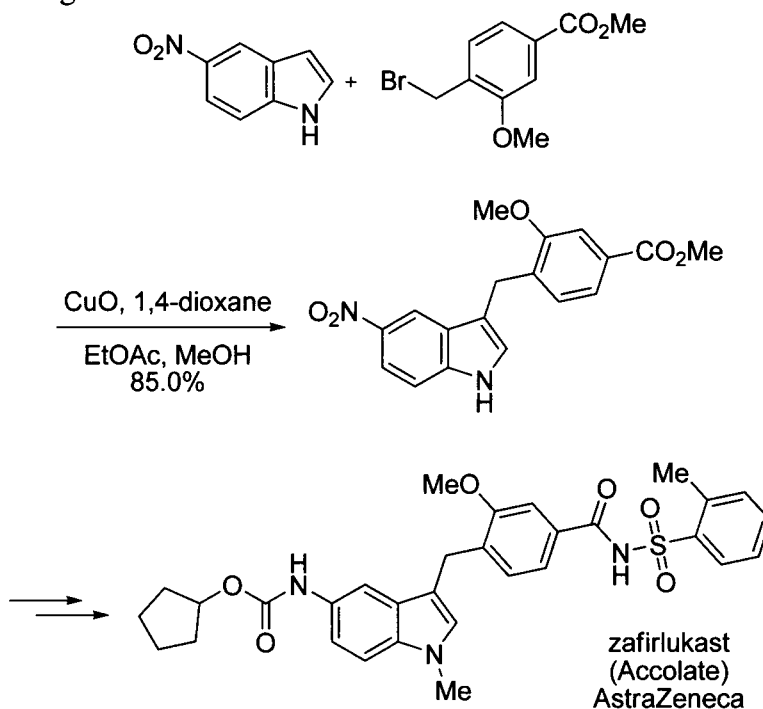


benzyl bromide in the presence of silver oxide and dioxane yielded the corresponding adduct.<sup>7</sup>



### 3.2.3 C2 Electrophilic Substitution

Electrophilic substitutions on the indole ring overwhelmingly favor the C3 position. However, when the energy outcome is favorable, C2 electrophilic substitutions do occur, especially for intramolecular substitutions. For instance, in the synthesis of tadalafil (Cialis), the Pictet–Spengler reaction is used to prepare the *cis*- $\beta$ -carboline where the C2 electrophilic substitution takes place. In the presence of trifluoroacetic acid (TFA), *D*-tryptophan methyl ester is condensed with piperonal. The C2-carbon of the indole adds to the resulting iminium ion to give a mixture of the *cis*- $\beta$ -carboline and the *trans*-isomer.<sup>8,9</sup>

