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Research paper

Bis-isatin hydrazones with novel linkers: Synthesis and biological evaluation as cytotoxic agents

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ABSTRACT

Many bis-isatins and isatins with hydrazide extension were reported to have a potential anti-proliferative effects against different cancer cell lines and cancer targets. In this study, four series of bis-isatins with hydrazide linkers were synthesized. These compounds were investigated for their antitumor activity by assessing their cytotoxic potency against HepG2, MCF-7 and HCT-116 cancer cell lines. Compound **21c** possessed significant cytotoxic activity against MCF-7 (IC_{50} = 1.84 μM) and HCT-116 (IC_{50} = 3.31 μM) that surpasses the activity of doxorubicin against both cell lines (MCF-7; IC_{50} = 2.57 μM and HCT-116; IC_{50} = 3.70 μM). Cell cycle analysis and annexin V-FITC staining of MCF-7 cells treated with **21c** suggested that the cytotoxic effect of the compound could be attributed to its pro-apoptotic activity.
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1. Introduction

Various combinations of bis-isatins were discovered to have significant biological activities towards different types of targets inside tumor cells. For example, different indigos **1** and indirubin **2** (Fig. 1) were having potential inhibitory action against CDK-2 (IC_{50} = 1 μM) [1–3]. Consequently, modification took place on these compounds to give meisoindigo **3** which was used for treatment of chronic myelogenous leukemia [4]. Additionally, 7,7′-azaindirubin **4** possessed inhibitory activity against casein kinase 2 [5].

Another strategy for synthesis of biologically active cytotoxic compounds from isatin nucleus was to replace the carbonyl group in position 3 with various substituents. For instance, the addition of hydrazine extension on position 3 would yield biologically active hydrazides as *N*-(2-oxoindolin-3-ylidene)hydrazide derivatives **5** (Fig. 1) reported as inhibitors of c-Met kinase (IC_{50} = 2.2 μM) [6]. Moreover, thiosemicarbazone extension at position 3 as in compound **6** resulted in compounds with selective activity towards multidrug-resistant cells [7].

Addition of certain heterocyclic rings on position 3 of indolin-2-one as pyrrole moiety was a successful strategy for synthesis of many anticancer compounds currently in clinical trials SU5416 (Semaxanib, **7a**), SU6668 (Orantinib, **7b)** and SU14813 [8]. Separation between indolin-2-one and heterocycles in position 3 such as pyrrole, pyridine or quinazoline by hydrazone linker elicits cytotoxic compounds as in **8a** (MCF-7; IC_{50} = 6.25 μM) [9], **8b** (MCF-7; IC_{50} = 6.3 μM and HepG2; IC_{50} = 8.7 μM) [10], **9a** (HepG2; IC_{50} = 1 μM) and **9b** (MCF-7; IC_{50} = 2.1 μM) [11], respectively (Fig. 1). Furthermore, connection of indolin-2-one with chromene ring through hydrazide link gave 2-oxo-*N*′-(2-oxoindolin-3-ylidene)-2*H*-chromene-3-carbohydrazide **10** that was identified to have anticancer activity against HT-29 colon cancer cell line (IC_{50} = 7.98 μM) [12].

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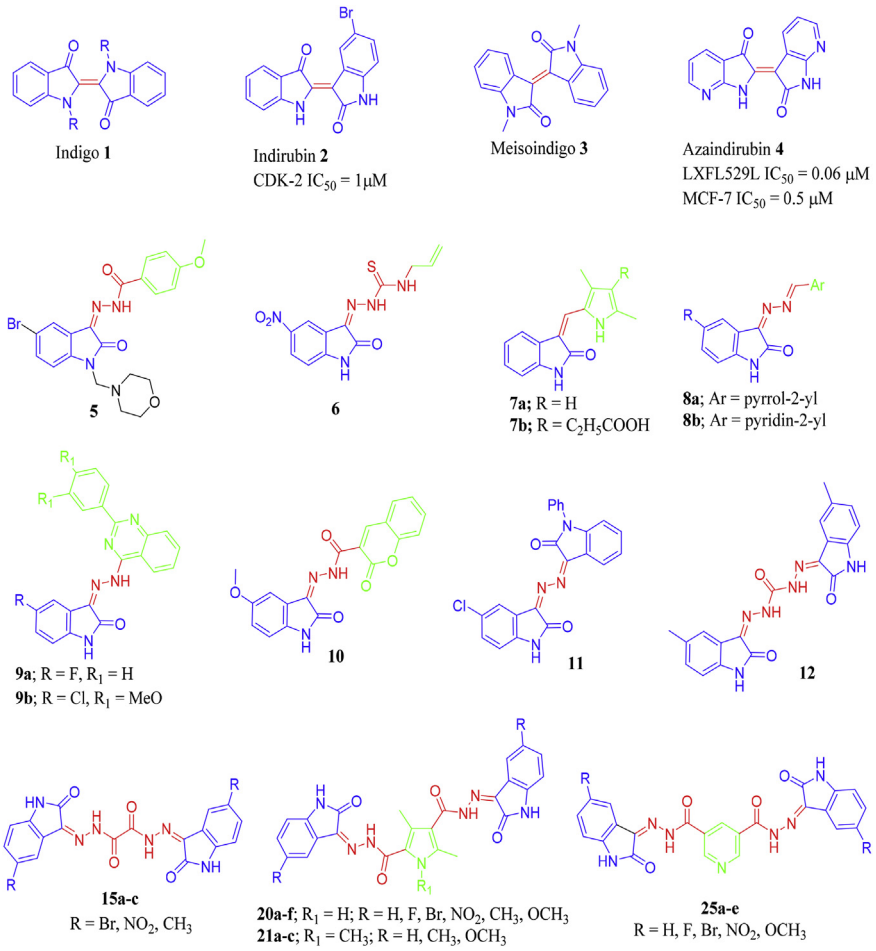

Fig. 1. Structure of isatins **1**–**12**, **15**, **20**, **21** and **25**.

Furthermore, joining two indolin-2-one rings with a short linker was a useful method to get the novel *N,N′*-hydrazine-bis-isatin derivative **11** with selective activity against multidrug resistant cancer cells (KB3-1; IC_{50} = 6.79 μM), (KBV1; IC_{50} = 6.07 μM) [13]. Recent studies on symmetrical derivatives of compound **11** illustrated compounds that could markedly inhibit the proliferation of cancer cell lines (HeLa, SGC-7901, HepG2, U251, and A549) *via* arresting the cell cycle at the G2/M phase with down regulation of cyclin B1 and cdc 2 expression [14]. Increasing the size of the linker between two indolin-2-one rings gave compound **12** that suppresses the proliferation of murine leukemia cells (L1210) (IC_{50} = 16 μM) [15] (Fig. 1).

Our target in this research is to design and synthesize four series of bis-isatins with novel linkers based on the previous data. The first series includes a bis-hydrazide linker as in compounds **15a-c**. The other three series feature a heterocyclic ring inside the bis-hydrazide linker. In compounds **20a-f** and **21a-c**, pyrrole was chosen to be the heterocyclic ring of the linker while in compounds **25a-e**, pyridine was selected (Fig. 1).

2. Results and discussion

2.1. Chemistry

The linker in the first series was inspired from oxalic hydrazide **14** that was synthesized by hydrazinolysis of diethyl oxalate **13** using hydrazine hydrate in ethanol at 0 °C [16]. The formed oxalic hydrazide **14** was subjected to reflux with various 5-substituted isatins in ethanol and in the presence of catalytic amount of acetic acid to give the target products **15a-c** (Scheme 1) [17]. The IR spectra of these compounds showed the appearance of NH stretching bands in the range 3178–3360 cm^{-1}. In addition, ^1H NMR spectra of **15a-c** showed two D_2O exchangeable signals due to 2 NH groups of indole in the range δ 10.81–11.48 in addition to the signals of 2 NH of the hydrazide linker in the range δ 11.95–14.16.

In the second group of compounds, **20a-f** and **21a-c**, the pyrrole ring embedded in the linker was first synthesized as diethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**17**) by Knorr-pyrrole synthesis [18,19]. *N*-methylation of compound **17** was performed *via* methyl iodide and sodium hydride to give diethyl 1,3,5-trimethyl-1*H*-pyrrole-2,4-dicarboxylate (**18**). The pyrrole dicarboxylates **17** and **18** were refluxed with excess hydrazine hydrate to give the corresponding hydrazides **19a** and **19b**. Both hydrazides were reacted with different isatins in refluxing ethanol and in the presence of catalytic amount of acetic acid to yield the target compounds **20a-f** and **21a-c** (Scheme 2). IR spectra of compounds **20a-f** revealed NH stretching bands in the range 3176–3365 cm^{-1} while for NH groups of **21a-c** in the range 3203–3398 cm^{-1}. Moreover, the IR spectra of compounds **20a-f** and **21a-c** revealed the presence of carbonyl groups in the range 1662–1728 cm^{-1}. ^1H NMR spectra of compounds **20a-f** showed the D_2O exchangeable singlet signal of the pyrrole NH near to δ 12.09. On the other hand, the characteristic

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