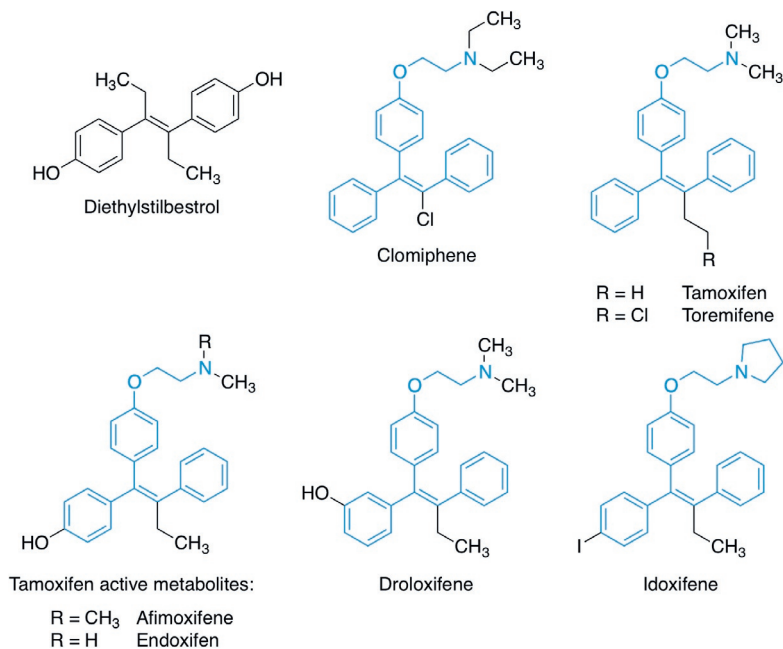


developed to treat menopause symptoms, have been studied. Other SERMS belonging to the family include toremifene (Fareston[®]),¹¹ droloxifene,¹² and idoxifene.¹³



Most of these compounds may lead to long-term toxic effects. For instance, tamoxifen induces liver cancer in rats after prolonged administration, which has been attributed to the generation of DNA-alkylating species from the metabolism of the stilbene framework. It has been proposed that in addition to other reactions, cytochrome P450 hydroxylates tamoxifen at the allylic position of the ethyl side chain leading to alcohol **3.5**, which can generate the highly delocalized allylic cation **3.6** and therefore alkylate DNA to give product **3.7** through an S_N1 mechanism (Figure 3.7).

This mechanistic proposal also explains the lack of carcinogenicity of toremifene, which can be attributed to destabilization of the positive charge in **3.8** by the inductive effect of the chlorine substituent at the position adjacent to the allylic carbon (Figure 3.8). Despite this advantage, toremifene is not often used due to other adverse side effects. Clinical trials with idoxifene and droloxifene have shown that they are no more efficacious or safer than tamoxifen.

Because of the toxic effects associated with the central double bond in triphenylethylene derivatives, a new family of antiestrogens was developed in which the incorporation of this double bond into a cyclic system increases its chemical and metabolic stability. Another structural difference of these compounds compared to the traditional triphenylethylene derivatives is the presence of a ketone group bridging the phenyl ring that contains the basic side chain. The main representative of this family is raloxifene (Evista[®]), which was identified as an antiestrogen and was first approved by the FDA only for the prevention of osteoporosis, whereas studies on its use as a treatment for breast cancer were discontinued. Interest in raloxifene as a means for breast cancer prevention was renewed and resulted in