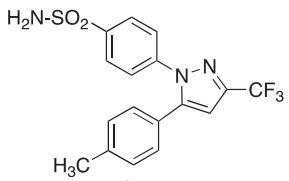
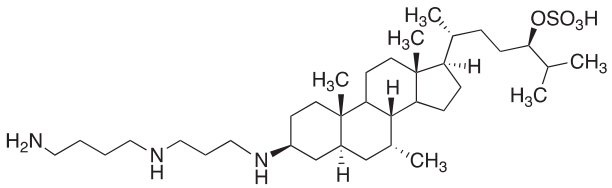


Celecoxib

6 MISCELLANEOUS ANTIANGIOGENIC COMPOUNDS

6.1 SQUALAMINE

Squalamine is an antiangiogenic aminosteroid isolated from tissues of several species of dogfish shark (*Squalus acanthias*). When discovered in 1993, it was reported to exhibit broad-spectrum antibiotic and fungicidal activity, being also an inductor of osmotic lysis in protozoa. In 2005, the FDA gave it fast track status for the treatment of "wet" age-related macular degeneration, which is mediated by inhibition of the choroidal neovascularization associated with this eye condition. In addition, squalamine has been the subject of clinical studies for several types of cancer.[88]



Squalamine

Similarly to the previously mentioned neovastat, squalamine interrupts and reverses multiple facets of the angiogenic process, such as VEGF activity, but it also induces endothelial cell inactivation and apoptosis through inhibition of integrin expression and disruption of cytoskeletal formation. In addition, it interacts with calmodulin and possibly other signaling pathways, and it specifically inhibits the isoform NHE3 of the Na^+/H^+ exchanger protein present on cell surfaces,[89] leading to changes in intracellular pH and subsequent inhibition of MAPK activity (Figure 11.24).[90]

6.2 THALIDOMIDE AND ITS ANALOGS

Thalidomide (Thalomid®) was introduced in the 1950s as a sedative prescribed for nausea and insomnia in pregnant women. Later, it was found to be the cause of severe birth defects in children whose mothers had taken the drug during the first trimester of pregnancy. In 1965, it was serendipitously discovered that thalidomide was effective at improving the symptoms of patients with erythema nodosum leprosum (ENL), and it was approved for this use in 1998. In 1994, thalidomide was found to inhibit angiogenesis through a complex mechanism that includes inhibition of the synthesis of TNF-α, which has a role in angiogenesis by upregulation of the expression of the endothelial integrin and VEGF growth factors, among others. In addition to the inhibition of angiogenesis, thalidomide is also involved