



Review

Application of Functionalized Indole Derivatives as Kinase Inhibitor and Potential Anticancer Agents

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ABSTRACT

Despite advances in cancer treatments and therapies, cancer still remains as major public health problem in modern world. Therefore, developments of novel cancer therapeutics are urgently needed to improve cancer prognosis. There is considerable interest exists in target based anti-tumor effects of synthetic molecule targeting various kinases such as tyrosine kinases (RTKs), vascular endothelial growth factor receptor (VEGFR), protein kinase B (Akt). This review is focused on the application & developments of functionalized indoles as kinase inhibitors & their anticancer activity.

Keywords: Indoles, Anticancer, Kinase inhibitors, Heterocycles

INTRODUCTION

In the history, the earliest written record related to cancer is from 3000 BC in the Egyptian pyramid describing breast cancer. Cancer is basically unregulated, uncontrolled cell growth [1]. Normally, body controls the process of cell division at various stages through various regulators. But somehow if this not happen, the cell division becomes uncontrollable and defected cell will produce and accumulated in the form of a tumor. One defining feature of the cancer is the rapid creation of the abnormal cells that grows beyond their usual boundaries, which can then invade adjoining part of the body through a process known as metastasis and spread to the other organs by the lymphatic system or bloodstream [2]. Thus, Cancer is a collective term used for a group of diseases that are characterized by the loss of control of the growth, division, and spread of a group of cells, leading to a primary tumor that invades and destroys adjacent tissues [2].

Cancer is a leading cause of death worldwide. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030[3-6]. The main types of cancer are: (i) Lung (ii) Stomach (iii) Liver (iv) Colorectal (v) Breast and (vi) Prostate cancer. About 90–95% of cases attributed to environmental factors which includes alcohols & smoking, diet and obesity, infections, radiation, stress, lack of physical activity, and environmental pollutants. Hormones are also related in the cancer of the breast, endometrium, prostate, ovary, and testis, and also of thyroid cancer and bone cancer [3-6]. In India, more than 50% cancer cases are due to tobacco which is really very high.

Cancer Therapy: The current cancer therapy is based on surgery, chemotherapy and radiotherapy. More often combinations of surgery and chemotherapy or radiotherapy found to be effective for cancer patients. Synthetic drugs are important regime of the modern cancer chemotherapy. The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumor cells by inhibiting some of the mechanisms implied in cellular division. Accordingly, the antitumor compounds developed through this approach are cytostatic or cytotoxic[7]. Recently, the knowledge of tumor biology has exploded during the past decades and this may pave the way for more active, targeted anticancer drugs [8,9]. However, drug resistance and lack of selectivity always been a problem for the better cancer prognosis & treatments [9]. Therefore, design and development of new anticancer agents with novel mechanism of actions remain as main focus areas of the modern medicinal chemistry research.

Bioactive Indole Derivatives: Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anticancer [10], antioxidant[11], antieducational and anti-HIV[12-13] and also play a vital role in the immune system[14,15]. Many indole derivatives are considered as the most potent scavenger of free radicals[16].

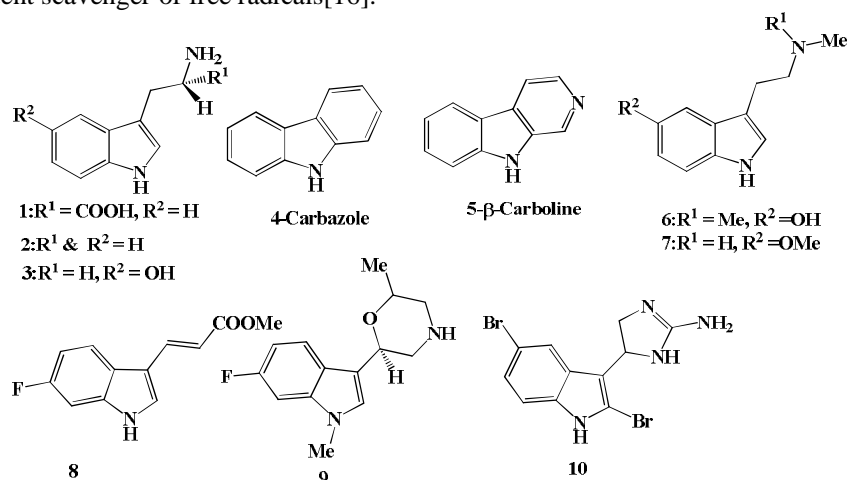


Figure 1

Artificial receptors for biologically active molecules have attracted attention from the view point of molecular recognition [17]. In addition, it was reported that various 3-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes[18].

At present, there are approximately 1500 indole alkaloids described [19], which includes simple and more complexly functionalized indole derivatives. The simple indole derivatives are comprised of a pyrrole ring fused with a benzene ring such as in the essential amino acid, tryptophan **1** as well as tryptamine **2** and serotonin **3** (Figure 1).

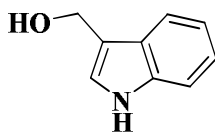
More complex indole derivatives usually contain an additional fused ring such as in carbazole **4** and β -carboline **5**. A number of indole derivatives known having important pharmacological activity. The medical uses of the simple tryptamine alkaloids are relatively few. Serotonin is one of the key neurotransmitters in animals. Several plants derived indole derivatives found to have hallucinogenic activity in humans, for instances bufotenine **6** and 5-methoxy N-methyl tryptamine **7**. Indole alkaloid derivatives isolated from marine sources. For example, methyl-(E)-3-(6-bromo-3-indolyl)-3-propeonate has been isolated from sponges. Bioactive indole alkaloids **9** and **10** are also marine natural products. Alkaloids chelonin A **9**, isolated from a marine sponge of *Chenolapysilla* sp., showed anti-inflammatory and antimicrobial activities. Compound **10**, isolated from *Discodermia polydiscus*

and showed anticancer activity. Beside these, several indoles are found to be antimicrobial activity against various microbial growths [20-21].

Kinases and Cancer: Cancer is a disease of worldwide importance. Its incidence in the developed countries is rising, and its mortality occupies the second rank in the order of death causes. Similar tendency can be observed in the developing world: the gradual improvement in the life expectancy is also associated with an elevated cancer incidence and mortality. Accordingly, we might assume that malignancy will be soon a global problem with its entire consecutive burden. Since the early history, chemistry has had varying roles in the discovery and development of anticancer drugs since the beginning of cancer therapies [22]. Synthetic chemistry has been extensively used to modify drug leads, especially those of natural origin, and to solve the problem of the often-scarce supply of natural products by developing semi-synthetic or synthetic strategies.

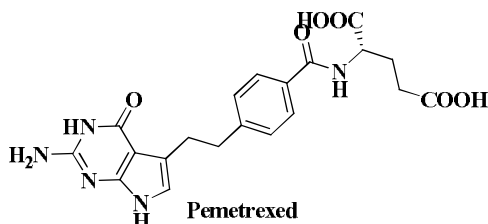
Since the 1950s, chemistry has also generated many antitumor drug leads through in vitro screening programs promoted by the National Cancer Institute (NCI) in the United States by using a range of cancer cell lines. Although DNA continues to be an essential target for anticancer chemotherapy, much recent effort has been directed to discover antitumor drugs specifically suited to target molecular aberrations which are specific to tumor cells [23]. This new generation of antitumor agents is based on research in areas such as cell signaling processes, angiogenesis and metastasis, and inhibition of enzymes that, like telomerase, are reactivated in the majority of cancer cells [24].

Indole Derivatives as kinase inhibitors: Indole nucleus is frequently found in medicinal chemistry and is considered as "privileged scaffolds"[25]. Therefore, the synthesis and selective fictionalization of indole have been the focus of active research over the years[26-28]. A brief literature review of the recent development in the functionalized indole as anticancer agents are described herein.



Indole-3-carbinol

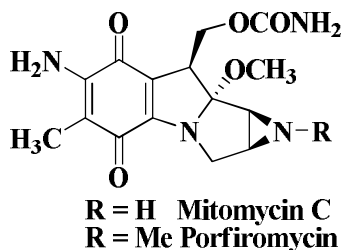
Indole-3-carbinol, a dietary component found exclusively in cruciferous vegetables, is known to suppress proliferation and induce apoptosis of various cancer cells, including breast, ovarian, lung, cervical, colon, prostate, and liver, and was the subject of several early-phase clinical trials for cancer prevention [29].



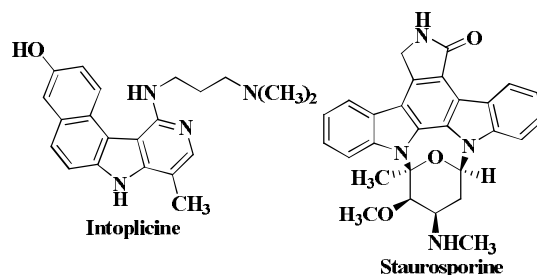
Pemetrexed

Pemetrexed was discovered during structure-activity studies of lometrexol by removal of the C-5 atom and concomitant replacement of the ring fused to the quinazolinone unit by an indole. It employs the RFC for entering the cells, and its polyglutamation product inhibits multiple targets in the folate pathway [30].

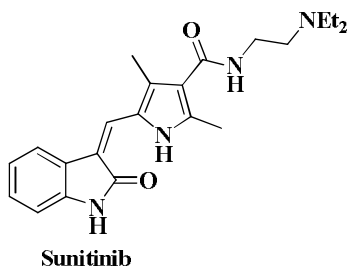
Mitomycin C is a naturally occurring antitumor quinone from *Streptomyces caespitosus*, which contains quinone and aziridine units, although not directly linked. It has been used as a cytotoxin since the 1960 decade and is active against a variety of tumors, including breast, stomach, oesophagus, and bladder, [31] as well as nonsmall cell lung cancer [32].



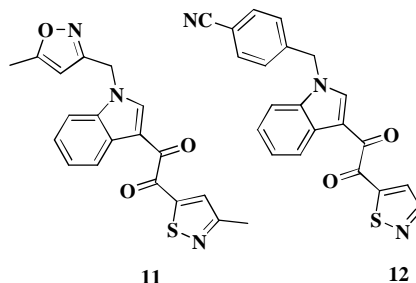
Intoplicine behaves as a dual topoisomerase I and II poison at cleavage sites different to those of other known topoisomerase inhibitors [33]. Staurosporine is well known for its antitumor activity [35].



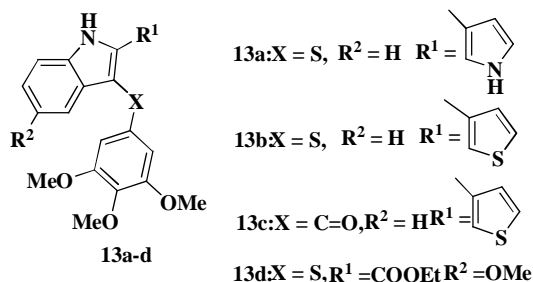
Indolinone derivatives have in common the presence of a hydrogen bond between the C-2 carbonyl and a hydrogen donor in a side chain, generally a pyrrole ring. Among these Sunitinib has been approved by the FDA for gastrointestinal and renal cancer [34, 35].



A series of *N*-heterocyclic indolyl glyoxylamides were synthesized and evaluated for in vitro and in vivo anticancer activities [36]. They exhibited a broad spectrum of anticancer activity not only in murine leukemic cancer cells but also in human gastric, breast, and uterus cancer cells as well as their multidrug resistant sublines with a wide range of IC_{50} values. They also induced apoptosis and caused DNA fragmentation in human gastric cancer cells [36].

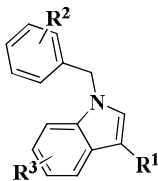


Among the compounds studied, **11** showed the most potent activity of growth inhibition (IC_{50} = 17-1711 nM) in several human cancer cells. Given orally, compounds **11** and **12** dose-dependently prolonged the survival of animals inoculated with P388 leukemic cancer cells [36].



Regina *et al.*, have reported several new arylthioindoles compounds which induced mitotic arrest and apoptosis at a similar level as combretastatin A-4 and vinblastine and triggered caspase-3 expression in a significant fraction of cells in both p53-proficient and p53-defective cell lines [37]. Importantly, **13a**, **13b**, and **13c** were more effective than vinorelbine, vinblastine, and paclitaxel as growth inhibitors of the P-glycoprotein-overexpressing cell line NCI/ADR-RES. On the other hand, methyl 3-[(3,4,5-trimethoxyphenyl) thio]-5-methoxy-1*H*-indole-2-carboxylate (**13d**), the most potent derivative, showed IC₅₀ 2.0 μM, 1.6 times more active than colchicine and about as active as combretastatin A-4 (CSA4). [38] Compound **13d** inhibited the growth of the MCF-7 cells at IC₅₀ 13 nM. Colchicine and CSA4 had 13 nM and 17 nM IC₅₀ values, respectively, with these cells.

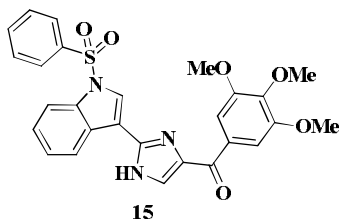
To optimize the antitumor activity of oncrasin-1, Wu *et al.*, have prepared several novel indole derivatives (**14**) for their cytotoxic activity against normal human epithelial cells and K-Ras mutant tumor cells [39]. Structure-activity relationship analysis revealed that most of the active compounds contained either a hydroxymethyl group or an aldehyde group as a substitute at the 3-position (R¹) of the indole. Both electron-donating and electron-withdrawing groups in the benzene ring were well tolerated (R²).



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The hydroxymethyl compounds ranged from equipotent with to 100 times as potent as the corresponding aldehyde compounds. Three active analogues' effect on RNA polymerase phosphorylation found that they all inhibited phosphorylation of the C-terminal domain of RNA polymerase II [39].

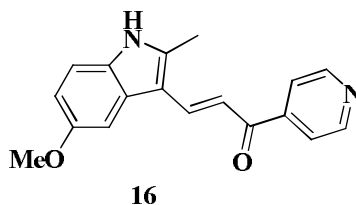
Jianjun Chen *et al.*, [40] have demonstrated that functionalized indole derivative is highly potent against a panel of melanoma and prostate cancer cell lines, with the best compound **15**, having an average IC₅₀ value of 3.8 nM. They are not substrate of Pgp and thus may effectively overcome Pgp mediated multidrug resistance [40].



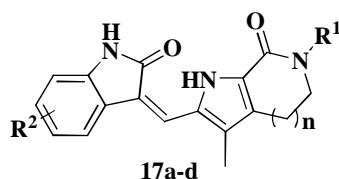
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The indole based chalcone 3-(5-methoxy, 2-methyl-1*H*-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (**16**), [41] showed to have novel caspase-independent mechanism form of cell death in which massive accumulation of vacuoles derived from macropinosomes ultimately causes cells to detach from the

substratum and rupture [41]. The potential significance of these studies is underscored by the finding that derivative **16** effectively reduce the growth and viability of Temozolomide-resistant glioblastoma and doxorubicin-resistant breast cancer cells.

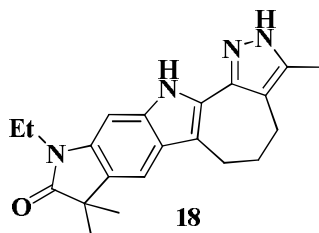


More recently, small-molecule kinase inhibitors have emerged as an important class of anti-cancer agents. The high-throughput technologies for gene resequencing, comparative genomic hybridization and single nucleotide polymorphism array analysis, and bioinformatics have made it possible to interrogate the cancer genome rapidly and comprehensively and to identify recurrent lesions that potentially contribute to the response to treatment [42]. For instances, the inhibition of receptor tyrosine kinases (RTKs) has become a successful approach in the development of anticancer agents. Many potent small-molecule kinase inhibitors have been discovered. A series of pyrrolo-fused-heterocycle-2-indolinone analogues as inhibitors of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-Kit[43]. Among them, some pyrrolo-fused six- and seven-membered-heterocycle derivatives such as **17a-d**, are potent inhibitors of VEGFR, PDGFR, and c-Kit both enzymatically (< 50 nM) and cellularly (< 50 nM).



a: $R^1 = (CH_2)_2N(C_2H_5)_2$, $R^2 = 5-F$, $n = 1$ **b:** $R^1 = (R)-CH_2CH(OH)CH_2N(C_2H_4)_2O$, $R^2 = 5-F$, $n = 1$
c: $R^1 = (CH_2)_2N(C_2H_5)_2$, $R^2 = 5-F$, $n = 2$ **d:** $R^1 = (R)-CH_2CH(OH)CH_2N(C_2H_4)_2O$, $R^2 = 5-F$, $n = 2$

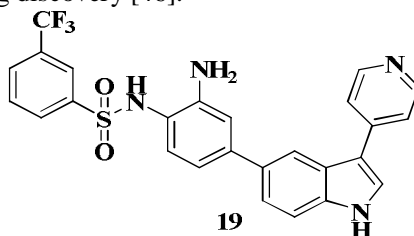
Furthermore, compounds **17a** and **17d** possessed favorable pharmacokinetic profiles and demonstrate good efficacies against human HT-29 cell colon tumor xenografts in nude mice [43]. Indole scaffolds is also found to have aurora kinase inhibitory and antimitotic activity[44]. The inhibitor **18**, exhibited low nanomolar potency against both Aurora A and Aurora B enzymes, excellent cellular potency ($IC_{50} < 100$ nM), and good oral bioavailability [44]. Phenotypic cellular assays showed that both Aurora A and Aurora B are inhibited at inhibitor concentrations sufficient to block proliferation. Importantly, the cellular activity translates to potent inhibition of tumor growth in vivo. An oral dose of 5 mg kg^{-1} QD is well tolerated and results in near stasis (92% TGI) in an HCT116 mouse xenograft model[44].



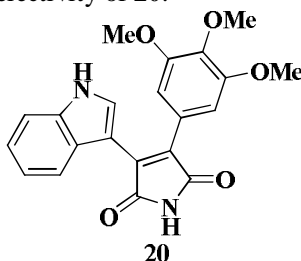
Hong *et al.*, [45] have reported a series of novel 7-azaindole-based Trk kinase inhibitors through the structure-based design strategy. Among the studied derivatives, compound **19**, On the basis of the docking results and SAR, we identified the binding mode and the detailed interactions responsible for

stabilizing in the TrkA homology model. The most potent inhibitor **19** was subjected to kinase selectivity profiling over a panel of 30 cancer related kinases at 1 μ M in a high-throughput binding assay [45]. Three kinases KIT, TrkA, and TrkB displayed tight binding to **19** (kinases with POC < 10). Subsequently the measured IC₅₀ demonstrated that **19** is about 100-fold selective for TrkA over KIT (TrkA IC₅₀ = 1.67 nM and KIT IC₅₀ = 145 nM)[45]. Moreover, **19** clearly induced cell deaths in MCF-7 and SKBr3 human breast cancer cells in a dose-dependent manner.

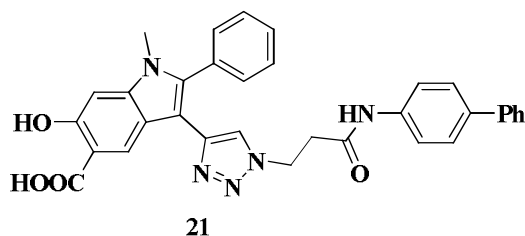
On the other hand, indole nucleolus-based agents also found to be active against Protein kinases (PKs) which comprise 22% of the druggable genome and are currently among the most important and promising target classes for drug discovery [46].



Selectivity profiling of **20** (Figure 6) in a panel of 20 protein kinases and molecular modeling indicating **20** to be highly active and selective for VEGF-R2/3 [46]. Sequence alignment analysis and detailed insights into the ATP binding pockets of targeted protein kinases from the panel result in a unique structural architecture of VEGF-R2 mainly caused by the hydrophobic pocket- I, determining the molecular basis for activity and selectivity of **20**.



The Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2) is also associated with various kinds of leukemias, and solid tumors [47]. The biological screening of a library derived from the functionalized indole scaffold led to the identification of a SHP2 inhibitor II-B08 (compound **21**) with highly efficacious cellular activity [47].

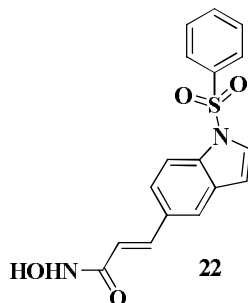


Compound **21** blocks growth factor stimulated ERK1/2 activation and hematopoietic progenitor proliferation, providing supporting evidence that chemical inhibition of SHP2 may be therapeutically useful for anticancer and antileukemia treatment. X-ray crystallographic analysis of the structure of SHP2 in complex with **21** reveals molecular determinants that can be exploited for the acquisition of more potent and selective SHP2 inhibitors [47].

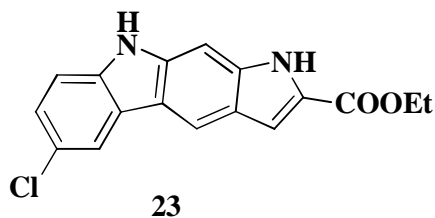
A series of 1-arylsulfonyl-5-(N-hydroxyacrylamide)indoles has been identified by Lai et al. as a new class of histone deacetylase inhibitors[48]. Among these indole derivatives, Lead compound **22**

showed remarkable HDAC 1, 2, and 6 isoenzymes inhibitory activities with IC_{50} values of 12.3, 4.0, 1.0 nM, respectively, which are comparable to drug SAHA. In in vivo efficacy evaluation against lung A549 xenograft model, **22** displayed better antitumor activity than compound SAHA [48].

Interestingly, Pyrrolo[2,3-*a*]carbazole, a 2,3-fused indole analog (ex. compound **23**) found to be active against Cyclin dependent kinase-1 exhibiting an IC_{50} in the low micromolar range and leading to 90% at higher concentrations[49].



By the use of a homology model of CDK1, CDK1-pyrrolo[2,3-*a*]carbazole complexes were modeled. The structural analysis of the simulated complexes attempts to illustrate the physicochemical and structure determinants for **23**'s high inhibitory potential toward CDK1.



In summary, it is evident from this review that functionalized indoles represented potent antitumor activity by inhibiting multiple kinases at low level concentration. A number of functional groups at different position of indole moiety (i.e.1,2,3) including benzyl, sulphonamide, aryl, heteroaryl, alkyl or fused heterocycles are well tolerated providing potent anticancer activity. Thus, targeting multi-kinases using functionalized indoles provide basis for the development of new potential anticancer agents.

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