In Silico-Based Drug Discovery Targeting HGF-Met

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To discover small molecule inhibitors for HGF-Met pathway, we organized a research group contributed by researchers in different fields and specialties (K. Matsumoto as a head researcher). In this research, specific structures involved in functional association between HGF and Met, and in their dimerization for Met activation were selected as target structures. First, about 3,000,000 chemical compounds were screened using successive combination of virtual techniques (docking simulation method, clustering technique of compounds, etc) and hundreds of compounds were selected (Fig. 1). These compounds were further screened by physical binding assay, ELISA assay, and in vitro biological assay. Through these screening, several lead compounds were obtained. These lead compounds inhibited biological activity of HGF.

Next to potentiate and optimize selected lead compounds, analysis of the crystal structure of the complex composed of a target protein and a compound is in progress (Fig. 2). Based on this "structure-based drug design", lead compounds will be potentiated and optimized.

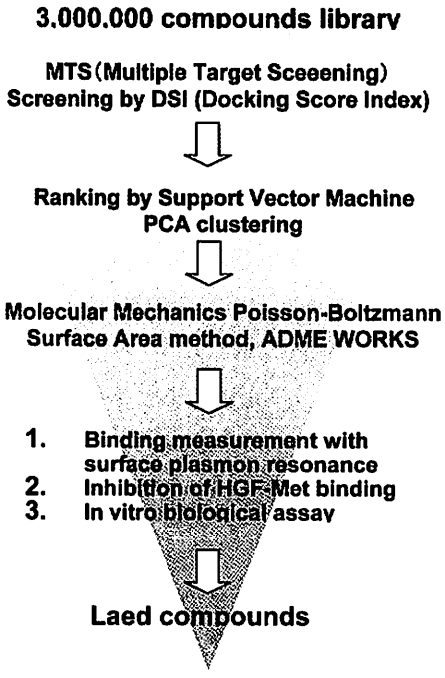

Fig. 1. Outline for screening of 3,000,000 chemical compounds, using in silico virtual screening techniques, biochemical and biological assay.

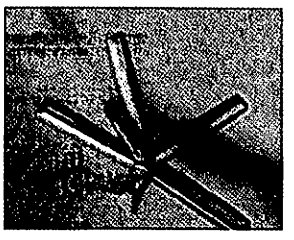

Fig. 2. Crystal of the complex composed of a target protein and selected compound.