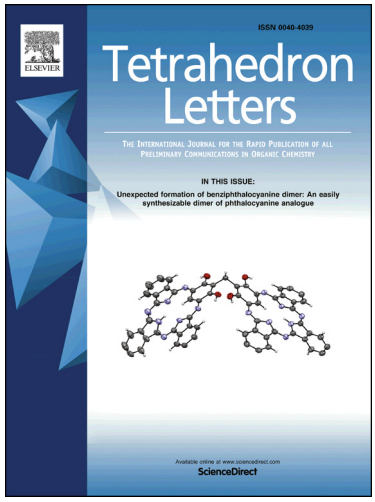

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Design, synthesis and cytotoxicity of Nitrogen-containing Tanshinone derivatives

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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.

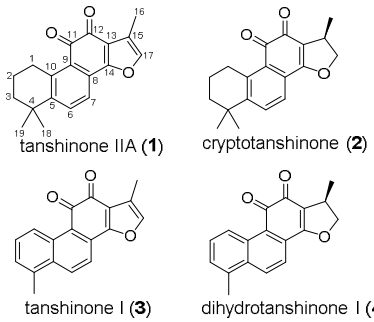

Fig. 1. Structures of tanshinone IIA, cryptotanshinone, tanshinone I, and deyhrotanshinone I.

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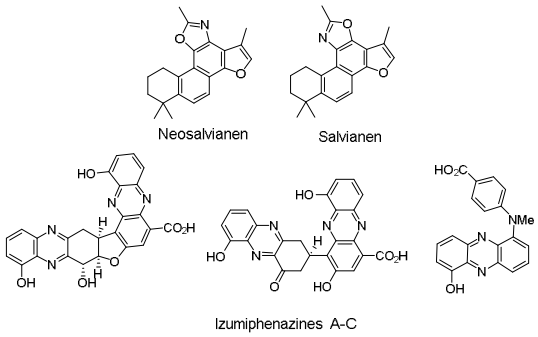


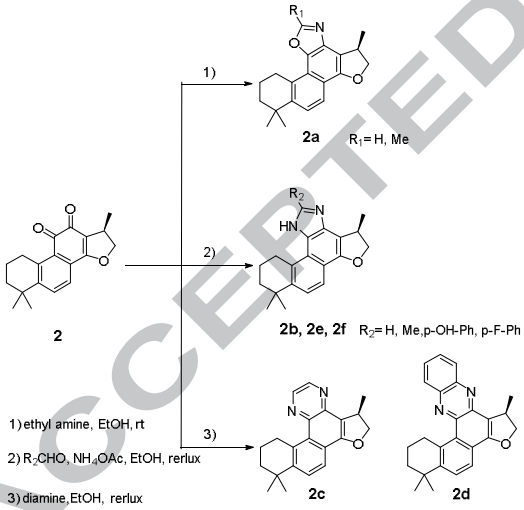
Fig. 2. Structures of N-containing natural products.

Three types of hetero atom containing derivatives were synthesized (**Scheme 1** and **Fig. 3**).

1) Oxazoline formation: tanshinones were treated with methyl amine or ethyl amine in EtOH. Salviamine A (**3a**) and isosalviamine A (**3b**), two known natural products reported from *Salvia* family, were synthesized biomimetically for the first time. The structures of 3a and 3b were determined by comparing the ^{1}H NMR and ^{13}C NMR date with salviamine A and isosalviamine A.[3a, 3d] Yields varied between 50%-76% when tanshinones **1-4** were used. Particularly, when methyl amine was used, no formation of N-Me imidazole was observed.[4a]

2) Imidazole formation: tanshinones were reacted with ammonium acetate, aldehyde in refluxing EtOH (y. 55-80%).

3) Pyrazine formation: tanshinones and diamine were reacted in refluxing EtOH (y. 40-60%).



Scheme 1. Representative synthetic route to oxazoline, imidazole and pyrazine.

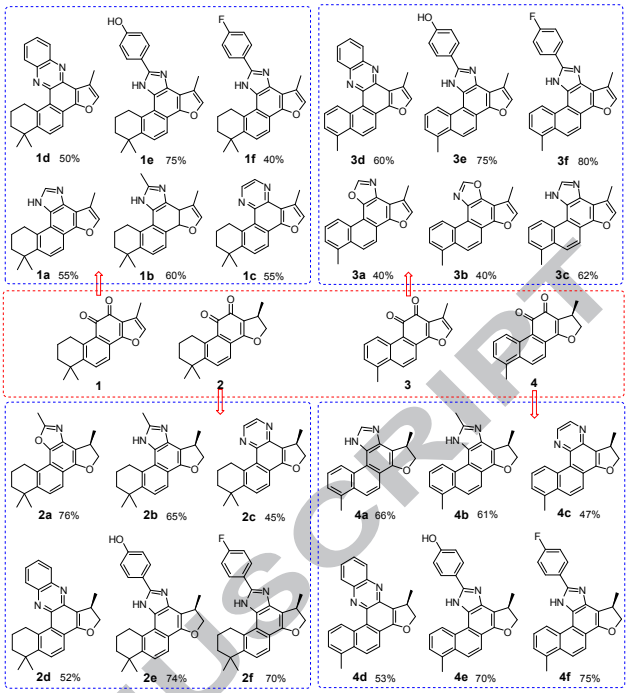


Fig. 3 synthesized tanshinone derivatives and isolated yield.

Next, these compounds were tested for in vitro inhibitory activities against HeLa, K562, MCF-7, PC3, and CNE human tumor cell lines using the MTT method described previously.[9] The results indicated that 11 tanshinone derivatives exhibited some cytotoxic activities against five human cancer lines in vitro (**Table 1**).

Table 1. Cytotoxicities of compounds against five cancer cell lines (IC_{50} μM)

Compounds[a]	HeLa	K562	MCF-7	PC 3	CNE
1	7.11	6.94	6.05	21.09	5.75
2	9.39	7.16	3.28	9.62	6.69
3	16.66	6.12	21.82	5.15	11.36
4	5.29	3.92	3.05	2.80	3.09
1b	17.1	3.9	13.6	20.6	23.8
1f	>100	>100	10.0	>100	>100
2b	>100	>100	10.0	>100	>100
2e	7.4	3.2	8.7	14.8	24.6
2f	>100	>100	10.0	>100	44.8
3b	19.3	41.4	14.7	>100	6.1
3c	5.6	10.7	7.8	46.6	8.5
3e	6.8	2.6	8.4	15.3	15.7
3f	11.6	3.8	10.8	21.2	22.9
4c	8.3	21.4	9.1	>100	13.9
4e	10.4	6.2	10.2	15.4	28.0
paclitaxel[b]	0.01	0.005	0.21	0.007	0.009

[a] Other derivatives with IC_{50} > 40 μM for all the cell lines are not listed.

[b] Positive control.

Our experiments revealed that, for the first time, modification of C11-C12 quinone have shown some antitumor activity. Especially, introduction of imidazole ring at C11-C12 (**2e**) maintained the activity to cell line (Hela, K562, MCF-7). All derivatives are not active towards PC 3 cell line and **3b**, **3c** showed activity to CNE. Therefore, imidazole derivatives showed higher activity when compared with oxazoline and pyrazine alternatives. Among imidazole derivatives, aryl substitution (**1f**, **2f**, **3f**, **2e**, **3e**, **4e**) on oxazoline ring is proved to be effective. The bioactivity of **2e** and

3e, compared with **2** and **3**, demonstrated that our modification strategy is promising.

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Supplementary data

The details of chemical transformation, and biological experimental procedures, MS and NMR spectra of the synthesized compounds associated with this article can be found in the online version at http://dx.doi.org/XXX.

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Highlights

- Nitro-containing tanshinone derivatives have been investigated.
- 22 derivatives, including oxazole, imidazole and pyrazine have been subjected to antitumor activity test.
- SAR of these heterocyclic compounds has been figured out and our modification strategy is promising.