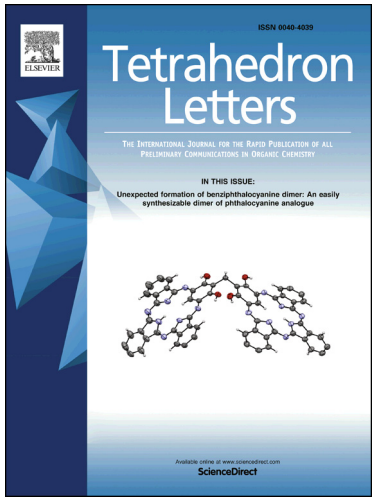

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Design, synthesis and cytotoxicity of Nitrogen-containing Tanshinone derivatives

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ABSTRACT

Tanshinones were used as starting material to synthesize a small library of nitrogen heterocyclic derivatives featured with oxazole, imidazole, and pyrazine ring between C-11/C-12 by simple methods. Except for salviamine A and isosalviamine A, 22 new derivatives were synthesized. Their structures were confirmed by spectroscopic analysis. Moreover, 11 derivatives exhibited moderate cytotoxic activities against five human cancer lines *in vitro*.

Tanshinones, possessing a characteristic 11,12-orthoquinone abietane skeleton, were first isolated by Nakao in 1930 from the roots of *Salvia miltiorrhiza* ('tanshen'), a well-known traditional Chinese medicine (TCM).[1] Extensive studies have demonstrated that tanshinones and their analogs exhibit various pharmacological activities, including antibacterial, antioxidant, anti-inflammatory, and antineoplastic. These diterpenoids attracted widespread attention in terms of organic synthesis, structural modification and biological evaluation.[1, 2]

Since 2005, a series of abietane diterpenoid alkaloids were characterized from the genus *Salvia*, which causing our attention for its special structure of the oxazole ring between C-11/C-12 as well as its cytotoxic activity.[3] Although series of structural modification products about tanshinone IIA and cryptotanshinone have been reported from 2001 to 2003, these N-containing derivatives were still an interesting concern from the chemical and pharmaceutical point of view. Furthermore, studies on the activity of these compounds are rare.[4] Therefore, studies on the 11,12-orthoquinone of tanshinones (tanshinone IIA, cryptotanshinone, tanshinone I, and dihydrotanshinone I, **Fig. 1**) will reveal more potent analogues with better biological activity.

Some N-containg natural products are collected in **Fig. 2**. Oxazolines from tanshinone IIA showed cytotoxicity with a CD50 range of 32-63 μM against HeLa cell lines. Izumiphenazines A–C exhibited activity in overcoming TRAIL (TNF-related apoptosis-inducing ligand) resistance in human gastric adenocarcinoma cells.[5] Meanwhile, Oxazoline[6], imidazole[7] and pyrazine[8] derivatives demonstrated the utilities in Oncology. Therefore, we planned to synthesize oxazole, imidazole, and pyrazine derivatives by treating Tanshinones (**1**-**4**) with various amines. As a result, 22 new derivatives were synthesized. In addion, salviamine A and isosalviamine A, two known natural products reported from *Salvia* famliy, were synthesized biomimetically for the first time.[3a, 3d] Subsequently, these synthesized compounds were tested against five human cancer cell lines (i.e., HeLa: Henrietta Lacks strain of cancer cells, K562: leukemia cell, MCF-7: human breast cancer, PC 3: Prostate cancer-3, and CNE: nasopharyngeal carcinoma cells) by MTT method.

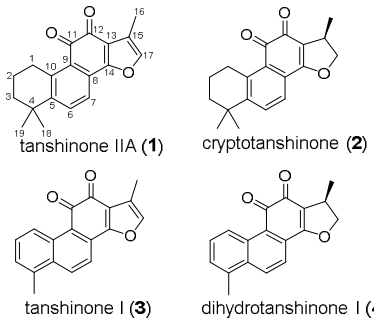

Fig. 1. Structures of tanshinone IIA, cryptotanshinone, tanshinone I, and deyhrotanshinone I.

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