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Antitumor agents 279. Structure–activity relationship and in vivo studies of novel 2-(furan-2-yl)naphthalen-1-ol (FNO) analogs as potent and selective anti-breast cancer agents

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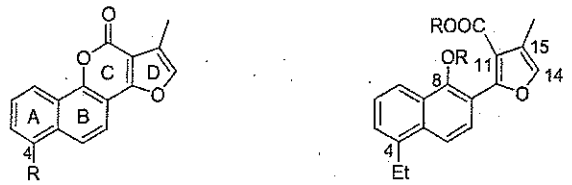
ABSTRACT

In our ongoing modification study of neo-tanshinlactone (**1**), we discovered 2-(furan-2-yl)naphthalen-1-ol (FNO) derivatives **3** and **4** as a new class of anti-tumor agents. To explore structure–activity relationships (SAR) of this scaffold, 18 new analogs, **6–12** and **14–24**, were designed and synthesized. The C11-esters **7** and **12** displayed broad anti-tumor activity (ED_{50} 1.1–4.3 μg/mL against seven cancer cell lines), while C11-hydroxymethyl **14** showed unique selectivity against the SKBR-3 breast cancer cell line (ED_{50} 0.73 μg/mL). Compounds **15** and **22** displayed potent and selective anti-breast tumor activity (ED_{50} 1.7 and 0.85 μg/mL, respectively, against MDA-MB-231). The SAR results demonstrated that the substitutions from the ring-opened lactone ring C of **1** are critical to the anti-tumor potency as well as the apparent tumor-tissue type selectivity. Treatment with **3** in *Brca1*$^{f11/f11}$*p53*$^{f586/f586}$*Cre*^{c} mice models significantly inhibited the proliferation of mammary epithelial cells and branching of mammary glands.

Neo-tanshinlactone (**1**), a natural product from *Salvia miltiorrhiza*, and its analog, 4-ethyl neo-tanshinlactone (**2**), are potent and selective anti-breast cancer agents (Fig. 1).[1–3] In our prior studies, they exhibited high tumor tissue-type as well as breast cancer cell line selectivity. The selective anti-breast tumor activity of **2** in mice models is consistent with the results in vitro.[3] In our continuing study, we explored how the individual rings A–D in the molecule influence the in vitro anti-breast tumor activity. The results led to the discovery of a novel class of anti-breast cancer agents, 2-(furan-2-yl)naphthalen-1-ol (FNO) analogs (e.g., **3** and **4**) by opening ring-C.[4] Our previous studies also explored the preliminary SAR and proved that the C8 and C11 substituents can greatly affect both potency and selectivity. FNO analog **3** showed significant potency (ED_{50} 0.3 μg/mL) and selectivity against the ZR-7-51 (ER+, HER2+) cell line compared with other cancer cell lines tested, while **4** exhibited activity against all cancer cell lines tested.[4] We wanted to use these promising results to design novel analogs with better pharmaceutical profiles and develop them as clinical trials candidates.

The initial studies showed that Et, H, and Me groups are preferred at the C4, C14, and C15 positions, respectively, of the FNO skeleton, and we retained this substitution pattern in our current study.[4] However, we expanded the identities of the groups at the C8 and C11 positions (**3** and **4** contain hydroxyl/carboxylic acid and methyl ether/methyl ester, respectively). Some of the different combinations at these positions included ether/carboxylic acid, ether/ester, ether/amide, and ether/substituted methyl. We



R = Me: Neo-tanshinlactone (**1**)
R = Et: 4-Ethyl neo-tanshinlactone (**2**)

3 : R = H
4 : R = Me

Figure 1. Structures of neo-tanshinlactone (**1**), 4-ethyl neo-tanshinlactone (**2**), and FNO analogs **3** and **4**.

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