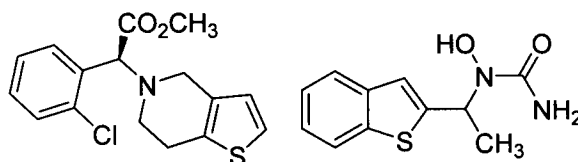


duloxetine (Cymbalta)

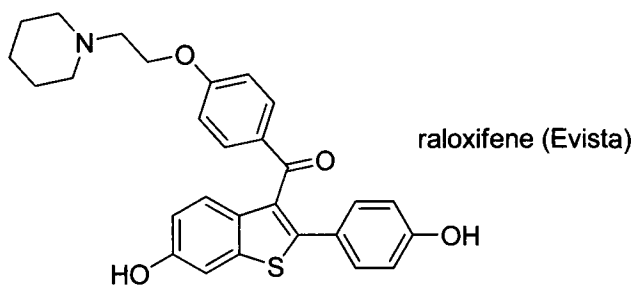
olanzapine (Zyprexa)

tiotropium (Spiriva)



clopidogrel (Plavix)

zileuton (Zyflo)



raloxifene (Evista)

## 4.2 Furans and Benzofuran

### 4.2.1 Reactions of Furans and Benzofurans

#### 4.2.1.1 Reactions at C2

There are few general methods for the functionalization of existing furan rings due to their low stability under acidic and aerobic conditions. For this reason, most functionalized furan derivatives are prepared by the cyclization of acyclic precursors using acid, base, or transition metal catalysis.

Despite the sensitivity of furans, several methods have been developed for the direct functionalization of these ring systems. The general reaction is shown below with C2 substitution preferred over C3. This is due to in part to the greater HOMO coefficient of the C2-carbon atoms as well as greater delocalization of the positively charged intermediate. Substitution at the C3 position can occur when the C2 position is occupied. Several examples, including halogenation, nitration, metal-halogen exchange,