International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.15 | Issue 1 | Jan - Mar -2026

www.ijrpp.com

ISSN: 2278-2648

DOI : https://doi.org/10.61096/ijrpp.v15.iss1.2026.506-517

Review

Indole as Anticancer Drug

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Published on:
27.03.2026

Published by:
Futuristic Publications

Abstract

Nitrogen-containing heterocycles play a central role in medicinal chemistry, particularly in the development of anticancer therapeutics. Among these, the indole nucleus has attracted sustained interest owing to its structural versatility, favorable physicochemical properties, and ability to interact with diverse biological targets. A wide range of indole-based compounds, including natural products, semi-synthetic analogues, and fully synthetic derivatives, have demonstrated significant antiproliferative activity across multiple cancer models. The anticancer effects of indole derivatives arise from their capacity to modulate key molecular pathways involved in tumor growth and survival, such as kinase-mediated signaling, epigenetic regulation, DNA-processing enzymes, and microtubule dynamics. Clinically approved drugs such as vincristine and vinblastine exemplify the therapeutic relevance of this scaffold and continue to inspire the design of next-generation indole analogues with improved selectivity and pharmacokinetic performance. This review highlights recent advances in indole-based anticancer agents, emphasizing their mechanisms of action, structural diversity, and future potential in oncology drug discovery.

Keywords: Antiproliferative activity, kinase-mediated signaling, epigenetic.

1. INTRODUCTION

The indole heterocycle, historically derived from natural indigo dyes, has evolved into one of the most widely explored structural motifs in contemporary drug discovery. Its bicyclic framework, incorporating

1.1. Indole as anticancer drug

a nitrogen atom within an aromatic system, enables favorable interactions with a variety of biological macromolecules. As a result, indole-containing compounds are frequently encountered among approved pharmaceuticals, particularly in the field of oncology.

Cancer remains a major global health challenge, characterized by uncontrolled cell division, resistance to programmed cell death, and the ability to invade distant tissues. Despite advances in surgery, radiotherapy, and chemotherapy, treatment resistance and systemic toxicity continue to limit therapeutic success. Consequently, the identification of novel chemical scaffolds capable of selectively targeting cancer-associated pathways remains a priority in medicinal chemistry.

Heterocyclic compounds have emerged as essential components of many modern anticancer agents due to their structural diversity and target adaptability. Within this class, indole stands out because of its balanced lipophilicity, hydrogen-bonding capacity, and planar aromatic nature, which together facilitate strong and selective binding to enzymes, receptors, and nucleic acids involved in tumor progression. Numerous studies have shown that indole derivatives can interfere with cancer development through multiple mechanisms, including inhibition of kinase signaling cascades, disruption of microtubule assembly, induction of cell-cycle arrest, and activation of apoptotic pathways.

Given its broad biological relevance and proven clinical success, the indole scaffold continues to serve as a valuable platform for the development of innovative anticancer agents. This review discusses the significance of indole-based compounds in cancer therapy, highlighting their structural features, mechanistic diversity, and emerging trends in rational drug design.

1.2. Indole as Anticancer Agent

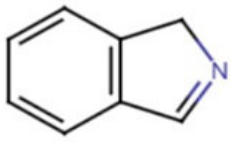
Natural indole alkaloids (for example, from Catharanthus roseus) are first isolated and then chemically modified (semi-synthetically process) to obtain drugs such as vincristine and vinblastine. Synthetic methods like Fischer indole synthesis, where phenylhydrazines react with aldehydes or ketones under acidic conditions, are used to prepare substituted indoles. Other important synthetic routes include the Bartoli indole synthesis, Madelung synthesis, and the Leimgruber-Batcho method.

Indole derivatives appear to play an important role in cancer therapy by acting through multiple mechanisms. Their activities include cell-cycle arrest, aromatase inhibition, and blockade of the NFkB/PI3K/Akt/Mtor pathway, all of which contribute to their promising anticancer potential.

Within the indole class, 2-arylindoles stand out as particularly promising leads for drug development. Derivatives of 2-arylindoles show antibacterial, anticancer, antioxidant, anti-inflammatory, antidiabetic, antiviral, antiproliferative, and antibacteriolytic activities, among others.

Several clinically used anticancer drugs contain indole as a key scaffold. Example include vincristine and vinblastine (used in leukemias, lymphomas, testicular cancer, breast cancer, and lung cancer), sunitinib (renal cell carcinoma and gastrointestinal stromal tumors), pazopanib (renal cell carcinoma and soft- tissue sarcoma), Osimertinib (EGFR-mutant non-small-cell lung cancer), alectinib (ALK-positive lung cancer), brigatinib (ALK-positive metastatic NSCLC), anlotinib (lung and thyroid cancers), nintedanib (lung cancer and idiopathic pulmonary fibrosis-associated tumors), indirubin (leukemia), and vinorelbine (breast and lung cancer).

1.3. Structure of Indole

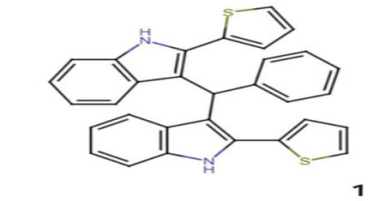


- IUPAC name: 1H-Indole
- MOLECULAR FORMULA: C8H7N

1.4. Derivatives of Indole

Docking results ensured the potency as anticancer agents especially in colo-rectal cancer and showed the possible mechanism through which these agents may exert their anticancer effect. Among the tested derivatives, this compound demonstrated superior antiproliferative activity against MCF-7 breast cancer cells, as reflected by its low IC_{50}

= 10.5±0.07.

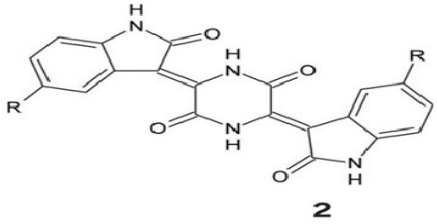


1

MCF-7 cancer cell-line
IC_{50} = 10.5±0.07µM

5-(1H-indolo[3,2-b]benzo[d]thiophen-12-yl)-2-phenyl-1,3-thiazole

The synthesized bis-isatin-piperazine-2,5-dione derivatives exhibited promising anticancer activity, with many analogues displaying IC_{50} values in the range of 1–10 µM against common human cancer cell lines such as MCF-7, HeLa, HCT-116, and HepG2. Unsubstituted derivatives (R = H) showed moderate potency (IC_{50} 10–50 µM), while those bearing electron-withdrawing groups (Cl, F, NO2) at the 5- or 6-position of the indole ring achieved sub-micromolar activity.

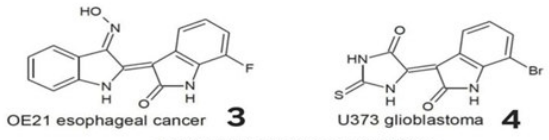


2

MCF-7, HeLa,
HCT-116, and HepG2 cancer cell-lines
IC_{50} =1–10 µM

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

A series of isatin-based heterocyclic compounds were synthesized (compounds 3 & 4) 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. Eldehna et al synthesized a series of 4/3- ((4-oxo-5-(2-oxoindolin-3-ylidene)thiazolidin-2- ylidene) amino)benzenesulfonamides and evaluated their antiproliferative activity against breast cancer MCF-7 and colorectal cancer Caco-2 cell lines.

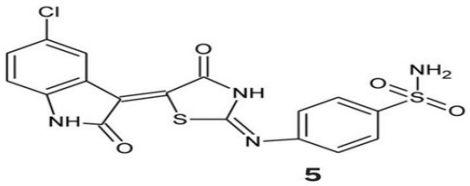


OE21 esophageal cancer 3 U373 glioblastoma 4

apoptosis-resistant cancer cell lines

IC_{50}=9.2µM IC_{50}=4.7µM

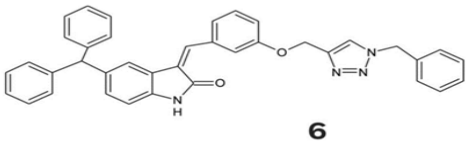
It emerged as the most potent against MCF-7 cells (IC_{50} = 3.96 ± 0.21 µM) and mechanistic studies indicated activation of mitochondria- mediated apoptotic pathways, supported by modulation of pro- and anti-apoptotic proteins and increased caspase activity.



5

MCF-7 cells
IC_{50} = 3.96 ± 0.21 µM

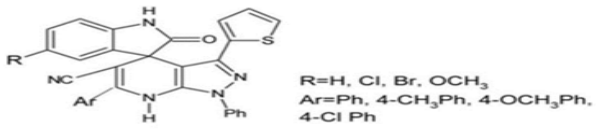
Compound proved the most potent among tested compounds against DU145 cells (IC_{50} = 3.7 ± 0.05 µM) and induced apoptosis in these cells. Furthermore, the 3-hydrazinoindolin-2-one derivative of isatin serves as a promising pharmacophore for anticancer activity and has been extensively reviewed.



6

DU145 cell-line
IC_{50} = 3.7 ± 0.05 µM

Patravale et al. described a facile, sustainable, catalyst-free, and bio- oriented multicomponent method for synthesizing 2-amino-3- cyanospiro[5H-indeno[1,2-b]pyran-4,3′-indoline]-2′,5-dione from isatin, malononitrile, and 1,3-indandione. They evaluated these compounds against breast carcinoma cell lines (MCF-7, MDA-MB- 435) and normal Vero monkey cells.

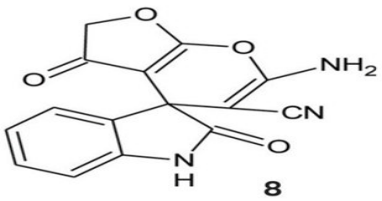


R=H, Cl, Br, OCH_3
Ar=Ph, 4-CH_3Ph, 4-OCH_3Ph, 4-Cl Ph

7

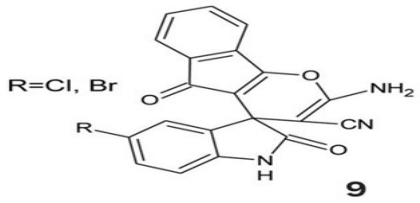
MCF-7,
MDA-MB-435 and
Normal Vero monkey
cells

Compounds 8 and 9 and chloro-substituted indeno-fused spirooxindoles—exhibited selective potency against MDA-MB-435 cancer cells, with GI_{50} values of 1.8 µM and 2.1 µM, respectively. These compounds also showed good to excellent selectivity when screened against the normal Vero monkey cell line.



8

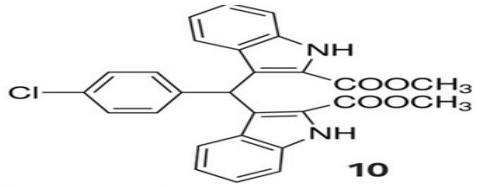
MDA-MB-435 cancer
cells
IC_{50} =1.8 µM



9

MDA-MB-435 cancer cells
GI$_{50}$ values 2.1 µM

It is a potential anticancer agents due to their ability to interact with DNA or enzymes via π-stacking and hydrophobic effects from thiophene and indole rings. Analytical characterization typically involves NMR (e.g., characteristic =CH proton around 5.8-6.2 ppm), IR (NH stretch ~3400 cm⁻¹), and HRMS. For similar chlorinated bis-indoles (e.g., 3b with Cl at indole position 4), IC50 values ranged from 3–8 µM in HL60 cells and 15–30 µM in other leukemic lines via MTT assays.

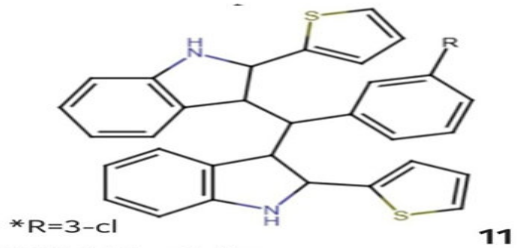


10

HL60 cancer cells
IC$_{50}$ =3–8 µM
Leukemic cancer cell-lines
IC$_{50}$ =15–30 µM

3, 3′-((3-chlorophenyl)methylene)bis(2-(thiophen-2-yl)-1H-indole) (4c)

All new compounds were initially tested at a single dose of 100 µg/ml against this panel of 5 human tumor cell lines indicated that the compounds under investigation exhibit selective cytotoxicity against HCT-116 cell line and compound showed potent anticancer activity against HCT-116 cell line with the inhibitory concentration IC50 = 11.9± 0.05 µM/ml and RPE-1 cells (IC$_{50}$ =28.61±0.02µM/ml).

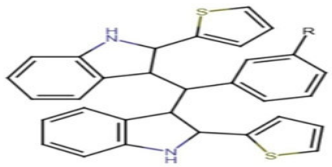


*R=3-cl

11

HCT-116 cell-line
IC$_{50}$ =11.9± 0.05 µM/ml
RPE-1 cancer-cells
IC$_{50}$ =28.61±0.02µM/ml

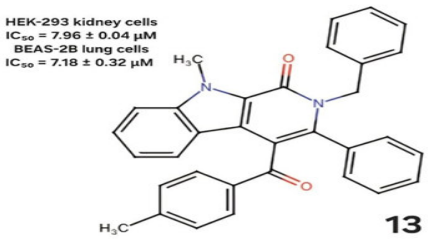
Among the tested derivatives, this compound demonstrated superior antiproliferative activity against MCF-7 breast cancer cells, as reflected by its low (IC$_{50}$ = 7.1±0.07µM/ml) and RPE-1 cells (IC$_{50}$ = 91.85±1.3 µM/ml).



12

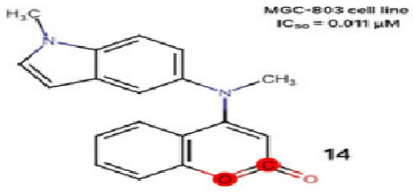
*R = 4-F
MCF-7 cancer-cells
IC_{50} = 7.1±0.07µM
RPE-1 cancer-cells
IC_{50} = 91.85±1.3 µM/ml

Compound 13 shows IC_{50} values of 7.96 ± 0.04 µM in normal HEK- 293 kidney cells and 7.18 ± 0.32 µM in BEAS-2B lung cells, revealing a ~10-fold selectivity for the highly aggressive MDA-MB-231 breast cancer cells. Further studies confirmed that compound 9c triggers cell cycle arrest in MCF-7, 4T1, and MDA-MB-231 breast cancer cells, resulting in dose-dependent apoptotic cell death.



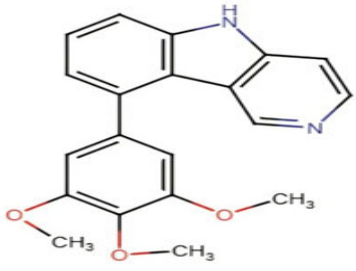
13

Compound 14 displayed the most potent anticancer activity, especially against the gastric cancer MGC-803 cell line (IC_{50} = 0.011 µM). It also showed strong inhibition across multiple cancer cell lines, with IC_{50} values <0.1 µM in 17 lines and <0.05 µM in 8 of them. Additionally, the compound potently inhibited tubulin polymerization (IC_{50} = 2.46 µM) and suppressed key MAPK pathway kinases involved in cancer progression.



14

Compound 15 which demonstrated the most potent antiproliferative activity against HeLa cells with an IC50 value of 8.7 µM. This compound effectively inhibited tubulin polymerization and disrupted the microtubule network, as confirmed by immunofluorescence staining.

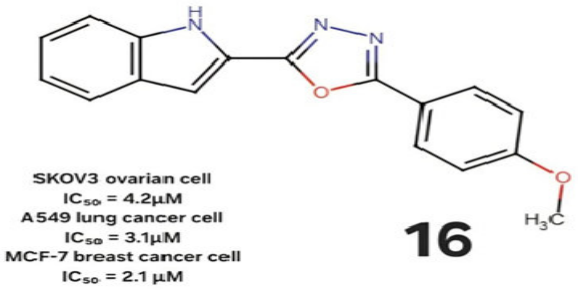


HeLa cell line
IC_{50} = 8.7µM

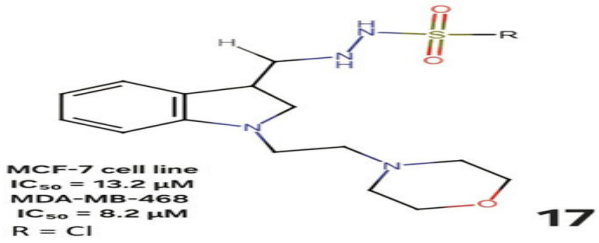
15

Boda et al. synthesized indole-1,3,4-oxadiazole hybrids and assessed their anticancer activity and tubulin polymerization inhibition. Compound 10 emerged as the most potent, with IC_{50} values of 4.2 µM (SKOV3

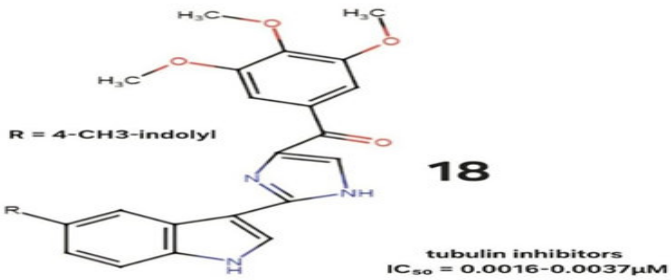
ovarian), 3.1 µM (A549 lung), and 2.1 µM (MCF-7 breast) cancer cells. It also exhibited superior tubulin inhibition (IC_{50} = 0.48 µM).

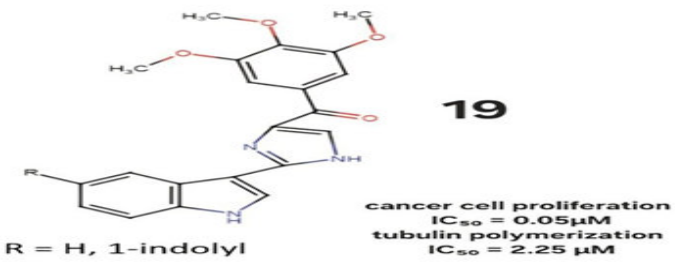


The chemotype 4-chloro-N′- ((1-(2- morpholinoethyl)- 1H- indol-3yl)methylene) benzenesulfonohydrazide (5f) potently inhibited MCF-7 and MDA-MB-468 breast cancer cells, with IC_{50} values of 13.2 µM and 8.2 µM, respectively. Compound 17 proved nontoxic to HEK-293 noncancerous cells across the tested concentrations, highlighting the selective antiproliferative activity of such chemotypes against cancer cells.

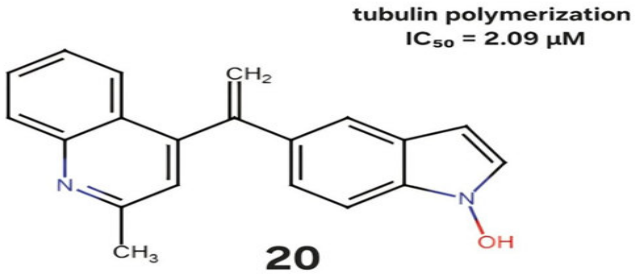


Wang et al. (2019) identified indole-imidazole hybrids 18 and 19 as potent tubulin inhibitors (IC_{50} 0.0016–0.0037 µM), 2–3 times more active than ABI-231, with SAR showing indolyl rotation impacts cytotoxicity; intraperitoneal 30 mg/kg dosing reduced tumor growth by 83.8% and weight by 62.8%. Benzimidazole-indole derivative 8 also potently inhibited cancer cell proliferation (average IC_{50} 0.05 µM) and tubulin polymerization (IC_{50} 2.52 µM).

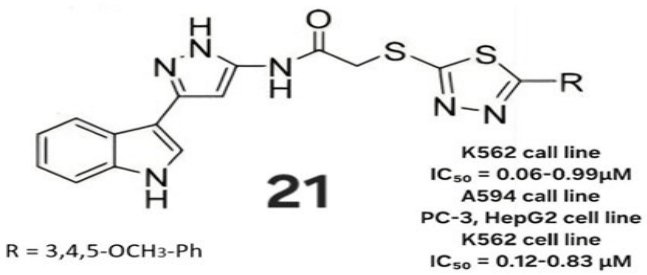




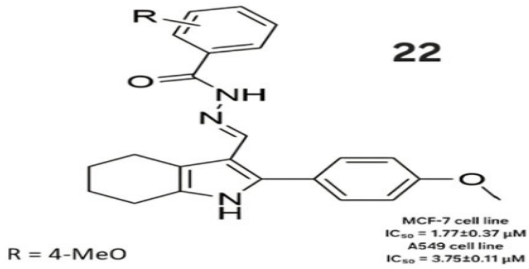
Quinoline-indole derivative, targeting tubulin's colchicine binding site, potently inhibited cancer cell lines (IC_{50} 2–11 nmol/L or 0.002–0.011 μM) and tubulin polymerization (IC_{50} 2.09 μM).



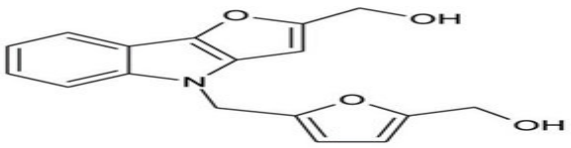
Compound 21 exhibited potent antitumor activity against K562 (IC_{50} 0.06–0.99 μM), A549, PC-3, HepG2, and K562 cells (IC_{50} 0.12–0.83 μM). It demonstrated 82-fold superior potency to gefitinib against A549 cells and 1225-fold greater activity than 5-fluorouracil against K562 cells.



2-phenyl-4,5,6,7-tetrahydro-1H-indole derivatives were evaluated as anticancer agents and tubulin polymerization inhibitors. They showed antiproliferative activity against MCF-7 (breast) and A549 (lung adenocarcinoma) cell lines in vitro. SAR analysis identified compound 7b (4-methoxylphenylhydrazone) as most potent, with IC_{50} values of 1.77 ± 0.37 μM (MCF-7) and 3.75 ± 0.11 μM (A549).



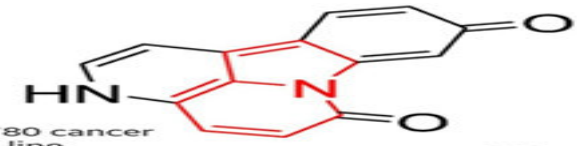
Zhuang et al. synthesized 2,4-disubstituted furo[3,2-b]indole derivatives, evaluated their anticancer activity, and determined SARs. Compound 7, (5-((2-(hydroxymethyl)-4H-furo[3,2-b]indol-4-yl)methyl)furan-2-yl)methanol, showed high selectivity against NCI- 60 human tumor cell lines and potent inhibition of A498 renal cancer cells.



23

A498 cancer cell-line IC_{50}=0.21µM
Colo 205 cancer cell-line IC_{50}=31.1µM

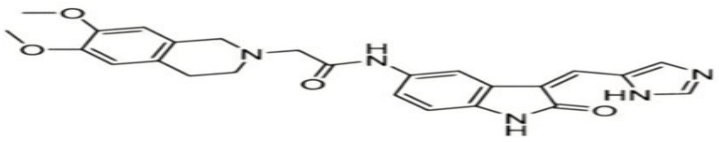
Ovarian cancer ranks as the eighth most common cancer in women and the 18th overall. The natural β-carboline alkaloid 9-Hydroxycanthin-6- one, isolated from Ailanthus altissima stem bark, shows potent antiproliferative effects (MTT assay) against A2780, SKOV3, and OVCAR-3 ovarian cancer cells with IC_{50} values of 17.4 ± 1.1, 13.8 ± 0.6, and 18.8 ± 0.7 µM, respectively. It induces apoptosis by activating caspases-3, -8, and -9 while elevating intracellular ROS levels.



24

A2780 cancer cell-line IC_{50} =17.4 ± 1.1µM
SKOV3 cancer cell-line IC_{50} =13.8 ± 0.6µM
OVCAR-3 ovarian cancer cell-line IC_{50}=18.8 ± 0.7µM

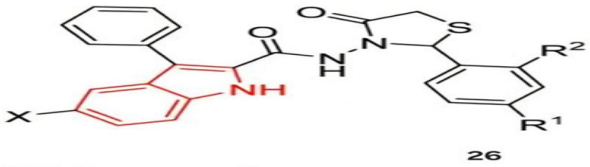
Compound 25 effectively reduced the viability of two temozolomide- resistant human GBM cell lines, ANGM-CSS and U118MG, in a concentration-dependent manner, with GI50 values ranging from 3.98 to 29.93 µM. Notably, its drug-likeness and high CNS multiparameter optimization (CNS MPO) score indicate excellent blood-brain barrier (BBB) penetration potential.



25

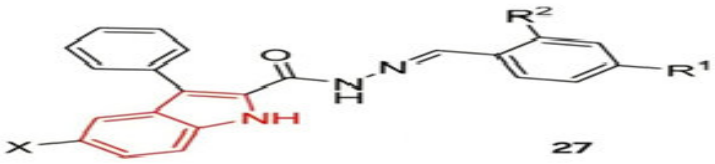
GBM cell-line,
ANGM-CSS cell-line,
U118MG cell-line
GI50=3.98 -29.93µM

Indole-2-carbohydrazones (Compound 26) were synthesized by reacting indole-2-carbohydrazides with aromatic aldehydes, followed by cyclization to yield thiazolidines (Compound 27).Compounds with X = Cl, R1 = CF3 or CN, and R2 = H exhibited strong antiproliferative activity against MCF-7 cells (IC50 = 0.42 ± 0.06 µM and 0.17 ± 0.02 µM, respectively; SRB assay), compared to combretastatin A-4 (IC50 = 0.016 ± 0.003 µM). These agents also inhibited tubulin polymerization effectively (IC50 = 1.7 ± 0.6 µM and 1.4 ± 0.02 µM), nearing the reference standard combretastatin A-4 (IC50 = 1.2 ± 0.08 µM).



26

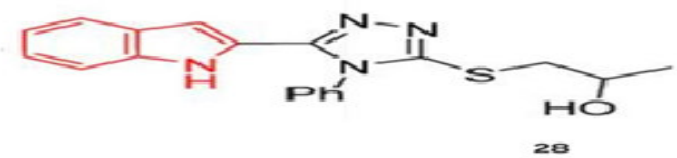
MCF-7 cancer cells
IC_{50} =0.42 ± 0.06 µM
Tubulin polymerization
IC_{50}= 1.7 ± 0.6 µM



27

MCF-7 cancer cells
IC_{50} = 0.17 ± 0.02 µM
Tubulin polymerization
IC_{50}= 1.4 ± 0.02 µM

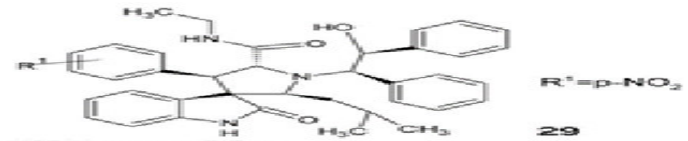
Compound 28 reveals better activity/inhibitory properties against PARP-1 "poly(ADP-ribose) polymerase-1" (IC50 = 0.35 ± 0.05) relative to olaparib (standard reference/drug IC50 = 1.8 × 10−3 ± 0.0001 µM). PARP-1 is a key enzyme in DNA repair. It represents an important target in combating oncology in breast cancer cells and is safe against normal cells with lethal mode selectivity.



28

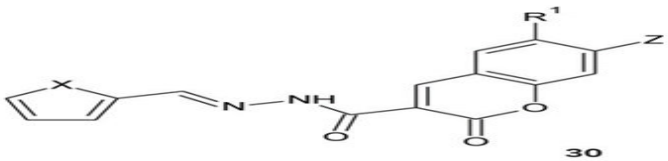
PARP-1 "poly(ADP-ribose) polymerase-1
Breast cancer cell-line
IC50 = 0.35 ± 0.05 µM

Konyar et al. synthesized, characterized, and evaluated the anticancer activity of spiro[pyrrolidine-3,3'-oxindole] derivatives. Cytotoxic effects were assessed on Huh7, MV, HCT116, and MCF7 cancer cell lines using the NCI-60 Sulforhodamine B assay. The compounds generally exhibited stronger activity against MCF7 and HCT116 cells, with compound showing the most potent inhibition: IC_{50} values of 4.8 µM (MCF7), 3.9 µM (HCT116), 14.9 µM (MV), and 8.2 µM (Huh7).



29

MCF-7 cancer cell-line
IC_{50}=4.8 µM
HCT-116 cancer cell-line
IC_{50}=3.9 µM
MV cancer cell-line
IC_{50} =14.9 µM
Huh-7 cancer cell-line
IC_{50}=8.2 µM



30

Panc-1cells
IC_{50}=6.50±0.16
Hep-G2 cells
IC_{50}=3.60±0.63

2. Future Perspective

- AI-designed polypharmacology: Future indole-based analogues may be designed using deep generative and graph-based computational models to rationally target multiple cancer- associated pathways to deliberately hit rational target constellations (e.g., VEGFR2/PD-L1, kinase/HDAC, or tubulin/topoisomerase), turning indole into a core for designed polypharmacology rather than single-target drugs.
- Tumor- and patient-specific tuning: Multi-omics and CRISPR screening can identify pathway "signatures" for each cancer subtype, after which virtual libraries of indole hybrids (indole– azole, indole–imidazole, indole–hydrazone, etc.) are optimized in silico for that signature, enabling subtype- and even patient-tailored lead series.
- Resistance-adaptive hybrids: Combining indole with second pharmacophores into single molecules (e.g., kinase–PARP, kinase–immunomodulator hybrids) offers a strategy to pre-empt common escape routes such as bypass signaling and DNA-repair up-regulation, especially in tumors already resistant to first-generation indole drugs like sunitinib, osimertinib, or alectinib.
- Green and rapid synthesis: Modern one-pot and green synthetic approaches to indole cores, coupled with automated parallel synthesis, will allow rapid physical realization of AI-proposed structures and fast SAR cycles focused on ADMET, brain penetration, and oral bioavailability, which are all already strengths of marketed indole anticancer agents.

3. Conclusion

Indole has progressed from a commonly encountered heterocyclic motif to a privileged and highly adaptable scaffold underlying numerous clinically successful anticancer agents, that anchors many of today's clinically used anticancer drugs and numerous preclinical candidates. The unique ability of the indole nucleus to engage diverse cancer-relevant targets (kinases, tubulin, topoisomerases, epigenetic enzymes, and apoptosis pathways), together with its favorable physicochemical and pharmacokinetic properties, firmly justifies its selection as a starting moiety in anticancer drug design. Looking ahead, integration of indole chemistry with AI-driven, multi-target design, hybrid scaffolds, and green, high-throughput synthesis is expected to deliver next-generation, polypharmacological and patient-tailored anticancer agents capable of overcoming resistance and toxicity limitations of current therapies. Consequently, the continued exploration of rationally engineered indole derivatives is likely to play a central role in shaping future precision oncology.

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