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Discovery of novel isatin–dehydroepiandrosterone conjugates as potential anticancer agents

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ABSTRACT

A series of isatin–dehydroepiandrosterone hybrids were synthesised via a convenient condensation procedure, and which were evaluated for their potential anticancer activities. The preliminary assays indicated that some of the newly obtained compounds exhibited good antitumor activities against human hepatocellular liver carcinoma (HepG2), heptoma (Huh-7), melanoma (A875) and 5-fluorouracil-resistant human hepatocellular carcinoma (BEL-7402/5-FU) cell lines compared with 5-fluorouracil (5-FU), which might be considered as promising lead scaffold for further design and synthesis of highly potential anticancer agents.

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With the ecological changes and environmental deterioration, cancer has gradually become a major threat to health of humans.¹ Among all current therapeutic methods, chemotherapy is still the most common options for cancer treatment.^{2–4} However, with the rapid increasing multidrug-resistance, one of the strategies to overcome this problem is to discover novel molecules with highly potential anticancer activities.

It is well known that isatin is a natural product consisted in a number of plants, and which has also been found to be a common scaffold in various drugs, agrochemicals, and dyes.^{5–7} Many isatin and its derivatives display diverse pharmacological activities mainly including antiviral, antitumor, anticonvulsants, antifungal etc.^{8–12} Especially, some isatin derivatives have been developed as commercial anticancer drugs such as Sunitinib, Intedanib, Semaxanib (Fig. 1), which identify isatin moiety is an attractive pharmacophore in the discovery of new drugs. On the other hand, dehydroepiandrosterone (DHEA), one of the natural steroids, arouse many researchers' interest in recent years, and many DHEA-type derivatives have been evaluated as potential antibacterial, anticancer, antiviral agents and CYP17 inhibitors.^{13–17} Recently, we have also synthesised a series of DHEA-dihydrazone derivatives¹⁸, and some of the obtained compounds significantly inhibited the proliferation of human tumor cells in culture,

suggesting that this natural four-ring scaffold might contribute to the cytotoxic activity.

In addition, pharmacophores hybridization and functionalization of natural products are the most widely used approaches for discovery of novel therapeutic agents in medicinal chemistry.¹⁹ In view of these observations, as part of our medicinal program aimed at the discovery of novel biologically important heterocyclic compounds, we integrated the structural features of isatin and DHEA unit to design and synthesize a new class of isatin–DHEA conjugates as shown in Figure 2, wishing to identify novel functional molecules with potent antiproliferative effects on tumor cells. The results may provide useful information for design of novel chemotherapeutic drugs.

In the present study, a series of novel isatin–DHEA derivatives were prepared via a convenient condensation procedure. The general method for the preparation of these derivatives **2a–e** and **4a–e** is outlined in Scheme 1.

The easily available steroid DHEA **1** was selected as starting materials, which was linked to various isatins via a =N–N= bridge to the corresponding isatin–DHEA conjugates **4a–e**. To study the possible structure–activity relationships, five imine derivatives **2a–e** have also been prepared using a similar condensation method. All the newly prepared derivatives gave satisfactory chemical analyses.

Structures of target compounds **2a–e** and **4a–e** were confirmed by their ¹H NMR, ESI-MS and elemental analyses, and all the spectra analyses were in good agreement with the proposed structures (Supplementary data). During the ¹H NMR studies, assignments of

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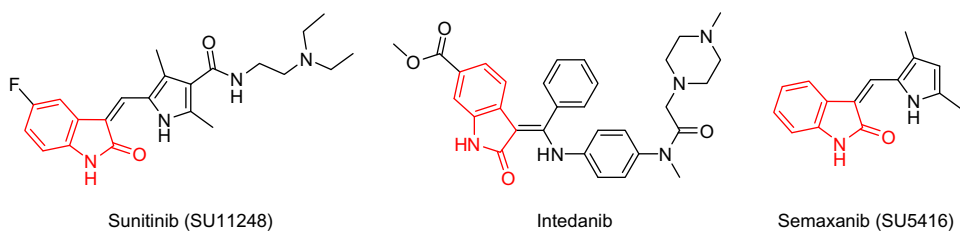


Figure 1. Structures for some anticancer drugs derived from isatin.

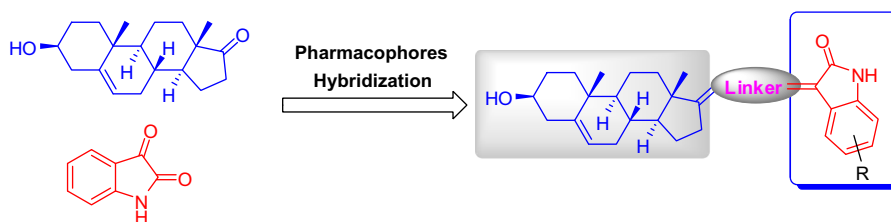
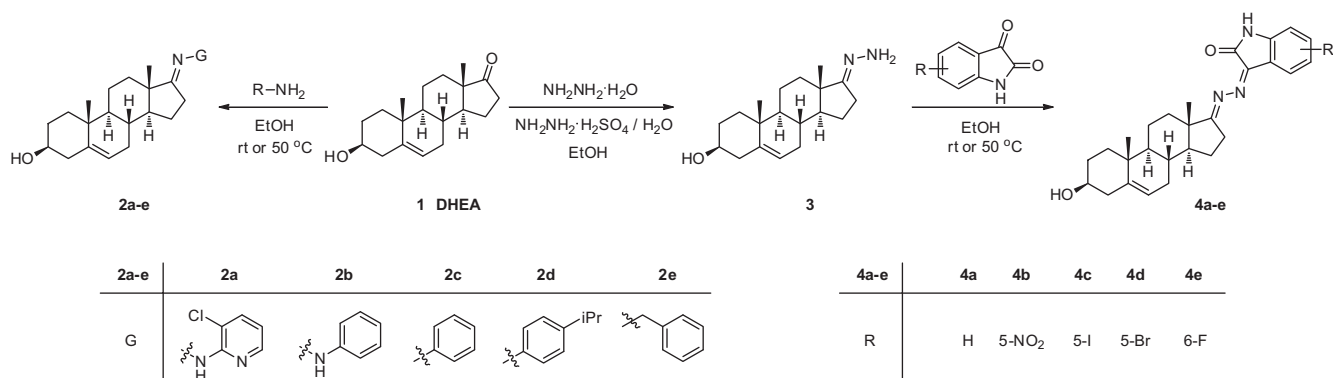


Figure 2. Design strategy of novel isatin–dehydroepiandrosterone conjugates.



Scheme 1. General scheme for the preparation of novel dehydroepiandrosterone derivatives.

the signals are based on the chemical shifts and intensity patterns. For all isatin–DHEA conjugates **4a–e**, the signals at lower fields in the range of 8.65–6.70 ppm were assigned to the aromatic protons in isatin moiety, and the signals at 11.49–10.06 ppm were attributed to NH protons as shown in general structures in Scheme 1. All ¹H NMR spectra of compounds **2a–e** and **4a–e** indicated distinctive signals for protons of alkene bond in the part of DHEA were resonated as a singlet between δ 5.30–5.37 ppm, and the signals of methine proton attached to hydroxyl group were presented at about 4.00 ppm. The several set of signals that appeared in their ¹H NMR spectra at higher fields were attributed to the other protons of DHEA unit. All the characteristic peaks observed within the ¹H NMR spectra for title compounds are given in Supplementary data.

All newly prepared compounds **2a–e** and **4a–e** were screened for their *in vitro* cytotoxic effects against HepG2 (human hepatocellular liver carcinoma), Huh-7 (human hepatoma), A875 (human melanoma) and BEL-7402/5-FU (5-fluorouracil-resistant human hepatocellular carcinoma) cell lines by the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay using 5-FU (5-fluorouracil) as a positive control.^{20,21} The preliminary antitumor results were summarized in Figure 3.

Generally, as shown in Figure 3, most of the synthesised steroidal analogues **2a–e** and **4a–e** displayed moderate to good antitumor activities against four human cancer cell lines compared

with the control. Notably, the isatin–DHEA conjugates **4a–e** exhibited significant better inhibitory activities against all tested cell lines at 20 μ g/mL concentration than that of the positive control 5-FU. However, the other DHEA derivatives containing imine unit **2a–e** indicated moderate to lower activities compared with the control. The preliminary results demonstrated that the strategy combined isatin and DHEA was right and effective, and these novel isatin–DHEA conjugates might be used as a high potential active scaffold for optimization of anticancer agents.

Subsequently, in order to further investigate the highly potential activities, the IC₅₀ values for all compounds were also evaluated. The cytotoxic activities expressed as IC₅₀ values for tested compounds are described in Table 1, which testified that the synthesised isatin–DHEA conjugates **4a–e** exhibited obviously higher inhibition activities than the commercial 5-FU. As indicated in Table 1, compounds **4a**, **4d**, and **4e** have higher cytotoxicity activities (entries 6, 9, and 10) against all tested cancer cell lines than that of the control 5-FU. However, compounds **2a–e** indicated poor activities at the same tested conditions. Especially, all isatin–DHEA conjugates **4a–e** displayed significant cytotoxic activities against BEL-7402/5-FU cell lines that resistant to 5-FU, and the IC₅₀ value for compound **4d** bearing a bromo group is up to 5.97 ± 2.67 μ M. In addition, compound **4b** bearing a nitro group exhibited selective inhibitory effect on HepG2, Huh-7 and BEL-7402/5-FU cell lines.

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