

FIGURE 5.26 Although carbenicillin is a useful antibiotic, its use is hampered by spontaneous decarboxylation in acidic media. The tetrazole analog is similarly effective as an antibiotic, but does not suffer from instability in an acidic media as a result of the non-classic bioisosteric replacement (highlighted in red).

replaced with a tetrazole (Figure 5.26). In this instance, antibacterial activity was maintained, and an increase in chemical stability was imparted. Carbenicillin can spontaneously decarboxylate, while the tetrazole derivative is incapable of decomposing in this manner.⁴²

In some cases, non-classic bioisosterism can be employed to replace one scaffold with another. Biological activity is maintained, but physicochemical properties and target selectivity may be very different. Further, synthetic accessibility may be simplified, and greater intellectual property space may also be available around the new scaffold. It has been demonstrated, for example, that the steroid framework of 17β -estradiol, a major female sex hormone, can be effectively replaced with a simple *trans*-stilbene (Figure 5.27).

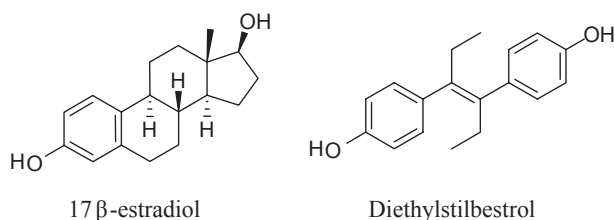


FIGURE 5.27 In this instance, three of the four rings in the steroidal framework are replaced by a stilbene framework. At the time of this discovery, this non-classical bioisosteric replacement provided novel intellectual property space and dramatically simplified the chemistry required to prepare novel estrogen receptor modulators.

Even though the two central rings of 17β -estradiol have been removed and a third ring has been replaced with a benzene ring, *trans*-diethylstilbestrol remains a potent estrogen receptor agonist.⁴³

Bioisosteric replacement, whether classical or non-classical, is an exceptionally important concept in the field of drug discovery and development. As indicated by the examples provided, even small bioisosteric changes can have a dramatic impact on the physicochemical and biochemical properties of a compound. There are hundreds of examples of potentially useful