Mithramycin is the most important member of the group of aureolic acid drugs, a small family of natural product anticancer antibiotics. Its biosynthesis is unusual, and full of unique enzymology. The drug itself was used in the 1960s and 70s mostly to treat testicular and bone cancers, but was discontinued to be used due to a too narrow therapeutic window and dangerous toxicities. The drug regained interest in 2011 when it was found to be the best drug against Ewing sarcoma, a rare bone cancer affecting only children and long adults, in an NCI screening encompassing 50,000 compounds, natural and synthetic products. We focused on both informations gained from biosynthetic and DNA binding studies and semi-synthetic methods following fragment-based drug development strategies to design novel mithramycin analogues with enhanced selectivity and broadened therapeutic window.