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Abstract:

Owing to their inherent three-dimensionality and structural novelty, spiro scaffolds have been increasingly utilized in drug discovery. In this brief review, we highlight selected examples from the primary medicinal chemistry literature during the last three years to demonstrate the versatility of spiro scaffolds. With recent progress in synthetic methods providing access to spiro building blocks, spiro scaffolds are likely to be used more frequently in drug discovery.

One widely used strategy in drug design is to rigidify the ligand conformation by introducing a ring.[1] The resulting cyclic analog will suffer a reduced conformational entropy penalty upon binding to a protein target. In addition to ring fusion, conformational restriction can also be imposed by introduction of a spiro-ring fusion. Spiro compounds are molecules containing two rings with just one shared atom (the spiroatom). Spiro rings such as spiroketals are present in numerous natural products;[2] simple spiroketals are known insect pheromones. A small number of spiro containing drugs has been investigated during the last several decades;[3] a few examples are shown in Figure 1. Recent progress on new synthetic routes to spiro building blocks will facilitate incorporation of spiro scaffolds into more pharmaceutically active molecules. Spiro containing systems not only have greater three-dimensionality than flat aromatic compounds, but also introduce structural novelty for patentability. Even though both spirocyclic and flat aromatic rings can impact ligand binding entropy, it has been suggested that compounds with too many flat rings have suboptimal physical properties and are less likely to be successfully developed as drugs.[4] As a result, spiro compounds have increasingly appeared in the recent literature.[5]

In this review, selected examples from medicinal chemistry literature published within the past three years (2011- March 2014) will be presented to illustrate the utility of spirocyclic scaffolds in drug discovery.