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Discovery of a small molecule direct Keap1-Nrf2 inhibitor as an anti-oxidant inflammation modulator

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Abstract

Keap1-Nrf2-ARE signaling has become an attractive target for the prevention and treatment of oxidative stress-related diseases and conditions including cancer, neurodegenerative, cardiovascular, metabolic and inflammatory diseases. Keap1-Nrf2 protein-protein interaction is considered as a critical point of the pathway that can be targeted for intervention. All currently known Nrf2-activating/ARE-inducing agents function as electrophiles and indirectly inhibit Keap1-Nrf2 interaction through covalent modification of the sensitive cysteine residues of Keap1 or Nrf2. LH601A (ML334), a first-in-class direct inhibitor of Keap1-Nrf2 interaction was identified through HTS of NIH's MLPCN library using a homogenous fluorescence polarization assay. LH601A is functionally active in both ARE gene reporter assay and Nrf2 nuclear translocation assay, and the binding constant (K_d = 1 μM) of LH601A to Keap1 Kelch domain was confirmed using asurface plasmon resonance solution competition assay. The stereospecific nature of binding between LH601A and Keap1, and preliminary structure-activity relationship studies supports that LH601A is a promising lead compound for developing improved and therapeutically applicable derivatives.

Biography

Dr. Magesh Sadagopan is a Scientist at Department of Medicinal Chemistry; Otsuka Maryland Medicinal Laboratories. He obtained his B. Pharm degree in 1999 from the Tamilnadu Dr. MGR Medical University, India and his MS. Pharm in Medicinal Chemistry in 2001 from NIPER (Punjab), India. He obtained his PhD in Bio-organic Chemistry in 2008 from Gifu University in Japan, under the guidance of Prof. Kiso Makoto. He held postdoctoral positions at Gifu University (iCeMS, Kyoto University) with Prof. Kiso Makoto and at Rutgers University with Prof. Longqin Hu.