



Title: Novel Nrf2 activators based on mechanism-based approach

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NF-E2-related factor-2 (Nrf2) is a transcription factor which induces cytoprotective enzymes via controlling the antioxidant response element (ARE)/electrophile response elements (EpREs). Nrf2 activity is regulated by the Keap1 protein through the formation of the Keap1-Nrf2 complex. Under oxidative stress, a disruption of the Keap1-Nrf2 complex induces the release of Nrf2 and the translocation of active Nrf2 into the nucleus, leading to ARE-dependent expression of HO-1. Recently endogenous 15d-PGJ2 was reported as a potent Nrf2 activator. Its Nrf2 activation is considered to be induced by a 1,4-nucleophilic addition of the reactive thiols in Keap1 to the cyclopentenone core of 15d-PGJ2. In this connection, we have been working on 15d-PGJ2 to elucidate its structural features, focusing on its electrophilic binding sites, and to confirm the proposed mechanism associated with the interaction with Keap1.

The mechanism-based chemical transformation of 15 deoxy-PGJ2 identified a series of novel Nrf2 activators and elucidated the key roles of each binding site of 15d-PGJ2 with regard to Nrf2 activation. These results enable us to develop novel 15d-PGJ2-based Nrf2 activators. The rationally designed chemical probes also supported that the concise tuning of the electronic states of the 15d-PGJ2 binding sites could ultimately enhance HO-1 expression. Homology modeling also predicted that the covalent adduct of α -chloro-15d-PGJ2 with Keap1 IVR is more stable than the 15d-PGJ2 adduct. Our systematic studies on Nrf2 activation associated with 15d-PGJ2 is anticipated to provide a facile access to novel chemopreventive therapeutics.

Biography

Seyeon Hwang was born in 1991 in Seoul, South Korea. She received her bachelor's degree in Pharmacy from Seoul National University in 2015. She is currently a M.S. candidate in the laboratory of Professor Young-Ger Suh at Seoul National University.

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