REVIEW ARTICLE

Indoles as anti-cancer agents

Mardia T. El Sayed¹*, Nehal A. Hamdy¹, Dalia A. Osman¹, Khadiga M. Ahmed²

¹Applied Organic Chemistry Department, Chemical Industries Division, National Research Centre, Egypt
²Natural Products Department, Pharmaceutical Industries Division, National Research Centre, Cairo, Egypt

Abstract: Indoles are natural products which are well known for its anti-cancer activity due to its ability to induce cell death for many cancer cell lines. This review addresses indoles as natural products, mechanism of indoles, facilitated induction and recent studies with indoles and related compounds that were investigated via anti-cancer screening and that led to drug approval.

Keywords: indoles; natural biosynthesis; cell death induction; screening; anti-cancer agents


A
n indole is an aromatic heterocyclic composite which has its heterobicyclic configuration as a six-membered ring fused to a five-membered pyrrole ring. 'Indole' is the name given to all indole derivatives which have an indole ring system¹. Indoles are obtained from coal pitch or a variety of plants and produced by the bacterial decay of tryptophan in the intestine. It has been synthesized by one of the oldest method that known as Fischer indole synthesis². Indoles function as signal molecules in plants and animals. They also serve as a raw material, nucleus building blocks and an efficient group of numerous imperative biochemical molecules and compounds, such as alkaloids, indigoids, etc. Most of these important molecules and compounds originate, either fully or partly, from bio-oxidation of indoles.

Naturally biosynthesized indole products

Indoles are natural compounds can be found in numerous types of plant. They are, however more predominantly found in cruciferous vegetables². Cruciferous vegetables comprise of cauliflower, cabbage, turnip, broccoli and brussels sprouts (Figure 1). Indoles fit in a class of phytонutrient compounds (plant compounds with health-protecting qualities) which have been systematically proven to profit the body in a number of imperative ways. Consuming of cruciferous vegetables has been associated with reduced of the risk of colon, breast and prostate cancers. Cruciferous vegetables are a rich source of many phytochemicals, including indole derivatives, dithiolethiones and isothiocyanates. Cruciferous vegetables are full of glucobrassicin (GB) which throughout metabolism, produce indole-3-carbinol (I3C), 3,3'-diindolylmethane (DIM) and ascorbigen (ASC) (Figure 2). The anti-carcinogenic property of I3C and DIM was exhibited in human cancer cells. It appears that these indolic compounds may be efficient anti-cancer agents for several cancer cell lines³-⁶.

Natural compounds found in fruits and vegetables are recognized to have anti-mutagenic and anti-carcinogenic properties. A high dietary intake of fruits and vegetables has proved to be beneficial against carcinogenesis. An inhibitory effect of indoles and cruciferous vegetables against tumorigenesis and cancer hazard has also been veri-
Epidemiological statistics reveal that populations that consume higher amounts of cruciferous vegetables have lower incidences of cancer or improved biochemical parameters, such as decreased oxidative pressure compared to controls. Cruciferous vegetables protect against cancer more successfully than fruits and other vegetables. The National Research Council, USA, has recommended consumption of cruciferous vegetables as a measure to diminish the commonness of cancer.[8-11]

Bio-oxidation of indoles and respective enzymes in microorganisms and in plants has been well documented in the recent review by Yuan et al.[3] In this review, the pathways of indole bio-oxidation which lead to configuration of indigo and indirubin in plant and the perspectives of the study in indole bio-oxidation have been discussed (Scheme 1). Where E1 is indole oxygenase, E2 is indole oxidase, E3 is indole 2,3-dioxygenase, E4 is indican synthase, E5 is indoxyl-UDP-glucosyltransferase, E6 is formylase, E7 is aldehyde oxidase, S is spontaneous reaction, P is plant tissues and organs, GT? is glucosyltransferase (unidentified) and GLU? is glucosidase (unidentified).[3]

The amino acid tryptophan is a biogenetic precursor of all indole alkaloids. The first step of synthesis is decarboxylation of tryptophan to form tryptamine. Dimethyltryptamine (DMT) is formed from tryptamine by methylation with the contribution of coenzyme of S-adenosyl methionine (SAM). Psilocin is produced from dimethyltryptamine by oxidation and is then phosphorylated into psilocybin. In the biosynthesis of serotonin, the intermediary product is not tryptamine but 5-hydroxytryptophan, which is sequentially decarboxylated to shape 5-hydroxytryptamine (serotonin) (Figure 3).[12-14]

Biosynthesis of β-carboline alkaloids takes place via formation of Schiff base from tryptamine and aldehyde (or keto acid) and consequent intramolecular Mannich reaction, where the carbon in position two of indole acts as a nucleophile (Figure 4). This is followed by the
Indoles as anti-cancer agents

aromaticity being restored via the elimination of a proton at the C two atom. The consequential tetrahydro-β-carboline frame steadily oxidizes to dihydro-β-carboline and β-carboline afterwards\textsuperscript{16,20}.

Scheme 1 Bio-oxidation of indole in higher plants.

Figure 3 Tryptophan as a biogenetic precursor of all indole alkaloids.
The biosynthesis of ergot alkaloids starts with the alkylation of tryptophan via dimethylallyl pyrophosphate (DMAPP), in which the carbon atom in position 4 of the indole ring acts an important facilitator of the nucleophile (Figure 5). The consequential 4-dimetallil-L-tryptophan is followed by N-methylation. Additional products that result from the biosynthesis are chanoclavine-I and agroclavine—the latter is hydroxylated to elymoclavine, that in turn oxidizes into paspalic acid which is converted to lysergic acid through the process of allyl rearrangement[16,21].

Biosynthesis of monoterpenoid indole alkaloids starts with the Mannich reaction of tryptamine and secologanin; this produces strictosidine, which is renewed to 4, 21-dehydrogeissoschizine (Figure 6). After that, the biosynthesis of alkaloids containing the composed monoterpenoid fraction (Corynanthe type) was shaped throughout cyclization with the configuration of
cathenamine, and following reduction reaction into ajmalicine in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). With the biosynthesis of previous alkaloids, 4,21-dehydrogeissoschizine changed into preaquamycin (an alkaloid of subtype Strychnos, type Corynanthe) which ascends to other alkaloids of subtype Strychnos and of the types Iboga and Aspidosperma.

**Indoles in medicinal chemistry**

Indole derivatives are imperative heterocycles in the drug-discovery studies. They are a very important category of compounds that play a key role in cell physiology and are probable intermediates for numerous biological reactions. Indole derivatives correspond to scores of important modules of therapeutic agents in medicinal chemistry such as anti-cancer, anti-oxidant, anti-rheumatoidal, anti-HIV, anti-microbial, anti-inflammatory, analgesic, antipyretic, anti-convulsant, anthelmintic cardiovascular, selective COX-2(cyclooxygenase-2) inhibitory activities (which is an enzyme accountable for inflammation and pain) and DNA binding ability. Furthermore, countless essential indole derivatives are used in disease management, for example, the non-steroidal anti-inflammatory drug indomethacin (Indocin®), the beta blocker pindolol (Viskin®) for management of high blood pressure (hypertension), the psychedelic, dimethyltryptamine (DMT) and BioResponse DIM® for estrogens for men and women (http://www.bioresponse.com/Home.asp) (Figure 7).

**Cell death induction by indoles**

Anti-cancer agents have been usually evaluated for their ability to induce apoptosis. Indoles have been verified to inhibit proliferation, expansion and invasion of human cancer cells. Many mechanisms of apoptosis stimulation of indole derivatives, I3C and DIM, were reported for, (a): down-regulation of anti-apoptotic gene products such as Bcl-2 (B-cell lymphoma 2) and Bcl-XI (B-cell leukemia-extra large), (b): down-regulation of the inhibitor of apoptosis proteins, e.g. CIAPs, X-chromosme linked inhibitor of apoptosis protein (XIAP) and survival, (c): up-regulation of pro-apoptotic factors such as Bax gene, (d): liberation of mitochondrial cytochrome C in addition to stimulating of caspase-9 and caspases-3 and (e): inhibition of the NF-κB signaling pathway. A vast number of diverse mechanisms of apoptosis induction by indoles have also been reported. Figure 8 demonstrates the extrinsic and the intrinsic pathways of apoptosis (programmed cell death). In the extrinsic pathway, signal molecules identified as ligands, which are released by the immune system’s natural killer cells possess the Fas ligand (FasL) on their exterior to connect to transmembrane death receptors on the target cell. After the binding of the death ligand to the death receptor the target cell triggers multiple receptors to aggregate together on the surface of the target cell. The aggregation of these receptors recruits an adaptor protein known as Fas-associated death domain protein (FADD) on the cytoplasmic side of the receptors. FADD, in turn, recruits Caspase-8. Caspase-8 will then be activated and will be now able to directly activate caspase-3 and caspase-7. The activation of caspase-3 will initiate the degradation of the cells. The intrinsic pathway is triggered by cellular strain, particularly mitochondrial stress caused by factors such as DNA damage from chemotherapy or UV exposure. Upon delivery of the stress signal, the pro-apoptotic proteins in the cytoplasm (Bcl-2-like protein 4 (BAX) and BAX-like Bcl-2 homology domain 3 protein (BID)) bind to the outer membrane of the mitochondria to signal the release of the internal content.
The interaction between the pro-apoptotic (BAX and BID) and the antiapoptotic proteins (Bcl-2) on the surface of the mitochondria is thought to be important in the formation of the PT pores in the mitochondria, and hence, the release of cytochrome c and the intramembrane content from the mitochondria. Following the release, cytochrome c forms a multi protein complex known as apoptosome which consists of cytochrome c, Apaf-1, procaspase-9 and ATP. Following its formation, the complex will activate caspase-9. The activated caspase-9 will then turn the procaspase-3 and procaspase-7 into active caspase-3 and active caspase-7. These activated proteins initiate cell degradation or cell death. Besides the release of cytochrome c from the intramembrane space, the intramembrane also releases Smac/Diablo proteins to inhibit the inhibitor of apoptosis (IAP). IAP is a protein family which consists of 8-human derivatives. Their function is to stop apoptotic cell death by binding to caspase-3, caspase-7 and caspase-9 and inhibit them, the schematic representation of these pathways are shown in Figure 8.[12,13,58].

*Figure 8 Intrinsic and extrinsic pathways leading to apoptosis. [Available from https://innspubnet.files.wordpress.com/2015/04/mitochondrial-pathway.jpg]*
Indoles for inhibition of invasion and metastasis

Cancer cells are able to travel through the lymphatic and blood vessels, pass through the bloodstream, and then occupy and produce in healthy tissues elsewhere. This ability to spread to other tissues and organs leads to malignancy and makes cancer a potentially life-threatening disease. Tumor angiogenesis is the propagation of a complex of blood vessels that penetrate into cancerous growths, supply blood and oxygen and eliminate waste products\[39\]. In reality, tumor angiogenesis starts with cancerous tumor cells releasing molecules that post signals to the neighboring host tissues. This signaling activates definite genes in the host tissue that, in turn, build proteins to support growth of new blood vessels. Indole derivatives, I3C and DIMs have been reported to restrain the invasion of cancer cells\[57-60\] and the expansion of new blood vessels (angiogenesis)\[59,60\].

Indole compounds for chemosensitization

Chemosensitization is the progression by which compounds, for example, indole compounds, I3C and DIM adapt the cellular signaling pathways leading to apoptosis and thus conquer the chemoresistance of well-known chemotherapeutic drugs\[1,61\]. I3C has been reported to sensitize multidrug resistant tumors to chemotherapeutic drugs without any related toxicity\[1,62-64\]. Mechanisms of anti-cancer and chemosensitizing effects of indole compounds were summarized in Figure 9. Indole compounds, such as I3C and its dimmer DIM, induce apoptosis through inhibition of several prosurvival pathways. Emerging evidence also documents the ability of indoles to reverse the process of EMT via regulation of key miRNAs. An efficient induction of apoptosis and reversal of EMT not only ensures increased sensitivity to conventional drugs (chemosensitization) but also results in significantly reduced invasion and metastasis\[1,62-64\].

Reported indoles as anti-cancer active agents

Nowadays, clinical association of human reproductive organ cancers requests new chemotherapeutics. In recent times, a lot of hard works have been done to organize antiproliferative signaling pathway of indole-3-carbinol and its foremost indole metabolite 3,3'-diindolylmethane (DIM)\[68-71\]. While DIM significantly reduces the occurrence of impulsive and carcinogen induced mammary tumor establishment (Figure 10)\[72-74\]. It also exhibits unpleasant promoting action in convinced investigation procedure\[75,76\]. As a result, the decision was to look for novel effective chemotherapeutics amongst 3,3'-diindolylmethane derivatives. Moreover, the X-ray studies of 5,5'-dimethoxy-3,3'-methanediyl-bis-indole\[77\] revealed its ‘butterfly’ conformation, which is analogous to the one proposed earlier for inhibitors of HIV-1 reverse transcriptase, sharing the mode of action of nevirapine\[78\]. Other diindolylmethane derivatives and their corresponding tetrahydroindolo-carbazoles have been synthesized and screened for anti-cancer activity in which two compounds indicated were significantly more sensitive for several cancer cell lines corresponding to their GI50 values. The highest antiproliferative activity recorded for the carbazole derivatives in a nanomolar scale towards the three certain cancers cell lines: non-small lung cell NCI-H460 with GI = 616 nmol/L, ovarian cancer cell line OVCAR-4 with GI = 562 nmol/L and breast cancer cell line 50 nmol/L scale MCF7 with GI = 930 nmol/L (Figure 10)\[16\].

![Figure 9](http://www.mdpi.com/cancers/cancers-03-02955/article_deploy/html/images/cancers-03-02955f1-1024.png)  
*Figure 9* Summary of mechanisms of anti-cancer and chemosensitizing effects of indole compounds. [Original source from http://www.mdpi.com/cancers/cancers-03-02955/article_deploy/html/images/cancers-03-02955f1-1024.png]

![Figure 10](http://www.mdpi.com/cancers/cancers-03-02955/article_deploy/html/images/cancers-03-02955f1-1024.png)  
*Figure 10* 3,3'-diindolylmethane derivatives and tetrahydroindolocarbazoles

Dorota et al\[79,80\] in 2005 synthesized the disubstituted diindolylmethanes fluoro and cyano derivatives which decrease the expansion of MCF7 (breast), NCI–H460
(lung) and SF-268(NCS) cells, considerably 5,5′-difluoro-3,3′-methanediyl-bis-indole and 5,5′-dicyano-3,3′-methanediyl-bis-indole were tested against the MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS) tumor cell lines. The results are reported as the proportion of growth of the tested cells to untested control cells (Figure 10). F-derivative at concentration 1.10 –4.00 mol/L reduces the growth of MCF7, NCI-H460, and SF-268 cell lines to 1%, 0% and 2%, whereas the CN derivative at concentration 5.10–5.00 mol/L to 4%, 1% and 9%, respectively. Both compounds are extremely cytotoxic in vitro towards those tumor lines. Their cytotoxicity indicates that they could be motivating as prospective antitumoral chemotherapeutics [79,80].

Indoles (I3C and DIM or its derivatives) have been revealed to induce apoptosis in breast [81-87], squamous cell carcinoma [88], cholangiocarcinoma [89], colon [90-93], cervical [94], ovarian [95], pancreatic [96,97] and prostate [98-101] cancer cells. Many other indole derivatives that were reported as active anti-cancer agents as follow: the potential prodrug (1,2-dimethyl-3-(N-(4,6-bis(dimethylamino)-1,3,5-triazin-2-yl)-N-trideuteronomethylamine(ethyl))-5-methoxyindole-4,7-dione), pentamethylmelamine (PMM) in which the labeled pentamethylmelamine is attached to an indole-4,7-dione moiety has attracted much interest as an anti-tumor agent for over 35 years (Figure 11). It entered clinics in the 1970s for the treatment of ovarian carcinoma but difficulties were encountered, as it was insoluble in water and thus is difficult to formulate. However, it has recently been recognised as a second-line treatment for ovarian carcinoma [12-19,102-104]. Schoentjes et al. [105] reported a patent of indole derivatives with general formula (I) in 2011 and reported its use for the treatment of cancers (Figure 11).

Numerous aroylamide indole derivatives have been synthesized and preliminarily screened for their in vitro anti-cancer activity in A431 and H460 cell lines (Figure 12). All the compounds examined exhibited strange effectiveness in a tumor cell cytotoxicity evaluation. The findings indicated that the indole derivatives would be talented candidates for the improvement of new anti-cancer agents. 3-aroylindole is a probable anti-cancer drug candidate designed and projected from in vitro human microsome studies with better pharmacokinetics and enhanced influence in the tumor xenograft represen-

cation [106,107].

Dragmacidin is an inaccessible bis-indole alkaloid (Figure 13) isolated from a deep water marine sponge [108,109] collected from the southern Australian coast [110]. Dragmacidin was set up to hold two indole groups fixed by a piperazine ring system. Dragmacidin exhibited in vitro cytotoxicity with IC₅₀ values of 15 µg/mL against P-388 cell lines and 1–10 µg/mL against A-549 (human lung), HCT-8 (human colon) and MDAMB (human mammary) cancer cell lines. In 1995, Murray et al. [110] reported the isolation of dragmacidin D (Figure 13). Dragmacidin D was found to be active against human lung tumour cell lines and inhibited in vitro growth of the P-388 murine and A-549 with IC₅₀ values of 1.4 and 4.5 µg/mL, respectively [108,109].

Four new bis-indole alkaloids nortopsentins A–D (Figure 13) were extracted from the Caribbean deep sea sponge Spongosorites ruetzleri [110]. These derivatives of nortopsentins A–C exhibited anti-cancer activity against P-388 cells with IC₅₀ values of 7.6, 7.8 and 1.7 respectively, and for Trimethylnortopeentin B derivative is 0.9 µg/mL.

Figure 11 Structure of prodrug indole-PMM derivative and tryptamine derivative

Figure 12 Molecular structure of aroyl- and aroylamide-indoles

Figure 13 Molecular structure of aroyl- and aroylamide-indoles
Topsentin showed self-conscious proliferation of cultivated human and murine tumor cells. It exhibited in vitro anti-cancer activity against P-388 with IC50 value of 3 μg/mL, human tumor cell (HCT-8, A-549, T47D) with IC50 value of 20 μg/mL and in vivo activity against P-388 (test/control (TC) 137%, 150 mg/kg) and B16 melanoma (T/C 144%, 37.5 mg/kg). Bromotopsentin showed antiproliferative activity against human broncopulmonary cancer cells (NSCLC-N6) with an IC50 = 6.3 μg/mL. Deoxytopsentin showed antiproliferative activity against human broncopulmonary cancer cells (NSCLC-N6) with an IC50 value of 6.3 μg/mL. It also displayed moderate activity against breast cancer and hepatoma (HePG2) with an IC50 of 10.7 and 3.3 μg/mL, respectively.[111-113].

Recently, Kobayashi et al. reported a new cytotoxic bisindole alkaloid hyrtinadine A (Figure 13) from an Okinawan marine sponge Hyrtios sp.[114-116]. Hyrtinadine reported to exhibit in vitro cytotoxicity against murine leukemia L-1210 and human epidermis carcinoma KB cells.

Schupp et al. isolated a couple of new indolocarbazole alkaloids, staurosporines (Figure 14) from the marine ascidians Eudistoma toaelensis and its predator.[116,117]. Schupp et al. reported the prospects of these staurosporine derivatives as inhibitors of cell explosion and macromolecule synthesis.[117]. Staurosporine D was found to be the main vigorous staurosporine candidate as a MONO-MAC-6 (human monocytic cell lines) inhibitor and inhibit the RNA and DNA synthesis. The IC50 values of staurosporine A, D and E for inhibiting MONO-MAC-6 cells were 24.4, 13.3 and 33.9 mg/mL, respectively while those of staurosporine B and C were >100 μg/mL. The percentage of inhibition of RNA and DNA synthesis of compounds staurosporine A and D were 93 and >98, 98 and >98, respectively. Analysis of structure activity relationship verified that hydroxylation of staurosporine at position 3 of the indolocarbazole moiety causes an increase in antiproliferative activity. The position of the –OH group is critical to determine the antiproliferative property of a range of staurosporine analogues. A novel carbazole alkaloid, coproverdine (Figure 14) was isolated from a nameless ascidians, Anchorina sp. collected from the North Island of New Zealand.[118]. Coproverdine was screened against a diversity of murine and human tumor cell lines such as P-388, A-549, HT-29, MEL-28 and DU-145 exhibiting IC50 values of 1.6, 0.3, 0.3, 0.3 and 0.3 μmol/L, respectively.

The hyrtioerectin alkaloid A (Figure 15) was inaccessible from a red coloured marine sponge Hyrtios erectus.[119,120]. Hyrtioerectin A was tested for its cytotoxic activity towards HeLa cells and showed sensible cytotoxicity with IC50 assessment of 10 μg/mL. Foderaro et al. published the isolation of a new tetrahydro-β-carboline alkaloid (Figure 15) bengacarboline from the Fijian ascidians Didemnum sp.[121]. Bengacarboline was found to be cytotoxic against a 26 human tumor cell line panel in vitro with a mean IC50 value around 0.9 μg/mL and also inhibited the catalytic activity of topoisomerase II at 32 μmol/L.

In 1994, Bifulco et al. reported the isolation of two tris-indole alkaloids, gelliusines A and B (Figure 15) from a deep water new caledonian sponge Gellius sp.[122]. Gelliusin A and B were found to be diastereomeric alternatives prepared by the coupling of three indole units in which two 6-bromo tryptamine units
are linked through their aliphatic chains to the C-2 and C-6 position of a middle serotonin moiety. The coupling of the indole unit appears to be non-stereoselective giving two enantiomeric pairs, having dissimilar comparative configuration at C-8 and C-8 named (±) gelliusines A and B. Gelliusines A and B showed anti-cancer activity with an IC50 value of between 10 and 20 μg/mL against KB, P-388, P-388/dox, HT-29 and NSCLCN-6 cell lines.

Dendridine A (Figure 16), a distinctive C2-symmetrical 4,4′-bis(7-hydroxy) indole alkaloid was isolated from an Okinawan marine sponge Hyrtios sp[123]. It exhibited reasonable cytotoxicity towards murine leukemia L-1210 cells with IC50 value of 32.5 μg/mL. Chetomin was acknowledged as a natural product anti-tumor candidate which prevents the configuration of the HIF-1, P300 complex (Figure 16). Universal management of chetomin inhibited hypoxia-inducible transcription within tumors and inhibited tumor growth[124].

It has been established by Lee et al. that 1,1,3-tri (3-indolyl)cyclohexane (Figure 17) inhibits cancer cell expansion in lung cancer cells of xenograft models[125]. Consequently, it is a potential anti-cancer product derived from its strong tumor growth inhibition and positive pharmacologic properties. It also increases the manufacture of reactive oxygen species (ROS) and triggers DNA damage[126-128]. Cyclohepta [b] indole and benzo[5,7] cyclohepta [1,2-b] indole (Figure 17) were subsequently screened for cytotoxic activity against human nasopharyngeal carcinoma (HOME-1) and gastric adenocarcinoma (NUGC-3) cell lines, where the product showed imperative cytotoxicity at a concentration of 4 μg[126]. In 2014, it has been proved that an indole and its derivatives NC001-8 could be novel therapeutic agents for spinocerebellar ataxias (SCA17). The development of indole-
based compounds offers a promising strategy for the treatment of polyglutamine (polyQ) diseases via activation of haperone expression to reduce polyQ aggregation in SCA17 neuronal cell and slice culture models[127].

Sandra et al.[129], reported the relevance of gold-containing indoles as anti-cancer agents. It displayed cytostatic effects against leukemia and adherent cancer cell lines. However, two gold-bearing indoles showed unique behavior by increasing the cytotoxic property of clinically relevant levels of ionizing emission (Figure 18). Quantification of the amount of DNA demonstrates that each gold-indole enhances apoptosis by restraining DNA fixation. Both Au(I)-indoles were screened for inhibitory property towards a mixture of cellular targets counting thioredoxin reductase, an identified target of numerous gold compounds and a variety of ATP-dependent kinases. Both compounds showed inhibitory property against numerous kinases connected with the beginning of cancer and its progression. The inhibition of these kinases provides a probable mechanism for the capability of these Au(I)-indoles to potentiate the cytotoxic effects of ionizing radiation. Clinical applications of combining Au(I)-indoles with ionizing energy are discussed with developing a new strategy to achieve chemosensitization of cancer cells[129].

A progression series of novel 5-(2-Carboxyethenyl) indole derivatives were designed and synthesized (Figure 19). Two of the seven recently prepared compounds were screened for their anti-cancer activities towards K562 and HT-29 cell lines resulting in 5-(2-Carboxyethenyl)indole derivatives being verified for major anti-cancer activity against HT-29 cell, their effectiveness was around 4.67, 8.24 and 6.73 μmol/L[130].

Kumar et al.[131] have synthesized 2,3-dimethyl-indoles and tetrahydrocarbazoles using Phenylhydrazine hydrochlorides and different cyclic and acyclic ketones in presence of antimony phosphate as catalyst (Figure 19). The products were tested for anti-cancer activity against five different cell lines such as kidney adenocarcinoma (ACHN), pancreas carcinoma (Panc1), lung carcinoma (GIII) (Calu1), non-small cell lung carcinoma (H460), colon cancer cell (HCT116) and normal breast epithelium (MCF10A) cell lines. The results showed that 2,3-dimethylindole (R1 = H, F) exhibited promising activity against both lung carcinoma and pancreas carcinoma cell line with IC_{50} value 2.7, 3.1, 2.8 and 3.2 nmol/L. Tetrahydrocarbazole (R1 = OCH3, R2 = F, R3 =
F, R4=PhCN) showed high activity against lung carcinoma cell line only, with IC50 2.5 nmol/L.

**Conclusion**

The current review covered three important topics about indoles: Firstly, indoles as natural products and its biosynthesis. Secondly, the mechanisms of induction of cell death for numerous cancers cell lines by indoles. Thirdly, recent studies with indoles and associated compounds that are investigated for anti-cancer screening and that are directly forwarded for drug approval.

**Conflict of interest**

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**

52. Ahmad A, Sakr WA, Rahman KMW. Role of nuclear factor-kappa B signaling in anticancer properties of...
78. Kim DJ, Han BS, Ahn B, et al. Enhancement by indole-3-carbinol of liver and thyroid gland neoplastic

Indoles as anti-cancer agents


