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REVIEW

Biosynthesis, total syntheses, and antitumor activity of tanshinones and their analogs as potential therapeutic agents

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Tanshinones are a series of abietane diterpenes, isolated exclusively from *Salvia miltiorrhiza* and related species. More than 40 tanshinones and their analogs have been isolated since the 1930s. Their biosynthetic pathway correlates with the MEP/DOXP pathway, and many key enzymes, such as SmCPS, are responsible for establishing their molecular scaffolds and stereospecificity. Because of their unique structural characteristics and promising biological activities, total syntheses of various tanshinones have attracted the interest of many synthetic chemists, including R. H. Thomson, H. Kakisawa, R. L. Danheiser, Y. Inouye and J. K. Snyder. Tanshinones and their analogs exhibit interesting and broad antitumor activity in various cell and animal models. Most recently, the tanshinone analog neo-tanshinlactone has shown potent and selective activity against breast cancer. This review will discuss the biosynthesis, total syntheses, and antitumor activities of tanshinones, especially neo-tanshinlactone and its analogs.

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1 Introduction

Tanshinones, which are abietane diterpenes, were first isolated by Nakao in 1930 from the roots of *Salvia miltiorrhiza* ('tanshen'), a well-known traditional Chinese medicine (TCM).[1,2] Tanshen has been used extensively for the treatment of coronary heart diseases, particularly angina pectoris and myocardial infarction,[3] as well as inflammatory diseases, including chronic hepatitis, arthritis, and endangitis.[4]

Over the past eight decades, natural product chemists have investigated the chemical constituents in tanshen, and so far more than 40 diterpenoids have been isolated from *S. miltiorrhiza*.[3] Tashinones are generally composed of four rings, including naphthalene or tetrahydronaphthalene rings A and B, an *ortho*- or *para*-quinone or lactone ring C, and a furan or dihydrofuran ring D. In the 1930s, Takiura[5–7] and Wessely[8,9] and their co-workers used spectroscopic data and degradative work to identify the structures of tanshinone I (**1**), tanshinone IIA (**2**), tanshinone IIB (**3**), and cryptotanshinone (**4**) (Fig. 1). These tanshinones are found exclusively in the *Salvia* genus. Structurally, all four compounds are characterized by an *ortho*-quinone