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Indole-3-carbinol as a chemopreventive and anti-cancer agent

Jing-Ru Weng^{a,b}, Chen-Hsun Tsai^c, Samuel K. Kulp^c, and Ching-Shih Chen^{c,*}

^aDepartment of Biological Science and Technology, China Medical University, Taichung 40402, Taiwan

^bChina Medical University Hospital, Taichung 40402, Taiwan

^cDivision of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, OH 43210

Abstract

During the course of oncogenesis and tumor progression, cancer cells constitutively upregulate signaling pathways relevant to cell proliferation and survival as a strategy to overcome genomic instability and acquire resistance phenotype to chemotherapeutic agents. In light of this clinical and molecular heterogeneity of human cancers, it is desirable to concomitantly target these genetic abnormalities by using an agent with pleiotropic mode of action. Indole-3-carbinol and its metabolite 3,3'-diindolymethane (DIM) target multiple aspects of cancer cell cycle regulation and survival including Akt-NFκB signaling, caspase activation, cyclin-dependent kinase activities, estrogen metabolism, estrogen receptor signaling, endoplasmic reticulum stress, and BRCA gene expression. This broad spectrum of antitumor activities in conjunction with low toxicity underscores the translational value of indole-3-carbinol and its metabolites in cancer prevention/therapy. Furthermore, novel antitumor agents with overlapping underlying mechanisms have emerged via structural optimization of indole-3-carbinol and DIM, which may provide considerable therapeutic advantages over the parental compounds with respect to chemical stability and anti-tumor potency. Together, these agents might foster new strategies for cancer prevention and therapy.

Keywords

indole-3-carbinol; 3,3'-diindolymethane; Akt-NFκB signaling; nuclear receptor signaling; endoplasmic reticulum stress; BRCA gene expression

1. Introduction

Epidemiological and dietary studies have provided a link between high dietary intake of cruciferous vegetables and lowered cancer risks (1–4). Considerable evidence attributes this chemopreventive effect to the antitumor activity of a common phytochemical, indole-3-carbinol, and its metabolic products. These indole derivatives have been shown to suppress the proliferation of various cancer cell lines at the concentration range of 50 – 100 μM, including those of breast (5–8), colon (9–11), prostate (12–14), and endometrium (15), by targeting a

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*To whom correspondence should be addressed: Division of Medicinal Chemistry, College of Pharmacy, Parks Hall, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210. Tel: (614)688-4008; Fax: (614)688-8556; chen.844@osu.edu.

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wide spectrum of signaling pathways governing hormonal homeostasis, cell cycle progression, and cell proliferation and survival [reviews:(16–20)]. Moreover, indole-3-carbinol inhibited spontaneous or chemical-induced tumorigenesis in mammary gland, liver, lung, cervix, and gastrointestinal tract in different animal model studies (21–27). These preclinical findings demonstrate the translational value of indole-3-carbinol in cancer prevention and therapy [review: (3)], which has led to its human trials in cervical dysplasia (28), breast cancer (29, 30), vulvar intraepithelial neoplasia (31), and recurrent respiratory papillomatosis (32).

From a mechanistic perspective, the *in vivo* efficacy of indole-3-carbinol arises from a dynamic interaction between its metabolic disposition and pleiotropic modes of action, which could be pharmacologically exploited to foster new strategies or to develop novel chemopreventive/therapeutic agents. Thus, this minireview addresses the multifaceted aspects of the chemical biology of indole-3-carbinol by giving an overview of the following subjects: (A) metabolic transformation of indole-3-carbinol and its pharmacological relevance, (B) pleiotropic effects of indole-3-carbinol on multiple signaling targets, and (C) pharmacological exploitation of indole-3-carbinol and DIM to develop novel antitumor agents.

2. Metabolic transformation of indole-3-carbinol and its pharmacological relevance

The intrinsic instability of indole-3-carbinol in acidic milieu arises from the vinyl hemiaminal moiety of the indole ring (Fig. 1, enclosed by dashed line) (33). This unique structural feature underlies the high susceptibility of indole-3-carbinol to acid-catalyzed dehydration and condensation to generate a complex series of oligomeric products *in vivo* (Fig. 1), including DIM (3,3'-diindolymethane), ICZ (indolo[3,2b]-carbazole), LTr₁ (a linear trimer), CTr (a cyclic trimer), and CTet (a cyclic tetramer) (34–37).

As each of these major metabolites exhibits pharmacological activities (Table 1), the observed chemopreventive effect of indole-3-carbinol *in vivo* might, at least in part, be attributable to these acid condensation products. Among them, DIM induces apoptosis and cell cycle arrest in cancer cells through signaling mechanisms analogous to those of indole-3-carbinol (14, 38–46), while the functions of ICZ, LTr₁, and CTr are associated with nuclear receptors such as the aryl hydrocarbon receptor (AhR) and/or estrogen receptor (ER) (47,48). It is noteworthy that the tetrameric product CTet suppressed breast cancer growth by inhibiting the expression of cyclin-dependent kinase (CDK)6 and other cell-cycle regulatory proteins, with fivefold higher potency than indole-3-carbinol (49).

3. Pleiotropic effects of indole-3-carbinol on multiple signaling targets

Substantial evidence indicates that the antitumor effect of indole-3-carbinol is attributable to its ability to target a plethora of signaling pathways governing apoptosis, cell cycle progression, hormonal homeostasis, DNA repair, angiogenesis, and multiple drug resistance [reviews: (16–20)]. Moreover, indole-3-carbinol proves to be an effective chemopreventive agent against estrogen-responsive cancers such as breast and cervical cancers, in part, because it functions as a negative regulator of estrogen by inhibiting ER α signaling (54,55) and altering cytochrome P450-mediated estrogen metabolism (56). It is important to note that the pharmacological responses of indole-3-carbinol in various cellular events might be contributed, in part, by its major metabolite, DIM as these two indole derivatives exhibit a high degree of similarity in their mode of action. Consequently, this section is aimed at providing an overview of the causative relationship between individual signaling targets and various indole-3-carbinol-induced cellular responses (Fig. 2).

3.1. Apoptosis Induction

Mounting evidence indicates that inactivation of Akt and its downstream effector, the nuclear transcription factor NF- κ B, plays a pivotal role in the proapoptotic action of indole-3-carbinol/DIM in tumor cells (6,12,57,58). It is well documented that Akt promotes cell survival by stimulating NF- κ B signaling through I κ B α kinase in conjunction with the phosphorylating deactivation of several proapoptotic proteins including glycogen synthase kinase (GSK)3 β , Bad, Forkhead transcription factors, and caspase-9, thereby constituting an important target for cancer therapy [recent reviews: (59–64)]. NF- κ B acts as an important survival factor in cancer cells by mediating the transcription of a series of antiapoptotic genes, including: *Bcl-2*, *Bcl-xL*, *survivin*, *p53*, and *p21* (65). In addition, indole-3-carbinol has been shown to activate the stress-induced MAP kinases p38 and c-jun N-terminal kinase (JNK) in prostate cancer cells (66), and to inhibit constitutively active STAT3, a transcription factor, in pancreatic carcinoma cells (67). Together, the concerted effects on these proapoptotic components underlie the ability of indole-3-carbinol/DIM to induce mitochondria-dependent apoptosis in tumor cells.

3.2. Cell cycle arrest

Indole-3-carbinol and DIM exhibit the ability to cause G1 arrest in breast and prostate cancer cells (68,69). This cell cycle arrest involves the upregulation of the CDK inhibitors p21^{WAF1} and p27^{kip1}, and the concurrent downregulation of cyclin D1, cyclin E, and CDKs 2, 4, and 6, which is, in part, attributable to the effect of indole-3-carbinol/DIM on regulating Sp1-promoter binding activity (50,70,71). In addition, indole-3-carbinol was reported to inhibit CDK2 kinase activity in MCF-7 cells through selective alterations in cyclin E composition, size distribution, and subcellular localization of the CDK2 protein complex (72). Together, inhibition of CDK4/6/cyclin D1 and CDK2/cyclin E activities led to decreased Rb phosphorylation, which causes the Rb protein to bind to the E2F transcription factor. This E2F sequestration blocks the transcription of S phase genes, resulting in G1 arrest (Fig. 3).

3.3. Modulation of the functional /expression status of nuclear receptors

3.3.1. Aryl hydrocarbon receptor (AhR)—AhR is a transcription factor that can be activated by several types of aromatic compounds such as dioxins and flavonoids. Indole-3-carbinol, DIM, and ICZ have been reported to bind and activate AhR with varying potencies (73,74). In addition, indole-3-carbinol has been reported to increase AhR expression in MCF-7 cells (75). AhR activation plays an important role in the chemopreventive effect of indole-3-carbinol and its metabolites. Specifically, AhR upregulates the gene expression of the Phase I enzyme CYP1A1 and the Phase II enzymes glutathione S-transferase and oxidoreductases in prostate and breast cancer cells (42,75) and in rat liver (76,77). These xenobiotic-metabolizing enzymes are involved in inhibiting the activation of chemical carcinogens. In addition, CYP1A1 mediates the 2-hydroxylation of estrone, one of the two major competing hydroxylation pathways of estrone metabolism, leading to increased levels of 2-hydroxyestrone (78). Relative to 16-hydroxyestrone, which is linked to stimulation of estrogen and DNA damage in mammary epithelial cells, 2-hydroxyestrone competes with estradiol for estrogen receptor binding, thereby abrogating the proliferative effect of estradiol (79). Consequently, I3C may act as a phytoestrogen by inducing a competing metabolic pathway that increases production of 2-hydroxyesterone and thus reduces the substrate available for production of 16-hydroxyesterone (80). Together, the ability of indole-3-carbinol to facilitate the metabolism of genotoxic agents, either environmental or endogenous, underlies its effect on cancer prevention.

3.3.2. Estrogen receptor (ER)—Indole-3-carbinol is a negative regulator of ER α signaling in human tumor cells (54). In addition to altering estrogen metabolism through CYP1A1, indole-3-carbinol and its metabolites also affect ER signaling through two different

mechanisms. First, indole-3-carbinol and DIM could bind to and inhibit the activity of ER (24,51), which diminished estradiol-mediated cellular and biochemical effects in estrogen-sensitive cells and tissues (81). Consequently, indole-3-carbinol could cooperate with tamoxifen to inhibit breast cancer proliferation (82). Second, indole-3-carbinol and DIM could suppress ER α expression in breast cancer cells (55,83), which might be attributable to the ability of these indole derivatives to bind to the nuclear AhR (55). Moreover, indole-3-carbinol was reported to increase the binding of ER β to the estrogen response element, resulting in a significantly higher ER β /ER α ratio that is associated with an antiproliferative status in human breast cancer cells (83).

3.4. Endoplasmic reticulum stress

Evidence indicates that indole-3-carbinol and DIM induced endoplasmic reticulum stress responses in cancer cells via unfolded protein response pathways, which led to the induction of a series of stress-related proteins including a series of GADD (Growth Arrest in response to DNA Damage) proteins (54,84,85). These endoplasmic reticulum stress-related proteins negatively regulate cell growth, leading to cell cycle arrest and apoptosis (86). For example, GADD153/CHOP, a nuclear transcription factor, represses the Bcl-2 promoter, and sensitizes mitochondria to the proapoptotic effects of BH3-only proteins (87). In addition, GADD153 enhances the expression of death receptor (DR)5, which underlies the effect of indole-3-carbinol on augmenting TRAIL-induced apoptosis in LNCaP prostate cancer cells (88). It is also noteworthy that there exists a mechanistic link between indole-3-carbinol/DIM-induced endoplasmic reticulum stress and upregulation of the expression of the tumor suppressor genes *BRCA1* and *BRCA2* in prostate and breast cancer cells (89). *BRCA1* and *BRCA2* genes represent main genetic elements associated with hereditary susceptibility to breast and ovarian cancer, and loss of these genes contributes to oncogenesis and tumor progression. The proteins encoded by the two genes play an important role in maintaining genomic stability by participating in DNA repair (90,91).

3.5. Tumor invasion and angiogenesis

Indole-3-carbinol has been reported to inhibit the migration and invasion of breast cancer cells by modulating the expression of a series of signaling proteins associated with invasion and migration, including E-cadherin, α , β , and γ catenin, *BRCA1* (92,93), the chemokine receptor CXCR4, and the matrix metalloproteinase (MMP)-9 (94). Moreover, indole-3-carbinol has been shown to inhibit the growth and phorbol ester-activated tube formation of endothelial cells, accompanied by decreased vascular endothelial growth factor (VEGF), increased interleukin-8 (IL-8) secretion, and decreased activities of MMP-2 and MMP-9 (95).

3.6. Reversal of multiple drug resistance (MDR)

Indole-3-carbinol has been reported to reverse the multiple-drug resistant phenotype of human leukemia cells and murine melanoma cells to doxorubicin and vinca alkaloids by down-regulating the expression of the MDR-1 gene product p-glycoprotein (96–98). Moreover, the ability of dietary administration of indole-3-carbinol to sensitize MDR tumors to chemotherapeutic drugs has also been demonstrated *in vivo* (98). Together, these findings indicate that indole-3-carbinol may be effective as a dietary adjuvant in the treatment of MDR cancers.

4. Chemo- and radiosensitizing effects of indole-3-carbinol/DIM

Considering the pleiotropic effects on multiple signaling targets relevant to cell survival, indole-3-carbinol/DIM exhibit the ability to sensitize cancer cells to apoptosis induced by various anticancer agents and radiation. As summarized in Table 2, indole-3-carbinol and

various therapeutic agents work through different signal transduction pathways in a synergistic manner to suppress cell viability of various types of cancer cells.

For example, indole-3-carbinol was shown to be an effective sensitizer of TRAIL treatment against TRAIL-resistant LNCaP prostate cancer cells by up-regulating the expression of two TRAIL death receptors, DR4 and DR5 (88). In addition, treatment of MCF-7 cells with indole-3-carbinol and tamoxifen synergistically ablated expression of the phosphorylated retinoblastoma protein (Rb), an endogenous substrate for the G1 cyclin-dependent kinases (CDKs), through specific down-regulation of the expression of CDK6 (82).

5. Pharmacological exploitation of indole-3-carbinol and DIM to develop novel antitumor agents

From a mechanistic perspective, the ability of indole-3-carbinol/DIM to target a broad spectrum of signaling pathways underlies their antitumor effect against a variety of cancer cells with different genetic and cellular abnormalities. However, indole-3-carbinol and DIM exhibit low - moderate potencies in suppressing tumor cell proliferation *in vitro*, and suffer from metabolic instability and/or unpredictable pharmacokinetic properties *in vivo* (29). Consequently, structural modifications of indole-3-carbinol/DIM to develop novel indole derivatives with improved potency have been the focus of many recent investigations. This medicinal chemistry effort has led to several different classes of novel agents with distinct pharmacological activities (Fig. 4).

5.1. Ring-substituted DIMs

Symmetrical disubstitutions at the 5,5' positions of DIM with methyl and bromo groups gave rise to two structural variants, 5,5'-diMeDIM and 5,5'-diBrDIM, respectively (Fig. 4) (102, 103). Despite structural similarity, these two ring-substituted DIM derivatives inhibited breast cancer cell growth through different mechanisms, indicating a subtle structure-activity relationship. While 5,5'-diMeDIM represents a selective AhR inhibitor (102), 5,5'-diBrDIM is a mitochondrial poison that induced cell death by decreasing mitochondrial membrane potential (103).

5.2. SR13668, an Akt inhibitor

Structural modifications after fusing the two indoyl moieties of DIM generated a novel class of antitumor agents, of which SR13668 represents an optimal agent (104). Unlike other DIM derivatives that are agonists of nuclear receptors, SR13668-mediated antitumor effect was facilitated by blocking growth factor-stimulated Akt phosphorylation. However, the mode of action of SR13668 in inhibiting Akt activation is distinct from that of many other Akt inhibitors, i.e., it does not target the ATP binding site.

5.3. 1-(p-Substituted phenyl)DIMs (C-DIMs)

Substitutions of a proton with bulky aromatic substituents on the methylene group of DIM alter the activity of resulting compounds, i.e., C-DIMs, in interacting with various types of nuclear receptors. It is noteworthy that these C-DIMs are no longer AhR agonists, but could activate peroxisomal proliferator-activated receptor (PPAR) γ and/or Nur77 (also known as nerve growth factor (NGF)I-B α) [PPAR γ C-DIMs: (105,106) Nur77 C-DIMs: (107,108)]. For example, of the three representative C-DIM derivatives depicted in Fig. 4, DIM-C-pPhTbu and DIM-C-pPhOCH₃ are PPAR γ -specific and Nur77-specific agonists, respectively, while C-pPhCF₃ transactivates both PPAR γ and Nur77. Transactivation of these nuclear receptors activates downstream responses including cell cycle arrest and induction of cell death pathways including caspase activation and poly(ADP-ribose)polymerase (PARP) cleavage.

5.4. OSU-A9, a multi-targeted agent

OSU-A9 was developed by using indole-3-carbinol as a scaffold via *N*-substitution of the vinyl hemiaminal function with a benzenesulfonyl moiety (66). This modification not only improves the acid stability, but also results in a 100-fold increase in apoptosis-inducing potency as compared to its parent compound. Equally important, OSU-A9 retains the pleiotropic mechanisms of indole-3-carbinol in mediating cell cycle arrest and apoptosis induction in cancer cells. Despite this broad spectrum of pharmacological activities, nonmalignant cells were less sensitive to the antiproliferative effect of OSU-A9 relative to cancer cell lines. Moreover, OSU-A9 has been shown to suppress prostate tumor growth *in vivo* without causing overt toxicity, underlying its potential use in cancer prevention and/or therapy.

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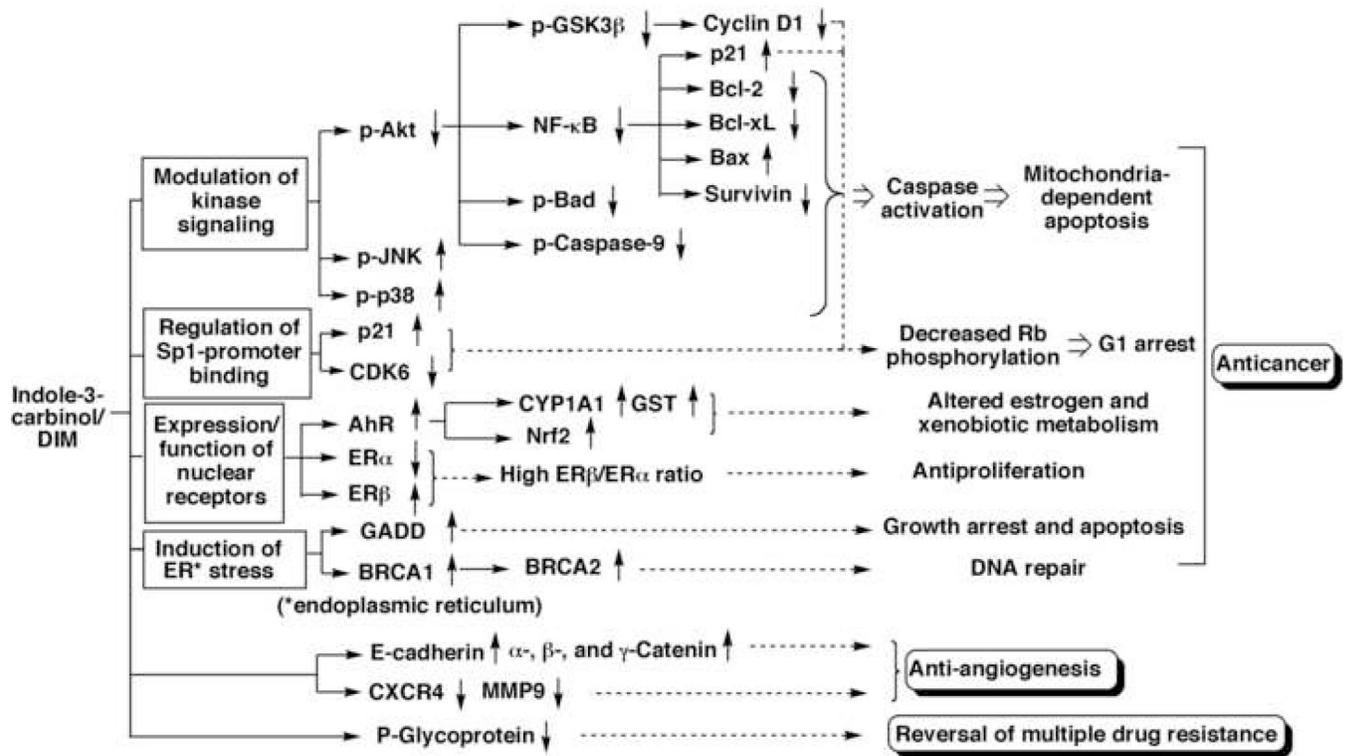


Fig. 2.
An overview of the signaling pathways targeted by indole-3-carbinol and DIM.

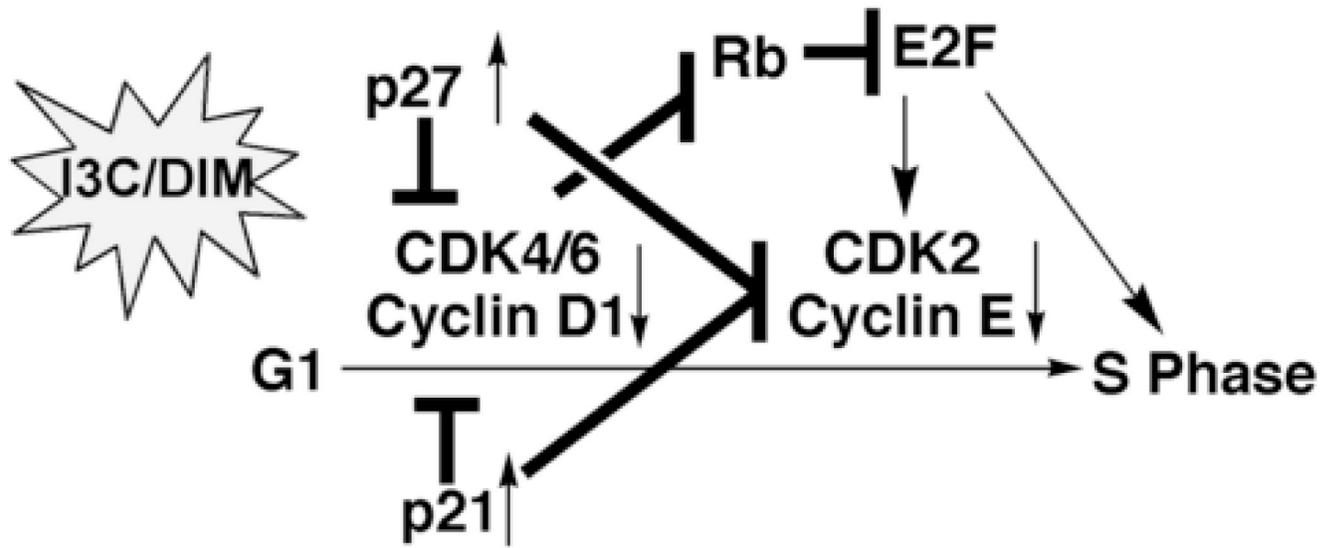


Fig. 3.
Effects of indole-3-carbinol/DIM on G1 cell cycle arrest.

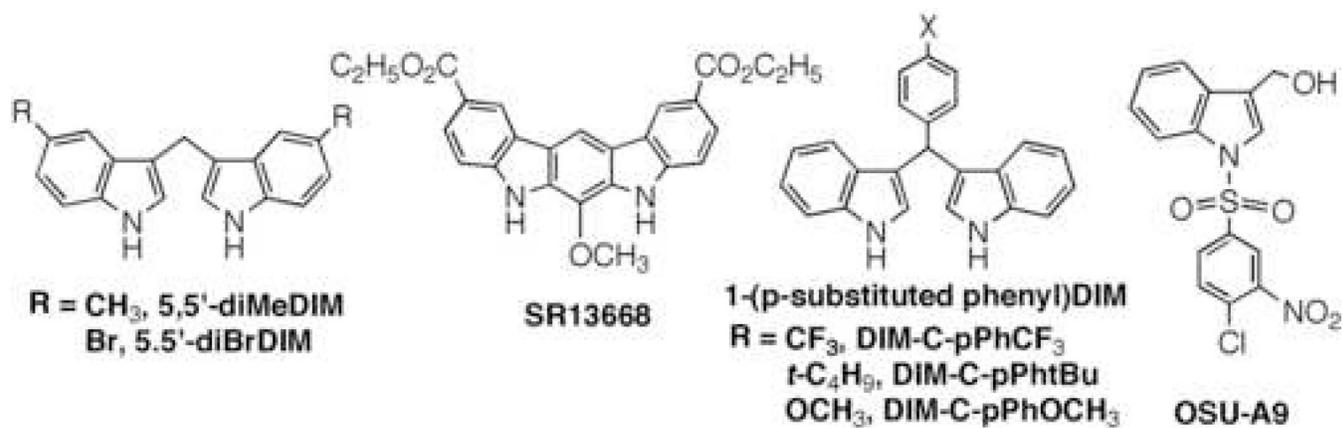


Fig. 4.
Structurally optimized indole-3-carbinol and DIM derivatives.

Table 1

Pharmacological effects of indole-3-carbinol metabolites in cancer cells

Metabolite	Cellular responses		Signaling targets	Ref.
DIM	<ol style="list-style-type: none"> 1 Apoptosis induction and cell cycle arrest 2 Inhibition of angiogenesis 3 Androgen receptor (AR) downregulation 4 Activation of aryl hydrocarbon receptor (AhR) and consequent activation gene expression of Phase I and II enzymes 5 Inhibition of ERα-dependent gene expression 	↓	Akt phosphorylation NF- κ B signaling Survivin expression Bcl-2 expression Cdc25A expression CDK 6 expression AR expression ER α signaling	(14,38–46,50,51)
			↑	
ICZ	Activation of AhR and consequent activation of gene expression of Phase I and II enzymes	↑	AhR signaling	(47,48)
LTr ₁	<ol style="list-style-type: none"> 1 An antagonist of estrogen receptor (ER)α 2 A weak agonist of AhR 	↓	ER signaling	(52)
		↑	AhR signaling	
CTr	A potent agonist of (ER) α	↑	ER signaling	(53)
CTet	Cell cycle arrest	↓	CDK 6 expression	(49)
		↑	p27 ^{kip1} expression	

(↓, downregulation; ↑, upregulation)

Table 2

Chemo-/radio-sensitizing effects of indole-3-carbinol and DIM

Treatment	Cell model	Proposed mechanism (ref)
Indole-3-carbinol		
Cisplatin	Cervical cancer cells	Downregulation of Bcl-2 expression (99)
	LNCaP prostate cancer cells	Inhibition of Akt/NF- κ B signaling (20)
Tamoxifen	MCF-7 breast cancer cells	Downregulation of CDK6 expression (82)
TRAIL	LNCaP cells (TRAIL-resistant)	Induction of death receptor (DR)4 and DR5 expression (88)
Ultraviolet B	Melanoma cells	Downregulation of Bcl-2 expression (100)
DIM		
Taxotere	MDA-MB-231 breast cancer cells	Inactivation of Akt/NF- κ B signaling (45)
Paclitaxel	Her2/Neu breast cancer cells	Downregulation of Bcl-2 expression and Her2/Neu activation (101)