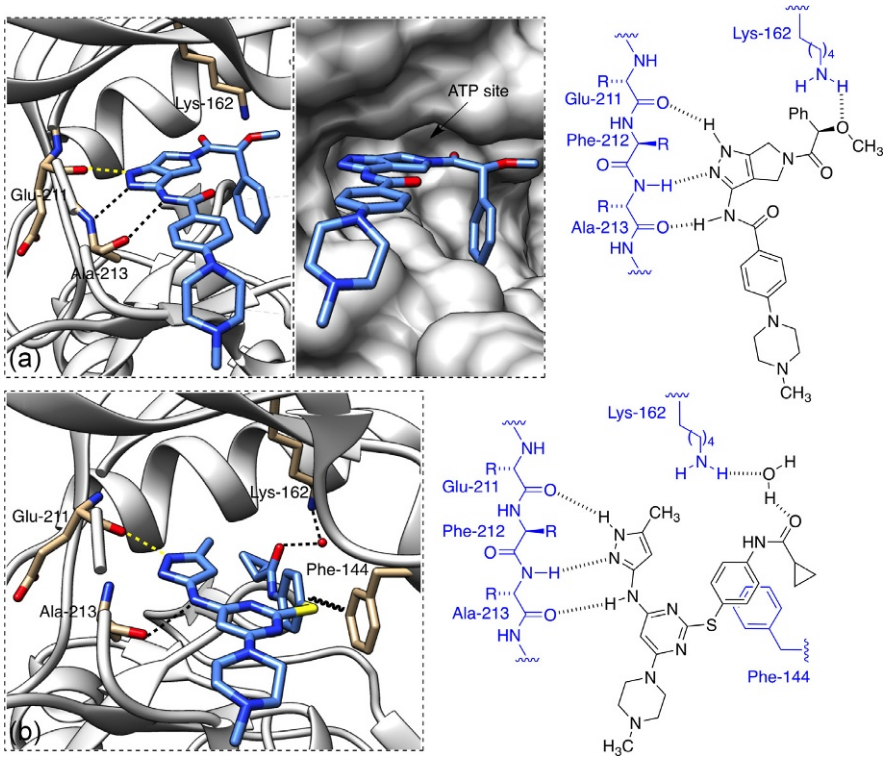

FIGURE 10.31

Recognition of danusertib (a) and tozasertib (b) by the ATP binding site of Aurora kinase A, which in the latter case was also bound to TPX2, a protein cofactor. The three-dimensional structures were generated from Protein Data Bank references 2 J50 (danusertib) and 3E5A (tozasertib) and displayed with Chimera 1.8.1.

These compounds were designed as adenine mimics at the ATP site of Aurore kinases, as shown in Figure 10.31 for two representative examples. In the case of danusertib, the aminotetrahydropyrrolo [3,4-*c*]pyrazole framework is responsible for the recognition of this site by H bonding to the peptidic framework at the Glu-111 and Ala-213 residues, whereas the methoxy substituent establishes an additional H bond with Lys-162 (Figure 10.31a).[206] In the case of tozasertib, the aminopyrazole fragment establishes similar H bonds with Glu-211 and Ala-213, and the carbonyl group of the cyclopropylamide moiety interacts with Lys-162. In this particular case, one of the loops in the kinase adopts a unique bent conformation that allows a $\pi-\pi$ interaction of the side chain of its Phe-144 residue with the phenyl group of the drug (Figure 10.31b).[207]

5.6 PROTEIN KINASE C (PKC) MODULATORS

PKC is a family of closely related serine–threonine kinases that can be activated by G protein-coupled receptors containing seven transmembrane domains. Activation of these receptors produces the activation of phospholipase C (PLC), which catalyzes the hydrolysis of the phosphatidylinositol