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Identification and structural analysis of novel Nrf2 activators via mechanism-based chemical transformation of 15-deoxy-$\Delta^{12,14}$-PGJ_2

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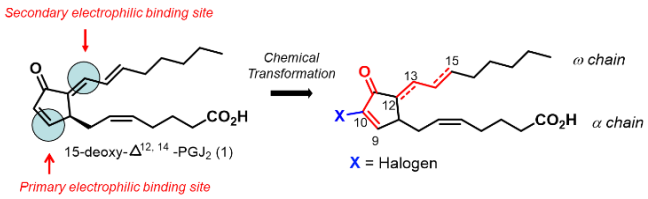
Abstract: The mechanism-based chemical transformation of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2) identified a series of novel NF-E2-related factor-2 (Nrf2) activators and elucidated the detailed function of each electrophilic binding site. In addition, HO-1 expression resulting from Nrf2 activation through the dissociaton enhancement of the Keap1-Nrf2 complex by the novel activators was proved via our chemical approach.

Cells have evolved defense systems to survive under various redox stresses, and understanding the molecular mechanisms by which cells detect oxidative or electrophilic stresses and transduce the signals to induce cytoprotective enzymes such as hemeoxygenase-1 (HO-1) has been a central focus in biology.[1] The induction of HO-1 is primarily mediated by the antioxidant response element (ARE)/electrophile response elements (EpREs) controlled by the transcription factor Nrf2.[2] Nrf2 activity is regulated by the Keap1 protein, a cytoplasmic repressor of Nrf2, through the formation of the Keap1-Nrf2 complex.[3] 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.[4] Keap1 is a cysteine-rich protein possessing twenty-seven cysteine residues, and chemicals that react with the thiol groups of cysteine are considered to be potential inducers of ARE activity. Various experimental approaches have been reported regarding how Nrf2-activating molecules bind to the thiol groups of Keap1 cysteines,[4, 5] although these studies have not fully elucidated the mode of action responding to oxidative stresses.[6, 7] Recently, endogenous 15d-PGJ_2 has received much attention due to its potent Nrf2-activating activity.[8] 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-PGJ_2, and a mutation study corroborated the evidence that Cys273 is the major site for 15d-PGJ_2 binding.[8a] Thus, these studies evoked the importance of the electronic features of the thiol binding sites[8a, 9] although the mechanistic questions about the role of the thiol binding sites of 15d-PGJ_2 remain unclear, despite the significance of Keap1-Nrf2 as a chemopreventive target. In addition, the limited structural information on the Keap1-Nrf2 complex has complicated the development of rationally designed Nrf2 activators based on 15d-PGJ_2 and confirmation of their interaction mode.[7] In this connection, we have been intensively working on 15d-PGJ_2 to elucidate its structural features, focusing on its electrophilic binding sites, and to confirm the proposed mechanism associated with the interaction with Keap1. We herein report an unprecedented chemical approach for the identification and structural analysis of novel and potent Nrf2 activators.



Scheme 1. Strategy for enhancing Nrf2 activation based on the 15d-PGJ_2 binding to Keap1.

We pursued appropriate structural modification of endogenous 15d-PGJ_2 to investigate the roles of each electrophilic carbon in Nrf2 activation. Initially, *rac*-15d-PGJ_2 (**4**) and *rac*-9,10-dihydro-15d-PGJ_2 (**5**) were prepared from *rac*-15d-PGJ_2 methyl ester (**3**), which was derived from known enone **2**.[10] The Me_3SnOH-mediated hydrolysis of **3** afforded **4** and the chemoselective 1,4-reduction of **3** with L-selectride followed by Me_3SnOH-mediated hydrolysis produced *rac*-9,10-dihydro-15d-PGJ_2 (**5**). The hydrolysis of **6**, which was prepared from known enone via a two-step sequence afforded *rac*-14,15-dihydro-15d-PGJ_2 (**7**). Next, *rac*-12,13,14,15-tetrahydro-15d-PGJ_2 (**8**) was synthesized by the Bu_3SnH reduction of enone olefins of *rac*-14,15-dihydro-15d-PGJ_2 methyl ester (**6**) and a selective Saegusa oxidation to yield the ring-olefin followed by ester hydrolysis.

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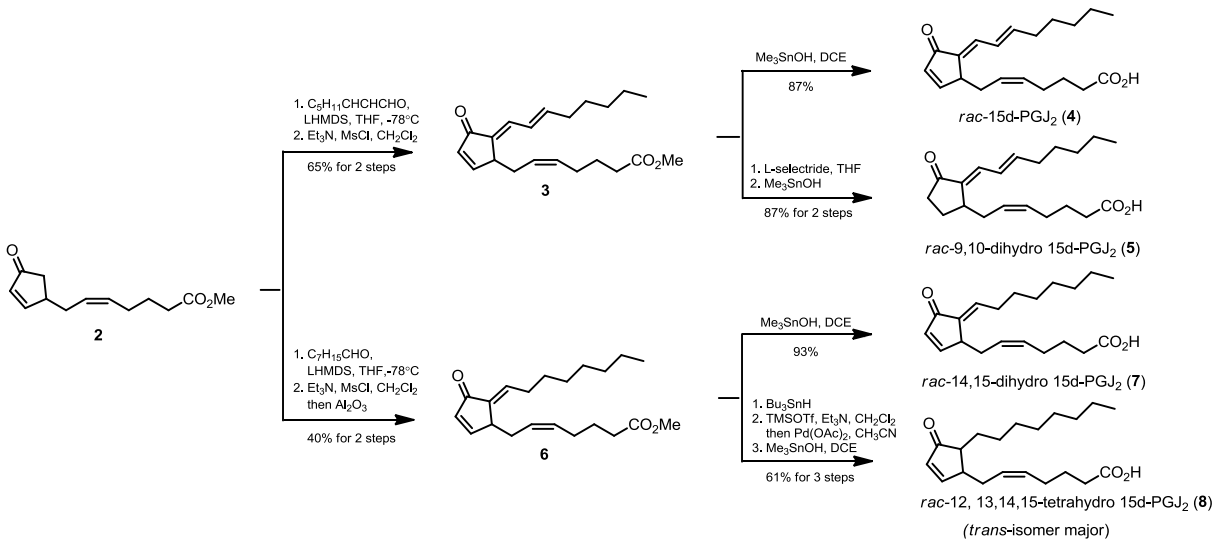


Scheme 2. Design and syntheses of 15d-PGJ_2 analogs.

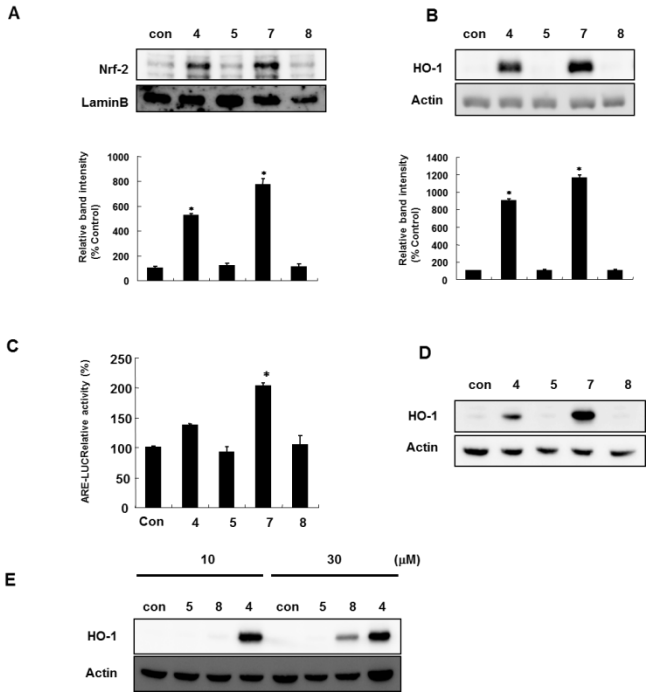
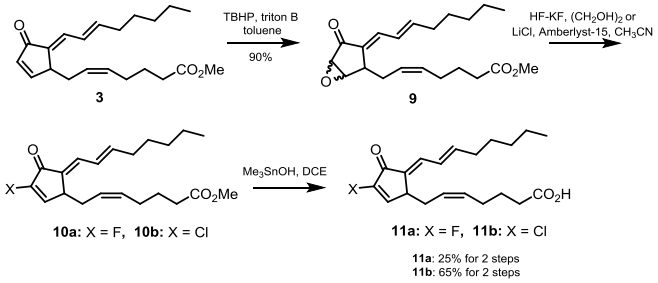


Figure 1. Effects of olefin-modified 15d-PGJ_2 analogs on the Nrf2 pathway. A) Nrf2 translocation in MCF10A cells (1 μM). B) HO-1 induction in MCF10A cells (1 μM). C) ARE activation in MCF7 cells measured by luciferase assay (1 μM). D) HO-1 induction in MCF7 cells (1 μM). E) HO-1 induction in MCF10A (10 and 30 μM, respectively). The data represent mean ± SD (n = 3). Significant differences between the compared groups are indicated (*P < 0.05 vs. control).

To confirm the influence of the electronic character of the thiol binding sites of 15d-PGJ_2 on its chemopreventive effect, sequential Nrf2 translocation, HO-1 expression and ARE activation by 15d-PGJ_2 and the 15d-PGJ_2-based cyclopentanones (or cyclopentenone) were evaluated. As shown in Figures 1A and 1B, Nrf2 translocation and HO-1 expression in non-tumorigenic human breast epithelial MCF10A cells were effectively induced by 15d-PGJ_2 (**4**) and **7**, whereas they were not induced by **5** or **8** at 1 μM. ARE luciferase activation (Figure 1C) and HO-1 expression (Figure 1D) in human breast adenocarcinoma MCF7 cells were observed in a similar pattern. These results indicate that both electrophlic sites are essential for Nrf2 activation, ultimately leading to HO-1 expression. Of interest, HO-1 expression was slightly induced upon treatment with **8** at a high concentration (30 μM), although it was not induced by **5** at the same concentration (Figure 1E). Again, these results confirmed the crucial role of the intracyclic olefin as a Michael acceptor for Nrf2 activation, with the exo-olefin being beneficial. The key function of the intracyclic olefin for thiol additions is also supported by the charge distribution (Supp. Figure S1) and chemical shifts of the electrophilic carbons (Supp. Synthesis Part) of both binding sites although the chemical shifts sometimes do not support the correlation well. These findings are consistent with the dienone moiety of prostaglandins reacting with thiols at higher rates compared with the simple enone.[13] Regarding the notably higher activity of **7** than 15d-PGJ_2, we assumed that the reduction of the 14,15-double bond might induce C9 more reactive for 1,4-addition partly due to decrease of the electronic density at C9, based on the charge analysis by molecular modeling and ^{13}C NMR analysis (160.6 to 161.6) although the enhanced activity of compound **7** might be associated with other factors including cell permeability, oxidative stress induction, and non-Keap1 mediated Nrf2 activation. To the best of our knowledge, this is the first report to demonstrate the substantial role of the second binding site of 15d-PGJ_2 in Nrf2 activation.



Scheme 3. Synthesis of α halogenated 15d-PGJ_2 analogs

Modifying the α-position of an *α,β*-unsaturated carbonyl system is quite attractive for enhancing the 1,4-additions of thiol, although it is not a common strategy.[14] Thus, we designed α halogenated analogs of 15d-PGJ_2 to evaluate with regard to the production of chemopreventive HO-1. The *α*-halo-15d-PGJ_2, **11a** and **11b** were synthesized via the epoxidation of **3**, the regioselective halogenation of the resulting epoxide, and dehydration and ester hydrolysis.[12]

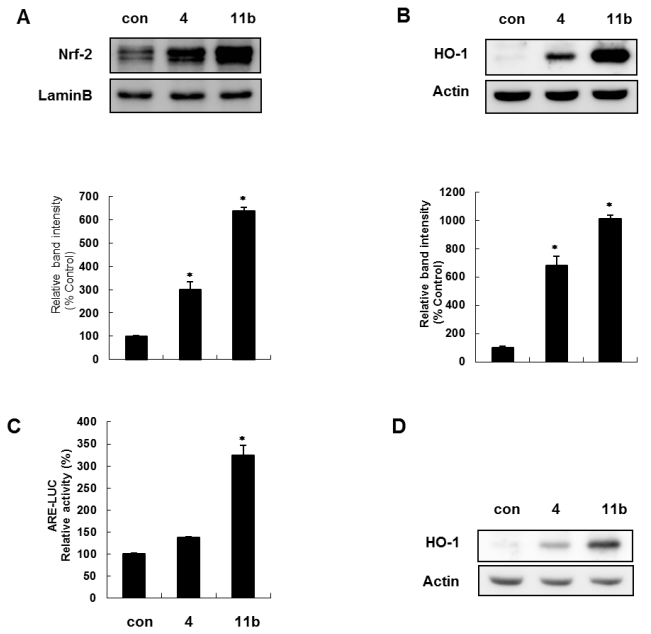
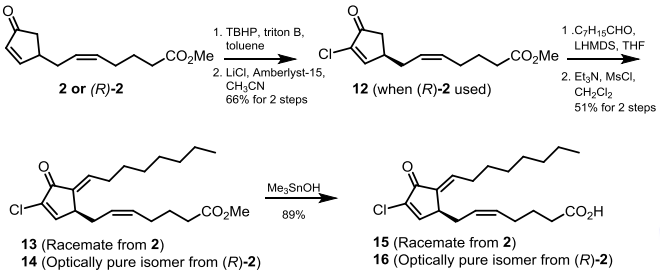


Figure 2. Effects of α-Cl-15d-PGJ_2 (**11b**) on the Nrf2 pathway. A) Nrf2 translocation (1 μM) in MCF10A cells. B) HO-1 induction in MCF10A cells (1 μM). C) ARE activation in MCF7 cells measured by luciferase assay (1 μM). D) HO-1 induction in MCF7 cells (1 μM). The data represent mean ± SD (n = 3). Significant differences between the compared groups are indicated (*P < 0.05 vs. control).

As anticipated, Nrf2 translocation (Figure 2A) and HO-1 expression (Figure 2B) in MCF-10A cells were highly induced by **11b** compared to the parent 15d-PGJ_2. In addition, **11b** significantly enhanced the ARE-luciferase activity (Figure 2C) and HO-1 expression (Figure 2D) in MCF7 cells. Based on the analysis of the chlorine substitution and 14,15-olefin effects on Nrf2 activation, we further prepared cyclopentenone **15**, which reflects the structural optimization of 15d-PGJ_2 for enhanced Nrf2 activation. Both racemic (**15**) and optically active (**16**) *α*-chloro-14,15-dihydro-15d-PGJ_2 were prepared from *rac* or (*R*)-**2**. Ketone **2** was first converted to *α*-chloro ketone **12** via epoxidation and chlorination. The synthesis of α-chloro analogs were completed by the same manner above**.**



Scheme 4. Synthesis of α chloro 14, 15 dihydro-PGJ_2 analogs

As anticipated, **15** exhibited the most potent ARE activation (Figure 3A), resulting in the highest HO-1 induction (Figure 3B) among the racemic compounds. Cyclopentenone **15** also showed dose-dependent HO-1 expression (Figure 3C). In addition, it was confirmed that the stereochemistry of 15d-PGJ_2 importantly influences the HO-1 inducing effect in favor of the (*S*)-configuration, as shown in Figures 3A and 3B. The improved activities of **11b** and **15** (or **16**) are obviously associated with electronegativity of the chlorine atom, and **16** appears to form the most energetically favorable complex with Keap1. The higher activity of **11b** versus **11a** (X= F; See Supp. Figure S3), in spite of the lower electronegativity of chlorine compared to fluorine, is not clearly explained. However, the higher biological activities of the chlorinated enones seem partly due to the lower electrophilic activity of fluoroenone **11a** caused by the overall electron-donating effect of fluorine, resulted from its strong resonance effect which can overrule its inductive effect.[15] The higher biological activities of **11b** was further supported by comparison of the binding and total free energies of the docked complexes between the Nrf2 activators and Keap1. (See Supp. Table S1 and S2). It was also predicted that the Keap1 complex with the most active chlorinated analog **16** was more stable than the Keap1 complex with any other halogenated analogs in terms of the total free energy of the ligand-receptor complex. (See Supp. Table S2).

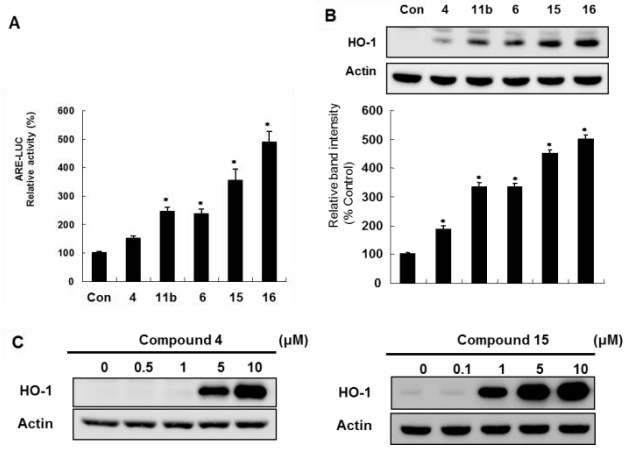


Figure 3. Effects of analogs **4**, **15** and **16** on the Nrf2 pathway. A) ARE activation in MCF7 cells measured by luciferase assay (1 μM). B) HO-1 induction in MCF10A cells (1 μM). C) Dose-dependent HO-1 induction in MCF10A cells. The data represent mean ± SD (n = 3). Significant differences between the compared groups are indicated (*P < 0.05 vs. control).

A hypothetical model of covalent adducts was established to examine the molecular interactions of **1** and **16** with Keap1. Previously, Kobayashi *et al* identified the covalent adduct of **1** with Cys273 of mouse Keap1 by MALDI-TOF MS analysis.[8a] Based on this result, we built covalent adduct models for **1** and **16** attached at Cys273, using a homology model of the IVR domain of mouse Keap1. In agreement with our experimental data showing that optically pure **1** and **16** are more active than racemate **4** (See Supp. Figure S2) and **15** (shown in Figure 3), only (*S*)-**1** and (*S*)-**16** fit well into the binding pocket to form a covalent bond with the sulfur atom of Cys273. The terminal carboxylic acid group forms hydrogen bonds with Arg240, and the hydrophobic *ω*-chain is positioned at the hydrophobic pocket, as shown in Figure 4. The low activity of 15d-PGJ_2 methyl ester **3** is likely due to the prevention of hydrogen bonding with Arg240. (See Supp. Figure S2) In addition, the 1,4-addition of the Cys273 thiol group to the cyclopentenone of **1** or **16** led to adducts with an *S* configuration at the electrophilic carbon C9, while the adduct with an opposite configuration was not able to be formed in the same binding pocket.

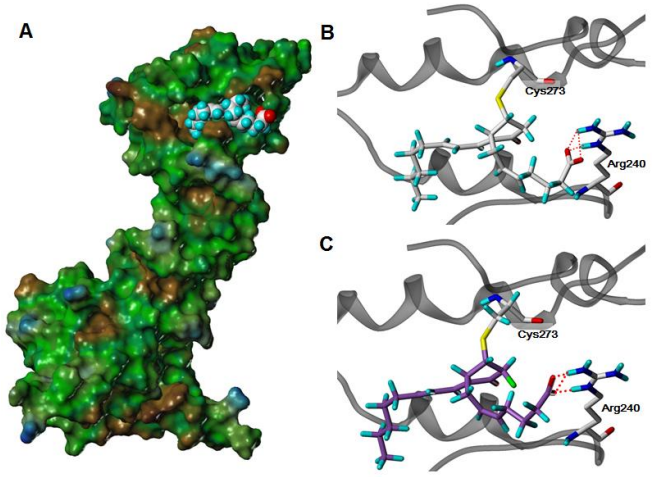


Figure 4. Modeling of covalent adduct of **1** and **16** with Cys273 in the Keap1 IVR domain. A) Covalently-bound **1** (space-fill atom type) in the binding site. The surface of the protein is represented by lipophilicity, which increases from blue (hydrophilic) to brown (lipophilic). B) and C) Covalent adducts of **1** and **16** in the binding site of Keap1. White carbon- capped sticks are the amino acids of Keap1. The ligand is rendered as a ball and stick models. Red dashed lines represent hydrogen bonding interactions.

To confirm the binding of **15** with Keap1, biotin-conjugates of **15** were prepared using amide coupling of the corresponding analogs with commercially available biotin cadaverine in the presence of 1,1'-carbodiimidazole (See Supp. Synthesis Part).[16] Initially, the induction of HO-1 expression by treatment of MCF10A cells with the biotin conjugates was examined. The biotin conjugates **17** and **18**, which were prepared from **4** and **15** resulted in HO-1 expression (Figure 5B). Finally, the binding of biotin conjugates **17** and **18** with Keap1 was confirmed via immunoprecipitation of cellular Keap1 and a subsequent immunoblot analysis (Figure 5C). In addition, the analysis well revealed better interaction of analog **18** with Keap1 than analog **17**. Again, these results suggested a direct interaction between 15d-PGJ_2 and its analogs and Keap1, which subsequently results in Nrf2 activation.

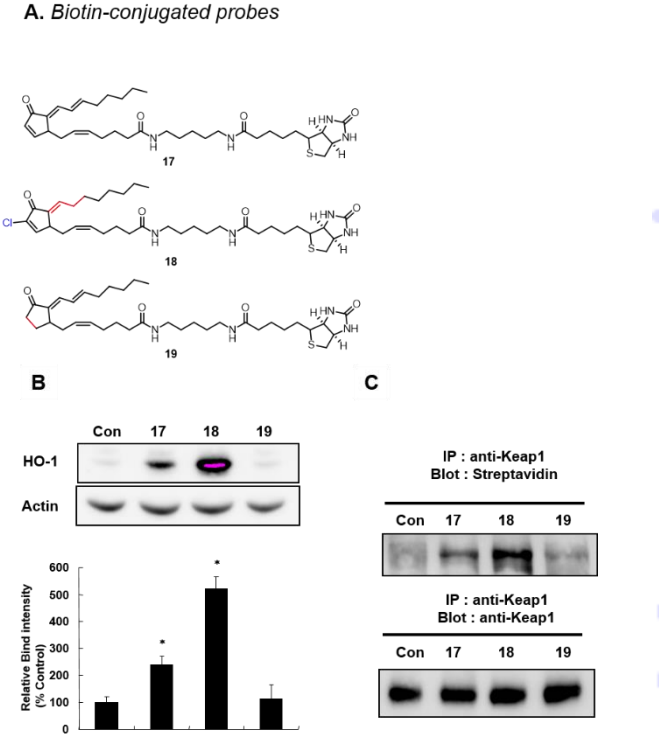


Figure 5. Immunoprecipitation of Keap1-biotin complex. A) Structures of biotin-conjugated probes **17**, **18** and **19**. B) HO-1 induction in MCF10A cells by the prepared probes at 30 μM. C) Immunoprecipitation and subsequent immunoblot analysis. The data represent mean ± SD (n = 3). Significant differences between the compared groups are indicated (*P < 0.05 vs. control).

In summary, we identified and structurally analysed novel Nrf2 activators via a chemical approach based on the interaction of 15d-PGJ_2 with Keap1. Our systematic investigation on the binding of 15d-PGJ_2 enabled us to elucidate the key roles of each binding site of 15d-PGJ_2 with regard to Nrf2 activation and to develop novel 15d-PGJ_2-based Nrf2 activators. The rationally designed chemical probes also supported that the concise tuning of the electronic states of the 15d-PGJ_2 binding sites could ultimately enhance HO-1 expression. Homology modeling also predicted that the covalent adduct of α-chloro-15d-PGJ_2 with Keap1 IVR is more stable than the 15d-PGJ_2 adduct. Our systematic studies on Nrf2 activation associated with 15d-PGJ_2 is anticipated to provide a facile access to novel chemopreventive therapeutics.

Experimental Section

Detailed procedures for chemical synthesis, cellular analysis, and docking study of the identified Nrf2 activators are described in Supplemental Experimental Methods.

Acknowledgements

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Keywords: Nrf2 • Keap1 • Michael addition • 15 deoxy-PGJ_2 • Chemical approach

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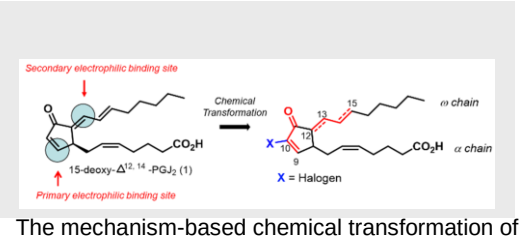

The mechanism-based chemical transformation of 15 deoxy-PGJ2 identified a series of novel NF-E2-related factor-2 (Nrf2) activators and elucidated the detailed function of each electrophilic binding sites. In addition, the HO-1 expression resulting from the Nrf2 activation through the dissociaton enhancement of the Keap1-Nrf2 complex by the novel activators was proved via our chemical approach.

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