Recent developments in ^{19}F NMR spectroscopy for fragment screening and drug design

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Over the last few years, fluorine NMR spectroscopy has gained significant attention in the pharmaceutical industry and academic institutions as an efficient and reliable method for performing functional and binding assays.[1] The high relative sensitivity of the binding experiments to protein interactions results in a large dynamic range, thus allowing the detection of very weak-affinity chemical fragments. This is due to two physical mechanisms that simultaneously contribute to the line width of the observed ^{19}F NMR signals: the ^{19}F chemical shift anisotropy (CSA) in the bound state and the exchange originating from the ^{19}F difference in chemical shift between free and bound state. In the binding assay a library of fluorinated molecules is first screened, and the identified binders are then used as *spy molecules* for subsequent screening experiments and for measuring the binding constant of the molecules interacting with the receptor. Different types of fluorinated libraries can be generated by using different selection criteria.[2] The choice of fluorinated motifs present in the library is fundamental in order to ensure a large coverage of chemical space and local environment of fluorine (*LEF*).[3] Complex mixtures of highly diverse fluorine motifs can be rapidly screened using optimized pulse sequences and deconvoluted in the same NMR tube with a novel combined procedure for the identification of the active molecule(s).[4] This allows for high throughput and fast data analysis.

The *LEF* determines the ^{19}F NMR chemical shift and the interactions of fluorine with the receptor. A correlation between the ^{19}F NMR isotropic chemical shifts and the type of close intermolecular contacts to the fluorine atoms was derived. Based on all these findings the *rule of shielding* was proposed for providing some insight into and guidelines for the judicious selection of appropriate fluorinated moieties to be inserted into a molecule for making the most favorable interactions with the receptor.[5] Novel chemical scaffolds, based on the *rule of shielding*, have been designed for recognizing distinct structural motifs present in proteins.

References

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