INDOLE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS: A REVIEW

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ABSTRACT

Heterocyclic moiety serve as perfect framework on which pharmacophores can be effectively attached to produce novel drugs. Among various heterocyclic compounds, nitrogen-based heterocycles have been extensively investigated as they constitute the core structures of numerous biologically relevant molecules and have been found to be active against different types of cancers. Due to the versatility of indole, it has been a highly "privileged motif" for the target-based design and development of anticancer agents. Moreover, it has been used as a synthon for the preparation of large number of bioactive heterocycles and paved a way to develop effective targets. This review article presents comprehensive overview of anticancer potentiality of diversely substituted indole derivatives including 1H-indole-2,3-dione and Spiro indole derivatives.

Keywords: Heterocyclic compounds, Nitrogen-based, Indole, Spiro-indole, Anticancer agents.

INTRODUCTION

Heterocyclic compounds have paid enormously to the society in the form of large number of drugs for the treatment of various ailments and have occupied a prominent place in medicinal chemistry due to their varied biological activities [1-5]. Owing to their specific chemical reactivity, they constitute 80% of the drugs which are in therapeutic use. Majority of the large number of marketed drugs viz., chlordiazepoxide (tranquillizer)[6], imipramine (antidepressant)[7], guanethidine (antihypertensive)[8], indapamide (diuretic and antihypertensive) [9,10], etc. are heterocyclic compounds and many antibiotics including penicillin, cephalosporin, norfloxacin, streptomycin etc., also contain heterocyclic ring[11-14]. Cancer is the major cause of death worldwide. Current cancer treatment possibilities include surgery, chemotherapy, and radiation therapy or a combination of these options [15]. Since past few decades, many heterocyclic compounds have been recognized as potential anticancer agents [16, 17]. Around 60% of the medications used for cancer treatment are based on heterocyclic moieties [18]. Although recommended quantity of anticancer drug is adequate to kill cancer cells but is generally harmful to the normal tissue and lead to many side effects, which restricts its treatment efficacy [15]. Hence, scientists are searching new anticancer drugs by designing and exploring new compounds for the treatment of various types of cancers which are devoid of side effects caused by conventional antineoplastic drugs.

Indole core has been continuously attracting the attention of researchers and has become a dynamic area of research due to its outstanding pharmacological properties [19-21]. It is designated as "privileged scaffolds" which bind to multiple receptors with high affinity, leading to the development of novel bioactive drugs [22-25]. It is used for the target-based design and development of anticancer agents [26]. In this context, therapeutic effect of multi-target directed indole based hybrid molecules in cancer therapy is recently reviewed by Sunil et al [27].

Indole core is widely distributed in the nature [28] and is present in many important alkaloids viz. auxins [29] and tryptophan [30]. The indole moiety is related to the neurotransmitter serotonin implicated for brain function and cognition as the endogenous receptor agonist [31]. Indole alkaloids, vallesiachotamine and iso-vallesiachotamine isolated from the fruits of *Anthocephalus cadamba* (Family: Rubiaceae) are found to exhibit potent anticancer activity[32] and indole alkaloids from marine natural products show numerous biological activity, including cytotoxic, antiviral, antimicrobial, antiparasitic, anti-inflammatory, antiserotonin, Ca^{2+}, calmodulin-antagonistic activity and antitopoisomerase-I activity, along with in vivo activity [33, 34]. Reserpine, an indole alkaloid, is used to treat high blood pressure and severe agitation in patients with mental disorders [35]. Compounds which contain cyclohepta[b] indoles possess broad spectrum of biological activities including inhibition of adipocyte fatty-acid-binding protein (A-FABP), deacetylation of histones, inhibition of leukotriene production p53, antituberculosis activities, and anti-HIV activities [36]. Monoterpenoid indole alkaloid from Melodinus khasianus [37] possess anticancer activity and from the African medicinal plant Tabernaemontana elegans serves as lead for targeting multidrug resistant cancer cells [38]. Dimeric monoterpene indole alkaloids, vincristine and vinblastine are used for the treatment of several types of cancers, including Hodgkin's disease, Kaposi's sarcoma, non-Hodgkin's lymphoma, and breast or testicle cancer [39, 40].

Indole derivatives have been extensively used as synthons for the preparation of large number of biologically relevant heterocycles [41]**(Chart 1)**. Moreover, indoles are found in important synthetic drug molecules with interesting pharmacological properties like SARS coronavirus 3CL protease inhibitors [42], anti-HIV activity [43], antituberculosis activity [44], anticonvulsant [45] and HIV-TB coinfection [46] including anti-cancer [47]. Indoles are also associated with the inhibition of NFkB/mTOR/PI3K/AkT and regulation of estrogen-mediated activity [48]. Several 3-substituted indole derivatives have been found to exhibit remarkable antineoplastic properties viz. inhibition of cell proliferation of human colon carcinoma (HT-29), human ovarian adenocarcinoma (SK-OV-3), and c-Src kinase activity [49]. Significantly, 3-pyranyl indoles have showed good anticancer activity against MCF-7 breast cancer cell lines in comparison with standards drugs [50].

Further, *(E)*-3-(5-substituted-1*H*-indol-3-yl)-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl) prop-2-en-1-one derivatives have anti-proliferative capacity in liver, breast and colon cancer cell lines [51] and indole-3-carbinol, bis(3′-indolyl) methane and synthetic analogs are associated with cancer chemotherapy as reported by Safe et al. [52] Furthermore, indole-3-carbinol and its metabolite 3,3′-diindoylmethane (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 [53]. This broad spectrum of anti-tumor activities in conjunction with low toxicity highlights the translational value of indole-3-carbinol and its metabolites in cancer prevention/therapy [53]. Anti-carcinogenic and anti-metastatic properties of indole-3-carbinol in prostate cancer has been reported by Garikapaty et al [54]. Several aroylindoles, arylthioindoles, diarylindoles and indolylglyoxyamides have shown good inhibition towards the tubulin polymerization [55]. Encouraged by the excellent and promising anticancer activities of indole derivatives and keeping in view of the several studies reported recently by the researchers altogether, it was thought to collect the literature consisting of new indole derivatives as potential anticancer agents.
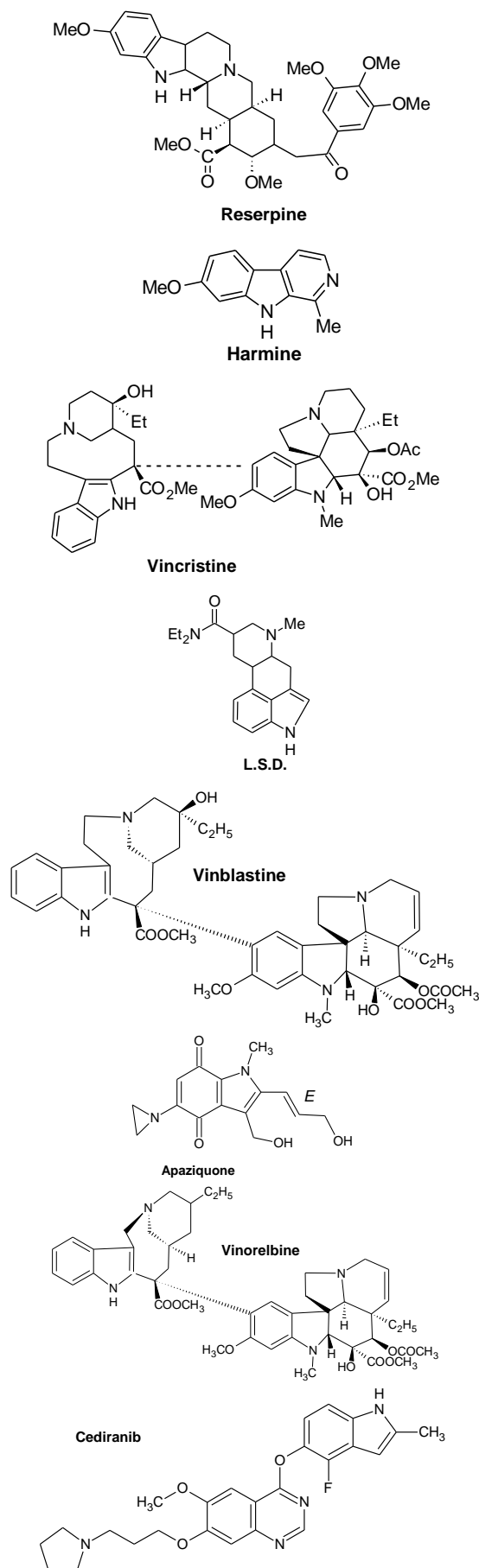
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**Chart 1**: Indole ring containing anti-cancer drugs

The present review article reflects overview of anticancer potentiality of variously substituted indole derivatives mainly N1-, C-2, C-3, C-5 substituted indoles, 1H-indole-2,3-dione (isatin) derivatives and Spiro indole derivatives that can be employed as a valuable support towards more potent drugs.

Anticancer activity of indole derivatives

Andreani et al [56] prepared and tested 3-indolylmethylene-2-indolinone derivatives for antitumor activities. Synthesized compounds were similar to 3-(2-chloro-3-indolylmethylene)1,3-dihydroindol-2-ones but with the two indole systems separated by an heterocycle (pyridine or piperazine) instead of a methine bridge and were evaluated for antitumor activity in the human cell line screen. The pyridine derivatives **(compound 1)** were far more active than the piperazine derivatives **(compounds 2, 3, 4)**. Interesting results were obtained with halogens, methoxy and dimethylamino groups. The compound containing chlorine at the 4 position of the indole **(compound 1, R^1= Cl)** was very active: the activity decreased by shifting the halogen from the 4 to the 5 **(compound 1, R^2=Cl)** and 6 position **(compound 1, R^3=Cl)**. The compound bearing the 5-methoxy-2-indolinone moiety was subjected to the first in vivo experiment (hollow fiber assay) and was found to be active.
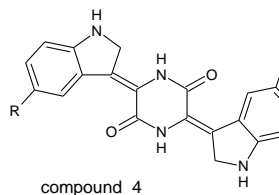

compound 1
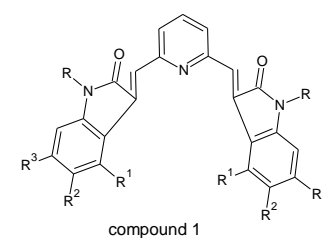
3,3'-[pyridine-2,6-diylbis(methylene)]bis(1,3-dihydroindol-2-ones)

compound 2
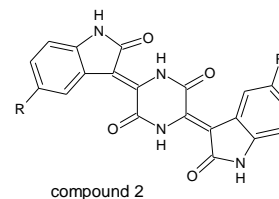
3,6-bis(2-oxo-1,2-dihydroindol-3-ylidene)piperazine-2,5-diones
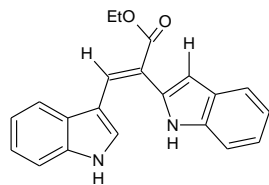

compound 3
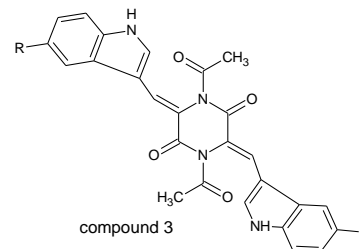
**1,4-diacetyl-3,6-bis(indol-3-ylmethylene)piperazine-2,5-diones**

compound 4

3,6-bis(indol-3-ylmethylene)piperazine-2,5-diones

Bis-indolinone derivatives having either 2,6-disubstituted pyridine core or 1,10-disubstituted phenanthroline core have been tested as potential G-quadruplex binders by Amato et al [57]. Sharma et al [58] carried out reaction of *C*-(3-indolyl)-*N*-phenylnitrone with allenic esters under mono-mode microwave irradiation to afford via a domino process, bis-indole derivatives **(compounds, 5**

& 6) which were evaluated against various human cancer cell lines [58] such as cancer of the breast (MCF-7), ovary (IGROV-1), lung (A-549, HOP-62) and colon (HCT-15 and SW-620) and were mainly found to be active against colon (HCT-15, SW-620) cancer cells. **Compound 5** showed inhibition of 61% at 100 μM and 58% at 50 μM against colon cell line (SW-620) with IC_{50} of 39.7 μM. **Compound 6** showed inhibition of 75% at 100 μM and 46% at 50 μM against colon cell line (SW-620) with IC_{50} of 39.7 μM; 85% at 100 μM and 56% at 50 μM against colon cell line (HCT-15) with IC_{50} of 46.6 μM.
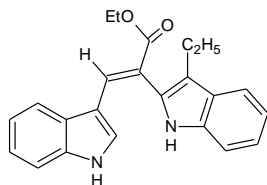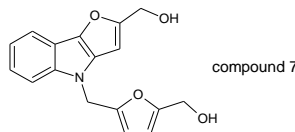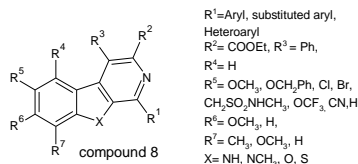
compound 5

compound 6

Zhuang et al [59] synthesized and evaluated a series of 2,4-disubstituted furo[3,2-*b*]indole derivatives for anticancer potentiality and established the structure–activity relationships (SARs) of these compounds. Among the tested compounds, (5-((2-(hydroxymethyl)-4*H*-furo[3,2-*b*]indol-4-yl)methyl)furan-2-yl)methanol (**Compound 7**) was found to exhibit highly selective anticancer activity against NCI-60 human tumor cell lines and significant inhibitory activity against A498 renal cancer cells.
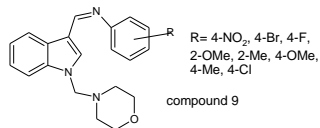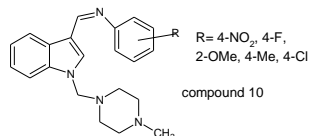
compound 7

compound 8

R^1=Aryl, substituted aryl, Heteroaryl
R^2= COOEt, R^3 = Ph,
R^4= H
R^5= OCH₃, OCH₂Ph, Cl, Br, CH₂SO₂NHCH₃, OCF₃, CN,H
R^6= OCH₃, H,
R^7= CH₃, OCH₃, H
X= NH, NCH₃, O, S

Patil et al [60] synthesized and tested series of pyrido[3,4-b]indoles **(compound 8)** for their antiproliferative activity against human cancer cell lines, comprising HCT116 colon, HPAC, MIA PaCa-2 and Panc-1 pancreatic, MCF-7 and MDA-MB-468 breast, A375 and WM164 melanoma, A549 lung, and LNCaP, DU145 and PC3 prostate cancer lines. Pyrido[3,4-b]indoles displayed SAR with respect to antiproliferative activity. 1-Naphthyl at C1 combined with methoxy at C6 (compound-1-naphthyl-6-methoxy-9H-pyrido [3,4-b]indole) provided the best antiproliferative activity hence the highest potency. Ali et al [61] synthesized micellar "nano" indole heterocyclic "anti-cancer compounds", DNA binding studies of synthesized molecules carried out and DNA binding constants were also calculated. The activities of the developed nano anticancer drugs were tested on HepG2 (C3A) cell lines. It was observed that **compound 9** (R=NO₂,4-Br,2-OMe) and **compound 10** (R=4-NO₂) at a micellar concentration of 670 μL mL⁻¹ displayed excellent anticancer activities against the HepG2/C3A line (25–50%). The potency of nano anticancer drugs was predicted by drug likeness using Lipinski's "rule of five". **Compounds 9 & 10** followed Lipinski's rule of five and could be used to treat cancers.
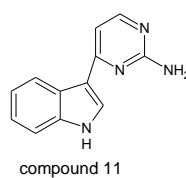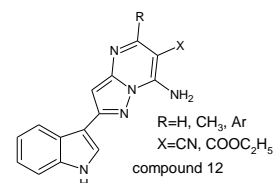
compound 9
R= 4-NO₂, 4-Br, 4-F, 2-OMe, 2-Me, 4-OMe, 4-Me, 4-Cl

compound 10
R= 4-NO₂, 4-F, 2-OMe, 4-Me, 4-Cl

Kamel et al [62] reported synthesis of bio isosteres of marine indole alkaloids, **Compound 11** (meridianins) and anti-proliferative activity against HCT-116 cell line. The 2-aminopyrimidine ring of meridianins was replaced with 5-aminopyrazole, pyrazolo[1,5-a]pyrimidine and pyrazolo[3,4-b]pyridine rings. The cytotoxic screening revealed that pyrazolo[1,5-a]pyrimidines **(compounds 12 and 13)** had the most potent cytotoxic activity with IC50 = 0.31 μM and 0.34 μM respectively. Compounds 12 and 13 were also investigated for their kinase inhibitory potencies toward six kinases (CDK5/p25, CK1δ/ε, GSK-3α/β, Dyrk1A, Erk2, and CLK1). They exhibited effective inhibition of GSK-3α/β (IC50 = 0.196 μM and 0.246 μM, respectively) and Erk2 (IC50 = 0.295 μM and 0.376 μM, respectively). 2-Aminopyrimidinyl ring of meridianins was replaced with pyrazolo[1,5-a]pyrimidine and pyrazolo[3,4-b]pyridine rings which showed promising cytotoxic activity compared to the five membered 5-aminopyrazole.
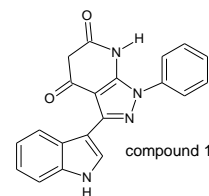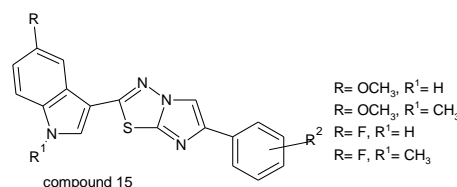
compound 11

compound 12
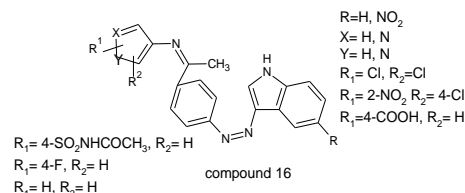R=H, CH₃, Ar
X=CN, COOC₂H₅
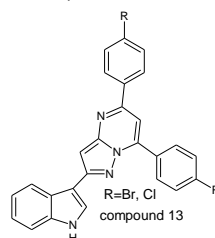
compound 13
R=Br, Cl

compound 14

Cascioferro et al [63] synthesized and studied indole-based imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **(Compound 15)** for their in vitro antiproliferative activity on a panel of pancreatic ductal adenocarcinoma (PDAC) cells, including SUIT-2, Capan-1 and Panc-1. **Compounds 15a (R=OCH₃, R¹=H, R²=4-NO₂)** and **15b (R=F, R¹=H, R²=H)**, showed relevant in vitro antiproliferative activity on all three pre-clinical models with half maximal inhibitory concentration (IC_{50}) ranging from 5.11 to 10.8 μM. In addition, compound **15a** significantly inhibited the migration rate of SUIT-2 and Capan-1 cells in the scratch wound-healing assay.
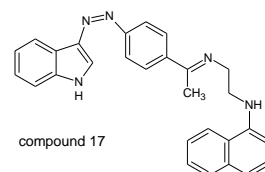
compound 15
R= OCH₃, R¹= H
R= OCH₃, R¹= CH₃
R= F, R¹= H
R= F, R¹= CH₃

Kaur et al [64] synthesized a series of indole hybridized diazenyl derivatives efficiently by condensation of diazotized p-aminoacetophenone with indole or nitroindole followed by reaction with different aromatic/heteroaromatic amines of biological significance and evaluated for cytotoxicity against human lung carcinoma cell line (HCT-116), breast cancer cell line (MDAMB231), leukemic cancer cell line (K562), and normal cell line (HEK293) by MTT assay using doxorubicin as the standard drug. The indole hybridized diazenyl derivatives, **Compound 16** (X=Y=R=R²=H, R¹=4-COOH) and **compound 17** were found to be active against breast cancer cell line and human colon carcinoma cell line having IC₅₀ in the range of 19–65 μg/ml.

compound 16
R=H, NO₂
X= H, N
Y= H, N
R₁= Cl, R₂=Cl
R₁= 2-NO₂ R₂= 4-Cl
R₁=4-COOH, R₂= H
R₁= 4-SO₂NHCOCH₃, R₂= H
R₁= 4-F, R₂= H
R₁= H, R₂= H

compound 17

1H-indole-2,3-dione derivatives

Among indole derivatives, 1*H*-indole-2, 3-dione (Isatin) has received considerable attention due to its potent biological activities [65-69] such as antioxidant, anti-inflammatory, antimicrobial, antituberculosis, anticancer, anti-HIV, antiviral, and anticonvulsant, etc. It was first obtained by Erdman [70] and Laurent [71] in 1840 as a product from the oxidation of indigo dye by nitric acid and chromic acids. The synthetic versatility of 1*H*-indole-2,3-dione has led to the extensive use of this compound in organic synthesis. In nature, It is found in plants of the genus *Isatis*, in *Calanthe* discolor LINDL. It is the biologically

active chemical produced by an *Altermones* sp. strain inhibiting the surface of embryos of the cardiean shrimp *Palaemon macrodectylus*, which protect them from the pathogenic fungus *Lagenidium callinectes* [72]. It undergoes several types of reactions due to the presence of several reaction centres Thus, keto group at position 2 and particularly, at position 3 can enter into addition at the C-bond and into condensation with release of the water molecule. Compounds of the 1*H*-indole-2,3-dione series are capable of entering into N-alkylation and N-acylation and into the Mannich and Michael reactions [73] through the NH group. Their Schiff bases and Mannich bases are known to possess a wide range of pharmacological properties including antibacterial (Pandeya et al [74]; Sarangapani and Reddy [75]; Varma and Nobles [76]), anticonvulsant (Sridhar et al [77]; Varma et al [78]), anti-HIV (Pandeya et al [79, 80]; Sriram et al [81]), antiviral (Singh et al [82]), and anticancer activity (Karki et al [83, 84]). Many fluorinated *1H*-indole-2,3-dione derivatives like 1-dialkylaminoacetyl-5/6-fluoroindole-2,3-diones, 2-([2-(fluoroaryl)-1*H*-indol-3- yl]methylene) hydrazine carbothioamides and 2-(fluoroaryl)-([5-(substituted benzylidene)-4-oxo-2-thiazolidinylidene]hydrazone)-1*H*-indole-3-carboxaldehydes possess antibacterial activity [85] and antifertility activity [86]. Jain et al [87] synthesized derivatives of 5-fluoroisatin with ethyl cyanoacetate and substituted ketones which show anticonvulsant activity.

### Anticancer activity of 1H-indole-2, 3-dione derivatives

Vine et al [88] synthesized a range of substituted 1*H*-indole-2,3-diones (isatins) and studied their cytotoxicity against the human monocyte-like histiocytic lymphoma (U937) cell line in vitro. SAR studies indicated C_5, C_6, and C_7 substitution greatly enhanced activity with some di- and tri-halogenated isatins giving IC_{50} values <10 μM. These compounds showed greater selectivity toward leukemia and lymphoma cells over breast, prostate, and colorectal carcinoma cell lines. The most active compound, 5, 6, 7-tribromoisatin **(compound 18)**, was found to be antiproliferative at low micromolar concentrations and also activated the effector caspases 3 and 7 in a dose-dependent manner. These results indicate that di- and tri-substituted isatins may be useful leads for anticancer drug development in the future [88].


compound 18

compound 19

X,Y:=O;H,H;H,OH;=N-OH;
R^1= Me, Et,
R^2= H, F, Cl, Br, CH$_3$,
OCH$_3$, But
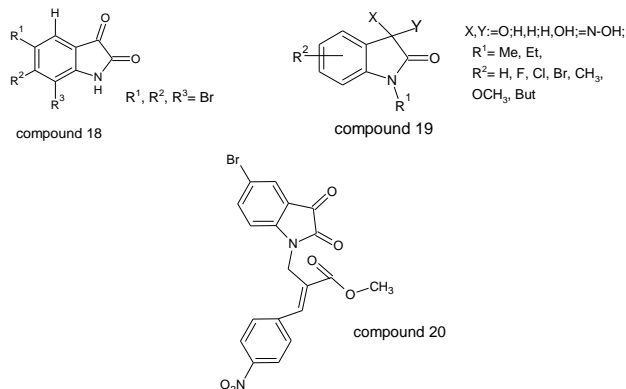
compound 20

A series of di- or trisubstituted isatin derivatives were synthesized **(compound 19)** and evaluated for anticancer activity against human T lymphocyte cells Jurkat by Teng et al [89]. SAR study suggested that the combination of 1-benzyl and 5-[*trans*-2-(methoxycarbonyl)ethen-1-yl] substitution greatly enhanced their cytotoxic activity. Baylis–Hillman adduct-derived *N*-cinnamyl-substituted isatin derivatives were synthesized and evaluated for their anticancer activity against four different cell lines Chinese hamster ovary (CHO cells), Colo 205 (human colon cancer), Sup-T1 (human lymphoma) and C6 glioma (rat glioma) by MTT assay method by Kumar et al [90]. The **compound 20** has shown specific cytotoxic activity. Gudipati et al [91] synthesized a series of 5 or 7 substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives, **compound 21** and studied for their anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependent inhibition of growth of the cells. The IC_{50} values of all the synthetic test compounds were found between 10.64 and 33.62 μM. Among the synthesized 2-indolinones, **compound 21** with halogen atom (electron withdrawing groups, F, Cl, Br) at C5 position showed the most potent activity. Kamal et al [92] synthesized and evaluated 3,3-diindolyl oxyindole derivatives against a panel of five human cancer lines and most of them showed potent cytotoxicity **(compound 22)**.

R^1=H, F, Cl, Br, CH$_3$, NO$_2$, COOH
R^2= H, Cl, NO$_2$, CH$_3$, COOH, COOCH$_3$

compound 21
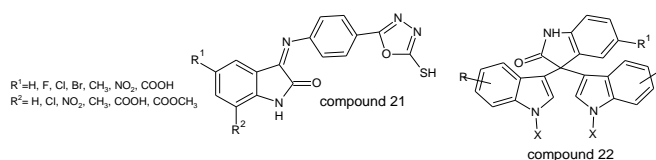
compound 22

A series of isatin-based heterocyclic compounds were synthesized **(compounds 23 & 24)** by the condensation of commercially available, active methylene heterocycles with isatin in moderate to excellent yields and found to inhibit proliferation of cancer cell lines resistant to apoptosis by Evdokimov et al [93].

compound 23

compound 24

OE21 esophageal cancer

U373 glioblastoma

apoptosis-resistant cancer cell lines
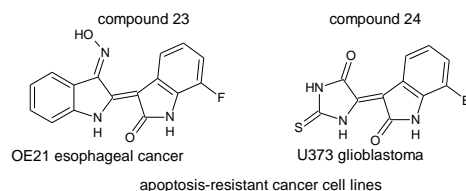
A series of 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene) thiazolidin-2-ylidene)amino) benzenesulfonamides were synthesized by Eldehna et al [94] and evaluated for their anti-proliferative activity against breast cancer MCF-7 and colorectal cancer Caco-2 cell lines. **Compound 25** was found to be the most potent derivative against MCF-7 ($IC_{50} = 3.96 \pm 0.21$ μM), **Compound 25** induced the intrinsic apoptotic mitochondrial pathway in MCF-7 cells; evidenced by the enhanced expression of the pro-apoptotic protein Bax and the reduced expression of the anti-apoptotic protein Bcl-2, and the up-regulated active caspase-9 and caspase-3 levels [94].

compound 25

compound 26
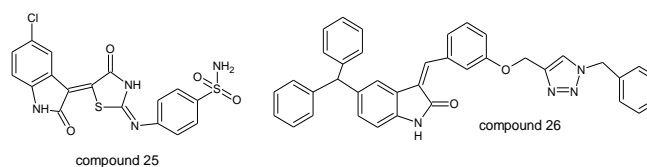
A series of triazole linked 3-benzylidene isatin hybrids were synthesized and assessed against DU145 (prostate), PC-3 (prostate), MDA-MB-231 (breast), BT549 (breast), A549 (lung) and HeLa (cervical) human cancer cell lines by employing MTT assay for their cytotoxic potential by Nagarsenkar et al [95]. **Compound 26** was found to be most potent amongst all the tested compounds with an IC_{50} value of (3.7 ± 0.05 μM) on DU145 cells and **Compound 26** can induce cell apoptosis in DU145 cells [95]. Moreover, 3-hydrazinoindolin-2-one derivative of isatin, represents a pharmacophore with potential anticancer activities and is extensively reviewed [96].

A sequence of isatin derivatives of podophyllotoxin were synthesized by Zhang et al [97] and evaluated for their cytotoxic activity against human leukemia K562 cells and adriamycin-resistant K562/ADR cells using CCK-8 assay *in vitro*. Among them, the cytotoxicities exhibited by **compounds 27a** and **27b** were found to be comparable or more effective than podophyllotoxin. In particular, **27a** exhibited significant cytotoxicity against resistance K562/ADR cells with IC_{50} value of 0.067 ± 0.010 μM. Furthermore, cell cycle analysis revealed that **27a** could remarkably induce K562/ADR cell cycle arrest in the G2/M phase [97].

27a: R=4-Br
27b: R=6-Cl

compound 27
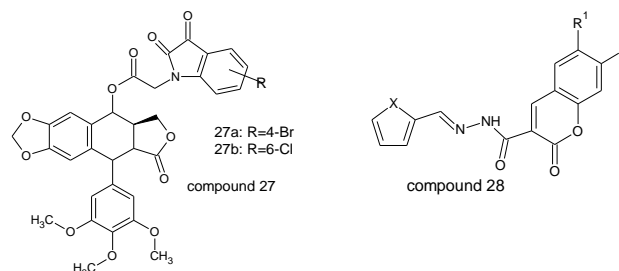
compound 28

Nasr et al [98] synthesized sixteen coumarins bearing hydrazide–hydrazone moiety **(compound 28)** and evaluated them against human drug-resistant

pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines *in vitro*. Bromocoumarins were found to be the most active antitumor agent against drug-resistant pancreatic carcinoma cells [98]. Similarly, Kakkar et al recently reviewed anticancer activities of diversely substituted isatin derivatives [99].

Spiro-indole derivatives

Furthermore, indole substituted with heterocyclic rings at the 3-position have been found in a fascinating array of bioactive natural products and pharmaceutical compounds [100]. It was found that several alkaloids and compounds obtained from marine molluscs and shell fish are heterocyclic compounds having a Spiro system at the position 3- of the 2-indolinone skeleton [101]. Spiro-indoles, with C-3 as Spiro atom act as precursors for the synthesis of novel heterocyclic systems and have received considerable attention as all sorts of rings beginning from one ring system to three ring systems with heteroatom can be incorporated by cyclization and rearrangement reactions [100]. Further, the other ring incorporated at C-3 of indole ring can have wide variation. This gives tremendous scope for the synthesis of novel pharmacodynamic indole heterocycles. Moreover, Spirooxindole derivatives occupy a special place in organic and medicinal chemistry because these compounds are well-known as microtubule assembly inhibitors (spirotryprostatin A and B)[102], Muscarinic M1, and serotonin receptor modulators (pteropodine and isopteropodine) [103] and nonpeptidyl growth-hormone secretagogues (MK-0677) [104]. Fredricamycin A, a Spiro heterocycle is an antitumor antibiotic agent [105]. Considerable attention has been paid on the development of new strategies to synthesize many kinds of Spiro oxindole ring systems because of their interesting biological and pharmacological properties, such as vasodilatory, hypoglycaemic, anti-inflammatory, antimicrobial, analgesic, and antipyretic activities [106, 107]. Several articles regarding anticancer activity of Spiro indole derivatives have been published during last decade [108, 109]. Owing to exclusive above-mentioned structural features and numerous biological activities associated with Spiro indole derivatives, they perform major and dynamic role in drug design and discovery (**Chart 2**).
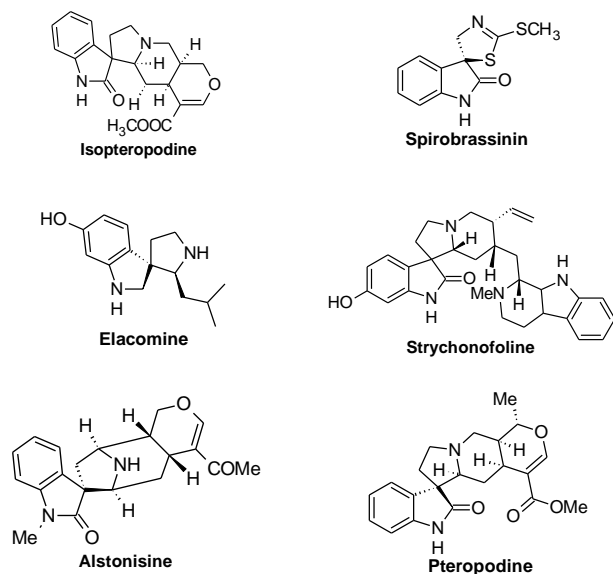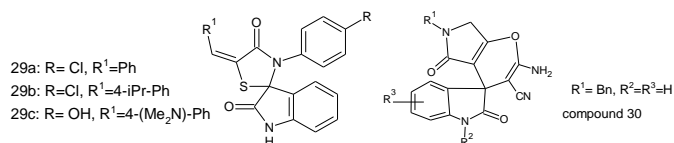

**Chart 2:** Biologically active Spiro indole derivatives.

Anticancer activity of Spiro-indole derivatives

Synthesis and evaluation of the anticancer activity of 3'-aryl-5'- arylidene-spiro [3*H*- indole-3,2'-thiazolidine]-2,4'(1*H*)-diones and spiro [3*H*-indole-3,2'-thiazolidine] -2,4'(1*H*)-dione-3'-alkanoic acid esters was described by Kaminskyy et al [110]. Among the tested compounds, (5'Z)-5'-(benzylidene) -3'-(4-chlorophenyl) spiro[3*H*-indole -3,2'- thiazolidine] -2,4'(1*H*)-dione (**29a**) and (5'Z)-3'-(4-chlorophenyl)-5'-[4- (1-methylethyl) -benzylidene]spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-dione (**29b**) were superior to other related compounds and may be considered due to the presence of 4-thiazolidinone group[110].

29a: R= Cl, R¹=Ph
29b: R=Cl, R¹=4-iPr-Ph
29c: R= OH, R¹=4-(Me₂N)-Ph

R¹= Bn, R²=R³=H
compound 30

A simple and efficient protocol for assembling novel Spiro[indole-pyranopyrrole] derivatives (**compound 30**) was developed and used to prepare a series of biologically important compounds by Han et al [111]. The cytotoxic activities of Spiro[indole-pyranopyrrole] derivatives were evaluated in vitro and found to exhibit significant cytotoxicities to Raji cell lines.

Synthesis, characterization and anticancer activity of Spiro[pyrrolidine-3,3'-oxindole] derivatives, **compounds 31** was carried out by Konyar et al [112]. Cytotoxic effects of the compounds were determined on Huh7, MV, HCT116 and MCF7 cancer cell lines by the NCI-60 Sulforhodamine B Assay, using (S)-(+)-Camptothecin as a positive control. Generally, target compounds showed better cytotoxic activities against the MCF7 and HCT116 cancer cell lines. It was found that **compound 31** exhibited the most potent inhibitory activity with IC50 values of 4.8 μM, 3.9 μM, 14.9 μM and 8.2 μM against the MCF7, HCT116, MV and Huh7 cell lines, respectively [112].

R¹=p-NO₂
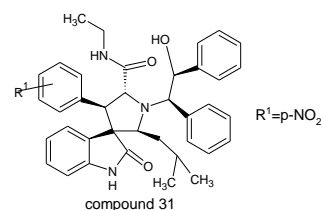
compound 31

Yong et al [113] synthesized 3'-spirocyclic-oxindole compounds, based on the Spiro[indole-3,5'-isoxazolidin]-2(1*H*)-one, the 2'*H*-spiro [indole-3,6'-[1,3]oxazinane] -2,2'(1*H*)-dione and the 2'*H*-spiro[indoline-3,3'-pyrrolo[1,2-c][1,3']oxazine]-1',2(1*H*)-dione heterocyclic compounds (**32-34**). These compounds were prepared from methyl α-(2-nitrophenyl)acrylate via [1,3]-dipolar cycloaddition reactions with two acyclic nitrones and one cyclic nitrone followed by reduction of the cycloadducts and then treatment with triphosgene. Two of these compounds showed significant cytostatic activity on three cancer cell lines with GI₅₀ values of 2.6–4.1 μM on the human breast cancer cell line, MCF-7.

32
GI₅₀=2.6 μM

33
GI₅₀= 4.1μM

34a: R=Me
34b: R=Ph
GI₅₀ >25 μM
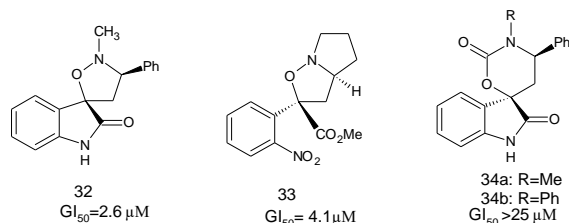
Barakat et al [114] investigated one-pot three-component reaction *via* a [3 + 2] cycloaddition/ring contraction sequence of a dipolarophile (activated alkene) with *in situ*-generated azomethine ylide (1,3-dipoles) without the use of any catalyst leading to the formation of biologically important spirooxindoles in high yield (69–94%) with high diastereoselectivity. The synthesized compounds were subjected to cytotoxicity evaluation using colorectal cancer (HCT-116), hepatocellular carcinoma (HepG2), and prostate cancer (PC-3) cells. **Compounds 35b**, **35c**, and **35d** showed potent cytotoxic activity and high selectivity against HCT-116 cells compared to cisplatin. Further, compound **35a** retained high cytotoxic activity and selectivity against HepG2 and PC-3 cells in comparison to cisplatin.
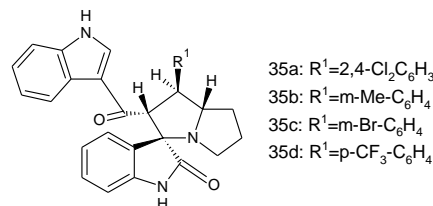
35a: R¹=2,4-Cl₂C₆H₃
35b: R¹=m-Me-C₆H₄
35c: R¹=m-Br-C₆H₄
35d: R¹=p-CF₃-C₆H₄

A series of functionalized Spirooxindole linked with 3-acylindole scaffold is synthesized starting from chalcones derived from 3-acetyl indole with isatin, a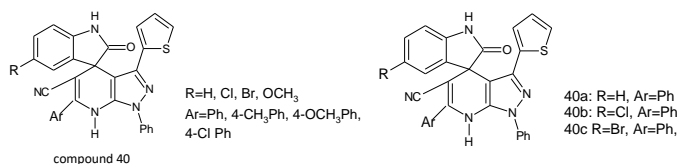nd l-4-thiazolidinecarboxylic acid by Islam et al [115] in high yield (71–89%). The spirooxindole hybrids have been evaluated *in vitro* for their antiproliferative effects against colon cancer (HCT-116), hepatocellular carcinoma (HepG2) and prostate cancer (PC-3). **Compound 36** proved to retain a high cytotoxic activity and selectivity against colon cancer cells HCT-116.

compound 36

compound 37   R=1-CH$_3$-7-F
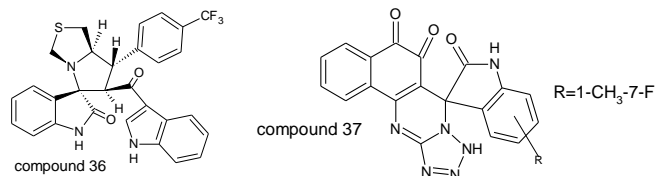
A series of Spiro oxindole-*O*-naphthoquinone-tetrazolo[1,5-*a*]pyrimidine hybrids were synthesized and evaluated as potent antitumor agents by Wu et al [116]. These hybrids exhibited relatively high cytotoxic activity against cancer cell line HepG2 (IC$_{50}$ = 2.86–36.34 μM), while normal cell line LO2 was less sensitive to these hybrids (IC$_{50}$ = 36.37–248.39 μM). Among all the compounds tested, **compound 37**, with a mean IC$_{50}$ value of 2.86 μM, was the most active. Furthermore, Lotfy et al [117] synthesized a new series of heterocycles containing spirooxindole and pyrrolidine rings by the 1,3-dipolar cycloaddition of an azomethine ylide, which was generated *in situ* by the condensation of a secondary amino acid (l-proline) and dicarbonyl compounds (isatin), with dipolarophiles and evaluated against breast cancer cell lines (MCF-7) and leukemia (K562). Among them, **compound 38** was identified as the most potent with IC$_{50}$ values of 15.49 ± 0.04 μM, against breast cancer cell lines (MCF-7) compared to standard drug 5-Fu (IC$_{50}$ = 78.28 ± 0.2 μM).

compound 38

compound 39   R^2= 3-indolyl
R^2=4-imidazolyl
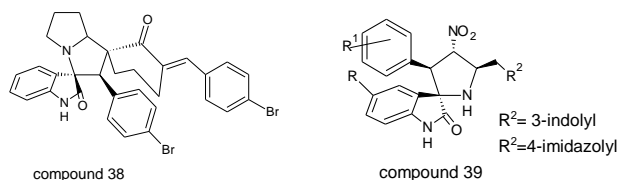
Arumugam et al [118] reported synthesis of a small library of hybrid Spiro heterocycles containing Spiro oxindole, pyrrolidine and indole/imidazole moieties **compound 39** with complete regio- and diastereoselectively from a three-component process starting from a series of variously substituted (*E*)-(2-nitrovinyl)benzenes, indoline-2,3-dione derivatives and l-tryptophan or l-histidine in an ionic liquid and evaluated for their anticancer activity. Compounds were shown to inhibit the proliferation of FaDu cells, a human epithelial cell line isolated from a squamous cell carcinoma of the hypopharynx, *via* apoptotic cell death. Eldehna et al [119] reported one-pot three-component synthesis of novel spirooxindoles (**compound 40)** and evaluated their potential anti-proliferative activity towards TNBC MDA-MB-231 cells. Spirooxindoles **40a**, **40b** and **40c** emerged as the most potent analogues with IC$_{50}$ = 6.70, 6.40 and 6.70 μM, respectively. Compounds **40a** and **40b** induced apoptosis in MDA-MB-231 cells, **40b** displayed significant increase in the percent of annexin V-FITC positive apoptotic cells from 1.34 to 44%. Furthermore, spirooxindoles **40b** and **40c** displayed good inhibitory activity against EGFR (IC$_{50}$ = 120 and 150 nM, respectively). These data established that **40b** might be a potential lead compound for the development of effective anti-TNBC agents [119].

R=H, Cl, Br, OCH$_3$
Ar=Ph, 4-CH$_3$Ph, 4-OCH$_3$Ph, 4-Cl Ph

40a: R=H, Ar=Ph
40b: R=Cl, Ar=Ph
40c R=Br, Ar=Ph,

compound 40

Patravale et al [120] described facile, sustainable, catalyst-free and bio-oriented multicomponent method for the synthesis of 2-amino-3-cynospiro (5H-indeno[1,2-*b*]pyran-4,3′-indoline)-2′5,-dione using isatin, malononitrile and 1,3-indandione and evaluated compounds against breast carcinoma cell lines (MCF7, MDA-MB-435) and normal Vero monkey cell lines. Among all the tested compounds, the bromo- and chloro- substituted indeno-fused spirooxindole

derivatives **(compounds, 41 & 42)** were found to show selective potency against the MDA-MB-435 cancer cell lines exhibiting GI$_{50}$ value of 1.8 and 2.1 μM respectively. The selected compounds were also screened against the normal Vero monkey cell line, which showed good to excellent selectivity against inhibition of cancer cells.

R=Cl, Br

compound 41   compound 42
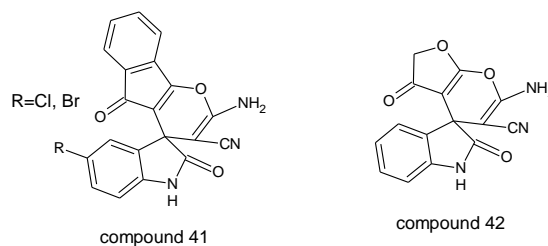
CONCLUSIONS

Due to aforementioned diverse structural features, indole ring is considered as a chief scaffold existing in various bioactive molecules which are known to prevent proliferation and invasion of many cancer cells and these derivatives have arisen as gifted core that need further expansion to obtain more potent and selective cytotoxic agents. It can be concluded that several indole derivatives such as (a) 3-indolylmethylene-2-indolinones derivatives containing pyridine ring display antitumor activity and interesting results were obtained with halogens, methoxy and dimethylamino groups. (b) Bis-indole derivatives were evaluated against various human cancer cell lines and were mainly found to be active against colon (HCT-15, SW-620) cancer cells. **(c)** (5-((2-(hydroxymethyl)-4*H*-furo[3,2-*b*]indol-4-yl)methyl)furan-2-yl)methanol was found to exhibit highly selective anticancer activity against NCI-60 human tumor cell lines and significant inhibitory activity against A498 renal cancer cells. (d) Pyrido[3,4-b]indoles displayed SAR with respect to antiproliferative activity. (e) 1-Naphthyl at C-1 combined with methoxy at C-6 (1-naphthyl-6-methoxy-9H-pyrido[3,4-b]indole) provided the best antiproliferative activity. (f) The indole hybridized diazenyl derivatives, Compound 16 (X=Y=R=R^2=H, R^1=4-COOH) and compound 17 were found to be active against breast cancer cell line and human colon carcinoma cell line having IC$_{50}$ in the range of 19–65 μg/ml. Further, a range of substituted 1*H*-indole-2,3-diones (isatins) were synthesized and studied for their cytotoxicity against the human monocyte-like histiocytic lymphoma (U937) cell line in vitro. SAR studies indicated C$_5$, C$_6$, and C$_7$ substitution greatly enhanced activity with some di- and tri-halogenated isatins giving IC$_{50}$ values <10 μM. These results indicate that di- and tri-substituted isatins may be useful leads for anticancer drug development in the future. Additionally, 5 or 7 substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives were studied for their anticancer activity against HeLa cancer cell lines. Among the synthesized 2-indolinones, compounds with halogen atom (electron withdrawing groups, F, Cl, Br) at C5 position showed the most potent activity. Similarly, various Spiro-indole derivatives have been synthesized viz. Spiro [3*H*- indole-3,2'-thiazolidine]-2,4'(1*H*)-diones, Spiro[indolepyranopyrrole], Spiro[pyrrolidine-3,3'-oxindole], Spiro[indole-3,5′-isoxazolidin]-2(1*H*)-one which show promising anticancer activity. Spiro-indoles, with C-3 as Spiro atom are one of the most important constituent of many drug molecules and can act as precursors for the synthesis of novel bioactive heterocyclic moiety containing varied rings incorporated at C-3 of indole ring. This gives tremendous scope for the synthesis of novel pharmacodynamic indole heterocycles.

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