

**RECENT ADVANCES IN THE SYNTHESIS OF INDOLE-BASED SCAFFOLD AND
THEIR ANTI-CANCER THERAPEUTIC APPLICATIONS****Saumya Rai¹, Dr. Shobhit Prakash Srivastava*¹**¹Research Scholar, Dr. M.C. Saxena College of Pharmacy Lucknow Uttar Pradesh 226101, India.¹Professor and Director, Dr. M.C. Saxena College of Pharmacy Lucknow Uttar Pradesh 226101, India.***Corresponding Author: Dr. Shobhit Prakash Srivastava**

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ABSTRACT

The indole scaffold represents a privileged structural motif in medicinal chemistry, celebrated for its remarkable chemical versatility, biological ubiquity, and clinical relevance. This review provides a comprehensive analysis of the recent research on the indole nucleus, emphasizing its physicochemical properties, reactivity patterns, and capacity to interact with a wide array of biological targets. Indole is one of the naturally occurring nitrogen-containing bicyclic heterocyclic ring systems where benzene and pyrrole rings are fused. It has been demonstrated to exhibit versatile biological activities. The indole scaffold regulates many proteins and genes which play a significant role in cancer development. US Food and Drug Administration (FDA) approved anti-cancer drugs having indole rings in their structure including alectinib, sunitinib, osimertinib, anlotinib, and panobinostat. Several research studies have focused on developing new indole derivatives for the treatment of cancer. Various studies have shown that indole C-3 atom; π -bond in between C-3 and C-2; and nitrogen atom can be substituted with varieties of other structural fragments to overcome the problem of drug resistance and toxicity. The anti-cancer potential of various indole derivatives, their synthetic strategies, and) for the further development and advancement of anticancer therapy. The article also summarizes how different proteins like TRK, VEGFR, EGFR, CDKs, ERK, BRD4, genes like Bcl2, intracellular pathways such as PI3K/AKT/mTOR, enzymes like tubulin and topoisomerase II are inhibited by indole derivatives. Synthetic strategies and SAR will help medicinal chemists to design and develop effective indole derivatives as anticancer agents.

KEYWORDS: Indole derivative molecular docking and synthesis of as anticancer. Application. scaffold.**1. INTRODUCTION**

Cancer is the major cause of human mortality second to cardiovascular diseases.^[1] According to the World Health Organization (WHO), 19.3 million new cancer cases are diagnosed and approximately 10 million cancer-related deaths occur every year.^[2] Cancer is defined as uncontrolled cell proliferation and its pathogenesis is complex involving multiple mechanisms that contribute to its development. It includes proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inflammation promoted by tumor, instability of genome and mutation, avoiding immune destruction, reprogramming energy metabolism, inducing angiogenesis, activating invasion, and metastasis. These mechanisms

are the basic ten hallmarks related to cancer.^[3] Numerous factors and biological pathways are involved in the development of cancer. The available conventional cancer therapy is associated with side effects, toxicity, and multidrug resistance.^[4] Indole and its derivatives form a group of interesting pharmacological agents and serve as promising pharmacophoric ring systems in medicinal chemistry research for drug design and development.^[5] The indole derivatives have been reported to possess CoV-2 inhibitory properties^[6], anti-malarial^[7], antimicrobial^[8], and anti-inflammatory^[9] activities, etc. The chemical structures of indole-containing approved marketed drugs for the treatment of various diseases are shown in Fig. 1. Indole heterocyclic ring system possesses significant biological

effects and is present in various natural products including the neurotransmitter serotonin, indole phytoalexins, and auxin, etc.^[10] Some of indole-based synthetic compounds with anticancer activities are utilized in clinics.^[11]

Furthermore, synthetic indole derivatives like sunitinib, a tyrosine kinase inhibitor, have been effectively utilized

as targeted therapies in renal cell carcinoma^[12] and gastrointestinal stromal tumors^[13], showcasing their efficacy in oncology. The versatility of indole scaffolds in interacting with various biological targets, such as kinases, has made them attractive candidates for anticancer drug development, intriguing and engaging researchers in the field.

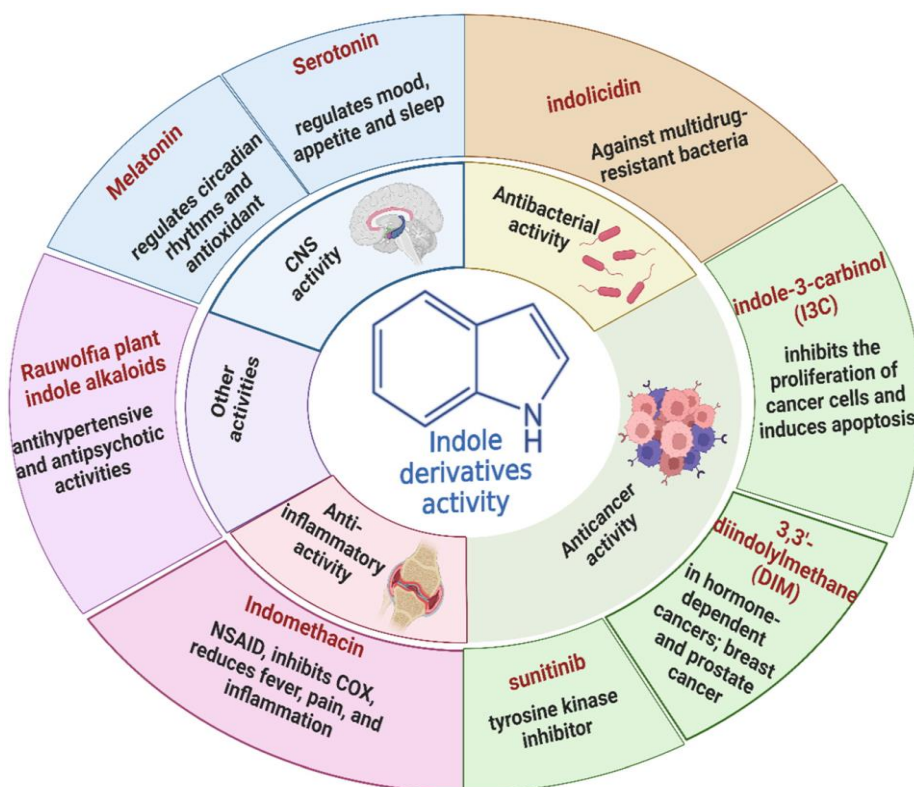
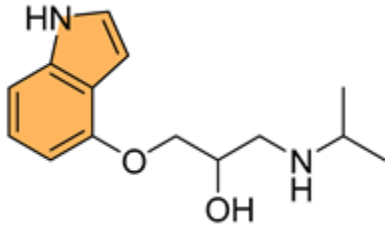
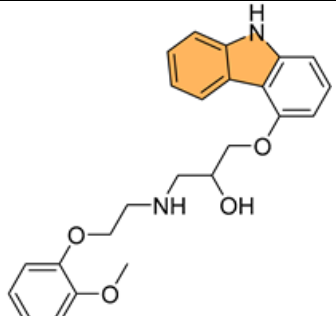
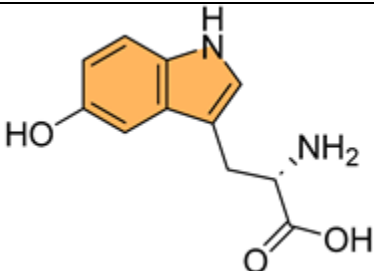
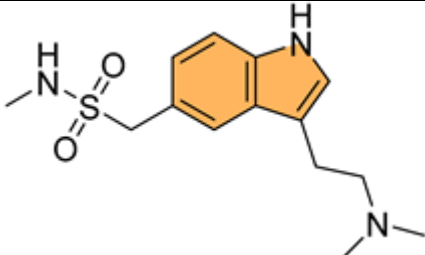
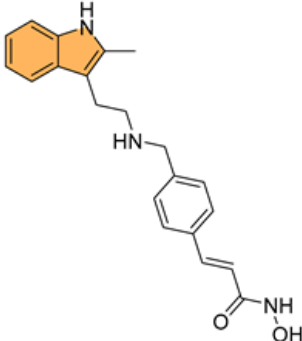
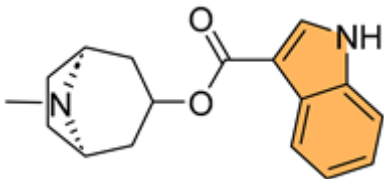
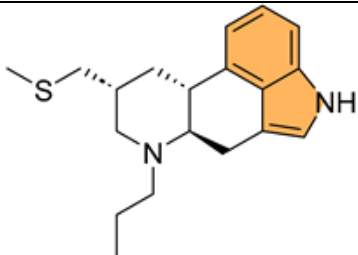
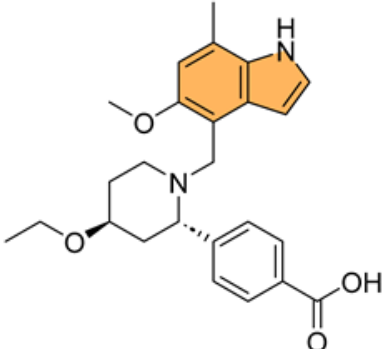
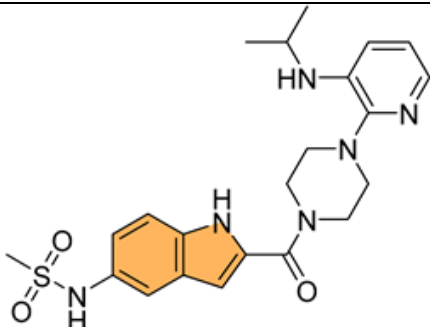
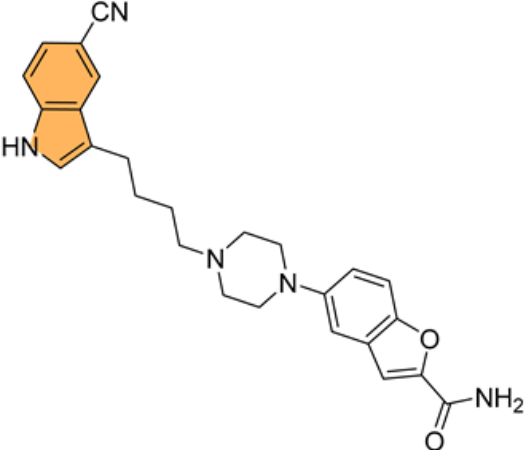
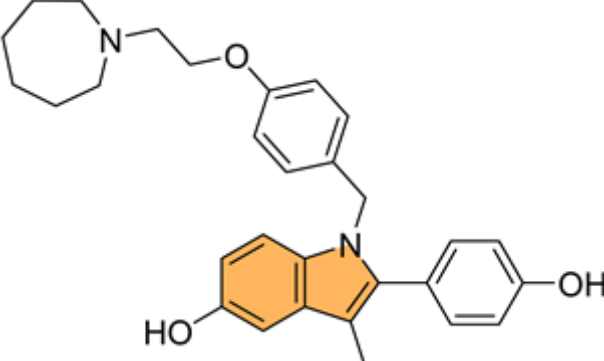
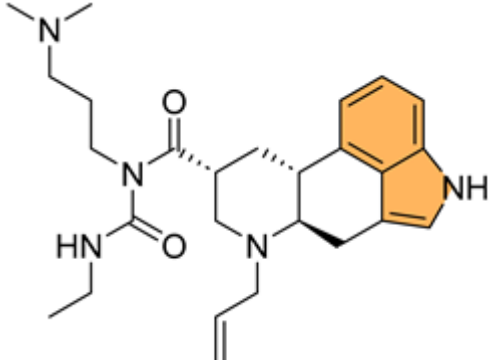
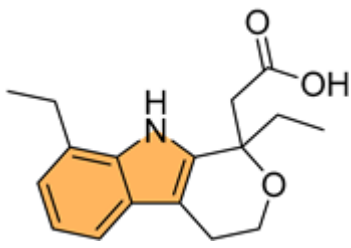


Figure 1: Different natural and commercially available indole derivatives and their biological activities.^[12]

Table 1: Examples of FDA-approved drugs containing indole structures and their therapeutic applications.

Drug Name	Chemical Structure	Indication	Mechanism of Action
Pindolol		Hypertension, angina pectoris. ^[14]	Non-selective beta-blockers decrease heart rate and blood pressure by blocking beta-1 and beta-2 adrenergic receptors. ^[14]
Carvedilol		Hypertension, heart failure, left ventricular dysfunction post-myocardial infarction ^[15]	Non-selective beta-blockers and alpha-1 blockers reduce heart rate, blood pressure, and myocardial oxygen demand. ^[15]

Oxitriptan		Depression, disorders, suppression ^[16] sleep appetite	Precursor to serotonin; increases serotonin levels in the brain. ^[16]
Sumatriptan		Migraine, headaches ^[17] cluster	Selective serotonin receptor agonist (5-HT1B/1D) causes vasoconstriction and reduces neurogenic inflammation. ^[17]
Panobinostat		Multiple myeloma ^[18]	Histone deacetylase inhibitor induces cell cycle arrest and apoptosis in cancer cells. ^[18]
Tropisetron		Nausea and vomiting induced by chemotherapy or surgery. ^[19]	5-HT3 receptor antagonist blocks serotonin receptors in the central nervous and gastrointestinal tract. ^[19]
Pergolide		Parkinson's disease ^[20]	Dopamine receptor agonists stimulate dopamine receptors in the brain. ^[20]
Iptacopan		Paroxysmal nocturnal hemoglobinuria (PNH) ^[21]	Complement factor B inhibitor prevents the formation of the membrane attack complex. ^[21]

Delavirdine		HIV-1 infection ^[22]	Non-nucleoside reverse transcriptase inhibitor (NNRTI) inhibits HIV-1 reverse transcriptase. ^[22]
Vilazodone		Major depressive disorder ^[23]	Selective serotonin reuptake inhibitor (SSRI) and partial agonist at 5-HT1A receptors. ^[23]
Bazedoxifene		Osteoporosis in postmenopausal women ^[24]	Selective estrogen receptor modulator (SERM) mimics estrogen in bones to maintain bone density. ^[24]
Cabergoline		Hyperprolactinemia, Parkinson's disease ^[25]	Dopamine receptor agonist inhibits prolactin secretion. ^[25]
Etodolac		Pain and inflammation ^[26]	Non-steroidal anti-inflammatory drug (NSAID) inhibits cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis. ^[26]

2. Docking Studies

In order to investigate the possible anti-cancer activity of compound 5, we used the crystal structure of tyrosinase from *Bacillus megaterium* (PDB ID: 3NM8), retrieved from the RSCB protein data bank. As illustrated in the compound presented a docking score in the order of -10.86 Kcal/mol which suggested that it could bind to tyrosinase spontaneously, indicating good protein ligand affinity. Enzymatic inhibition can theoretically occur

through the ligand occupancy of the enzyme active site by non-covalent interactions.^[27] Accordingly, compound 5 potentially possesses potent inhibition capacity as it effectively fits into the active site of tyrosinase and forms favorable interactions with its amino acid residues. This includes hydrogen bonds with Lys47, Π -alkyl, and alkyl-alkyl with Ala 44, Ala 40, Lys 47, Thr 267, Ile 139, and Phe 48 as well as an amide- Π stacking interaction with Ile 39, as shown in.

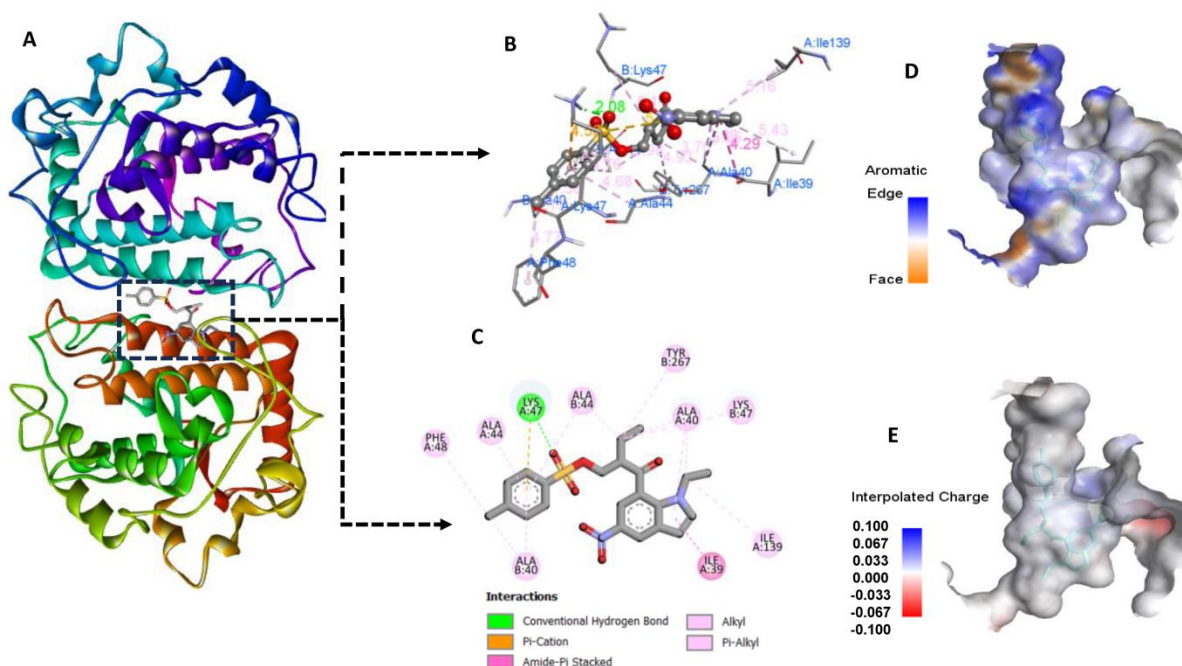


Figure 2: (A) Compound 5 fits in the active site of tyrosinase; (B,C) 3D and 2D representations of interacting residues; (D,E) surface representations of 5 within tyrosinase active site.^[27]

Table 2: Docking results of compound 5.^[27]

Compound	Docking Score (Kcal/mol)	Interactions	Interacting Residues
4	-8.53	H-bond Π -alkyl Alkyl-alkyl	Ala 44 Lys 47 Ala40, Phe 48
5	-10.86	H-bond Π -alkyl Alkyl-alkyl Amide- Π stacking	Lys 47 Ala 44, Ala40, Lys 47, Thr267 Ile 139, Phe 48 Ile 39

Furthermore, a significant observation was made when comparing compound 5 with its hydroxy analog compound 4. The introduction of the tosyl group in compound 5 increased its affinity for the target enzyme tyrosinase. This is evidenced by a difference of -2.15 kcal/mol in the docking scores, indicating that compound 5 requires less energy to form a complex with tyrosinase compared to compound 4. Additionally, while the hydroxy group of compound 4 engages in a single interaction with Ala 44 the tosyl group engages in

several interactions with amino acid residues, making the ligand-protein complex more stable. These interactions include the benzene ring of the tosyl group forming π - π and π -alkyl interactions with Ala 44 and Phe 48, as well as the sulfonyl group forming hydrogen bonds with Lys 47. While several N-tosyl indole derivatives are currently reported as antioxidant agents^[28], these findings indicate that O-tosyl indole derivatives also hold promise as effective antioxidant agents.

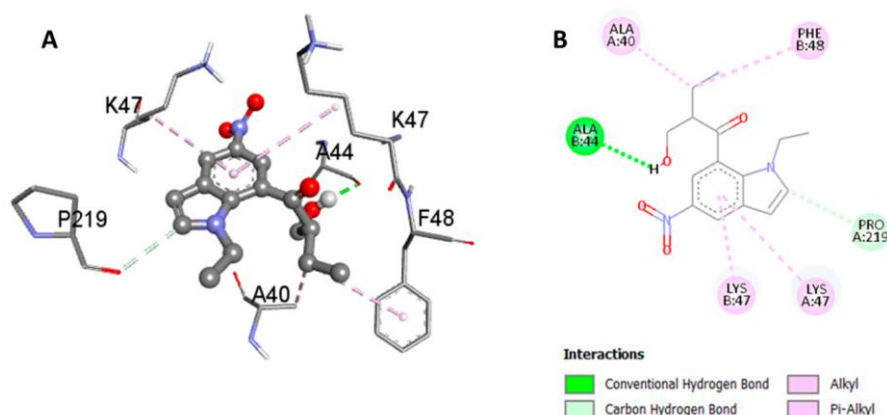


Figure 3: Three-dimensional (A) and two-dimensional (B) representations of interacting residues with compound 4.^[29]

3. INDOLE SYNTHESIS PROCESSES

3.1 Fischer Indole Synthesis^[30]

- This reaction was discovered in 1983 by Emil Fischer and so far remained the most extensively used method of preparation of indoles.
- The synthesis involves cyclization of arylhydrazones under heating conditions in presence of protic acid or lewis acids such as ZnCl_2 , PCl_3 , FeCl_3 , TsOH , HCl , H_2SO_4 , PPA etc.
- The starting material arylhydrazones can be obtained from aldehydes, ketones, keto acids, keto esters and diketones etc.

- Reaction produces 2,3-disubstituted products. Unsymmetrical ketones can give a mixture of indoles.

3.2 Reissert Synthesis^[31]

- Reissert indole synthesis is a multistep reaction:
- Step 1: Base catalysed condensation of *o*-nitrotoluene with oxalic ester (methyl oxalate) to give *o*-nitrophenylpyruvic ester
- Step 2: Reduction of the nitro group to an amino group,
- Step 3: Cyclization to indole-2-carboxylic acid
- Step 4: Decarboxylation

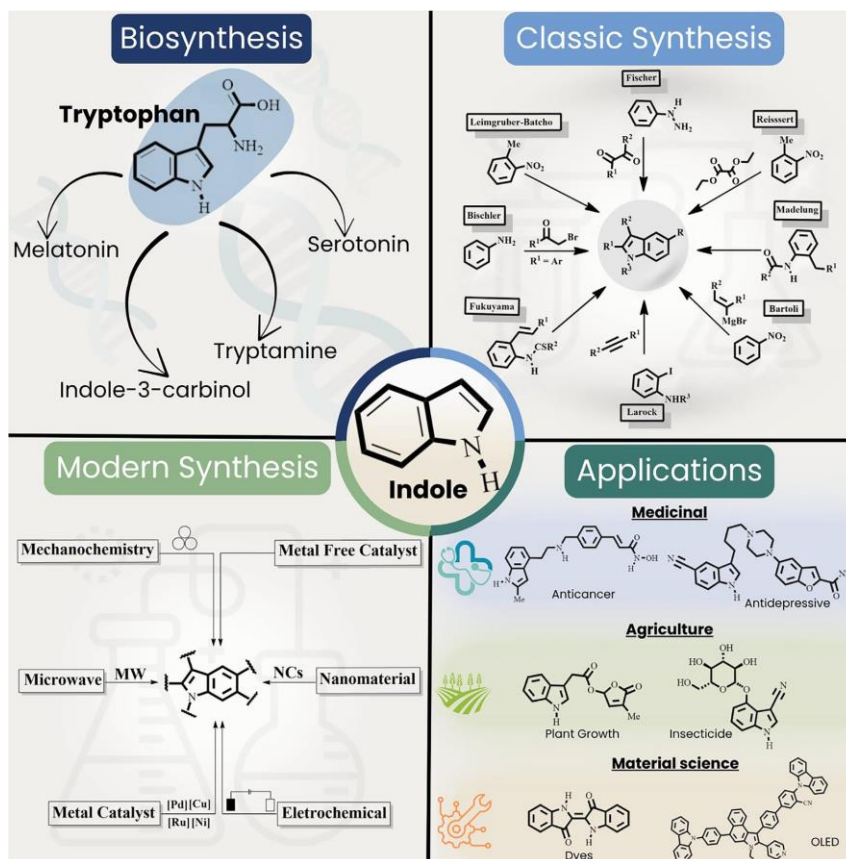


Figure 4.^[32]

4. Anticancer Activity

Cancer remains one of the leading causes of morbidity and mortality worldwide, with an estimated 19.3 million new cases and nearly 10 million cancer-related deaths reported globally in 2020.^[33] The disease's burden is expected to rise significantly in the coming decades, driven by aging populations and increasing exposure to risk factors such as tobacco use, unhealthy diet, and environmental pollutants. Despite advances in cancer treatment, including surgery, radiation, and chemotherapy, the need for more effective and targeted

therapies is paramount.^[34] Indole derivatives have emerged as promising anticancer agents due to their ability to act on different key biological targets such as tubulin^[35], protein kinases, HDAC (Histone Deacetylase), etc. The structural versatility of indoles allows for the design of compounds that can specifically target cancer cells while minimizing toxicity to normal tissues. Here, we highlight recent advancements and key examples of indole derivatives demonstrating significant anticancer activity.^[36]

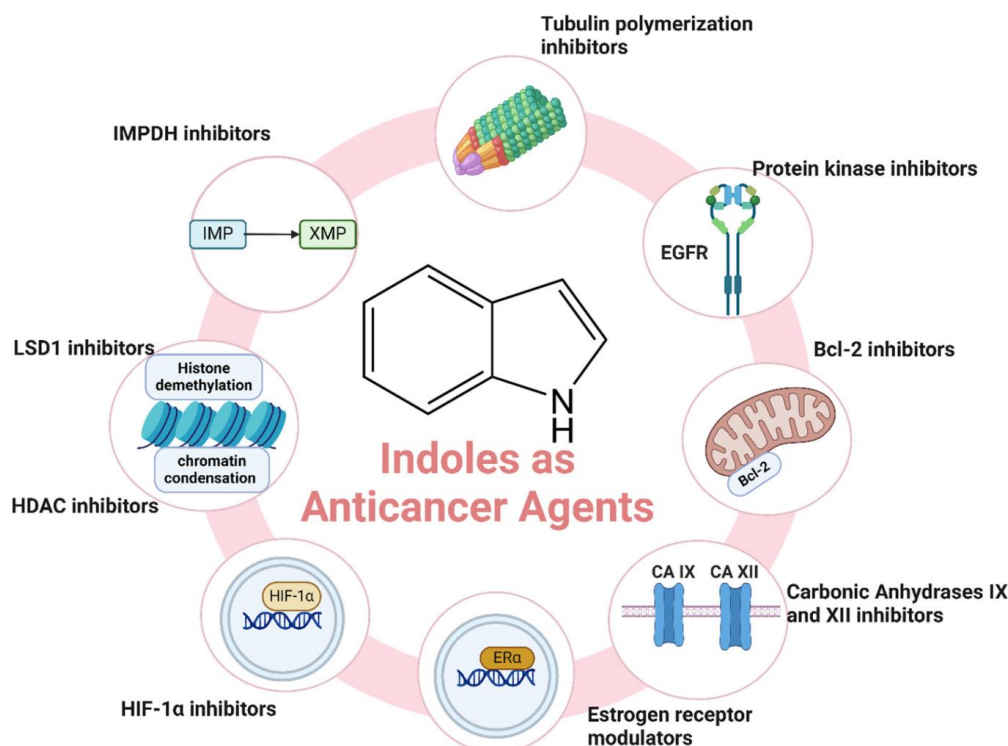


Figure 5: Different mechanisms of indole derivatives as anticancer agents.^[37]

5. Therapeutic Applications

5.1 Oncology

Indole-based compounds have a storied and ongoing role in cancer therapy. Several natural indole alkaloids were among the earliest effective chemotherapeutics and remain in use. The vinca alkaloids, isolated from *Catharanthus roseus* in the 1950s, include vinblastine and vincristine—complex bis-indole compounds (dimeric indole–indoline structures) that bind tubulin and inhibit microtubule polymerization, causing mitotic arrest of cancer cells. Vincristine and vinblastine were FDA-approved in the early 1960s and dramatically improved cure rates for leukemias, lymphomas, and other malignancies. Semisynthetic vincristine analogs like vinorelbine and vindesine were later developed to broaden activity and reduce neurotoxicity.^[38] These drugs exemplify how an indole scaffold can interfere with a fundamental process (spindle formation) in rapidly dividing cells. Another renowned natural product is camptothecin, a quinoline-indole alkaloid from *Camptotheca acuminata*. Camptothecin's planar indole-containing structure intercalates into DNA at

topoisomerase I cleavage sites, stabilizing the DNA–enzyme complex and leading to lethal DNA breaks. Its derivatives irinotecan and topotecan are important agents in colorectal and ovarian cancer, respectively.^[39]

Indole-3-carbinol (I3C), found in cruciferous vegetables, represents a nutraceutical approach to oncology. I3C itself is not the active agent *in vivo*—in the acidic stomach, it dimerizes into 3,3'-diindolylmethane (DIM) and other oligomeric products. These indoles have been shown to induce phase I/II drug-metabolizing enzymes, modulate estrogen metabolism (favoring less estrogenic catechol estrogens), and cause cell-cycle arrest and apoptosis in cancer cells. For example, I3C/DIM can downregulate cyclin-dependent kinases and upregulate tumor suppressor p21, particularly in hormone-responsive tumors. Though I3C/DIM are available as supplements and have shown anti-cancer effects in preclinical models of breast, prostate, and colon cancer, clinical evidence is still limited, and high doses are required. Nonetheless, they highlight the potential of indole diet-derived agents as cancer

chemopreventives.^[40,41,42] Several indole derivatives target hormone-related pathways in cancer. Tamoxifen (for breast cancer) is not an indole, but researchers have explored indoles as selective estrogen receptor modulators (SERMs) and as aromatase inhibitors. For instance, some indole3-carboxyethyl piperazines showed SERM activity, and indole-derivatives like aminogluthethimide (though not a true indole) pioneered aromatase inhibition. Indole-structured antiandrogens have also been investigated for prostate cancer. Additionally, as noted earlier, indoleamine 2,3-dioxygenase (IDO1) is an immunosuppressive enzyme often overexpressed in tumors; inhibitors such as indoximod (1-methyl-tryptophan) aim to counteract the “tryptophan starvation” strategy of tumors and restore T-cell activity. Indoximod and analogs entered clinical trials in melanoma and other cancers. While the first major trial of an IDO1 inhibitor (epacadostat, a hydroxyamidine that is not indole-based) in combination immunotherapy did not meet its endpoint, interest remains in modulating the Trp–kynurenine–AhR axis in cancer. Endogenously, accumulations of kynurenine (from Trp via IDO) activate AhR in tumor cells and regulatory T-cells, aiding immune evasion. Indole-based drugs that block IDO or AhR are being explored to tilt the immune balance against tumors.^[43]

In oncology-related indoles, clear structure–activity relationships (SAR) have emerged. Minor substitutions on the indole ring can significantly impact potency and selectivity. For example, N-substitutions and catharanthine modifications in vinblastine/vincristine derivatives modulate efficacy and toxicity. Electron-withdrawing groups and halogenation (e.g., 6-bromoindoles) enhance antiproliferative and antimicrobial activity by altering electronics and lipophilicity. A 5-methoxy group on thiazolidinedione–indole hybrids improved activity against breast cancer cells, likely via favorable electronic and steric effects. The indole scaffold allows extensive derivatization at N-1 and C-2 to C-7, with medicinal chemists also employing heterocyclic bioisosteres (e.g., indazole, benzimidazole) to refine drug-like properties while maintaining target affinity. In conclusion, the indole scaffold’s contribution to oncology spans cytotoxic natural products, targeted kinase inhibitors, hormonal pathway modulators, and emerging immunotherapeutics. Its privileged structure has enabled binding to diverse cancer targets (tubulin, kinases, receptors, enzymes), and ongoing SAR refinements continue to produce novel anticancer leads.^[43]

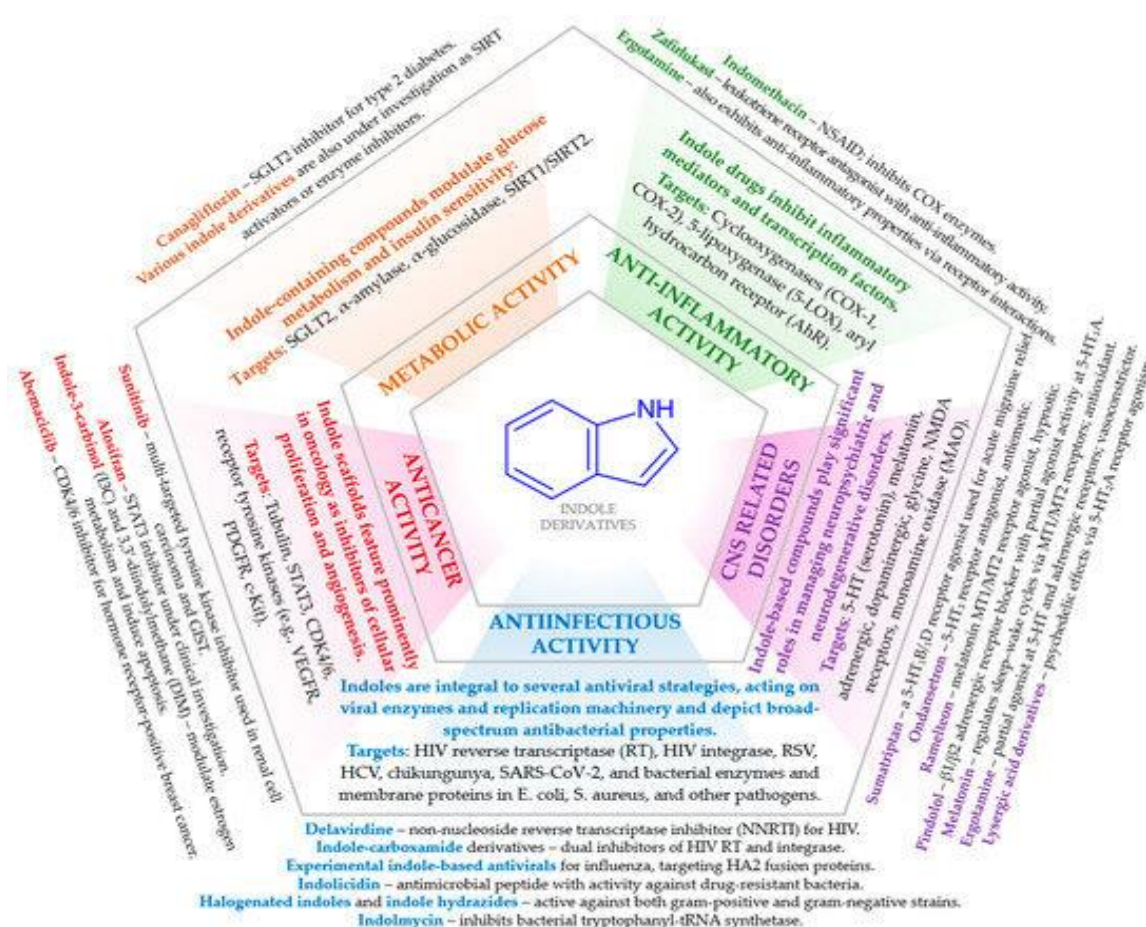


Figure 6: Overview of the main therapeutic domains of indole-containing compounds.

The figure highlights key pharmacological classes (CNS, oncology, anti-infective, metabolic, and antiinflammatory), representative drugs, and their principal molecular targets such as GPCRs, nuclear receptors, enzymes, and ion channels. This schematic representation underscores the structural adaptability of the indole scaffold and its privileged status in drug discovery across diverse disease areas. Figure adapted from.^[44]

6. Limitations and Future Directions

While the indole scaffold is celebrated for its versatility, it is not without challenges. Recognizing these limitations is important for guiding future research and drug development. Each limitation discussed below is paired with optimization strategies and concrete design approaches to mitigate it. Indole is a privileged scaffold known for binding many targets, but this same quality can lead to off-target effects. Indole-based drugs sometimes hit multiple receptors or enzymes, which can cause side effects. For example, an indole compound developed as a kinase inhibitor might unintentionally bind to serotonin receptors or hERG cardiac ion channels, leading to undesirable effects. Achieving high specificity with an indole can be difficult when closely related proteins have binding pockets that readily accommodate indoles.^[45]

7. CONCLUSION

Approved anticancer drugs, while effective, are associated with toxicity and resistance. Despite their toxicity, chemotherapeutic agents are crucial and prescribed due to limited safer alternatives and the pressing need to address cancer incidence and mortality rates. Indole is a potent scaffold with great inhibitory activity against different enzymes and receptors and has emerged as a promising anticancer pharmacophore. Many new drugs that were approved for the treatment of cancer have indole rings as a core motif. There has been significant effort in recent years in synthesizing indole derivatives as targeted therapy against cancer and some are currently under clinical research. However, there remains a critical need to develop more potent and safer anticancer drugs utilizing the versatile indole scaffold. The indole ring because of its structure flexibility can be easily substituted particularly at the C-3 atom; π -bond in between C-3 and C-2; and nitrogen atom to synthesize diverse bioactive compounds. This review article highlights the recent developments of the indole derivatives as inhibitors of BRD4, Bcl-2, CDK, Tyrosine kinase, Tubulin polymerization as potent anticancer agents. The indole-containing compounds act as good BRD4, ERK and topoisomerase inhibitors when the NH of the indole ring is blocked with some substituents. For tyrosine kinase inhibition (EGFR, CDK, VEGFR, TRK, CDK), Bcl-2 and PI3K/AKT/mTOR free nitrogen are more important and substituted at the C-3 carbon. Apart from free nitrogen, the C-2 and C-3 positions of indole are substituted to act as both potent tubulin and topoisomerase II inhibitors. Synthetic strategies, SAR,

and *in silico* studies showing the important interaction within the receptors offer valuable insights for the medicinal chemists and this might help them to design more potent molecules. The continued research on indole derivatives will help the researcher to make advancements in multi-drug therapies and improved cancer treatments in the future.

The indole scaffold's journey in medicinal chemistry is far from over. Its limitations— off-target activities, metabolic quirks, poor solubility, and potential toxicities—are wellrecognized, and each is an active area of research aimed at turning these weaknesses into strengths. As discussed above, researchers are now explicitly linking each challenge with targeted solutions: improved computational modeling, including AI-driven drug design, enables the prediction and rational optimization of indole–target interactions to enhance binding specificity; smart chemistry modifications and prodrug approaches help us sidestep metabolic and solubility issues; and advanced biological models together with pharmacogenomic data enable us to flag and mitigate toxicity risks early.

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