NMR-guided and fragment-based design of protein-protein interaction inhibitors. Application to CK2 kinase.

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Fragment-based approaches that rely on the screening of small libraries (thousands of compounds) against purified therapeutic targets are particularly well suited for the design of protein-protein interaction inhibitors. This is mainly due to the fact that protein-protein interfaces consist of discontinuous hot-spots as compared to more conventional protein pockets. Examples of successful application of fragment screening for the discovery of PPI modulators include XIAP/caspase-9, Bcl-2/Bax, and bromodomains.

The design of compounds from initial fragments typically requires structural information, and X-Ray crystallography is the method of choice. Here we will show how NMR combined to docking can be a robust, rapid and efficient approach for fragment screening, fragment growing and for hit to lead optimization. This will be exemplified using kinase CK2 as therapeutic target.

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