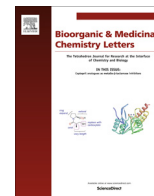




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Isatin derivatives with activity against apoptosis-resistant cancer cells [☆]



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ABSTRACT

In a search of small molecules active against apoptosis-resistant cancer cells, a series of isatin-based heterocyclic compounds were synthesized and found to inhibit proliferation of cancer cell lines resistant to apoptosis. The synthesis of these compounds involved a condensation of commercially available, active methylene heterocycles with isatin proceeding in moderate to excellent yields. The heterocyclic scaffolds prepared in the current investigation appear to be a useful starting point for the development of agents to fight cancers with apoptosis resistance, and thus, associated with dismal prognoses.

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Cancers with intrinsic resistance to apoptosis are generally poorly responsive to current chemotherapeutic agents, most of which work through the induction of apoptosis. These cancers, which include tumors of the lung, liver, stomach, esophagus, pancreas, as well as melanoma and glioblastoma, represent a major challenge in the clinic in terms of treatment strategies.¹ For example, patients afflicted by glioblastoma multiforme,^{2,3} have a median survival expectancy of less than 14 months when treated with the best available protocol that involves chemotherapy with temozolomide.⁴ Indeed, due to their high resistance to apoptosis, glioblastoma cells respond poorly to conventional chemotherapy with proapoptotic agents.³ In addition, the majority of cancer patients die from tumor metastases. Metastatic cells have acquired resistance to cell death known as anoikis, which is normally triggered due to the loss of contact with the extracellular matrix or neighboring cells.⁵ The ability to survive anoikis renders metastatic cells resistant to the large majority of proapoptotic agents as well.^{3,6} Therefore, a search for novel anticancer agents that can overcome cancer cell resistance to apoptosis is an important pursuit.

In this connection, natural products represent a valuable source of not only cytotoxic compounds, but also those molecules capable of overcoming the intrinsic resistance of cancer cells to apoptosis.^{7–10}

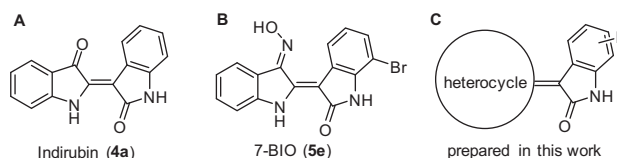


Figure 1. Structures of natural and synthetic isatin derivatives relevant to the current study.

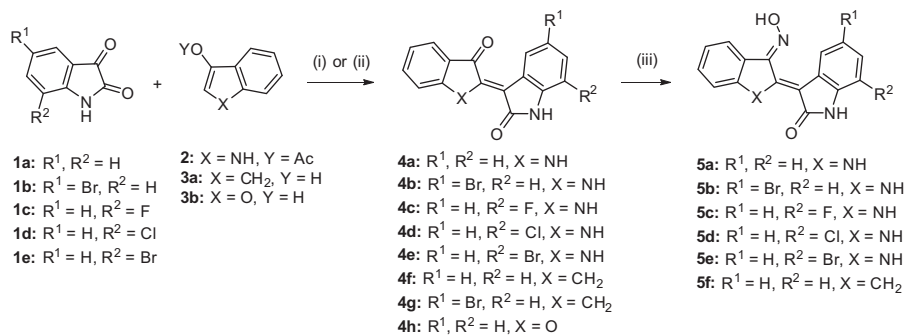
Our recent studies have focused on the class on natural products known as indirubins (Fig. 1A).¹¹ The 2,3'-bis-indoles have been reported to modulate glycogen synthase kinase (GSK)-3,^{11,12} 5-lipoxygenase (5-LO),¹³ tyrosine kinases,¹⁴ and aryl hydrocarbon (Ah) receptor.¹⁵ Indirubin derivatives that attracted our interest were indirubin-3'-oximes based on a report from Meijer's group, showing that 7-bromoindirubine-3'-oxime (7-BIO, Fig. 1B) triggers necrotic, caspase-independent cancer cell death,¹⁶ indicating the promise of this type of compounds in overcoming apoptosis resistance.¹⁷ This discovery prompted us to synthesize a series of indirubin derivatives, as well as related isatin-based heterocyclic scaffolds (Fig. 1C), and evaluate them against apoptosis-resistant cancer cells.

For the synthesis of indirubin analogs (4a–g), most of which bear a halogen atom in the ring (as in 7-BIO), we employed a base-catalyzed condensation of substituted isatins (1a–e) with indoxyl acetate (2) and 1-indanone (3a). 3-Coumaranone (3b)

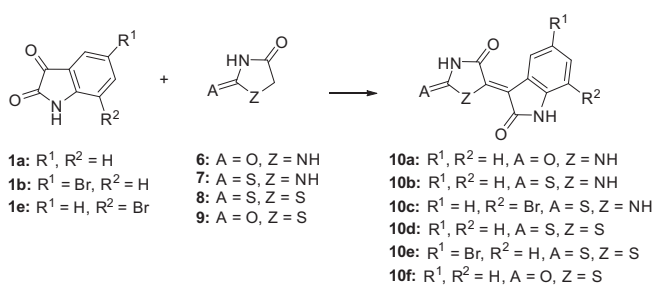
[☆] In remembrance of Dr. Igor V. Magedov.

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Scheme 1. Synthesis of isatin derivatives **4a–h** and their 3'-oximes **5a–f**. Reagents and conditions: (i) Na₂CO₃, MeOH, rt, 6–24 h (73% (**4a**), 81% (**4b**), 93% (**4c**), 88% (**4d**), 91% (**4e**), 86% (**4f**), 59% (**4g**)); (ii) AcONa, AcOH, 110 °C, 24 h (54% (**4h**)); (iii) NH₂OH·HCl, pyridine, 120 °C, 2 h (71% (**5a**), 59% (**5b**), 65% (**5c**), 73% (**5d**), 69% (**5e**), 36% (**5f**)).



Scheme 2. Synthesis of compounds **10a–f**. Reagents and conditions: AcONa, AcOH, 110 °C, 24 h (65% (**10a**), 52% (**10b**), 64% (**10c**), 58% (**10d**), 85% (**10e**), 66% (**10f**)).

failed to react with **1a** neatly due to a rapid self-condensation, but a switch from basic to acidic conditions facilitated a clean reaction and we were able to obtain a high yield of **4h**. Compounds **4a–f** were further reacted with an excess of hydroxylamine hydrochloride in pyridine providing 3'-oximes **5a–f** (Scheme 1).

To extend the series beyond the indirubin scaffold, we synthesized compounds resulting from the condensation of isatin with other active methylene heterocycles (Scheme 2). Our selection of suitable heterocycles was based on their previously described biological and therapeutic relevance. Thus, hydantoin (**6**) derivatives are represented by approved drugs (Phenytoin, Fosphenytoin), pesticides (Imiprothrin, Iprodione), or inhibitors of matrix metalloproteinases (MMPs).¹⁸ Thiohydantoin (**7**) derivatives have been identified as antimicrobials¹⁹ and antitumor²⁰ agents with topoisomerase I inhibitory activities.²¹ Rhodanine (**8**) derivatives are well known beta-lactamase inhibitors.^{22,23} Analogs of thiazolidinedione (**9**) are peroxisome proliferator-activated receptor (PPAR) agonists and have been used as antidiabetic drugs.²⁴ Condensation of isatins with the above mentioned heterocycles was found to work best with sodium acetate in acetic acid, providing the desired isatin derivatives **10a–f** in satisfactory yields (Scheme 2).

Having synthesized the library, we proceeded with the in vitro evaluation of their growth inhibitory activity against the panel of nine cancer cell lines (Table 1). The panel included cell lines with demonstrated resistance towards the induction of apoptosis, such

Table 1
In vitro antiproliferative activities of the synthesized compounds

Compound	IC ₅₀ in vitro values ^a (μM)								
	Resistant to apoptosis				Sensitive to apoptosis				Unknown
	U373 (GBM)	A549 (NSCLC)	OE21 (esophageal cancer)	SKMEL-28 (melanoma)	HS683 (Glioma)	B16F10 (melanoma, mouse)	PC-3 (prostate cancer)	MCF-7 (breast cancer)	LoVo (colon cancer)
4a	^b	^	30.5	^	^	0.2	^	^	^
4b	8.6	^	3.8	^	14.1	3.8	^	37.3	12.0
4c	45.8	^	29	^	38.7	16.3	^	44.8	42.0
4d	^	^	35.3	^	55.2	15.7	^	^	^
4e	8.1	^	8.7	^	6.9	3.2	^	52.8	32.3
4f	^	^	25.1	^	^	^	^	70.2	52.6
4g	41.4	^	56.0	^	47.3	69.1	^	65.2	52.8
4h	27.7	23.3	25.9	23.8	25.7	<0.01	36.1	0.3	4.1
5a	18.0	27.0	8.1	26.6	6.0	5.4	24.3	9.2	8.9
5b	8.0	7.2	3.6	17.3	8.4	0.5	6.8	5.8	6.6
5c	19.7	33.3	9.2	44.6	9.3	7.8	26.0	26.2	9.0
5d	31.5	45.2	19.6	40.1	25.3	12.9	29.7	27.5	10.2
5e	6.6	13.9	3.9	9.8	8.1	5.3	7.8	4.9	5.6
5f	28.0	28.7	27.8	33.7	22.9	32.6	33.1	38.5	18.7
10a	^	66.5	52.3	^	84.7	73.3	95.5	94.6	76.1
10b	51.9	45.8	38.7	62.9	52.9	41.6	75.5	87.8	60.2
10c	4.7	3.8	20.2	11.7	40.8	5.0	22.8	51.0	37.0
10d	85.3	99.0	47.2	96.6	93.3	73.5	^	^	69.3
10e	41.7	36.2	62.5	53.5	93.6	0.1	44.3	82.9	52.1
10f	86.4	60.7	38.0	^	89.7	2.8	67.5	^	5.2
β-Lapachone	0.4	0.8	0.6	0.6	0.4	0.3	<0.01	0.5	0.3

^a IC₅₀ is the compound concentration that reduces by 50% the growth of a given cell line (as compared to the control value) after having cultured the cells for 72 h with the compound of interest, as determined with the MTT assay. Each experiment was carried out in sextuplicates, numbers in table are arithmetic mean values.

^b ^—more than 100 μM.

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