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Original article

Design, synthesis and biological evaluation of novel 4-thiazolidinones containing indolin-2-one moiety as potential antitumor agent

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ABSTRACT

A series of novel 4-thiazolidinone and indolin-2-one hybrid derivatives **5a**–**5s** and **10a**–**10s** have been designed and synthesized and their cytotoxic activities were evaluated *in vitro* against three human cancer cell lines including HT-29 (human colon cancer), H460 (human lung cancer), MDA-MB-231 (human breast cancer) by MTT assay. Several potent target compounds (**5m**, **5p**, **5s**, **10a**, **10c**–**10g**, **10m**, **10p**) were further evaluated against one cancer cell line SMMC-7721 (human liver cancer) and one normal cell line WI-38 (human fetal lung fibroblasts). Most of the prepared compounds exhibited significant antitumor activities against different human cancer cell lines. Compound **10c** (IC_{50} = 0.025 μM, 0.075 μM, 0.77 μM, 1.95 μM) was 52, 36, 4.8 and 3.3 times more active than Sunitinib (IC_{50} = 1.3 μM, 2.7 μM, 3.7 μM, 6.47 μM) against HT-29, H460, MDA-MB-231 and SMMC-7721 cancer cell line, respectively.

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1. Introduction

4-Thiazolidinone derivatives are an important group of heterocyclic compounds possessing a variety of biological effects [1], including antitumor [2–4], anti-inflammatory [5], antimicrobial [6], antiviral [7], anticonvulsant [8], antifungal [9], antibacterial [10] activities and so on. Among them, 5-benzylidene-4-thiazolidinone derivatives have been reported to show marked antitumor activities with different biotargets and mechanism, such as phosphatase of a regenerating liver (PRL-3) [11], Sphingosine Kinase (SK) [12], JNK-stimulating phosphatase-1 (JSP-1) [13] and nonmembrane protein tyrosine phosphatase (SHP-2) [14]. Moreover, 5-benzylidene-4-thiazolidinone derivatives exhibited potent antitumor activities against non-small cell lung cancer cell line H460, paclitaxel-resistant $H460_{taxR}$, human colon cancer cell line HT-29 and human breast cancer cell line MDA-MB-231 (Fig. 1) [15–17].

The indolin-2-one ring system belongs to the privileged structure in modern medicinal chemistry, particularly in discovery of new antitumor and antiangiogenic agents. Various kinase inhibitors containing indolin-2-one moiety have been intensively studied for the inhibition of VEGFR, c-Kit, FLT3, PDGFR-α/β, and CSF-1-R [18]. Sunitinib, a multitargeted receptor tyrosine kinase inhibitor, interfering with tumor blood vessel formation, is approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST) (Fig. 1) [19]. BIBF 1120, a triple angiokinase inhibitor reported by Boehringer, is currently in phase III clinical trials in non-small cell lung cancer (Fig. 1) [20]. Indirubin, an active ingredient of a traditional Chinese medicine recipe, has been applied to treat chronic myelocytic leukemia (Fig. 1) [21].

The aforementioned compounds have inspired us to attach substituted indolin-2-one to the 5-benzylidene-4-thiazolidinone scafford, and the combination of two privileged structures in one molecule leads to drug-like molecules. To our knowledge there are hardly any studies about introduction of indolin-2-one group at the 2-position of the 4-thiazolidinone ring so far. Thus, indolin-2-one group was introduced at the 2-position of the 4-thiazolidinone ring and a basic side chain was introduced at the 3-position of the 4-thiazolidinone ring, in order to improve the solubility and bioavailability of these structures.

Here, we report the newly synthesized target compounds (Fig. 1) and their cytotoxic activities against HT-29, H460, MDA-MB-231 and SMMC-7721 human cancer cell lines.

2. Chemistry

The preparation of target compounds **5a**–**5s** and **10a**–**10s** was described in Scheme 1. The indolin-2-ones **11a**–**11f** were synthesized from appropriate anilines according to the reported procedures [22,23].

The 5-benzylidene-3-substitutedrhodanine intermediates **3a**–**3h** and **8a**–**8f** were synthesized by reaction of the primary amine **1** or **6** and carbon disulfide under basic conditions followed by ring closure

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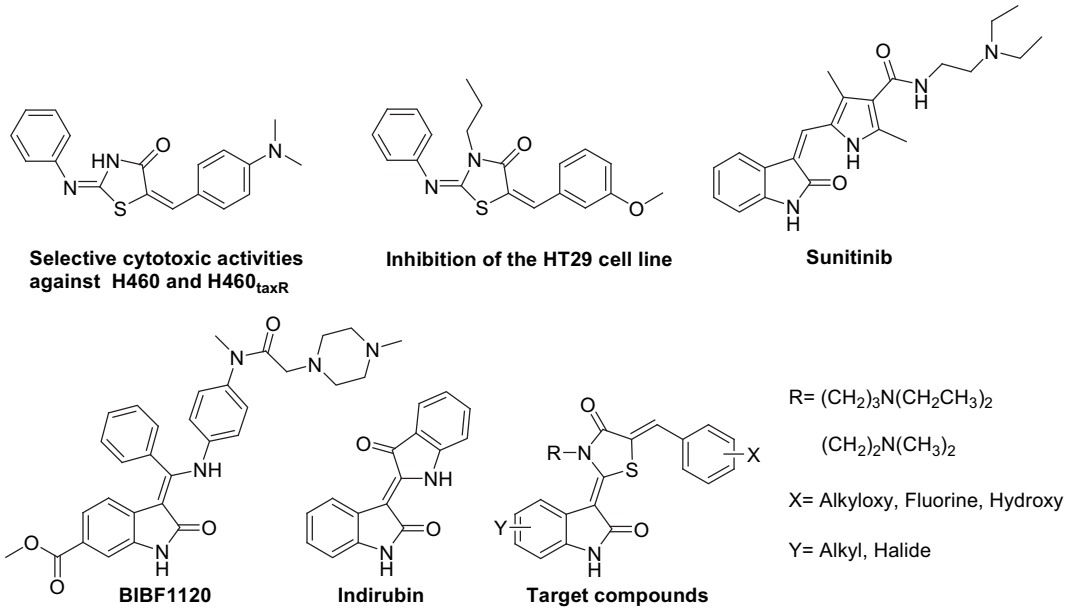
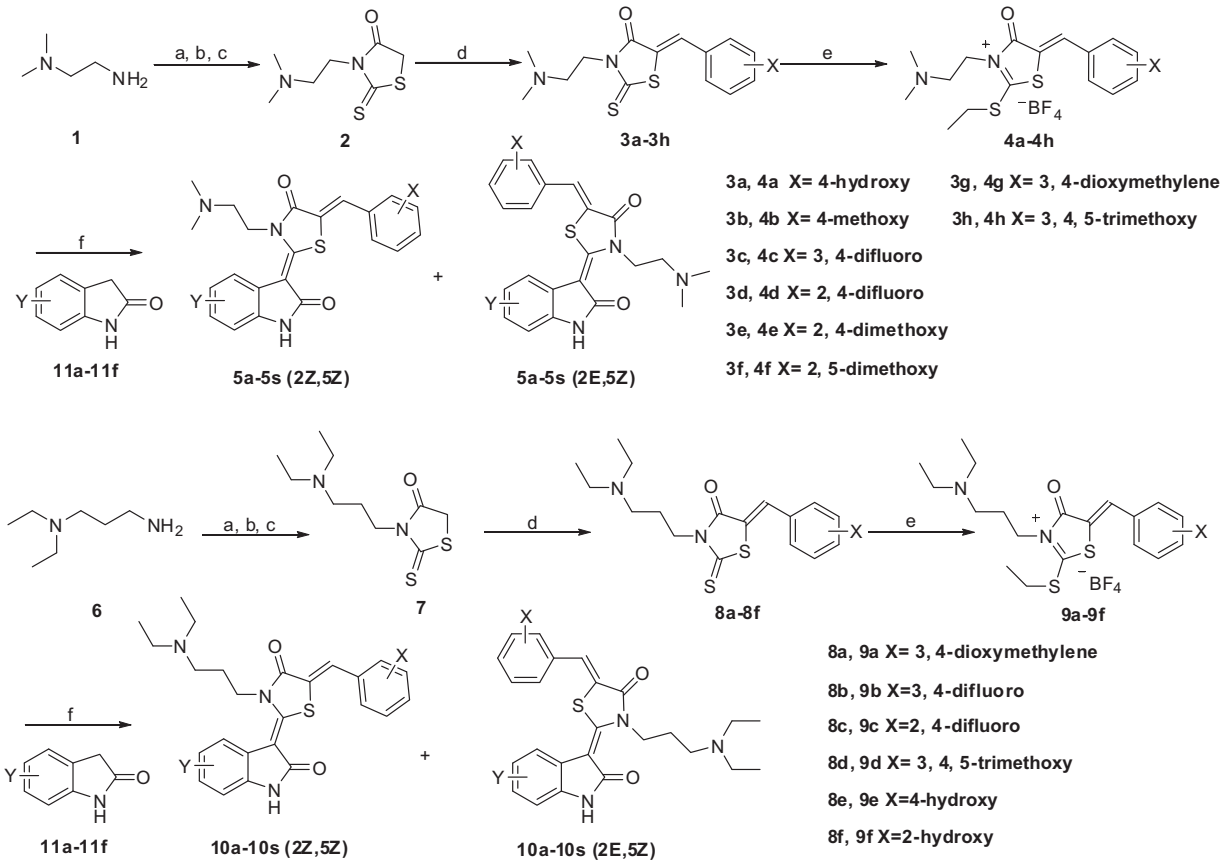


Fig. 1. Structures of 4-thiazolidinones, indolin-2-ones and target compounds.

with chloroacetic acid and subsequent the intermediate **2** or **7** was subjected to Knoevenagel condensation with suitable benzaldehydes in refluxing ethanol (Scheme 1).

The Knoevenagel condensation reaction of **2** or **7** with benzaldehydes provided only the Z isomer, as determined by the chemical shift of the methine proton in **3a**–**3h** and **8a**–**8f** ranging from 7.70 to 8.00 ppm as a singlet. The exclusive formation of the thermodynamically stable Z-isomers is in agreement with which was reported for similar structures in literature [24,25]. This downfield movement of methine proton in **3a**–**3h** and **8a**–**8f** was due to the deshielding effect of the adjacent carbonyl group at the 4-position. The *S*-Ethylation of **3a**–**3h** and **8a**–**8f** with boron trifluoride diethyl



Scheme 1. Reagents and conditions: (a) CS_2, Et_3N, Et_2O, 25 °C, 0.5 h; (b) $ClCH_2COOH$, K_2CO_3, MeOH, H_2O, 25 °C, 7–8 h; (c) concd.H_2SO_4, pH = 4.0, 35–40 °C,12 h; (d) Benzaldehyde, piperidine, EtOH, reflux 3–4 h; (e) $BF_3.Et_2O$, $HC(OEt)_3$, 1,4-dioxane, 80 °C; (f) Et_3N, CH_3CN, 25 °C, 4 h.

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