As in the case of other antagonists, the binding of ICI-164384 or fulvestrant to the estrogen receptor obstructs the folding of the H12 helix of the receptor and therefore prevents its interaction with coactivators. In this case, the H12 rotation is physically prevented by the presence of the bulky C-7 side chain of the antagonist (Figure 3.12).

Fulvestrant is a competitive inhibitor of estradiol, binding at the estrogen receptors with an affinity of 89% that of estradiol. A consequence of fulvestrant binding is the impairment of the dimerization of estrogen receptors, leading to accelerated receptor degradation due to the lower stability of the monomer (Figure 3.13).[22]

Figure 3.14 summarizes the events associated with fully activated transcription by estrogen receptor agonists, partially inactivated transcription by SERMs, and full inactivation by antiestrogens. In the

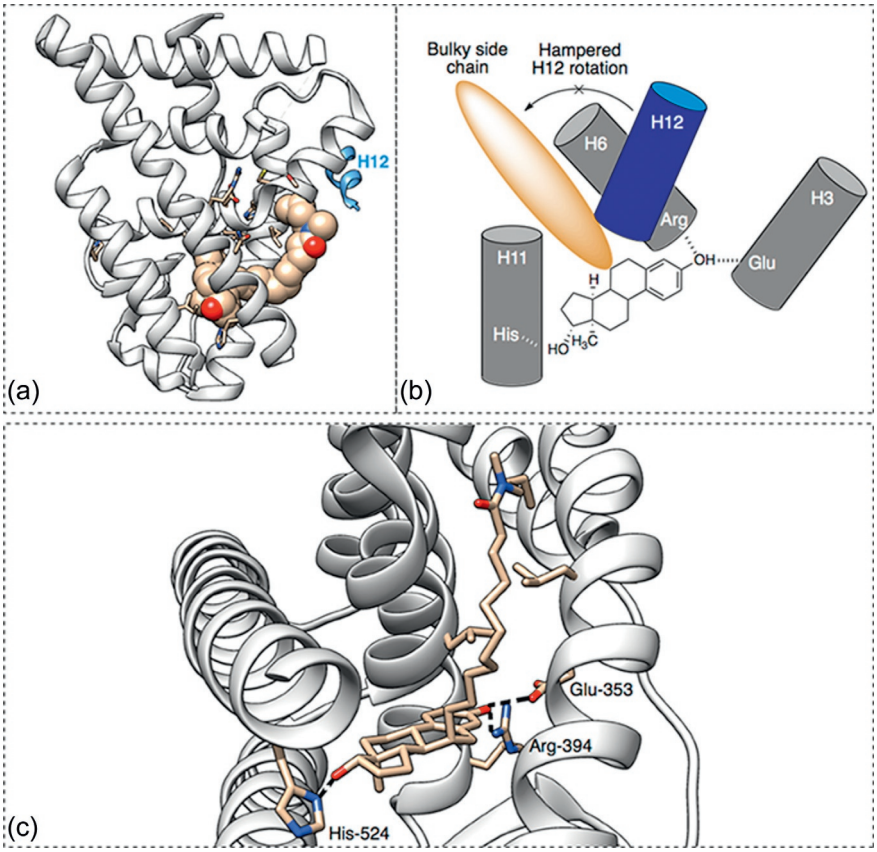

FIGURE 3.12

(a) Binding of ICI-164384 to the estrogen β receptor. (b) Schematic depiction of the blockade of the H12 chain of the receptor by the antagonist side chain. (c) ICI-164384 binds to the receptor active site by the same hydrogen interactions as estradiol, but its C-7 side chain protrudes from the cavity. The three-dimensional structures were generated from Protein Data Bank reference 1HJ1 and displayed with Chimera 1.8.1.