

# Anti Cancer Activity of Naturally Occurring Heterocyclic Compound

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**Abstract:** *Indole compounds present in cruciferous vegetables have powerful anti-cancer capabilities. Indole-3-carbinol (I3C) and its dimeric form, 3, 3'-diindolylmethane (DIM), have been shown to block a number of cellular signaling pathways, including the PI3K/Akt/mTOR signaling pathway. These chemicals can block angiogenesis, overcome drug resistance, invasion, and change the phenotype of the epithelial-to-mesenchymal transition (EMT). It is becoming known that the PI3K/Akt/mTOR and NF-Kb signaling pathways play an important role in EMT and control novel miRNAs. It has been examined how parental I3C and DIM, as well as their analogues and derivatives, regulate PI3K/Akt/mTOR/NF-B signaling.*

**Keywords:** indole-3-carbinol, epithelial-to-mesenchymal transition, angiogenesis, cruciferous vegetables.

## 1. Introduction

Worldwide and in the US, cancer is a serious general medical illness [1]. Chemotherapy is still an important treatment option for cancerous patients, and a variety of therapeutic substances are being investigated for their potential role in the management of cancer. It has become clear that natural substances might potentially be used to treat cancer instead of synthetic ones because they are generally safe and well tolerated [2].

Indole is an aromatic heterocyclic organic compound comprising a six-membered ring combined with a five-membered nitrogen-containing pyrrole ring (a bicyclic compound). A review of 22 animal studies and 206 epidemiological examinations revealed the great impact of I3C against tumorigenesis [3]. Cruciferous vegetables are a great source of various phytochemicals, including dithiolthiones, indole derivatives, and isothiocyanates [4]. The most discussed two indoles which were studied for their consequences for PI3K/Akt/mTOR/NF- $\kappa$ B signaling with anticancer properties are I3C and its dimer [5].

### Indole-3-carbinol

A variety of fruits and vegetables contain I3C, including those from the cruciferous family and the genus Brassica. It may be used as a chemopreventive agent since it has anticancer properties in humans and experimental animals [6]. In cruciferous vegetables, I3C is produced by the hydrolysis of glucosinolate glucobrassicin.

### 3, 3'-diindolylmethane, the dimer product of I3C

In the stomach's acidic environment, I3C molecules can react with one another to create a complex mixture of physiologically active chemicals [7]. Dimer DIM is the primary acid condensation byproduct of I3C (DIM can be a

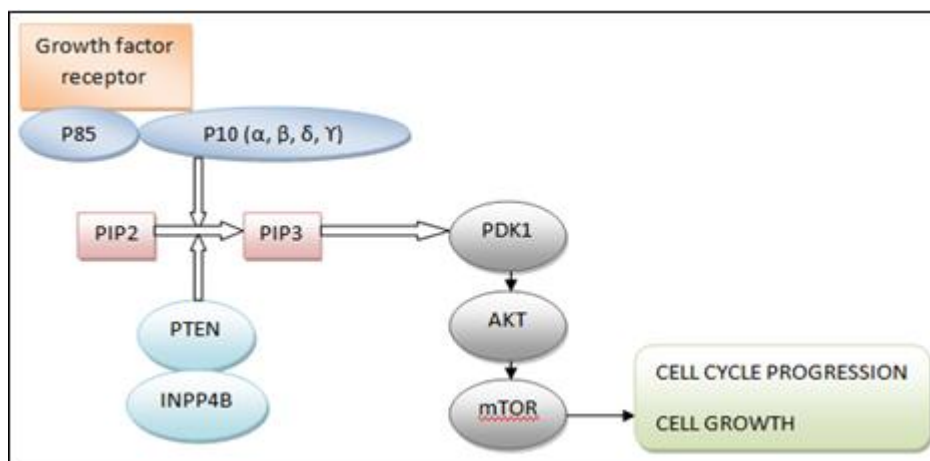
plausible prerequisite for I3C-induced anti-carcinogenesis) [8].

### PI3K/Akt/mTOR signaling as a potential target in cancer research

In all human cancers, the PI3K/Akt/mTOR signaling pathway has been identified as one of the most frequently targeted pathways. Mutations in a single component of this pathway may be responsible for up to 30% of all known human cancers, been estimated [9]. When receptor tyrosine kinases (RTKs) or Ras activate PI3K, (Akt being the most favored downstream target of PI3K) other intracellular signaling molecules are also activated, the components that are downstream of Akt affect four major processes: cell growth, cell-cycle progression, cell survival, and metabolism. When Akt reverses the inhibitory effects of the tumor suppressor tuberin on mTOR. An essential molecule that functions as Akt's downstream target, mTOR, is activated. This pathway's involve in developing primary cancer and resistance to targeted therapy [10].

### The association between NF- $\kappa$ B and PI3K/Akt/ mTOR signaling

A key signaling component in human cancer formation and progression and the acquisition of a drug-resistant phenotype in extremely aggressive malignancies is NF- $\kappa$ B [11]. The NF- $\kappa$ B pathway contains several significant molecules, including NF- $\kappa$ B, IKK, I- $\kappa$ B and others; nevertheless, NF- $\kappa$ B is the primary protein that has been identified as a key therapeutic target in human cancers as it is a significant causative factor in human cancers [12]. There is proof that the PI3K/Akt/mTOR signaling pathway and NF- $\kappa$ B interact [13]. Since NF- $\kappa$ B and mTOR are both downstream effectors of Akt, it would seem that the signaling through Akt may go in one of two distinct and mutually incompatible directions, either through NF- $\kappa$ B or through mTOR [14].



Diagrammatic representation of PI3K/AKT/mTOR pathway

### Inhibition of PI3K/AKT/ mTOR/ NF- $\kappa$ B signaling by indole-3-carbinol:

Epidermal growth factor (EGF) has been prevented by I3C which induced activation of PC3 prostate cancer cells in addition to directly inhibiting Akt phosphorylation and activation. I3C was discovered to prevent even PI3K activation by EGF. This mechanism also works against breast cancer cells because I3C exclusively damaged the malignant cells generated from MCF-10A and spared the parental MCF-10A non-tumorigenic cells. The relationship between Akt and NF- $\kappa$ B was studied and states that ectopic Akt expression can induce NF- $\kappa$ B. I3C can greatly reduce the amount of lung adenocarcinoma that vinyl carbamate-induced lung adenocarcinoma in mice [15]. Demonstration of I3C anti-carcinogenic effect was done against 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone plus benzo[a]pyrene-induced lung cancers in mice. The mechanism of action in HBEC and A549 lung cancer cells was examined in vitro using cigarette smoke condensate therapy. Cells treated with I3C, shows a clear suppression of Akt and NF- $\kappa$ B.

I3C had an in vivo anticancer impact against an experimental lung cancer model, but considerable toxicity was also seen, particularly at the high dose of I3C, hence it is coupled with silibinin and I3C dosages were lowered [16]. A considerable inhibition of Akt and activation of apoptosis were seen in in vitro experiments using A549 and H460 lung cancer cells.

I3C was coupled with another natural substance, genistein (obtained from soy), the combination of these two anticancer medicines was more efficient in inhibiting Akt, increasing the induction of apoptosis in HT-29 colon cancer cells [17]. I3C has a poor metabolic profile in addition to the observed in vivo toxicity. As a result, a novel family of indole analogues was developed to improve and possibly augment I3C's anticancer capabilities [18]. These analogues were created as a result of computer-aided rational drug design. One of the analogues, SR13668, stood out as the most promising one throughout testing since it had the least amount of toxicity and the strongest oral anticancer efficacy. When several oral squamous cell carcinoma cells were used to test OSU-A9, an I3C derivative, the results showed that it

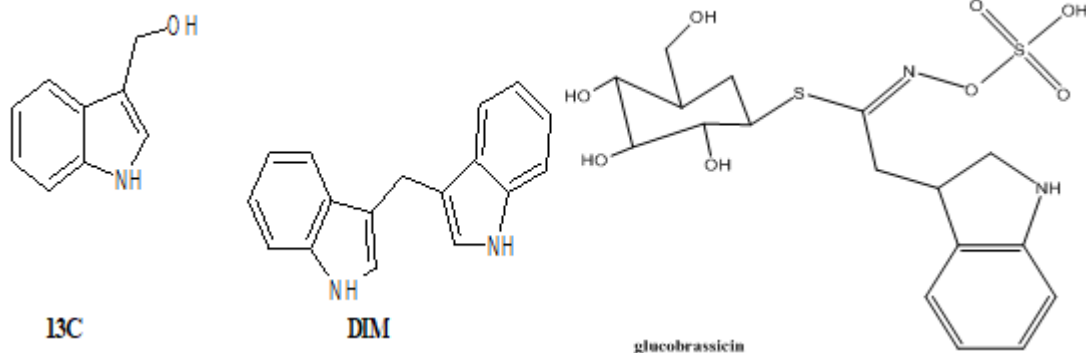
had an anticancer activity that was two orders of magnitude better than I3C [19].

### Inhibition of PI3K/AKT/ mTOR/ NF- $\kappa$ B signaling by 3,3'-diindolylmethane:

Similar to I3C, the cancer cell-specific activity of DIM had been discovered using prostate cancer PC3 cells [20], where it selectively caused apoptosis in cancer cells but not in the non-tumorigenic CRL2221 cells. DIM was discovered to affect several NF- $\kappa$ B signaling stages in addition to inhibiting Akt and NF- $\kappa$ B activation. DIM prevented I $\kappa$ B from being phosphorylated, which caused the NF- $\kappa$ B inhibitory complex to form. A comparison of DIM was done against I3C, which states that DIM is a better anti-proliferative drug than I3C, with a much lower IC<sub>50</sub> against both androgen-dependent and androgen-independent prostate cancer cells [21]. DIM was discovered to suppress PI3K and Akt activation in these two experiments. The inhibition of Akt by DIM and the inhibition of Akt-NF- $\kappa$ B were seen in both hormone-responsive and hormone-nonresponsive prostate cancer cells [22]. Multiple cancer cells have been demonstrated to be prevented from migrating and invading when Akt is inhibited by DIM. DIM recently demonstrated the ability to cause cell cycle arrest and death in oral squamous cell carcinoma cells by acting on Akt and NF- $\kappa$ B [23].

### Derivatives and analogues of indole-3-carbinol:

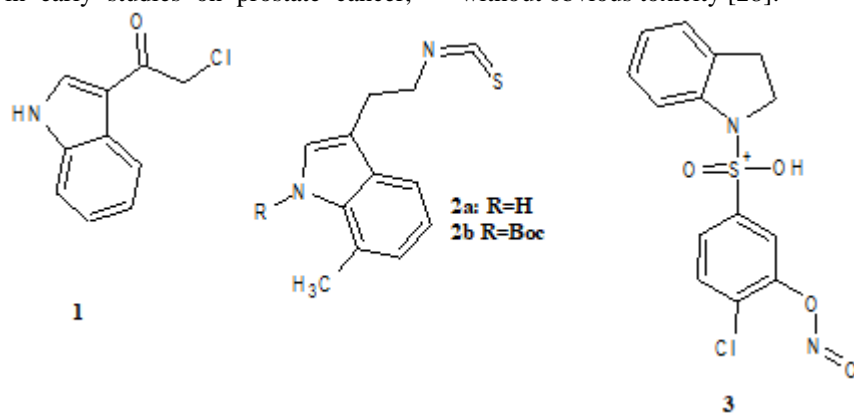
A straightforward and widely accessible I3C congener, 3-chloroacetylindole, is produced when indole reacts with 2-chloroacetyl chloride while in the presence of pyridine [24]. When compared to I3C (IC<sub>50</sub> > 200  $\mu$ M), compound 1 showed greater suppression of HCT-116 colon cancer cell proliferation [25]. AKT1 was specifically inhibited by 1  $\mu$ M in a screen of 85 kinases, and AKT2 was inhibited by 4  $\mu$ M. One hydrogen bond was found with Glu17 and a configuration parallel to Ins (1,3,4,5) P4 in the AKT1 PH domain, and three hydrogen bonds were found with Lys14, Leu52, and Arg86 and a configuration perpendicular to Ins (1,3,4,5) P4 in the AKT2 PH domain, according to docking studies on the binding mechanism of 1. In vitro pull-down tests with 1 revealed direct binding in an ATP non-competitive manner; as a result, 1 binds to an AKT allosteric site rather than the ATP binding site.



Brand and his coworkers studied a brand-new indole ethyl isothiocyanate (2a). Along with its function in the activation of SAP/JNK and pro-apoptotic p38, this substance (3  $\mu\text{M}$ ) decreased AKT in SMS-KCNR neuroblastoma cells. Additionally, a panel of four neuroblastoma cell lines demonstrated a strong growth inhibitory effect ( $\text{IC}_{50} = 2.5\text{--}5.0 \mu\text{M}$ ) (SMS-KCNR, SK-N-SH, SH-SY5Y, and IMR-32). Indole 2b (NB7M) was created by the same team based on the 2a molecule, and researchers researched its effects on ovarian cancer and neuroblastoma. Compound 2b was more hazardous than compound 2a in the four aforementioned neuroblastoma cell lines ( $\text{IC}_{50} = 1.0\text{--}2.0 \mu\text{M}$ ), and at a concentration of 1.5 M, it inhibited the pro-survival proteins PI3K in SMS-KCNR, SH-SY5Y, and AKT in neuroblastoma cells [26].

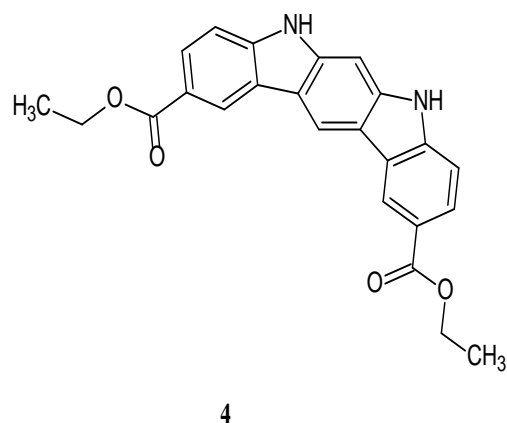
Chen and colleagues revealed another I3C congener, OSU-A9, with strong anticancer potential. Significant similarities between I3C and 3, in early studies on prostate cancer,

revealed in terms of their modes of action, albeit at a considerably lower concentration [27]. For instance, the phosphorylation of AKT was suppressed by 3 at 2  $\mu\text{M}$  compared to I3C at 200 min in PC-3 prostate cancer cells. In line with this result, the tumor-selective growth inhibitory action was significantly higher for indole-3 than that of I3C in both androgen-responsive LNCaP ( $\text{IC}_{50} = 3.8 \mu\text{M}$ ) and androgen-nonresponsive PC-3 ( $\text{IC}_{50} = 2.0 \mu\text{M}$ ) prostate cancer cells. Treatment of PC-3 xenograft tumours for 45 days with 3 (25 mg/kg, i.p.) resulted in an 85% reduction in tumor growth, and a significant decrease in phosphorylated AKT showed by Western blot analyses of the tumor remnant. As a result, 3 might be a good candidate for additional clinical testing as a prostate cancer treatment. Similar encouraging outcomes were attained in hepatoma (80% growth suppression in Hep3B xenografts using 50 mg/kg) and breast cancer (70% growth suppression in MCF-7 breast cancer xenografts using 50 mg/kg of compound 3) without obvious toxicity [28].

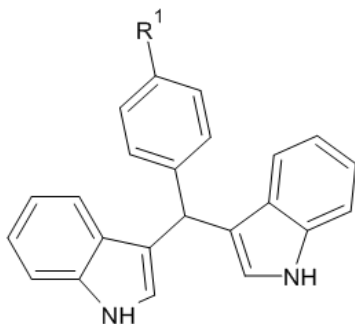


#### Derivatives and analogues of 3, 3'-diindolylmethane:

Effective anticancer drugs could result from the creation of fresh DIM analogues and their manufacturing. Jong, et al. identified a powerfully fused DIM analogue 4. It proved to be significantly more cytotoxic to MCF-7 breast cancer cells than control cells ( $\text{IC}_{50} = 0.19 \mu\text{M}$ ), when given orally (10 mg/kg/day), significantly inhibiting the growth of MDA-MB-231 xenografts in vivo and preventing AKT activation (phosphorylation). Therefore, compound 4 is a good option for more clinical research [29].



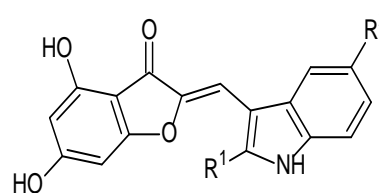
Recently, at AstraZeneca, the research team made public the active indole-based pyrazolo [1, 5-a] pyrimidines 5a and 5b [30]. CK2 kinase was targeted by both drugs, and also showed potent suppression of AKT phosphorylation ( $IC_{50} = 34$  nM for 5a, 27 nM for 5b). Additionally, inhibition of the proliferation of HCT-116 colon cancer cells ( $IC_{50} = 0.7$   $\mu$ M) was seen by compound 16b. Gilbert and colleagues looked at PI3 kinase and mTOR inhibitors by a variety of benzofuran-3-one indole compounds [31].

5a: R=CF<sub>3</sub>

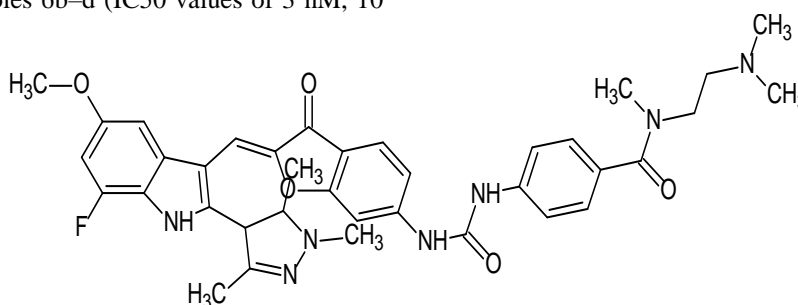
5b: R=Ph

5-methoxy indoles 6a–d shows the greatest PI3K inhibition. Results from docking for 6a as PI3K showed that the 5-methoxy group binds to the hinge region (Val 851) and hydroxyl groups bind to the catalytic Lys 802. It was discovered that higher PI3K-inhibition, when compared to 6a ( $IC_{50} = 30$  nM), can be obtained by the addition of more indole substituents at position 2 (6b–d, methyl-, phenyl-, and 3-pyridyl-). In addition, dramatically decreased mTOR activity was seen in indoles 6b–d ( $IC_{50}$  values of 3 nM, 10

nM, and 1 nM for indoles 6b, respectively). On day 6, the most potent PI3K- and mTOR inhibition was seen ( $IC_{50} = 1$  nM). Zhang et al. found that in LoVo colon carcinoma, the highest growth inhibitory action was demonstrated by 6c ( $IC_{50} = 1.2$   $\mu$ M), as well as by inhibiting Thr308 phosphorylation on AKT proteins at 1 M and PC-3 prostate carcinoma cells ( $IC_{50} = 0.8$   $\mu$ M) [32].

6a: R<sup>1</sup>=H, R<sup>2</sup>=OMe6b: R<sup>1</sup>=Me, R<sup>2</sup>=OMe6c: R<sup>1</sup>=Ph, R<sup>2</sup>=OMe6d: R<sup>1</sup>=3-Py, R<sup>2</sup>=OMe

A strong dual inhibitor of PI3K and mTOR was later demonstrated by a novel 5-ureidobenzofuranone-indole 7. Suppressed proliferation of MDA-MB-361 breast cancer cells was seen by indole 7 with an  $IC_{50}$  value of less than 3 nM and sub-nanomolar kinase inhibition ( $IC_{50} = 0.2$  nM, PI3K;  $IC_{50} = 0.3$  nM, mTOR). Compound 7 (25 mg/kg) effectively prevented AKT phosphorylation (activation) in nude mice and caused MDA-MB-361 breast cancer xenograft tumours to significantly shrink. These encouraging outcomes call for more thorough research on compound 7 [32].



## 2. Conclusion

Significant reduction of the invasion and metastasis of several cancers has been demonstrated for indole compounds, particularly I3C and DIM, while the exact mechanism of action remains unknown. These pleiotropic drugs influence P3K/Akt/mTOR/NF-B as one of the signaling networks. Data states that these compounds will specifically decrease Akt and NF-B activity, indicating that Akt and NF-B are two of their main targets. Questions have been raised about the stability and bioavailability of indoles as pre-clinical research on these indoles has progressed.

The vast majority of these compounds either directly or indirectly inhibit AKT/mTOR signaling through interactions with proteins. This indicates that additional, in-depth biological research is necessary. There are still many natural

indole compounds available as anticancer agents about which we know very little, aside from those that have been the focus of this review article. However, further research would be important for assessing their applicability in clinical settings. Our opinion is that the vast pool of prospective novel therapies represented by the indole-associated class of medicines represents a resource that must be thoroughly utilized for evaluating their anti-cancer effects in both clinical and pre-clinical settings. However, few brand-new indole derivatives with outstanding in vivo activity have this already included in their review involving cancer patients, which is a requirement for the planning of clinical studies.

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