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Antitumor agents 281. Design, synthesis, and biological activity of substituted 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one analogs (ATBO) as potent in vitro anticancer agents

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ABSTRACT

In our exploration of new biologically active chemical entities, we designed and synthesized a novel class of antitumor agents, substituted 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (ATBO) analogs. We evaluated their cytotoxic activity against seven human tumor cell lines from different tissues, and established preliminary structure–activity relationships (SAR). All analogs, except **8**, **9**, and **25–27**, displayed potent tumor cell growth inhibitory activity. Especially, compounds **15** and **33** with a 4-methoxyphenyl group at position C-4 were extremely potent with ED_{50} values of 0.008–0.064 and 0.035–0.32 μM, respectively. Compound **15** was the most potent analog compared with structurally related neo-tanshinlactone (e.g., **1**) and 4-amino-2*H*-benzo[*h*]chromen-2-one (ABO, e.g., **4**) analogs, and thus merits further exploration as an anti-cancer drug candidate.

One of the most challenging areas of research in both industry and academia is the discovery and development of new medicines.[1,2] In 2009, 103 new drugs were approved by the FDA's Center for Drug Evaluation and Research (CDER).[3] Nineteen new molecular entities (NMEs) and six biologics license applications (BLAs) were filed among these approvals.[3] The pharmaceutical industry's demand for new leads with new scaffolds has never been greater.[4] These facts prompted us to design and discover new biologically active chemical entities.

Previously, our group successfully developed new cytotoxic chemical entities, including neo-tanshinlactone (**1**, Fig. 1) and its 4-ethyl analog **2**,[5,6] for treating breast cancer, and these compounds are now in extended preclinical study. Structural simplification and optimization is a powerful tool for analog design and lead exploration. For example, this strategy was applied to the natural product halichondrin B, a potent mitotic inhibitor, which led to a new therapeutic medicine, eribulin mesylate.[7] In our continuous exploration of new chemical entities, we also designed and developed several additional series of novel anticancer agents according to this strategy. These agents include 2-(furan-2-yl) naphthalen-1-ol (FNO),[8] 6-phenyl-4*H*-furo[3,2-*c*]pyran-4-one (AFPO),[9] tetrahydronaphthalene-1-ol (TNO),[10] and 4-amino-2*H*-benzo[*h*]-chromen-2-one (ABO, **3**, Fig. 1)[11] analogs. Lead compounds showed potent antitumor activity and different tumor tissue type selectivity. Braccio et al. first reported four compounds with the ABO scaffold and their cytotoxic activity against Ehrlich ascites tumor cells.[12] We also designed and explored this scaffold based on our studies of neo-tanshinlactone analogs (**1** and **2**). Compound **4** showed potent and broad antitumor activity compared with **1** and **2**.[11] Structure–activity relationship (SAR) studies on **3** indicated that (1) 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 R^2/R^3 position, (3) 3′-bromophenyl group can cause dramatic loss of potency, and (4) hydrogen is better than an ethyl group at R^1 position. Our prior studies also suggested that a non-aromatic ring can greatly affect the antitumor activity and cancer cell line selectivity.[10] Consequently, we have now designed scaffold **5** with a non-aromatic five- or six-membered A-ring (Fig. 1). Different amino (R^2/R^3) and A-ring (R^1) substituents were incorporated to establish SAR and identify potent analogs. This Letter reports the design, synthesis, and biological activity of 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one, (ATBO) analogs.

All target compounds **8–27**, **32**, and **33** were synthesized from the related 4-hydroxy compounds, **6**, **28**, and **29**, respectively, according to the methods reported before (Scheme 1). Chlorides **7**, **30**, and **31** were synthesized by treatment of **6**, **28**, and **29**,

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