The main biotargets of indole or 2-oxoindole-based hybrids acting as promising antiproliferative agents


Department of Medicinal Chemistry, Faculty of Pharmacy, Minia University, 61519-Minia, Egypt.

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Abstract

Indole moiety is considered a unique core scaffold that can bind with different types of genes and proteins and also has easy synthetic techniques and exclusive chemical characteristics. These characteristics make indole-based scaffolds a prime probe for medicinal chemistry drug research chemists. Hybridization technique utilizing indole moiety could improve the efficacy, combating drug resistance and lowering side-effects of the final compound. Consequently, many indole and 2-oxoindole-based hybrids have been reported recently and entered pre-clinical and clinical studies. But still, more research efforts are essential for a clear understanding of the cancer origin and drug resistance mechanisms in cancer therapy, in addition to getting more achievements in multitargeting drug therapy by developing more potent indole-based scaffolds in the near future. Behind the promising antiproliferative activities of these indole and 2-oxoindole-based hybrids introduced within this review study, there are four main mechanisms which are protein kinases, DNA topoisomerases, histone deacetylase (HDAC), and tubulin polymerization inhibitory activities. Herein, this review will briefly illustrate the newly synthesized indole and 2-oxoindole-based hybrids along with their multiple mechanisms to display their promising antiproliferative activity, which will be a valuable step for more improvement of drug invention and elimination of drug resistance problems’ approaches.

Keywords:
Indole; 2-Oxoindole; Anticancer activity; Protein tyrosine kinases (PTK); DNA Topoisomerases; Tubulin polymerization

* Correspondence: Heba A. Hassan
Tel.: 01068390918; Fax: (+20) 086-236-9075
Email Address: heba.hasan@mu.edu.eg
1. Introduction

Cancer is the most challenging disease, responsible for the highest mortality rate globally after cardiovascular diseases [1–3]. However, developing an optimum special cure for various cancer types remains a serious problem for humanity. In relation, chemotherapy is exposed to failure because of acquired resistance [4]. From 1949 until now, the USFDA organization approved over 150 new drugs for combating cancer spread aggressiveness [4]. Therefore, the invention of new novel anticancer drugs with higher efficacy, selectivity, and more economic becomes a must for researchers. Consequently, the hybridization technique, including using two or more pharmacophores working on two distinct cancer targets, becomes an urgent trend to withstand this fast carcinogenic violence [5–7].

It is commonly comprehended that heterocyclic-based scaffolds represent a valuable source of bio-actives, which could be gained through organic synthesis or natural sources [8–10]. The existence of not less than one heteroatom, such as sulfur, oxygen, and nitrogen, in addition to one carbon atom in the ring is essential to act as hydrogen bond donating or accepting candidates, effectively forming intermolecular hydrogen bonding with bio-targets. Considerably, they can emphasize the lipophilicity and aqueous solubility of drug biomolecules to afford their pharmacological significance [11].

1.1 Indoles and 2-o xoindoles:

Among heterocyclic core scaffolds, indole-based scaffolds have exhibited significant potency in various biological activities as antimicrobial, antiviral, antitubercular, antioxidant, and analgesic activities, to name a few [12, 13]. The indole scaffold is incorporated in various natural alkaloids acting as powerful antitumor agents via their tubulin inhibitory activity, like vinblastine (I) and vincristine (II). Many research scientists have recently focused on incorporating indole as a core scaffold in many compounds owing to its antiproliferative properties. The main cytotoxic mechanisms behind this antitumor character of indole-based compounds are either protein kinases, DNA topoisomerases, histone deacetylase inhibitors, or destabilizing agents for tubulin polymerization. In addition, they may act as apoptosis-triggering agents [14–18].

Additionally, there are various indole-based scaffolds that display versatile biological activities like anti-inflammatory, antibacterial, antiviral, antimalarial, anticonvulsant, and anticancer agents. For instance, indomethacin III is a highly common NSAID used in many inflammatory conditions, such as rheumatoid arthritis [19]. For example, as a leukotriene receptor antagonist, zafirlukast IV is the first orally active indole medication licensed for treating asthma with few side effects, such as headache and GIT disturbance [20]. Indole-based drugs are also used in cardiovascular disorders, such as pindolol V, which is considered a serotonin (5-HT1A) receptor antagonist and has been used for hypertension and depression disorders under the brand name Visken® [21]. Moreover, among the receptor tyrosine kinase inhibitors (RTKIs) that reached the clinics, osimertinib (VI), midostaurin (VII), and lestaurtinib (VIII) are indole-based anticancer agents [13, 22].

The 2-o xoindole chemical structure comprises a benzene ring directly attached to the pyrrole ring and the carbonyl group at the C-2 position with the chemical formula C₉H₇NO (Figure 1a) [23, 24]. 2-O xoindoles, named scientifically as 1,3-dihydro-2H-indole-2-one(s), are an important category of heterocyclic compounds that naturally occur in human body fluids and tissues and as natural products in various plant types [25, 26]. The first oxindole derivative was extracted from the bark of cat claw’s plant species (Uncaria tomentosa) as an alkaloid product incorporated into traditional medicine for treating bacterial and fungal infections, versatile cancer types, peptic ulcers, and some inflammatory diseases. For many decades ago, 2-oxindole-based compounds have acquired significant importance owing to their broad pharmacological activities such as antimicrobial, antiangiogenic, anticancer, antiviral, antileishmanial, antitubercular, antioxidant, and analgesic effects, etc [12]. It is highly common in cancer therapy clinics as multiple kinase inhibitors. A deep view of different structural properties of 2-oxoindole-based kinase hampering agents illustrates three various oxindole frameworks: 3-alkenyl-2-oxoindole, 3-imino-2-oxoindole, and 3,3'-spirocyclic-2-oxoindoles (Figure 1b). Away from their biological valuability, these C₃-substituted-2-oxoindoles are readily obtained owing to well-ascertained synthetic techniques. Most of the 2-oxoindole-based protein kinase inhibitors (PKIs) establish 3-alkenyl-2-oxoindole moiety as a major framework already present in many clinically reported drugs [27]. Specifically, 2-oxoindole derivatives exhibit their cytotoxic antiproliferative activity via acting either as stabilizing or destabilizing agents for tubulin polymerization or as inhibitors for protein kinases, DNA topoisomerases, and histone deacetylase, in addition to acting as apoptosis inducers [12]. In addition to C₃-substituted-2-oxoindoles, substitution on positions 5 and 6 also afforded fundamental kinase inhibition [28, 29]. For instance, sunitinib (IX) and nintedanib (X) are 5- and 6-substituted 3-alkenyl-2-oxoindole-based clinically FDA-approved anticancer drugs used for renal cell carcinoma and adenocarcinoma therapy respectively [30]. Furthermore, naturally, extracted oxindole-based scaffold-like indirubin (XI) has displayed significant CDK inhibition [31]. Therefore, many research and pharmaceutical institutions have shown an obvious interest in developing novel oxindole-based scaffolds with unique pharmacokinetic properties and outstanding biological activities.
inhibitors (EGFR-TKIs), such as gefitinib (XII) and erlotinib (XIII), which were orally active agents that reversibly bonded to EGFR and were more efficient for those patients with sensitive mutation types (L858R or exon 19 deletion) [44, 45]. Unfortunately, the clinical usage of these drugs revealed the drug resistance to these gene mutations, specifically the T790M mutation associated with most NSCLC patients [46]. The 2nd generation EGFR-TKIs were majorly represented by afatinib (XIV), the α,β unsaturated ketone scaffold that could bind irreversibly to the EGFR kinase. Herein, this category of drugs showed powerful therapeutic efficacy in cancer patients with the EGFR T790M mutation. In contrast, the wild type of EGFR kinase is remarkably inhibited, which may lead to severe toxic side effects such as diarrhea, nausea, vomiting, urticaria, etc. [47, 48]. The 3rd generation EGFR-TKIs were membered by osimertinib (VI), which could irreversibly inhibit the T790M mutated cancer cells without inhibiting the EGFR-wt kinase [49–51]. Recently, there are many EGFR TKIs are also USFDA reported for NSCLC therapy, including nazartinib (XV) and torceteranib (XVI) [52]. In relation, indole-pyrimidine-based derivative (XVII) showed inhibitory activities with IC50 values of 0.094 μM, 0.099 μM, and 0.595 μM against EGFR (T790M), EGFR (L858R), and c-MET, respectively [53]. Moreover, indole-3-acrylamide derivative (XVIII) exhibited highly remarkable antiproliferative activities. It exerted a remarkable circumventing activity with about twenty-two times selectivity versus EGFRL858R/T790M over EGFRWT kinase with IC50 values of 1.7 nM and 37 nM, respectively [54]. Also, this indole-3-acrylamide derivative (XVIII) was evaluated against A549 and H1975 cancer cell lines with IC50 values of 4.17 μM and 0.052 μM, respectively, compared to the reference osimertinib with IC50 values of 2.91 μM and 0.064 μM, respectively [54].

1.2.1. Epidermal growth factor receptor (EGFR):

Briefly, there are four main members representing the ErbB subfamily, specifically epidermal growth factor receptor (EGFR) (HER1/ErbB1), HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4; all these members can act as heterodimers for signal cascades proliferation [36, 37]. Midst these factors, EGFR is the most critical one and has gained great attention from many researchers. It was found that ligand interaction such as EGF with the extracellular region of EGFR stimulates the intracellular region of tyrosine kinase and therefore promotes initiation of signaling cascades which result in cellular differentiation, migration, angiogenesis, and apoptosis [38–40]. Furthermore, mutations within EGFR activity represent one of the main causes in the progression of several human carcinomas, such as ovary, pancreas, lung, skin, breast, prostate, colorectal, kidney, and brain tumors [41–43]. The 1st generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib (XII) and erlotinib (XIII), which were orally active agents that reversibly bonded to EGFR and were more efficient for those patients with sensitive mutation types (L858R or exon 19 deletion) [44, 45]. Unfortunately, the clinical usage of these drugs revealed the drug resistance to these gene mutations, specifically the T790M mutation associated with most NSCLC patients [46]. The 2nd generation EGFR-TKIs were majorly represented by afatinib (XIV), the α,β unsaturated ketone scaffold that could bind irreversibly to the EGFR kinase. Herein, this category of drugs showed powerful therapeutic efficacy in cancer patients with the EGFR T790M mutation. In contrast, the wild type of EGFR kinase is remarkably inhibited, which may lead to severe toxic side effects such as diarrhea, nausea, vomiting, urticaria, etc. [47, 48]. The 3rd generation EGFR-TKIs were membered by osimertinib (VI), which could irreversibly inhibit the T790M mutated cancer cells without inhibiting the EGFR-wt kinase [49–51]. Recently, there are many EGFR TKIs are also USFDA reported for NSCLC therapy, including nazartinib (XV) and torceteranib (XVI) [52]. In relation, indole-pyrimidine-based derivative (XVII) showed inhibitory activities with IC50 values of 0.094 μM, 0.099 μM, and 0.595 μM against EGFR (T790M), EGFR (L858R), and c-MET, respectively [53]. Moreover, indole-3-acrylamide derivative (XVIII) exhibited highly remarkable antiproliferative activities. It exerted a remarkable circumventing activity with about twenty-two times selectivity versus EGFRL858R/T790M over EGFRWT kinase with IC50 values of 1.7 nM and 37 nM, respectively [54]. Also, this indole-3-acrylamide derivative (XVIII) was evaluated against A549 and H1975 cancer cell lines with IC50 values of 4.17 μM and 0.052 μM, respectively, compared to the reference osimertinib with IC50 values of 2.91 μM and 0.064 μM, respectively [54].

1.2.1.1. Protein kinase inhibitors:

Protein kinases are classified into two main categories: tyrosine and serine/threonine protein kinases [32]. Protein-tyrosine kinases’ receptors are two main categories: receptor and non-receptor proteins [32]. Regarding these proteins, tyrosine residue phosphorylation could be accomplished by tyrosine kinases. Tyrosine receptors’ phosphorylation outcomes initiate vital downstream signalling cascades, which are fundamental in critical bioprocesses such as cell adhesion, growth, survival, and proliferation [33–35]. In view of the human genomics, about 52 RTKs were identified, which are categorized into various multiple member subfamilies, counting insulin receptors ErbB, and other growth factors, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [32].

1.2.1.2. Vascular endothelial growth factor receptor (VEGFR):

VEGF (vascular endothelial growth factor) is another RTK, including 5 growth factors, VEGFA, VEGFB, VEGFC, VEGFD, and PLGF (placental growth factor). Additionally, VEGF has three receptor types, namely VEGFR-1 (Flt-1), VEGFR-2 (KDR), and VEGFR-3 (Flt-4) [55]. Among these VEGFR types,
VEGFR-2 or KDR exemplifies a critical target to afford novel anticancer scaffolds owing to the essential role of VEGFR-2 in both traditional physiological and tumor pathophysiological angiogenesis [56, 57]. Angiogenesis is the proliferation of new blood vessels from the previous old ones. It is considered a key and complicated bioprocess in both physiological and pathological conditions [58]. This bioprocess is controlled by making an equilibrium between pro- and antiangiogenic factors and is disturbed in multiple diseases, specifically cancer. Three main angiokinase signaling biomolecules influence the angiogenesis process, including VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), which are vital for blood vessels' propagation, solidity, and preservation. Overexpression of VEGFR-2 has been marked in versatile cancer types, such as breast cancer, non-small cell lung cancer, malignant melanoma, colorectal cancer, etc [59–62]. From a medicinal chemistry point of view, a wider range of EGFR and VEGFR-2 inhibitors can be considered a well-established antiangiogenic milestone that can facilitate cancer eradication [63, 64]. Herein, many indole-based VEGF-2 TKIs are clinically FDA-approved drugs, namely sorafenib (XIX) and sunitinib (IX); for advanced renal cell carcinoma and adenocarcinoma therapy, respectively [22, 65–67]. Many experimental studies found that both the VEGFR-2 and EGFR have the same usual downstream signaling pathways, contributing to the oncogenesis process. Interestingly, it has been detected that the elevation of the EGFR signaling scale rises the VEGF level, which is responsible for the resistance appearance to EGFR inhibitors [63, 64]. Herein, dual VEGFR-2/EGFR inhibition in clinical research trials is a prime strategy for potential antiproliferative activity. For instance, vandetanib (XX) is a prime antiproliferative agent that acts as a dual EGFR/VEGFR-2 inhibitor [63, 64, 68]. For example, an aniline-indole-based hybrid (XXI) showed dual inhibitory activities versus EGFR and VEGFR-2 with IC\textsubscript{50} values of 18 nM and 45 nM, respectively [69]. Also, morpholinoo-indole-based hybrid (XXII) exhibited hampering activities versus both EGFR and VEGFR-2 with IC\textsubscript{50} values of 0.007 μM and 1.2 μM, respectively [69].

\begin{figure}
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\includegraphics[width=0.5\textwidth]{sorafenib_vandetanib}
\caption{Sorafenib (XIX) and Vandetanib (XX)}
\end{figure}

### 1.2.1.3. Platelet-derived growth factor receptor (PDGFR):

Platelet-derived growth factor (PDGF) is another type III receptor tyrosine kinase (RTK) highly overexpressed in cancer cells resulting in resistance to conventional chemotherapy. However, PDGFRs' circumvention downregulates propagation, metastasis, being invasive, and angiogenesis of multiple tumor cells, specifically malignant ones [70]. PDGF is a critical pro-angiogenic agent with a significant supervisory role on both normal and diseased blood vessels [71]. Critically, the receptors of PDGFs (PDGFR\textalpha and PDGFR\textbeta) are overexpressed in several cancer cells such as pancreatic cancer, non-small cell lung cancer (NSCLC), ovarian carcinoma, gastrointestinal stromal tumor (GIST), breast cancer neuroendocrine tumors, and hepatocellular carcinoma [72, 73]. PDGFR inhibitors are classified into two main categories, specific and non-specific hampering agents regarding their binding interactions with PDGFR\textalpha and/or PDGFR\textbeta [74]. For instance, CP-673451 (XXIII) is a new, adenosine triphosphate (ATP)-competitive antiangiogenic agent, PDGF circumventing agent that could act as a dual inhibitor for PDGFR\textalpha and PDGFR\textbeta kinases, but it was ten folds more specific for PDGFR\textbeta than PDGFR\textalpha. CP-673451 (XXIII) hampers the PDGFR-β expression and tumor mass proliferation in lung carcinoma-bearing mice [75, 76]. Furthermore, sorafenib (XIX) is a dual kinase inhibitor, which acts as a type IIA tyrosine kinase inhibitor of VEGFR-2 which fits into the front cleft within the DFG-out area, the gate area, and extends through the gatekeeper into the back cleft hydrophobic pocket, this expansion into the less common back hydrophobic pocket potentiates type IIA inhibitors’ efficacy and selectivity compared to type IIB and platelet-derived growth factor receptor (PDGFR) [52, 77, 78]. Moreover, sunitinib (IX) and nintedanib (X) are indole-based type IIB tyrosine kinase inhibitors for VEGFR-2, which interact with the DFG-out front cleft and the gate area (Figure 2). Also, both sunitinib (IX) and nintedanib (X) can inhibit PDGFR [52, 77, 78]. Anlotinib (XXIV) was an indole-based anticancer agent that targets numerous angiogenic receptor tyrosine kinases, including platelet-derived growth factor\beta (PDGF\beta), vascular endothelial growth factor receptor-2 and 3 (VEGFR-2 and 3), and fibroblast growth factor 2 (FGF-2), [79]. Therefore, erlotinib (XXIV) as anti-lung cancer was more potent than that sunitinib (IX), nintedanib (X), and sorafenib (XIX). In advanced NSCLC patients, anlotinib (XXIV) has been considered as a promising 3rd line therapeutic agent [79]. In relation, 2-oxoindole-based uredo compound (XXV) was reported with circumventing activities versus VEGFR-2, PDGFR\beta, and FGFR-1 with IC\textsubscript{50} values of 0.18 μM, 0.10 μM, and 0.23 μM, respectively (Figure 2) [80]. The 2-oxoindole based uredo compound (XXV) was evaluated versus four human cancer cell lines, namely, HepG2, MCF-7, A549, and A498 with IC\textsubscript{50} values of 2.67 μM, 16.03 μM, 39.53 μM, and 1.00 μM, respectively compared to the positive references; doxorubicin with IC\textsubscript{50} values of 4.10 μM, 2.60 μM, 4.36 μM, and 1.10 μM, respectively and sorafenib with IC\textsubscript{50} values of 5.23 μM, 4.27 μM, 6.11 μM, and ND (not determined), respectively (Figure 2). Moreover, compound (XXVI), 2-oxoindole based amido congener, was presented as a potent multiple kinase inhibitor versus VEGFR-2, FGFR-1, and PDGFR\beta with IC\textsubscript{50} values of 0.28 μM, 0.46 μM, and 0.09 μM, respectively (Figure 2) [80]. This 2-oxoindole-based amido analog (XXVI) was also examined versus the same four human cancer cell lines like compound (XXV) with IC\textsubscript{50} values of 2.89 μM, 11.79 μM, 73.10 μM, and 8.90 μM, respectively compared

\begin{figure}
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\includegraphics[width=0.5\textwidth]{sorafenib_nintedanib_vandetanib}
\caption{Anlotinib (XXIV), Erlotinib (XXIV), and Nintedanib (XX)

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to the same two previously mentioned references. In relation, Eldehna et al. adopted a hybridization strategy between sorafenib (type IIA VEGFR-2 inhibitor) on one side and sunitinib and nintedanib (type IIB VEGFR-2 inhibitors) on the other side to afford hybrids (XXV and XXVI) (Figure 2) [80]. Briefly, these hybrids (XXV and XXVI) can be well fitted into the gate area and the hydrophobic back pocket with their biaryl urea or amide linking moieties, respectively, from one side and into the front cleft hinge area by the linking 2-oxoindole core from the other side (Figure 2) [80]. So, these hybrids (XXV and XXVI) can be well dipped into the tyrosine kinase binding site. Therefore, they can act as potent multiple tyrosine kinase inhibitors significantly included in cancer proliferation and development (Figure 2) [80].

1.2.2. DNA-Topoisomerases inhibitors:

Mammalian topoisomerases are considered a critical target for numerous clinically useful anticancer drugs. DNA topoisomerases represent catalytic enzymes that may alter the topology of DNA as well; it contributes to processes such as DNA replication and transcription [81]. Topoisomerase I displays transition breaks within the DNA strand by cleaving a single DNA strand, whereas topoisomerase II allows transient fractures in DNA by cleaving double strands [82, 83]. There are many FDA-approved drugs as DNA topoisomerases' inhibitors; for instance, camptothecin (XXVII), doxorubicin (XXVIII), and mitoxantrone (XXIX) are used as anticancer through DNA intercalation [84]. Briefly, camptothecin (XXVII) is an anticancer drug that inhibits type I topoisomerases, circumvents resealing of cleaved DNA strands, and potentially results in apoptosis [84]. Doxorubicin (XXVIII) is a well-known anticancer agent inhibiting specifically type II topoisomerases. Like these agents disrupt the promoting function of type II topoisomerases either by stabilizing the enzyme complex with cleaved DNA, inhibiting the process of resealing by potentiating the synthesis of cleavable complexes, or by intercalating DNA and hampering the enzyme from affording it's promoting function. DNA topoisomerase II stands among the most significant beneficial targets in the evolution of anticancer medicines [85]. Most of these drugs are now used in human carcinomas' therapeutic protocols. In 2020, a series of 3-methyl-2-phenyl-1H-indoles was designed, affording two highly potent compounds, XXX and XXXI, against cervical, ovarian, and lung cancers with IC_{50} values less than 4 μM [17].

1.2.3. Histone Deacetylase inhibitors (HDACIs):

Histone deacetylases (HDACs) represent promising therapeutic milestones owing to their participation in numerous human disorders, including cancer [86, 87]. Histone Deacetylases (HDACs) represent a group of reversible enzymes which are in authority of the detachment of acetyl moiety from the lysine side chain in the NH_{2} peripheral tail of both histone and non-histone protein (tubulin and p53) [88, 89]. This process strengthens the intercalation between the positively charged histone and the negatively charged DNA, results in chromatin coiling, and inhibits gene expression [88]. HDACs act parallelly with HAT.
(histone acetyltransferases) in the deacetylation and acetylation of histone protein and display a fundamental role due to their participation in genetic expression, cellular propagation, proliferation, protein DNA interaction, and finally in apoptosis [90, 91]. An imbalance between HDACs and HAT results in pathological conditions of numerous diseases such as cancer, neurodegeneration, cardiovascular, and inflammatory diseases. Owing to this reason, HDAC inhibitors (HDACIs) elucidate a new gate for affording a novel class of drugs acting as potent anticancer agents via regression of cell migration and mobility, triggering apoptosis, and hampering cell proliferation and invasion [90, 92, 93]. Commonly, HDACIs should include three main frameworks: cap region, zinc-binding group, and the linker [94]. For many decades, there have been many HDAC inhibitors that are FDA-approved for clinical use: vorinostat (SAHA) (XXXII), panobinostat (XXXIII), and mocetinostat [95–97]. Vorinostat (XXXII) has been used to treat peripheral and cutaneous T-cell lymphoma [98]. Panobinostat (XXXIII) (indole-based drug) was approved in 2015 for various myeloma therapy [96]. Recently, an indole-based scaffold named quinazolost (XXXIV) has entered different phases of clinical trials [99]. In 2022, Jiang et al. designed indole-based compounds (XXXV and XXXVI) [95]. Compound (XXXV) was the most potent one (IC₅₀_HDAC1 = 1.16 nM; IC₅₀_HDAC6 = 2.30 nM), and displaying remarkable antiproliferative activity against the MDAMB-231 (IC₅₀ =0.46 µM), A549 (IC₅₀ = 0.96 µM), SGC7901 (IC₅₀ = 0.04 µM), HL60 (IC₅₀ = 0.02 µM), and HCT116 (IC₅₀ = 0.14 µM) human cancer cell lines; relative to SAHA that exhibited IC₅₀ values of 8.25 µM, 7.32 µM, 0.64 µM, 0.93 µM, and 3.59 µM in these five cell lines, respectively [95]. Besides, Compound (XXXVI) was also potent one (IC₅₀_HDAC1 = 3.16 nM; IC₅₀_HDAC6 = 4.64 nM) and exhibited remarkable antiproliferative activity against the MDAMB-231 (IC₅₀ =1.77 µM), A549 (IC₅₀ = 0.92 µM), SGC7901 (IC₅₀ = 0.18 µM), HL60 (IC₅₀ = 0.51 µM), and HCT116 (IC₅₀ = 0.68 µM) human cancer cell lines relative to SAHA in these above mentioned five cell lines, respectively [95]. Indole-based hydroxamic acid derivative (XXXVII) showed highly potent HDAC inhibition and antiproliferative activities through in vitro studies. The IC₅₀ values of compound (XXXVII) against HDAC1, HDAC3, and HDAC6 were 13.9 nM, 12.1 nM, and 7.71 nM, respectively, compared with SAHA with IC₅₀ values of 50.7 nM, 164.1 nM, and 169.5 nM, respectively [100]. Also, it displayed increased antiproliferative activities versus U937, U266, and HepG2 cancer cells with IC₅₀ values of 0.16 µM, 1.92 µM, and 1.85 µM, respectively, with SAHA (1.40 µM, 0.88 µM, and 8.68 µM) [100]. Therefore, compound (XXXVII) displayed about six and five folds more potent than SAHA in inhibiting both U266 and HepG2 cells, respectively [100]. Moreover, indole-based N-hydroxy benzamide derivative (XXXVIII) via HDAC class I cellular assay (specifically: HDAC1 and HDAC2); exhibited highly fundamental inhibitory activity with IC₅₀ values of 33.2 nM and 60.1 nM, respectively, compared to SAHA with IC₅₀ of 447.6, and 3052.4 nM, respectively [101]. In relation, compound (XXXVIII) showed highly promising activity than the reference SAHA against PC-3, HCT116, U937, U266, and K562 cell lines with IC₅₀ of 0.74 µM, 1.45 µM, 1.09 µM, 1.01 µM, and 1.67 µM, respectively; relative to SAHA (IC₅₀ = 5.36 µM, 6.15µM, 3.35 µM, 1.35 µM, 3.89 µM, respectively) [101].

1.2.4. Tubulin polymerization inhibitors:

Microtubules are synthesized through the non-covalent intercalation of both α- and β-tubulin heterodimer subunits and act as a critical cytoskeleton constituent. Microtubules contribute to many key cellular processes, especially controlling the mitotic spindle functions during mitotic division, stabilizing the cell shape, intrinsic transport, and motility [102, 103]. Their influence in controlling cellular consistency and function and their previously reported utilization in cancer chemotherapy make microtubules a critical target for developing new potent anticancer agents [104]. Moreover, microtubule targeting agents (MTAs) are divided into 2 types depending on their disturbing capability, with microtubule polymerization and depolymerization as tubulin stabilizing or destabilizing agents. Tubulin-stabilizing compounds, e.g., taxol, prevent microtubule depolymerization and promote polymerization. Whereas tubulin destabilizing agents, e.g., vincristine, prevent polymerization and cause microtubule depolymerization, resulting in microtubule shortening [105, 106]. The homologic structure of tubulin should include 3 different ligand binding sites: the paclitaxel (taxol), vinblastine (vinca alkaloid), and colchicine binding sites (CBS, e.g., combretastatin A-4 (CA-4)) [107]. CA-4 (XXXIX) (Fig. 3) represents a prominent anticancer agent that can selectively target cancer angiogenesis [108, 109] but with limited antiproliferative activity due to the fact related to CA-4 that it is metabolically unstable and has low hydrophilicity [110, 111]. Consequently, to overcome this drawback, numerous cyclic derivatives have been tried to preserve the efficacy and potentiality of CA-4, but with diverse pharmacokinetic properties [112–116]. Compound XL exhibited good anticancer activities versus many types of cancer cells. Also, it showed good anti-tubulin activity compared with the reference CA-4 with IC₅₀ values of 18 µM and 0.54 µM.
respectively [117]. Moreover, 3-substituted indole scaffold XLI displayed a potent competitive inhibition with a percent of 50% at the colchicine binding to tubulin, which is more preferred than the positive reference colchicine with IC₅₀ s of 1.30 and 2.93 μM, respectively [118]. Additionally, 3- substituted indole-quinoline compound XLII showed notable antiproliferative activities against HCT-116, MCF-7, A-549, HT-29, K-562, and K-562R cancer cells with IC₅₀ s of 2.2 nM, 10.1 nM, 8 nM, 9.1 nM, 4.5 nM, 2 nM, respectively; in comparison to CA-4 with IC₅₀ values of 2.7 nM, 170 nM, 200 nM, > 8000 nM, 5.5 nM, and 25 nM, respectively [119]. Compound XLII circumvented tubulin polymerization in a dose-dependent regimen where the detected concentration to cause 50% polymerization inhibition was found half a fold lower than CA-4 with IC₅₀ values of 5 μM and 2.5 μM, respectively. Thus, compound XLII has a little lower activity than CA-4 [119]. Moreover, 3-(2,4,6-trimethoxybenzylidene) indole-based hybrid XLIII showed potent activity against the colon cancer COLO-205 cell line affording the same IC₅₀ value of the reference IC261 (IC₅₀ = 0.2 μM) [120]. Additionally, compound XLIII was a potent inhibitor for EGFR compared to gefitinib with IC₅₀ values of 0.19 μg/mL and 0.05 μg/mL, respectively; besides, compound XLIII exhibited good efficacy in inhibition of tubulin polymerization compared to CA-4 with IC₅₀ values of 1.66 μM and 0.42 μM, respectively [120]. In 2020, Mukherjee et al. designed bis(indoly)hydrazide-hydrazone derivative (XLIV) that displayed remarkable inhibitory activity versus HeLa cells, with IC₅₀ value of 1.5 μM, besides it showed moderate cytotoxicity against MDA-MB-231, MCF-7, HepG2, and PA1 with IC₅₀ values of 8 μM, 5.25 μM, 29.7 μM, and 24.7 μM, respectively [121]. Also, compound (XLIV) showed good tubulin polymerization circumvention activity with IC₅₀ value of 13 μM [121]. In 2022, Shi et al. synthesized pyrido-indole hybrid (XLV) that exhibited highly potent antiproliferative activity against HeLa cells compared to the reference CA-4 with IC₅₀ values of 8.7 μM and 0.088 μM, respectively [122]. In relation, compound (XLV) could show remarkable inhibition against tubulin polymerization compared to the positive control CA-4 [122]. In 2020, Iacopetta et al. reported a new indole derivative (XLVI) that displayed promising antiproliferative activities versus HeLa cells and MCF-7, with IC₅₀ values of 3.6 μM and 3.8 μM, respectively, relative to the reference drug vinblastine with IC₅₀ values of 0.067 μM and 0.045 μM, respectively [123]. Also, compound (XLVI) exhibited potent circumvention against tubulin polymerization reaction [123].

Conclusion

Cancer, uncontrolled cellular proliferation, is considered the 2nd leading cause of mortality worldwide, following cardiovascular diseases. Indole moiety is a core scaffold of great importance in medicinal chemistry for affording novel anticancer leads. Also, 2-Oxindoles, 1,3-dihydro-2H-indole-2-one derivative, have acquired prime attention because of their broad pharmacological activities, specifically as anticancer agents via acting as multiple kinase inhibitors. For instance, many FDA-approved drugs that enter clinics and the market are indole and 2-oxoindole-based compounds such as sunitinib, nintedanib, panobinostat, osimertinib, and anlotinib. Also, these indole and 2-oxoindole-based hybrids display their antiproliferative activity utilizing other inhibitory mechanisms such as DNA topoisomerases, histone deacetylases (HDAC), tubulin polymerization, apoptosis, etc. This review summarizes recent examples of promising antiproliferative indole and 2-oxoindole-based hybrids acting as multitargeting drugs utilizing two or more antiproliferative bio-targets mentioned before. These antiproliferative bio-targets are majorly engaged in the proliferation and survival of various types of cancer cells. Hence, this research work aims to pave the way for future medicinal research studies to design and briefly study the pharmacokinetic properties of these recent promising antiproliferative indole and 2-oxoindole-based hybrids to enter to clinical trials stage and consequently afford more potent indole-based antiproliferative agents.

References


