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Chapter 8

DIINDOLYLMETHANE: AS A POTENT ANTICANCER AGENT

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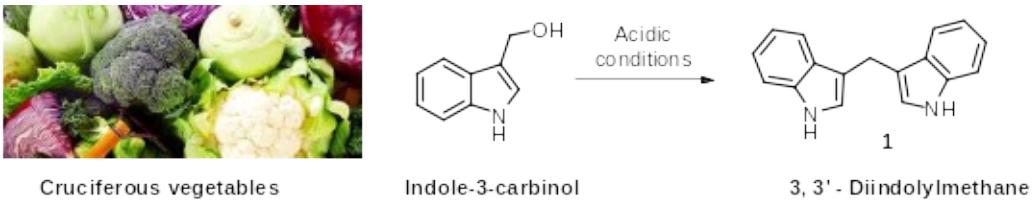
Indoles are ubiquitous heterocycles found in natural products endowed with a plethora of biological activities. Bis(3′-indolyl)methane or 3, 3′- diindolylmethane **1** (DIM), a disubstituted methane with two indole units is an active metabolite of indole-3-carbinol (I3C), a glucosinolate conjugate present in various *Brassica* vegetables such as cabbage, broccoli, brussels sprouts, etc and is renowned for its potential anticancer properties. Many epidemiological studies have shown that the high dietary intake of cruciferous vegetables can reduce the risk of cancer and is due to the anticancer property of I3C. In the acidic pH of the stomach, I3C molecules are unstable and are converted into acid condensation products of biologically active compounds, out of which one of the most prominent by-product is the dimer DIM-**1** (Scheme 1). Hence the effects induced by I3C *in vivo* could be attributed to its condensation product DIM-**1**, which highlighted it as the prime target for anticancer investigations. In the 1970s, Wattenberg first described the chemo protective abilities displayed by DIM-**1** in crucifers, through many studies. The studies revealed the role DIM-**1** in aryl hydrocarbon hydroxylase induction, carcinogen metabolism, and inhibition, and chemical neoplasia inhibition (www.diindolylmethane-dim.com). Since then, DIM-**1** has been found to target multiple proteins and pathways for the attenuation of cancer progression. The major molecular targets of DIM-**1** are shown in the Figure 1. Due to its low toxicity and cytotoxic ability to inhibit the growth of a multitude of cancer cell types *in vitro* and *in vivo*, DIM-**1** has gained precedence as a potential cancer therapeutic agent and has been extensively investigated. In addition, DIM-**1** and its derivatives are good plant growth

promoters and potent inhibitors of *Leishmania donovani* topoisomerase I and also exhibit antimicrobial activities against human pathogens.



Scheme 1. Formation of DIM-**1** from I3C

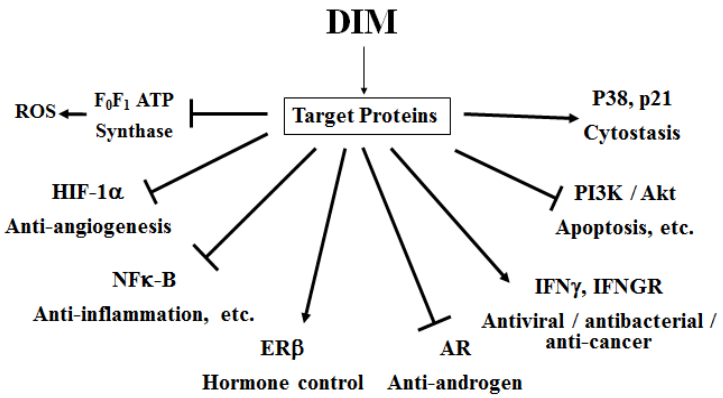


Figure 1. Molecular targets of DIM-**1**

In search of conceivably more powerful anticancer agent than DIM-**1**, many derivatives of DIM-**1** have been synthesized and screened for their increased potency and pharmacological properties like specificity, bioavailability, toxicity, stability, etc. For instance, Studies on 2,2′-Diphenyl-3,3′-Diindolylmethane (DPDIM) carried out by Ghosh and co-workers in 2013, revealed that it significantly induces apoptosis in carcinogen-induced Sprague-Dawley rat mammary tumor by inhibiting EGFR pathway. Many studies have been published by Dr. Safe's lab on the promising anticancer activity of DIM analogues. They disclose the efficiency of the 1,1-Bis(3-indolyl)-1-(p-substitutedphenyl)methane (C-DIM) analogues as potent anticancer agents for the treatment of metastatic lung cancer. Their studies found that both DIM-C-pPh-OCH_3 and DIM-C-pPhOH inhibit lung cancer cell and tumor growth in a metastasis model. Another study from the same laboratory reported that 1,1-bis (3′-indolyl)-1-(p-biphenyl) methane (DIM-C-pPhC_6H_5) could be used alone or in combination with other drugs for the treatment of lung cancer. Many novel modified analogues of DIM-**1** have been identified to exhibit improved anticancer activity than the natural counterpart.

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Chapter 9

BIOMEDICAL APPLICATIONS OF POLYMERS

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