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Tautomerism occurrence and intrinsic importance in the development of new drugs

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Tautomerism is a phenomenon quite common in biomolecules that also appears in many drugs, and strategies to control the corresponding desired species and related equilibrium conditions leading to efficient chemical speciation are frequently required. The presence of isomers is a huge challenge in the development of new medicinal or pharmaceutical agents because the main goal is to obtain the most active compound with high purity and yield. In the literature, there are significant works about the presence of tautomers, although some articles do not properly emphasize their occurrence or their importance for the differences verified in biological activity. Nucleobases are examples of molecules presenting tautomers that differ in the position of protons, and such structural differences play crucial roles in their hydrogen bonding interactions, leading to altered base pairing and consequently to serious effects on biochemical processes where nucleic acids are involved. For instance, minor tautomers that are transiently formed during replication could generate undesirable mutations. Herein tautomers observed both in metalated and non-metalated compounds and their importance in the biological properties of promising drugs is discussed. Mainly, keto-enol equilibria among imines, hydrazones, and oxindole derivatives are showcased, based on noteworthy examples investigated in our laboratory or described in the literature. Strategies to improve their speciation or to better elucidate their modes of action are suggested.

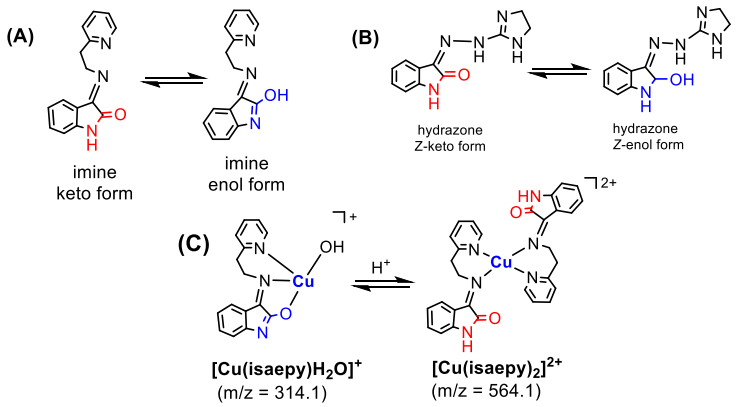

Figure 1 - Some oxindolimine (A) and hydrazine (B) ligands and corresponding metal complexes (C) showing keto-enol tautomerism.

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