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Antitumor agents 287. Substituted 4-amino-2*H*-pyran-2-one (APO) analogs reveal a new scaffold from neo-tanshinlactone with in vitro anticancer activity

Yizhou Dong [a], Kyoko Nakagawa-Goto [a], Chin-Yu Lai [a], Susan L. Morris-Natschke [a], Kenneth F. Bastow [b], Kuo-Hsiung Lee [a,c,*]

[a] Natural Products Research Laboratories, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7568, USA
[b] Division of Medicinal Chemistry and Natural Products, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7568, USA
[c] Chinese Medicine Research and Development Center, China Medical University and Hospital, Taichung, Taiwan

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ABSTRACT

4-Amino-2*H*-benzo[*h*]chromen-2-one (ABO) and 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (ATBO) analogs were found to be significant in vitro anticancer agents in our previous research. Our continuing study has now discovered a new simplified (monocyclic rather than tricyclic) class of cytotoxic agents, 4-amino-2*H*-pyran-2-one (APO) analogs. By incorporating various substituents on the pyranone ring, we have established preliminary structure–activity relationships (SAR). Analogs **19**, **20**, **23**, and **26–30** displayed significant tumor cell growth inhibitory activity in vitro. The most active compound **27** exhibited ED_{50} values of 0.059–0.090 μM.

In 2004, our group first isolated and synthesized neo-tanshinlactone (**1**).[1] Compound **1** was 10-fold more potent and 20-fold more selective as compared with tamoxifen citrate against the ER+ human breast cancer cell lines MCF-7 and ZR-75-1. Further structural optimization led to its 4-ethyl analog **2**, which displayed significant and selective anti-breast cancer activity both in vitro and in vivo.[2,3] Moreover, **2** was selective for a subset of breast cancer-derived cell lines and significantly less active against normal breast-derived tissue. In order to explore the effect of individual rings on the anticancer activity, identify new lead compounds, and discover new chemical entities, we designed and reported five classes of new anticancer agents, including 2-(furan-2-yl) naphthalen-1-ol (FNO),[4] 6-phenyl-4*H*-furo[3,2-*c*]pyran-4-one (AFPO),[5] tetrahydronaphthalene-1-ol (TNO),[6] 4-amino-2*H*-benzo[*h*]chromen-2-one (ABO, **3**, Fig. 1),[7] and 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (ATBO, **4**, Fig. 1)[8] analogs. Interestingly, the neo-tanshinlactone-inspired synthesis of a breast cancer selective ABO series was reported independently by others.[9]

Importantly, ABO and ATBO compounds displayed much higher potency than **1**-analogs, which encouraged us to further investigate these scaffolds. Structure–activity relationship (SAR) studies on **3** and **4** indicated that (1) a secondary amine (R^2 or R^3 = H) is preferred over tertiary amine (R^2 and $R^3 \neq$ H), (2) bulky groups are favored at the R^2/R^3 position, (3) a 3′-bromophenyl group can cause a dramatic loss of potency, and (4) a non-aromatic ring-A can increase potency and cancer cell line selectivity for certain

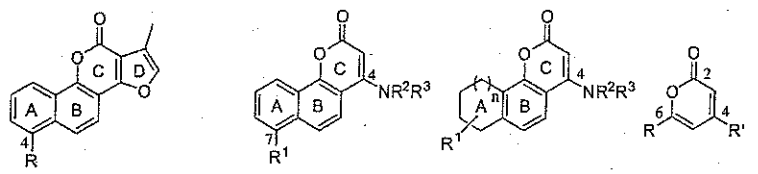

Figure 1. Structures of neo-tanshinlactone (**1**), 4-ethyl neo-tanshinlactone (**2**), previously reported ABO (**3**) and ATBO (**4**) scaffolds, and newly designed APO scaffold (**5**).

* Corresponding author. Tel.: +1 919 962 0066; fax: +1 919 966 3893.
E-mail address: khlee@unc.edu (K.-H. Lee).

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