

## In situ Ortho-Quinone Methide Reactions for Construction of Flavonoids with Fused Ring Systems

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**Abstract :** Flavonoids are naturally occurring compounds that have been shown to exhibit a wide range of biological properties including anticancer and anti-inflammatory activities. However, flavonoids suffer from low bioavailability, which limits their overall utility for therapeutic applications. One of the methods to overcome this limitation is through structural modification of natural flavonoids. In this study, flavanone, isoflavanone, and isoflavene, were structurally modified through the introduction of additional fused-ring systems via ortho-quinone methide intermediates (o-QMs). These intermediates can readily undergo a [4+2] cycloaddition through an inverse-electron-demand Diels-Alder reaction with electron-rich dienophiles. A regioselective Mannich reaction using bis-(N,N-dimethylamino)methane was employed to generate the o-QM precursors of flavanone, isoflavanone, and isoflavene. The o-QM intermediates were subsequently generated in situ through thermal elimination of the dimethylamine functionality and reacted with a variety of dienophiles to produce novel flavonoids with fused-ring systems. A total of 21 novel flavonoid analogs were successfully synthesized. The X-ray crystal structure of cycloaddition adducts, particularly those derived from 3,4-dihydro-2H-pyran and p-methoxystyrene revealed a special case of enantiomeric disorder, where two enantiomers in equal amounts superpose with one another, with the exception for atoms that have opposite configuration. The anticancer properties of fused-ring systems derived from isoflavene were evaluated against the neuroblastoma SKN-BE(2)C, the triple negative breast cancer MDA-MB-231, and the glioblastoma U87 cancer cell lines. One of these cycloaddition adducts had displayed improved anti-proliferative activity against MDA-MB-231 and U87 cancer cell lines as compared to the parent compound. Further anticancer and anti-inflammatory activities of the flavanone and isoflavanone analogs are currently being investigated.

**Keywords :** Diels-Alder reaction, flavonoids, Mannich reaction, ortho-quinone methide.

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