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Affinity-based Compound Screening Using NMR for the Discovery of a New Drug Candidate

HJ Han, JW Moon, SS Kang, KH Kim, JH Kim, JH Lee, DK Shin, SG Ro, YH Jeon

LG Biotech Research Institute

A critical aspect of the drug discovery process is the ability to reliably detect and identify small molecules that bind to macromolecular targets. For the initial stage of the compound screening which employs a lot of structurally diverse compounds, it is important to detect weakly binding compounds to the active site of the target receptor. The recently developed NMR techniques, which detect complexation of a small molecule with a target receptor promises to be a valuable tool for this purpose. These techniques include relaxation-edited NMR, transferred-NOE spectroscopy, diffusion dependent signal observation, monitoring the amide chemical shift changes of 15N-labeled proteins, etc.

Here, we present some examples for the application of these techniques to the pharmaceutical target proteins. Tens of compounds were selected by the affinity-based compound screening by NMR, and their binding site were identified by the competition with known inhibitors, monitoring the 15N-labeled amide chemical shifts, and TRNOE measurement. To diversify the initial hits, amide-aldehyde coupling was carried out to generate second library. We could select some aldehyde compounds that coupled to the initial hits and increase their affinity. To get an insight for the design of new scafold, or pharmacophore, the computer-aided ligand docking process can be used. These methods may lead us to the discovery of the novel drug candidate in a short time.