

Dactinomycin can also form some reactive oxygen species (ROS) and is a substrate of P450 reductase (Figure 2).

Formation and Elimination of Reactive Oxygen Species (ROS)

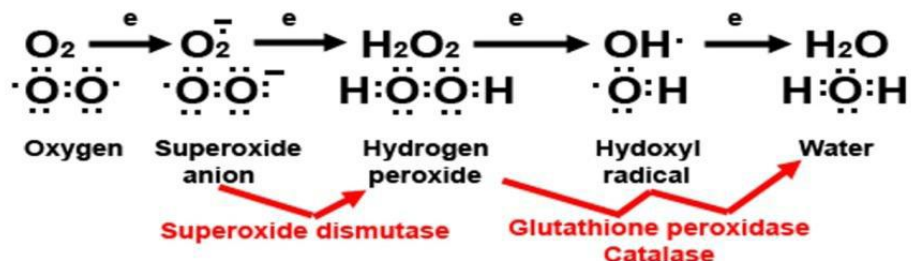


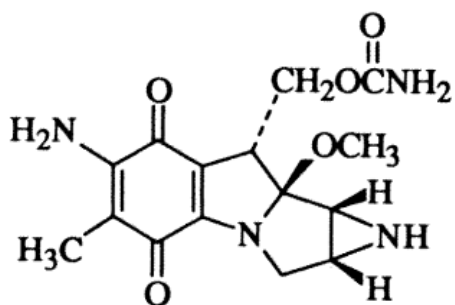
Figure 2. Molecular oxygen can be reduced by stepwise addition of electrons catalyzed by Fe^{++}

Toxicities: Myelosuppression, hepatotoxicity, fatigue, N/V, infection*, local inflammation if extravasation occurs, veno occlusive disease (liver toxicity can also occur).

ADME: Long $t_{1/2}$ due to minimal metabolic breakdown.

Note(s): Originally isolated from various bacteria, especially *Streptomyces*. *Because dactinomycin is also a bacterial antibiotic, it can interfere with diagnostic assays used to identify the bacteria causing an infection in patients.

Mitomycin (Mutamycin):



Uses: Gastric cancer, pancreatic cancer, bladder cancer. Administered IV. Also, intravesically for bladder cancer (directly into the bladder).

Mechanism: Like other macrolide antibiotics, intercalates into DNA, and can bind irreversibly through quinone system. Interferes with the transcription of DNA in mRNA. Can be activated by P450 reductase and NADPH quinone oxidoreductase (NQO1) and for ROS. Also a substrate of thioredoxin reductase (see clearance below). However, note presence of aziridine in the molecule. Thus, recent research has shown that mitomycin need not enter the nucleus and it can also inhibit cytosolic ribosomal (rRNA). This can cause inhibition of all (genome wide) translational silencing. This could be the most important mechanism.

Toxicities: Myelosuppression, nephrotoxicity, pulmonary toxicity, mucositis, alopecia; rare but potentially serious cardiotoxicity.*

ADME: Metabolism is hepatic and extrahepatic; renal excretion of parent and metabolites is important and about 10% of parent drug excreted renally. Metabolism routes are easily saturated and clearance of the agent is inversely proportional to dose (higher the dose → slower the clearance); recent data (2012) show that mitomycin can irreversibly inhibit thioredoxin reductase.

Note(s): *Cardiotoxicity almost always in association with previous anthracycline use. Remember the important cardiotoxicity of the anthracyclines (daunorubicin, doxorubicin, idarubicin).

Bleomycin: Actually a mixture but mainly bleomycin A2; isolated commercially as Cu⁺⁺ chelate. In vivo it becomes an Fe⁺⁺ chelate (Figure 3).

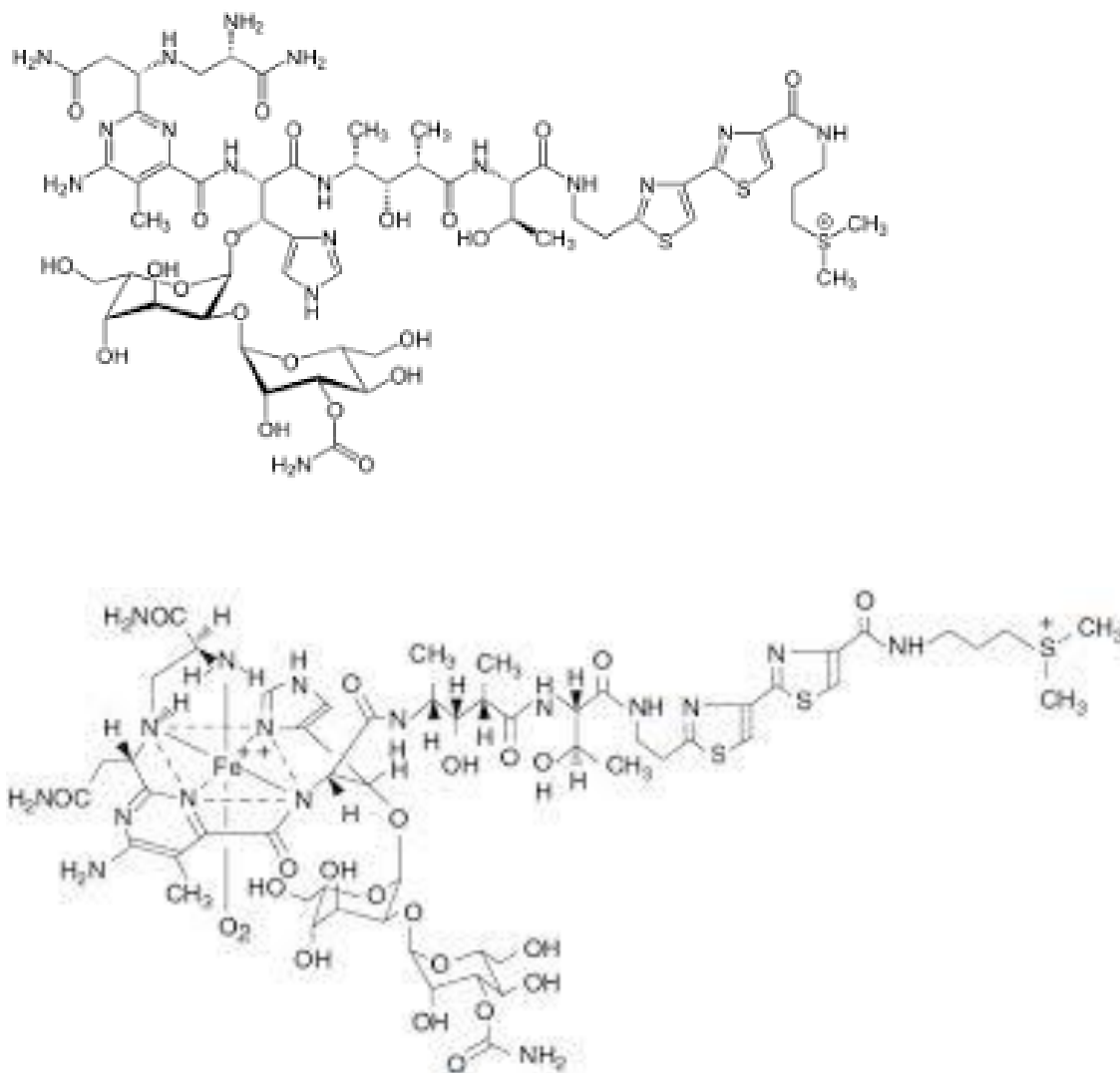


Figure 3. Iron chelated by bleomycin A2

Uses: Hodgkin's lymphoma as component in ABVD

(adriamycin/**bleomycin**/vinblastine/dacarbazine) regimen, NHL, squamous head and neck cancer, testicular cancer. A small test dose of bleomycin can be given to check for an allergic reaction to the agent prior to full dose.

Mechanism: Intercalates into DNA, then binds DNA covalently. Importantly, the agent also binds Fe^{++} and in vivo the chelate leads to generation of reactive oxygen species (ROS). Iron can catalyze the addition of electrons to oxygen (refer back to Figure 2).

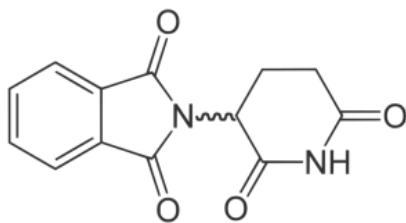
Toxicities: Myelosuppression, but mild (neutropenia, thrombocytopenia), pulmonary toxicity.* Allergic reaction can occur (rarely) but can be serious and lead to anaphylaxis.

ADME: *Important inactivating enzyme (bleomycin hydrolase); hydrolysis of terminal amide leads to the inactive carboxylate metabolite. Major change in charge (to -1) alters binding to DNA in a big way and reduces Fe⁺⁺ chelation. Finally, typical t_{1/2} is about 2-4 hrs; renal excretion is important for the agent and impairment of renal function can increase t_{1/2} to more than 20 hrs.

Note(s): Pulmonary toxicity is perhaps the most serious complication of bleomycin. It specifically involves pulmonary fibrosis. Studies support the role of ROS and proinflammatory cytokines (IL-18 and IL -1 beta) in the mechanism of lung injury.

Immunomodulators (we will discuss 3)

Thalidomide



Uses: Previously for multiple myeloma in combination with dexamethasone. Being studied in several other cancers because of its novel mechanism of action. Administered PO.

Because of its notable toxicity involving teratogenesis (see Toxicities below) a special program is in place that physicians and pharmacists must enter in order to dispense this drug. Program is called STEPS (**S**ystem for **T**halidomide **E**ducation and **P**rescribing **S**afety). Also approved for cutaneous erythema nodosum leprosum (ENL).

Mechanism: An immunomodulator and can increase in the number of circulating natural killer cells, and increase plasma levels of interleukin-2 and interferon-gamma. Both these cytokines are associated with cytotoxic activity. Thalidomide also possesses anti-inflammatory and antiangiogenic properties*.

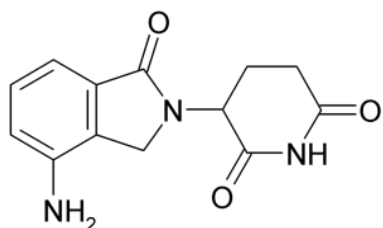
Toxicities: Teratogenic (phocomelia; limb shortening), but also can cause venous thrombotic events (deep vein thrombosis and pulmonary emboli); **black box warnings**. In addition, it can cause peripheral neuropathy, sedation, constipation. No or minimal myelosuppression. Any agent without myelosuppression is interesting to study further.

ADME: Spontaneously hydrolyses in vivo to multiple “metabolites”; also a substrate of CYP2C19 so potential PM concern. However, CYP pathway is not major. Notice the molecule has a chiral center but it is located adjacent to a carbonyl group. This causes the enantiomers of the molecule to racemize easily in solution. Therefore, there is no rationale for pursuing pure enantiomeric forms of this drug.

Note(s): Originally developed as a sedative and an anti-emetic for morning sickness in pregnant women but found to cause extreme birth defects in the late 1950s and early 1960s. Notably, the agent was never approved by FDA. However, it was approved in Europe and some U.S. citizens got access to the drug there, e.g. military personnel stationed in Europe for extended time periods. Also has some activity against leprosy.

*Angiogenesis is the formation of new blood vessels in tissues. As solid cancers grow they need to generate additional vasculature to supply the growing mass of cells with sufficient nutrients and oxygen. Inhibiting the angiogenesis process with anti-angiogenic drugs is therefore a reasonable approach (more on this topic later).

Lenalinamide (Revlimid): analog of thalidomide



Uses: Mainly multiple myeloma in combination with dexamethasone, melphalan, and doxorubicin. Being studied in several other cancers, in particular myelodysplastic syndrome (MDS), Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, pancreatic cancer. Administered PO.

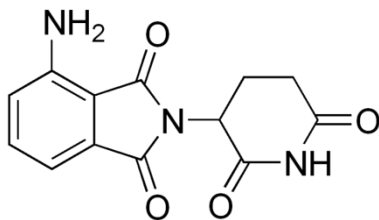
Mechanism: Multiple anti-cancer effects: A direct anti-tumor effect by inhibition of the microenvironment support for tumor cells, an immunomodulatory role like thalidomide, induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, anti-angiogenic and anti-osteoclastogenic effects. Nearly 10-fold more potent than thalidomide (e.g. 25 mg for L vs 200 mg for T daily dose).

Toxicities: Myelosuppression (neutropenia and thrombocytopenia) is much more severe than that of thalidomide and can be dose-limiting. Can be assumed to be teratogenic because so close in structure to thalidomide. Also causes venous thrombotic events (DVT and PE); **black box warnings**.

ADME: Much less breakdown compared to thalidomide; about 2/3 of the drug is excreted in the urine. Lenolinamide is not a substrate or an inducer of CYP450 enzymes.

Note(s): *Approved by the FDA on December 27, 2005 for patients with low or intermediate-1 risk MDS with 5q deletion, with or without additional cytogenetic abnormalities. Presently being monitored by FDA because it might be associated with an increased incidence of acute myelogenous leukemia and B-cell lymphoma.

Pomalidomide (Pomalyst): analog of thalidomide; approved in 2013



Uses: Multiple myeloma but only after patients have received at least two prior therapies including lenalidomide and bortezomib and have disease progression on or within 60 days of completion of the last therapy.

Mechanism: Multiple anti-cancer effects and similar to above.

Toxicities: Myelosuppression (neutropenia and thrombocytopenia) is much more severe than that of thalidomide and can be dose-limiting. Can be assumed to be teratogenic because so close in structure to thalidomide. Also causes DVT and PE; possibly worse than agents above; **black box warnings**.