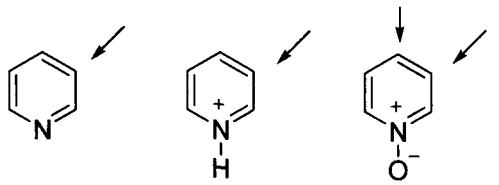
enzymes and display slow-offset kinetics.[10] For these reasons, binding assays for representative CYP450 enzymes are often included in the secondary pharmacology screening panels.

Several researchers investigated the structural requirements for the induction of hepatic microsomal cytochrome P450 2B1/2 and cytochrome P450 1A1/2. It was revealed that pyridine-containing compounds having lipophilic groups are inducers of hepatic P450, and compounds having aromatic groups and taking coplanar conformational structures are potent inducers of P450 1A1/2.[11]

Because of the potential liability of pyridine containing compounds as potent inhibitors or inducers of CYP450s, potential drug–drug interactions (DDI) need to be carefully considered. For instance, esomeprazole (**22**) is a competitive inhibitor of the enzymes CYP2C19 and CYP2C9, and it may therefore interact with drugs that depend on them for metabolism, such as diazepam and warfarin; *i.e.*, the concentrations of these drugs may increase if they are used concomitantly with esomeprazole.

10.2 Reactivity of the Pyridine Ring

10.2.1 Electrophilic Attack at Nitrogen of the Pyridine Ring[12]



General reactivity pattern for electrophilic substitution

Most pyridines do not undergo electrophilic substitution reaction (S_EAr) at the ring carbon atoms due to the decreased electron density compared with benzene. And if the S_EAr reaction does occur, it occurs exclusively at the 3-position. Strong nucleophiles, such as amide ion, hydroxides, and organolithium compounds, can attack the ring carbon atoms of pyridines via an S_NAr reaction preferably at the 2- or 4-positions. Electron-withdrawing groups on the pyridine ring, such as nitro and nitrile, favor the S_NAr reaction. S_NAr reactions with halogen or alkoxyl substituted pyridines proceed much faster than the corresponding unsubstituted pyridines with the halogen or the alkoxy group as the leaving group.

On the other hand, pyridine is a weak base (p*K*a = 5.22) that can be protonated or can form salts with strong protonic acids. Some of the resulting pyridinium salts are commercial reagents. For instance, pyridinium perbromide is used as brominating agent, and pyridinium dichloromate