# Small Bicyclic Amines: Unexplored Motifs For Drug Discovery

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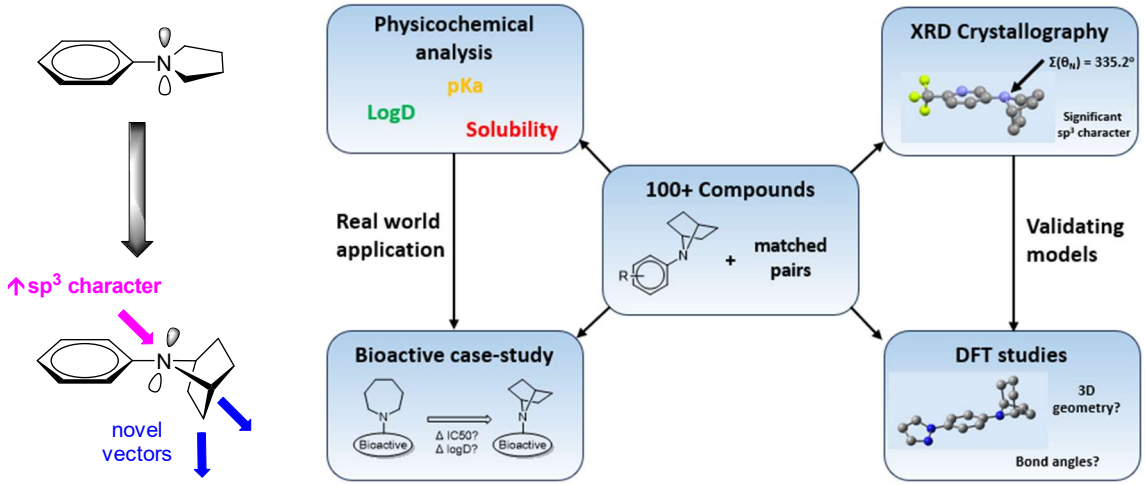
The potential for novel structural motifs to impact beneficially on the drug-like properties of molecules is well documented: for example, the introduction of BCP motifs as sp3-rich bioisosteres of aromatics by Pfizer lead to improved aqueous solubility and metabolic profile[1]. AstraZeneca demonstrated that addition of a bridging carbon atom to azacycles can counterintuitively *lower* log D, with positive impacts on metabolism and hERG inhibition profiles[2]. In this work, we introduce *small bicyclic amines* (SBAs) as underexplored structural motifs that, when linked to (hetero)aryl groups, retain a pyramidalized nitrogen configuration. This unique property, owing to the bicyclic effect[3], not only expands the three-dimensional design space for medicinal chemists but can also improve drug-like characteristics such as aqueous solubility, logD, and metabolic stability. To demonstrate this, we synthesised a fragment library of (hetero)aryls containing SBAs and their non-SBA isomeric analogues; characterised the physicochemical and structural properties of these fragments and used the observed structural properties to validate models that predict structures of currently unknown SBA derivatives. Finally, the potential of SBAs in bioactive discovery applications was validated in collaboration with GSK on a previous discovery programme.

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