

qHTS for Identifying the Cell Membrane Permeable Inositol Monophosphatase Inhibitors with HTRF IP-One Reagents

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Lithium has been used for the treatment of Bipolar Disorder in last 50 years with a narrow therapeutic index. Despite its severe adverse effects, it remains a main therapeutic choice for the patients with acute mania. Inositol monophosphatase (IMPase) has been speculated as a target of lithium therapeutic action. The traditional enzyme-based assays have failed to discover the cell-membrane permeable and bioavailable IMPase inhibitors. Cell-based enzyme assay offers a new approach for identifying inhibitors of intracellular enzymes. We have optimized and miniaturized the HTRF inositol-1-phosphate (IP1) assay in 1536-well plate format and applied it for a screen of ~100, 000 compounds. A total of 30 potential IMPase inhibitors were identified from the primary screening. The confirmation and follow-up assays on these active compounds are currently carrying out. Our results indicated that this HTRF IP-One assay is cost effective and robust for high throughput screening.