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Design, synthesis and biological evaluation of novel indolin-2-ones as potent anticancer compounds

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ABSTRACT

The indolin-2-one core is a privileged structure for antitumor agents, especially kinase inhibitors. Twenty-three novel indolin-2-ones were designed by molecular dissection of the anticancer drug indirubin. Seventeen of them exhibited significant inhibition against the tested cell lines, and two of them (**1c** and **1h**) showed IC_{50} values at the submicromolar level against HCT-116 cells. Compounds **1c** and **2c** were also potent inhibitors of the triple-negative breast cancer (TNBC) cell line MDA-MB-231. Flow cytometry was utilized to explore the antitumor mechanism of **1c** and **2c** with MDA-MB-231 cells, and distinct effects were observed on **2c**. Furthermore, immunocytochemical examination of **1c** suggested a destabilization of microtubules, which was significantly different from the effect of **IM**, an indirubin derivative.
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The indolin-2-one core is regarded as a privileged structure for antitumor agents, in particular, kinase inhibitors, and numerous indolin-2-one derivatives have been reported as potent kinase inhibitors.[1] Among the examples shown in Fig. 1, Sunitinib[2] and Toceranib phosphate[3] have been approved for cancer therapy by the US FDA, and SU5416,[4] SU6668,[5] SU5614, SU14813, SU9516, and SU4984[1] have been investigated in either clinical trials or preclinical development.

Indirubin (Fig. 2) is a natural product with the bis-indole scaffold. As the active ingredient of the traditional Chinese prescription Danggui Longhui Wan, indirubin is used to treat chronic myeloid leukemia in China.[6,7] It is also reported to possess various biological activities, including anti-HIV,[8] anti-angiogenesis[9] and anti-inflammatory[10,11] effects. However, the therapeutic application of indirubin and its derivatives is often hampered by their poor solubility, which is at least in part attributed to the bis-indole scaffold.

We have previously explored the SAR of a series of indirubin-3'-monoxime (**IM**, Fig. 2) derivatives.[12] As a follow-up study and also to expand the SAR of this compound class, two series of indolin-2-one derivatives were designed by molecular dissection of indirubin (Fig. 3). Series **1** was designed by dividing between N1' and C2' to provide a 2-oxo-2-phenylethylidene side chain. From previous SAR studies, fluoro-substitution on ring B might be favored for antitumor activity.[12] Thus, fluorine was maintained at R^1 for most series **1** compounds and substituted phenyl and other aromatic rings were introduced in R^2. In compound **1a**, an isosteric OH group replaced the residual N1' amino. In contrast, series **2** was obtained by breaking the covalent bond between C2' and C3' to leave a (phenylamino)-methylene side chain. To enhance water-solubility, 3-(p-methylpiperazinyl) phenyl was incorporated as R^4 in series **2** compounds, whereas various aromatic and aliphatic substituents were introduced as R^3.

The series **1** and **2** compounds were prepared following previously published protocols[13,14] as presented in Schemes 1 and 2. Briefly, nucleophilic addition of indoline-2,3-dione **3** (Scheme 1) and various ethanones **4** provided the key intermediate **5**. Elimination of H_2O from **5** produced series **1** compounds. The preparation of series **2** compounds began from 5-nitroindolin-2-one (**6**, Scheme 2). After treating **6** with ethylorthoformate and acetic anhydride, the enol ether intermediate **7** was obtained, and **7** was subsequently converted into the enamine **8**. Hydrolysis of the acetyl and reduction of the nitro group in **8** afforded intermediate **10**, which was reacted with different acids to give series **2** compounds.

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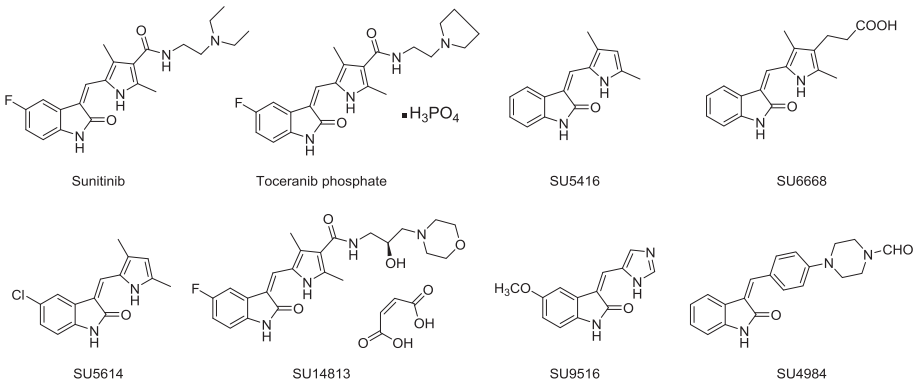


Fig. 1. Representative indolin-2-ones as kinase inhibitors

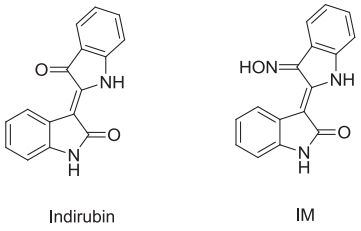


Fig. 2. Structure of indirubin and **IM**

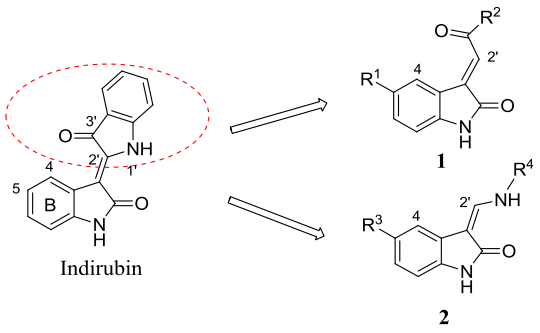


Fig. 3. Molecular design of the target compounds based on indirubin

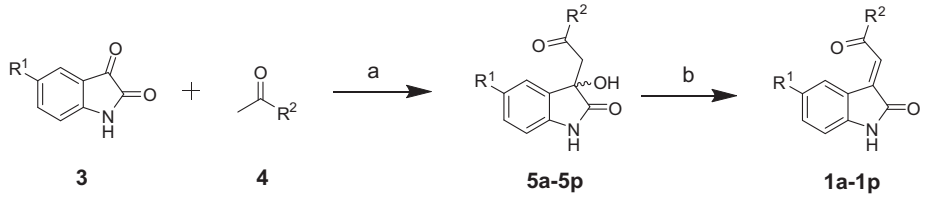
All compounds in both series **1** and **2** were obtained as a single stereoisomer. The downfield chemical shifts of H-4 and H-2' (Fig. 3) suggested an (*E*)-configuration in series **1** compounds,[13,15] which was further confirmed by the lack of correlation between H-4 and H-2' in the NOESY spectra of compound **1c** (Supporting Data). Similarly, the stereochemistry of compounds in series **2** was assigned as (*Z*)-configuration based on the downfield chemical shifts of H-4 and the apparent correlation between H-4 and H-2' in compound **2c** (Supporting Data).

To explore their potential as antitumor agents, compounds in series **1** and **2** were tested in an MTT assay for their inhibitory activity against HCT-116, HepG2, BGC-823, NCI-H1650 and A2780 tumor cell lines. The results are shown in Tables 1 and 2. With regard to series **1** in Table 1, ten compounds showed significant inhibitory activity against all the tested tumor cell lines, and compounds **1c** and **1h** exhibited submicromolar IC_{50} values against HCT-116 cells. According to the data given in Table 1, it appears that R^1 can accommodate a range of different substituents and might have little effect on the tumor inhibitory activity of this compound class (**1e** *vs* **1f**, **1g** *vs* **1h**). In contrast, the R^2 substituents have a significant impact on the tumor inhibitory activity, although no obvious trends could be deduced from the currently available data. Five compounds in series **2** also displayed significant inhibitory activities against the tested tumor cell lines (Table 2). As observed in series **1**, many various substituents were well-tolerated at R^5 in series **2**. However, aliphatic substituents and heteroaromatic rings might be unfavorable for the cytotoxicity of this compound class (**2a-2d** *vs* **2e-2g**). Surprisingly, the indirubin derivative **IM** was tested in parallel and was inactive against all the tested cell lines.

Compounds **1c** and **2c**, the most active compound from each series, were selected as representative compounds for further evaluation against MDA-MB-231, MCF-7, A594, KB and KB-vin cells in a sulforhodamine B (SRB) assay, and **IM** was tested in parallel (Table 3). Notably, all three compounds were potent against MDA-MB-231, which are triple-negative breast cancer (TNBC) cells, a clinically aggressive form of breast cancer and generally unresponsive to chemotherapies.

Since **IM** is an effective inhibitor of CDK2 and CDK9,[12] compounds in series **1** and **2** were initially evaluated against CDK2/Cyclin E1 and CDK9/Cyclin T1 at a concentration of 10 μM. However, neither compound inhibited either CDK system. This observation implied that the molecular dissection of the bis-indole scaffold in **IM** to the indolin-2-one core in **1c** and **2c** resulted in significantly altered pharmacological profiles and an implicit shift in molecular mechanism.

To shed light on the underlying antitumor mechanism of compounds **1c** and **2c**, their effects on cell cycle progression were evaluated in the TNBC cell line MDA-MB-231 by employing flow



Scheme 1. Synthesis of compounds **1a-1p**. Reagents and conditions: (a) Et_2NH, C_2H_5OH, r.t.; (b) hydrochloric acid, C_2H_5OH, 60 °C, 2–24 h.

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