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Potential in Vitro Anti-Tumor Effects of Novel Indole Derivatives

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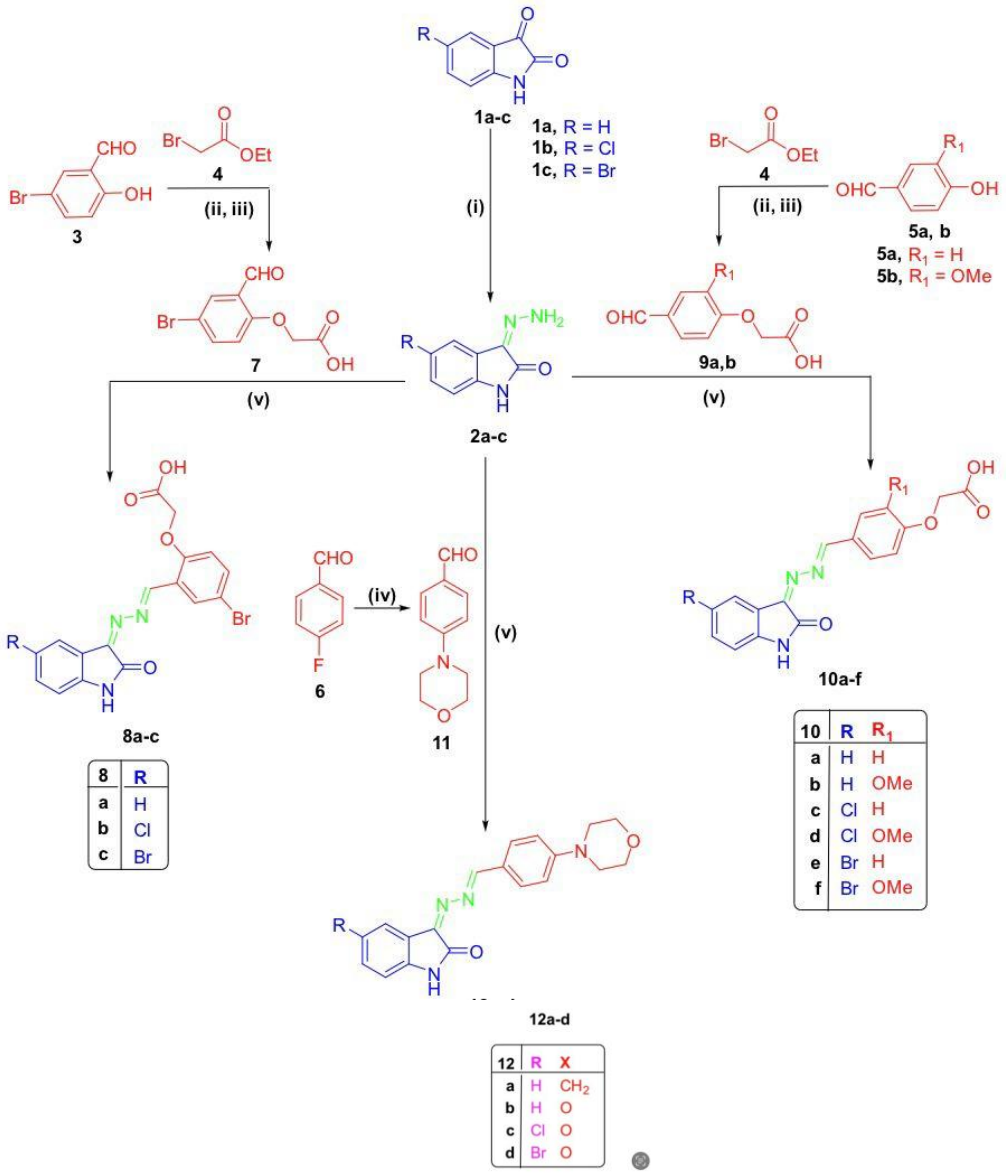
Indole alkaloids, such as isatin, are one of the most abundant and complex alkaloids, which ubiquitously exists in natural products. Isatin compound is derived from indole with formula $C_8H_5NO_2$. Isatin is a well-known natural product that can be found in plants of the genus Isatis in *Couroupita guianensis* and in humans, as a metabolic derivative of adrenaline. Isatin is widely recognized for its antibacterial, antiviral, anticonvulsant, anti-inflammatory, as and anti-cancer properties [1]. The current study continues searching for new biological activities for the active novels of isatin derivatives, highlighting its importance as potential anti-cancer compounds

In scheme 1, the key starting compound was 2a-c (hydrazones) prepared by the reaction of isatin 1a-c with hydrazine hydrate [2]. 4-Morpholinobenzaldehyde (11) was prepared by the reaction of 4-fluorobenzaldehyde (6) with the morpholine [3]. Hydrazones 2a-c reacted with the aldehydes 11 in ethanol, in the presence of acetic acid under reflux to afford the corresponding hydrazones 12a-d, respectively. The structures of the compounds were confirmed through their IR, ^{1}HNMR, ^{13}CNMR and CHN thermal analyses. The structure of the latter newly synthesized hydrazones was confirmed through their IR, ^{1}HNMR, ^{13}CNMR and CHN thermal analyses [4].

Out of 12 indole compounds synthesized, we studied, in this phase, the effect of 4 novel compounds on normal (Wi38, fibroblast cell line) and cancer cell lines (A549 lung cancer cell line) after 48 h as compared to no treatment and cells and after treatment with doxorubicin (DOX) as an anti-cancer reference drug. We tested four compounds, including compound 12a: 5-Chloro-3((4-morpholinobenzylidene)hydrazineylidene) indolin-2-one, compound 12b: 5-Bromo-3-((4-morpholinobenzylidene)hydrazineylidene) indolin-2-one, 12c: 5-Chloro-3-((4-morpholinobenzylidene)hydrazineylidene)indolin-2-one, and 12d: 5-Bromo-3-((4-morpholinobenzylidene)hydrazineylidene)indolin-2-one.

The IC_{50} measured after 24 h of treatment of Wi38 was 0.047 mM for DOX, 4.97 mM for compound 12a, 5.6 mM for compound 12b, 1.192 mM for compound 12c, and 0.019 mM for compound 12d. The IC_{50} after 24 h of treatment of A549 lung cancer cell line was 0.07 mM for DOX, 3.8 mM for compound 12a, 3.44 mM for compound 12b, 3.79 mM for compound 12c, and 9.218 mM for compound 12d.

By analyzing cell apoptosis (programed cell death) and cell cycle by flow cytometry, we found that the four-compound increased apoptosis and arrested the cel cycle of the tumor cells. Altogether, these data indicate that isatin compounds derivatives from indole have potential anti-tumor effects by increasing cell death and arresting cell division.



8	R
a	H
b	Cl
c	Br

10	R	R1
a	H	H
b	H	OMe
c	Cl	H
d	Cl	OMe
e	Br	H
f	Br	OMe

12	R	X
a	H	CH_2
b	H	O
c	Cl	O
d	Br	O

Figure 1. Reagents and conditions: (i) $NH_2NH_2.H_2O$, MeOH, reflux 1 h; (ii) DMF/K_2CO_3, stirring 12 h; (iii) NaOH/MeOH, reflux 1 h; (iv) Morpholine, DMF/K_2CO_3, stirring 24 h; (v) EtOH/AcOH, reflux 8 h.

Further structural characterization of indoles is crucial for understanding their anti-tumor mechanisms and optimizing their applications. Spectroscopic techniques such as UV-visible spectroscopy, fluorescence spectroscopy, and NMR spectroscopy are pivotal in elucidating the absorption, fluorescence, and detailed molecular structure of indole derivatives, respectively.

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