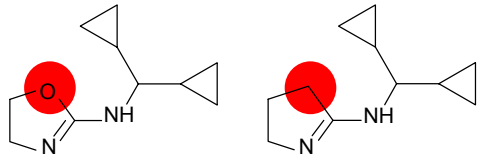
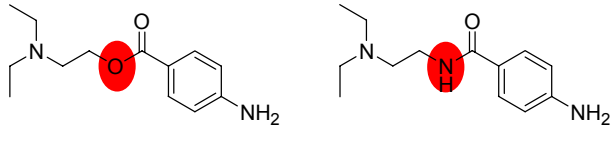


Rilmenidine Methylene isostere

FIGURE 5.23 In this example of classic bioisosterism, exchanging a carbon atom for an oxygen atom (highlighted in red) eliminates an undesired off-target activity. While both compounds are potent modulators of the I_1 imidazoline receptor, rilmendine's potent α_2-adrenoceptor binding is eliminated by this simple change.

(Figure 5.23). Both compounds share similar potency at the I_1 imidazoline receptor, a key player in the regulation of blood pressure. On the other hand, the new series of compounds demonstrated improved target selectivity, as although rilmendine potently binds to the α_2-adrenoceptors, the methylene analogs showed no affinity for this receptor. This successful application of classic bioisosterism clearly demonstrates that simple changes in chemical structure can be employed to alter some properties (abolishing α_2-adrenoceptor binding), while successfully preserving others (potency at the I_1 imidazoline receptor).[40]



Procaine Procainamide

FIGURE 5.24 While both procaine and procainamide block the same sodium channel, only procainamide can be used as a treatment for arrhythmia. In this instance, bioisosteric replacement of an oxygen atom with a nitrogen atom provides a compound with similar biological activity and substantially improved metabolic stability.

Procaine and procainamide (Figure 5.24) are also excellent examples of the impact that can be achieved with a classic bioisosteric replacement. Both of these compounds exert their pharmacological impact via sodium channel blockade. Procaine, more commonly referred to as Novocain, is only useful as a topical anesthetic, while procainamide is an orally administered antiarrhythmic agent. In this instance, a classic bioisostere exchange is employed to improve metabolic properties. The ester linkage of procaine is hydrolyzed quickly *in vivo*, limiting its utility to topical application, while the amide linkage in procainamide is significantly more stable *in vivo*. The enhanced metabolic stability conferred