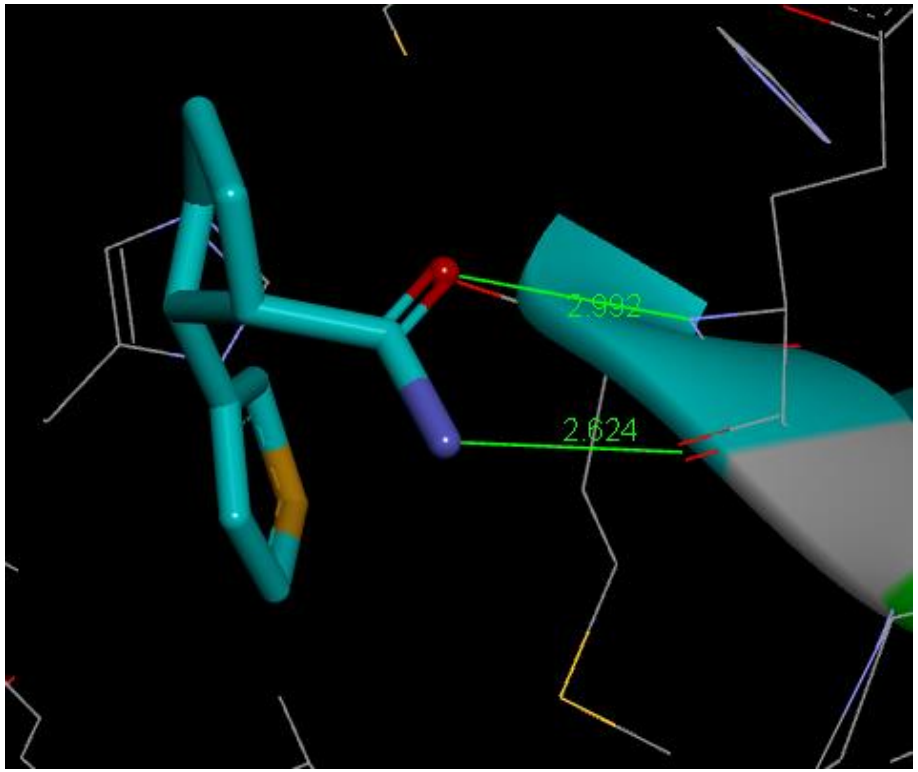
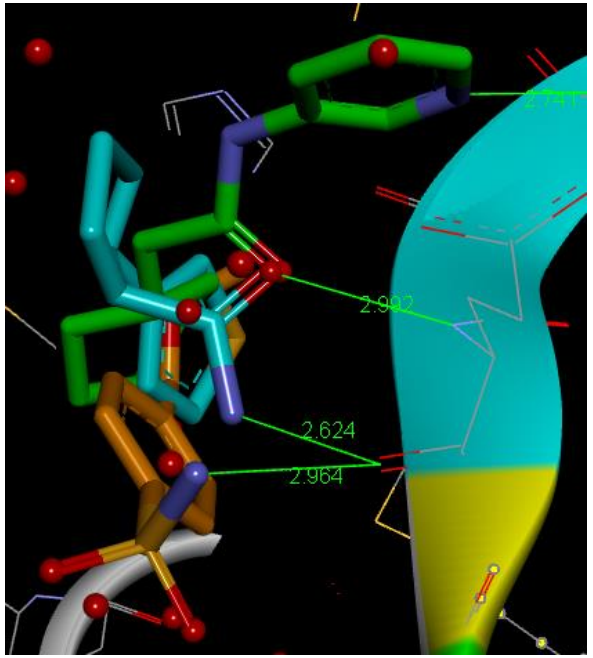
Fragment 874: Amide bidentate interaction with backbone

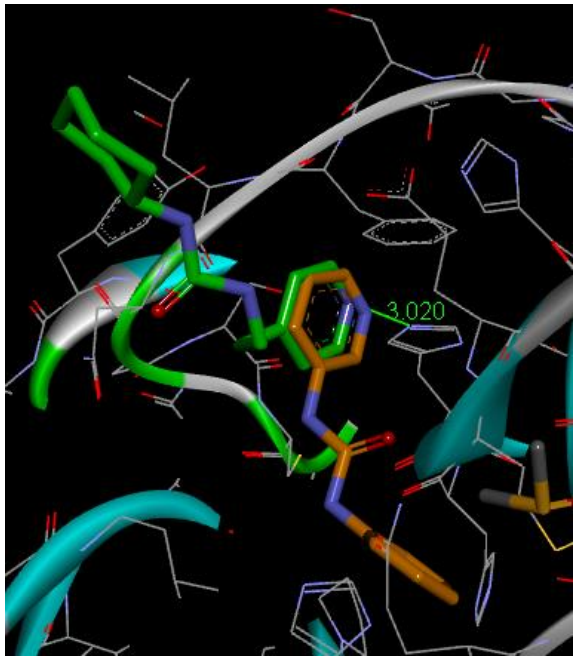


Could be a key interaction
c.f. hinge binder in kinases

Other ligands H-bond with one or other of these backbone carbonyl or NH

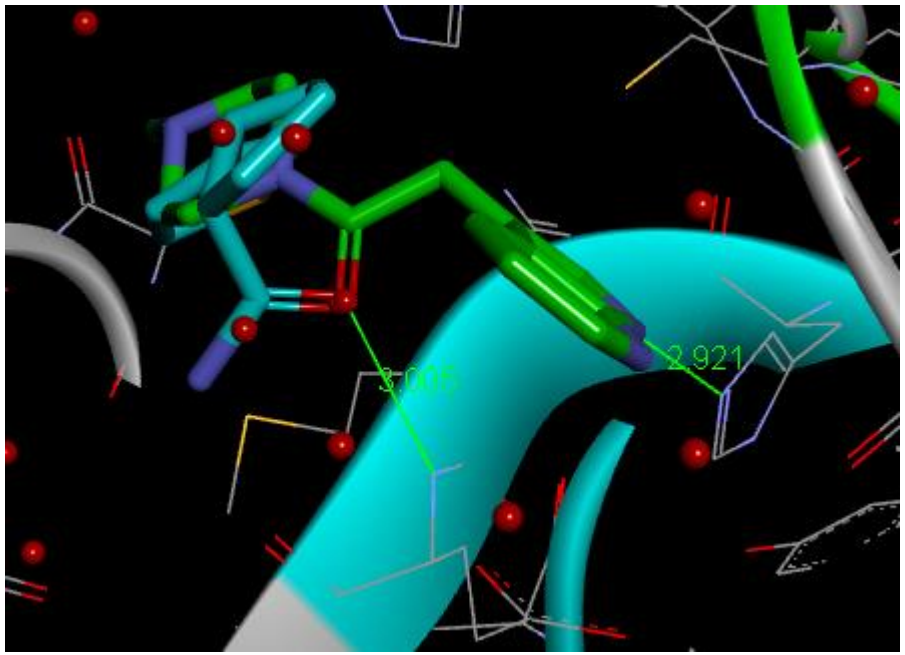


Pyridine to His163 conserved polar interaction



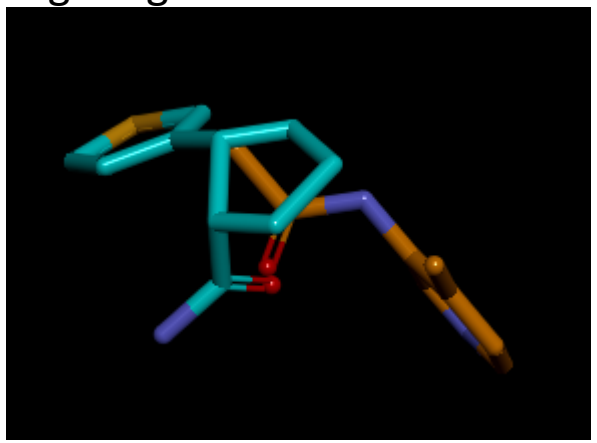
Green ligand appears to make no other productive interactions?

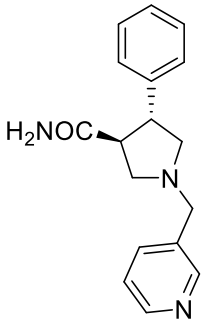
Azaindole His163 interaction



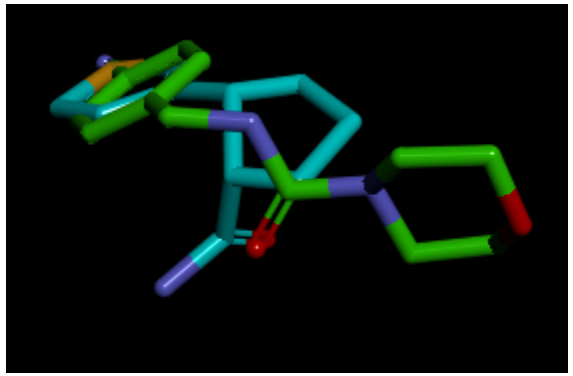
Non-covalent x0874 hybrids

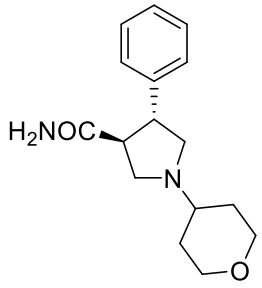
Targeting His163 interaction





x0874 x x0107

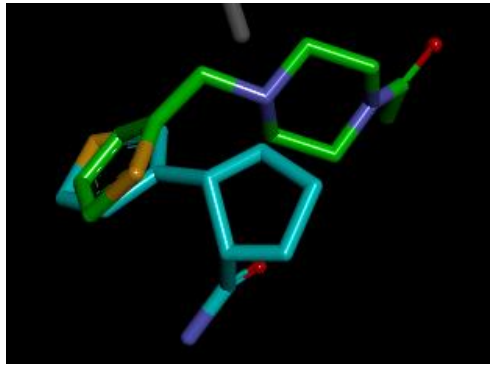


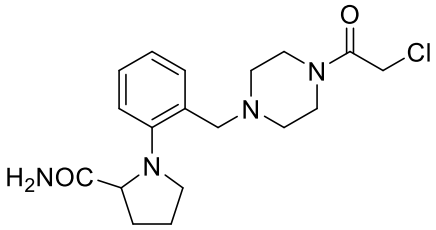


x0874 x x1249

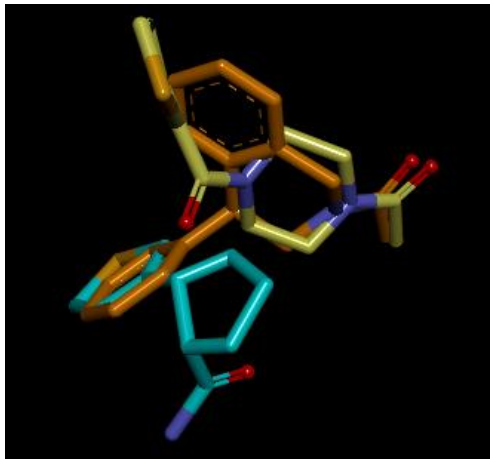
3+2 cycloaddition chemistry

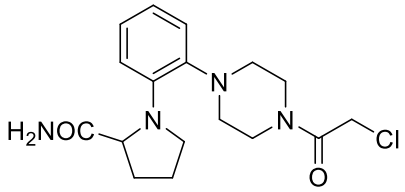
Covalent x0874 Hybrids





x0874 x x1418



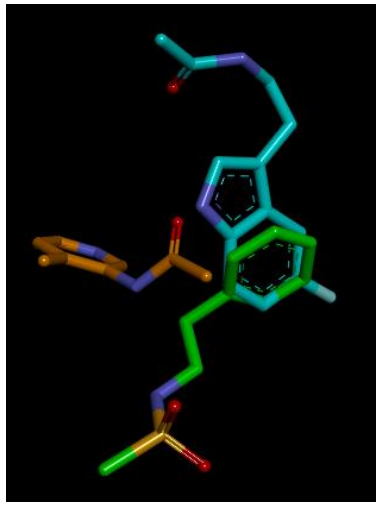


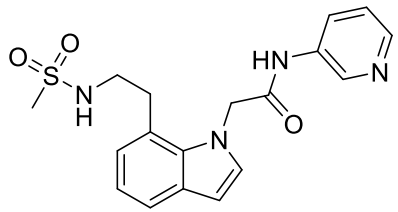
x0874 x x1392 x x1385

Ortho-substituents may clash, but may still be able to access targeted interactions

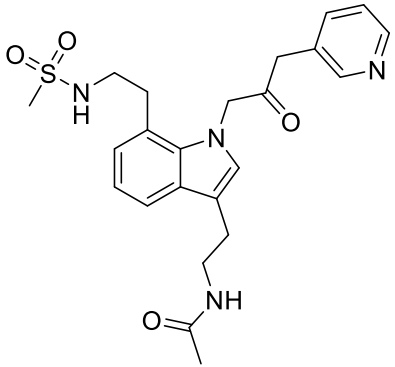
All synthetically feasible

Introducing His163 Interaction into other Fragments (Non-covalent)

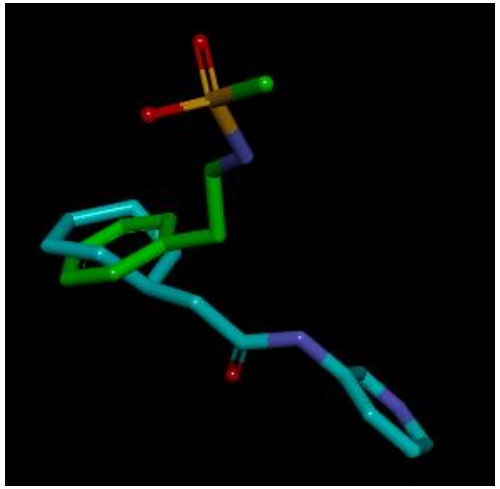


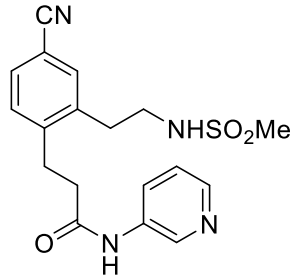


x0104 x x0107

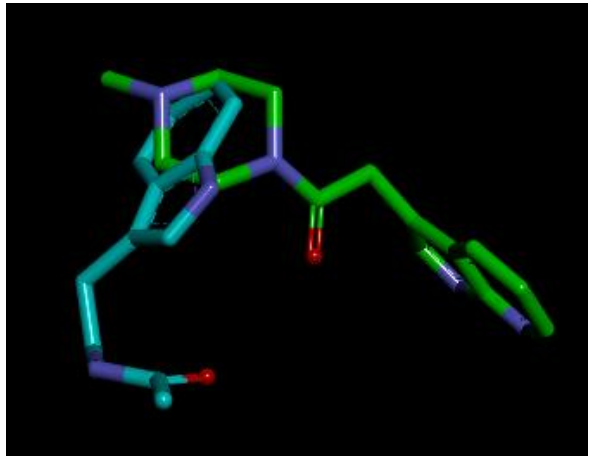


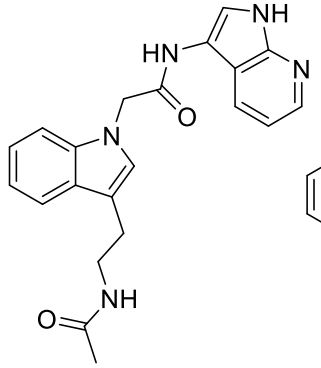
x0104 x x0107 x x0072



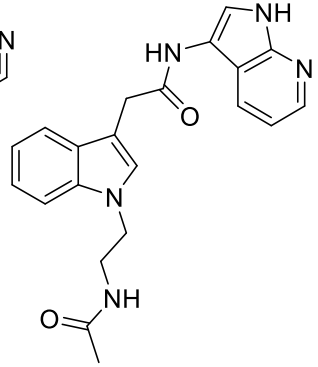


x0072 x x0678

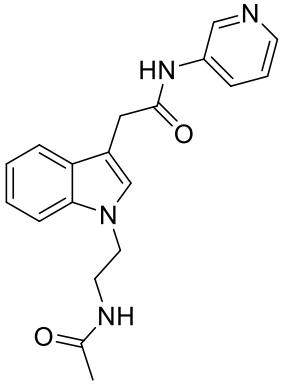




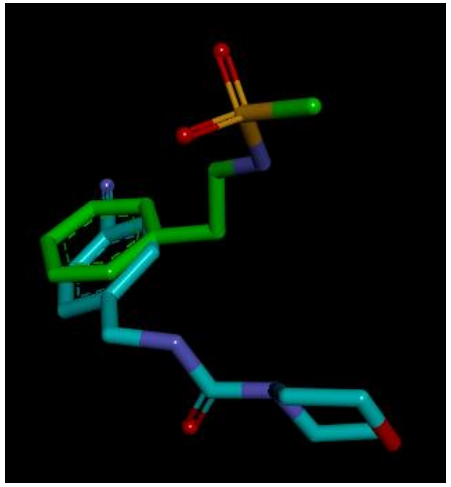
x0104 x x1093

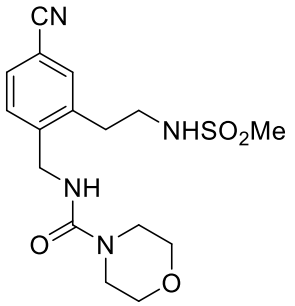


x0104 x x1093



x0104 x x1093

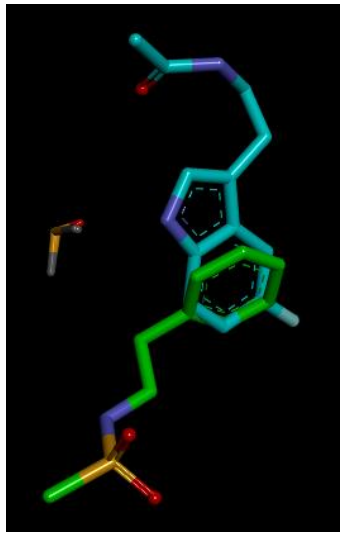


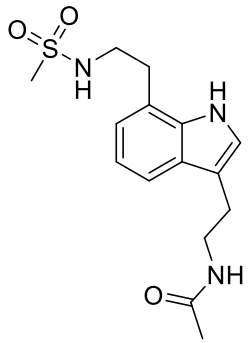


x0072 x x1249

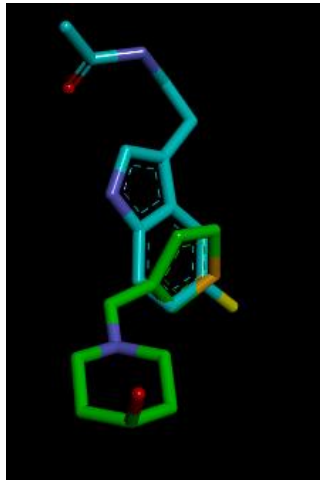
Moving indole nitrogen may
aid synthetic accessibility

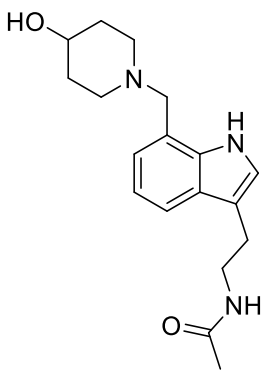
Other Non-Covalent Fragment Merges



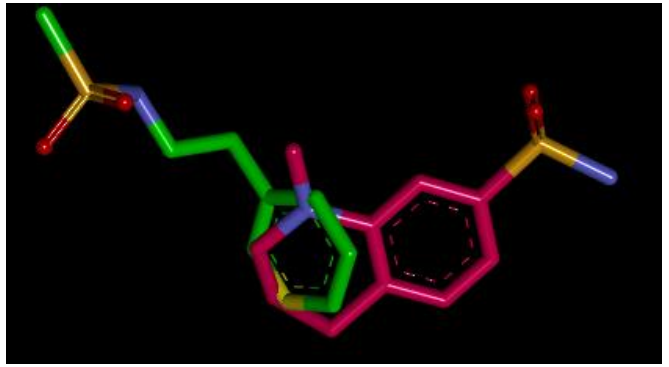


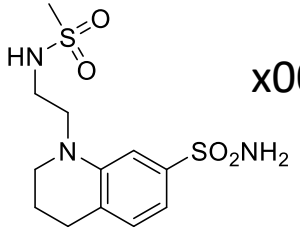
x0104 x x0072



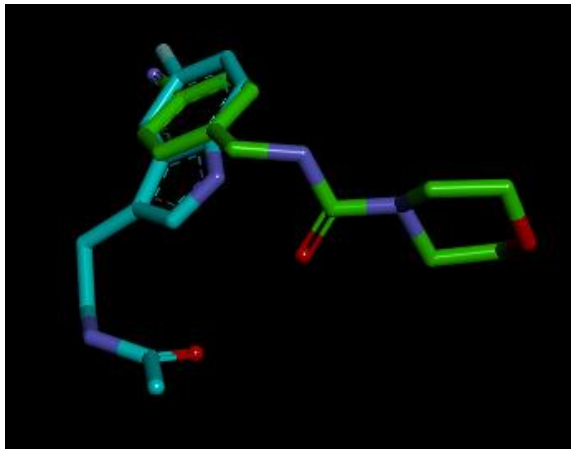


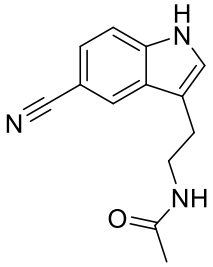
x0104 X x0387



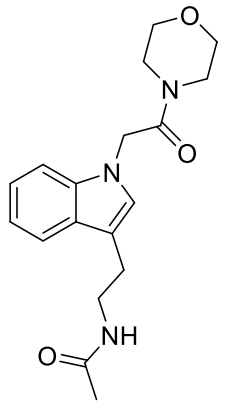


x0072 x x0195



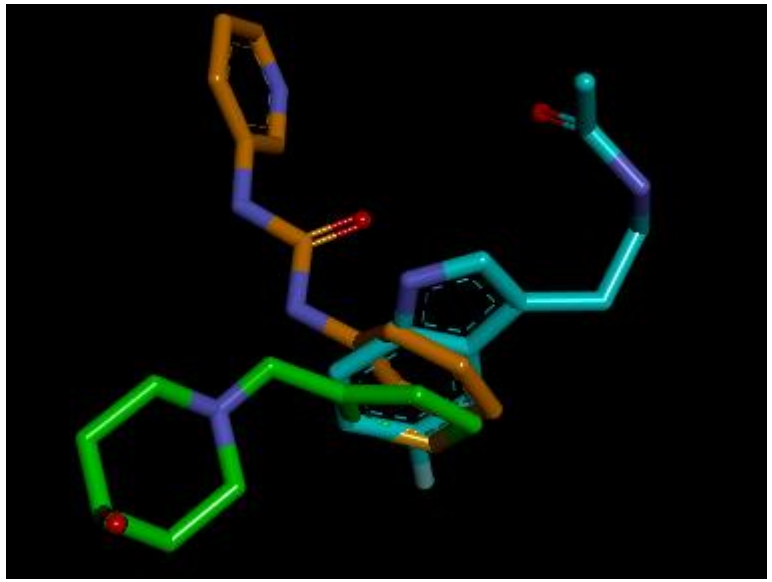


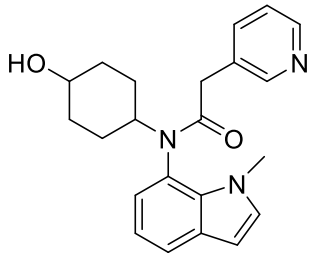
x0104 X x1249



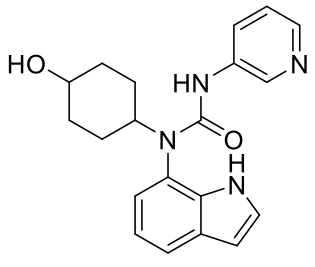
x0104 X x1249

Three-way non-covalent fragment merges

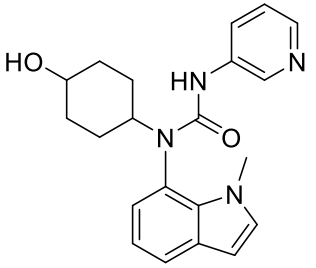




x0104 x x0434 x x1249

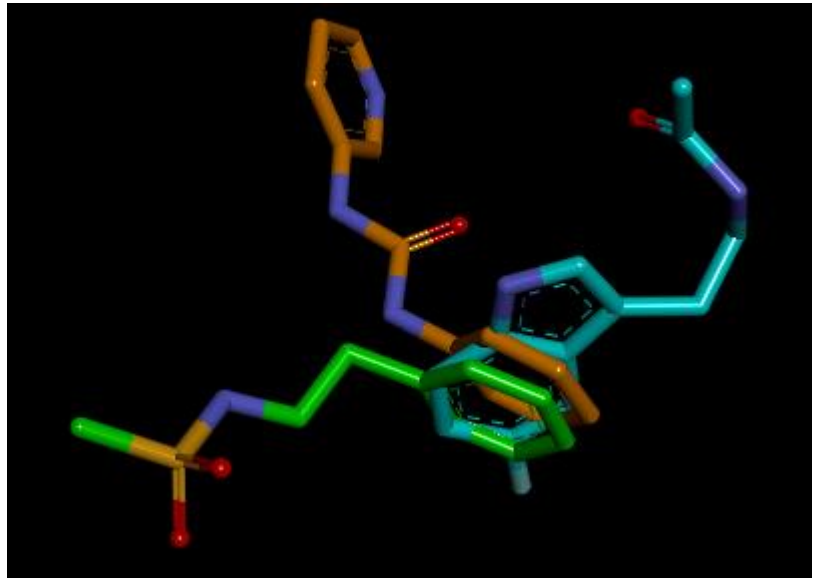


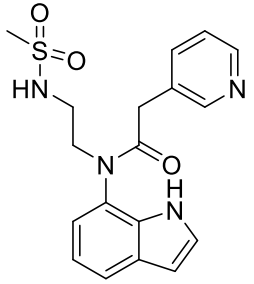
x0104 x x0434 x x1249



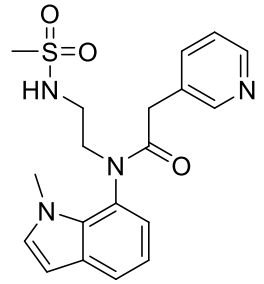
x0104 x x0434 x x1249

Pyridyl and sulfonamide groups out of plane of the indole. Methylation of the indole nitrogen may favour this conformation



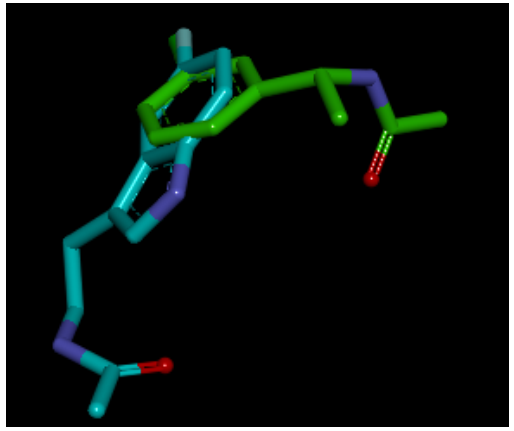


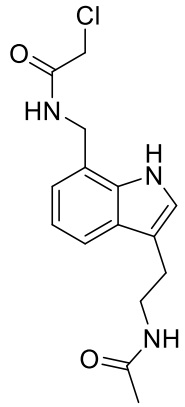
x0104 x x0434 x x0072

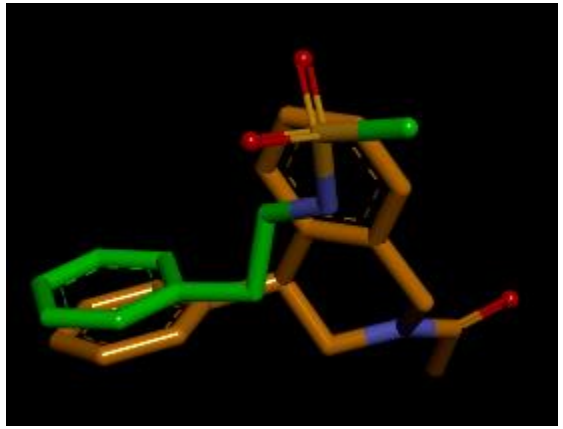


x0104 x x0434 x x0072

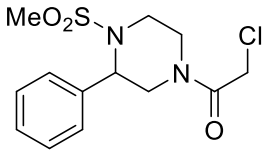
Covalent Merges

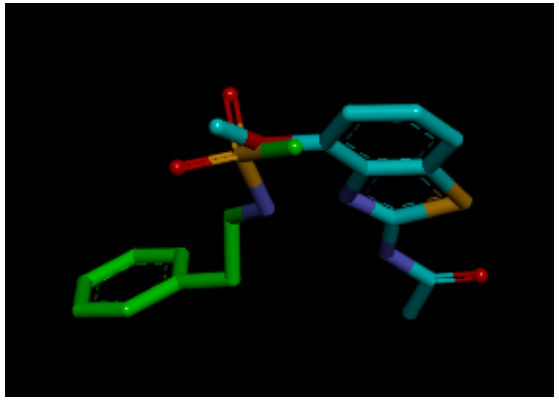




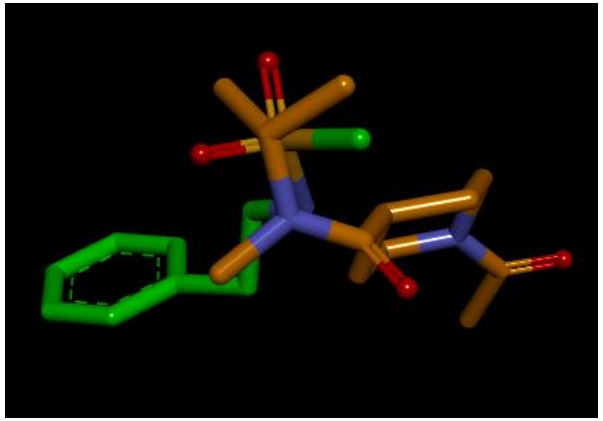


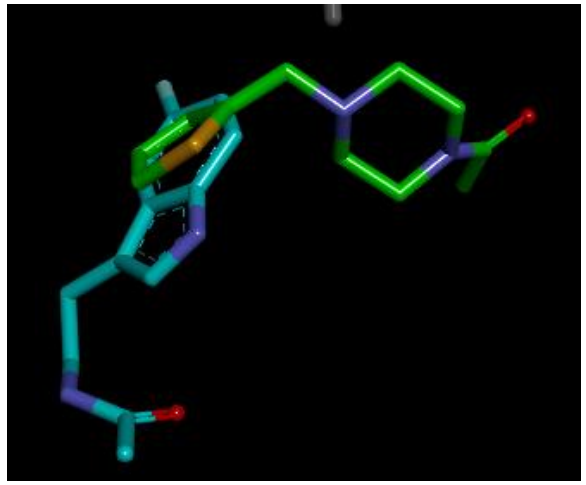
x0104 x x1382

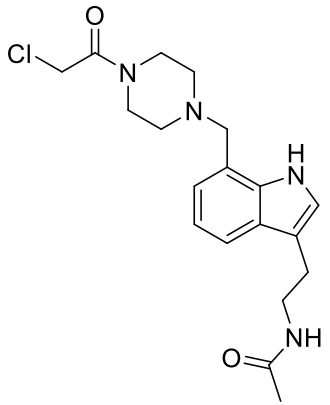




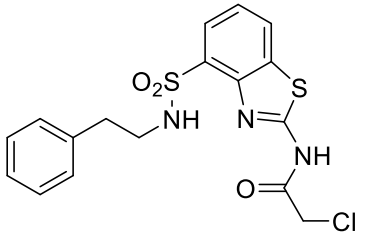
x0072 x x1392



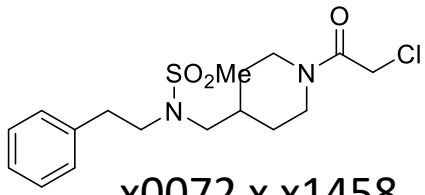




x0104 x x1418



x0072 x x1348



x0072 x x1458