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

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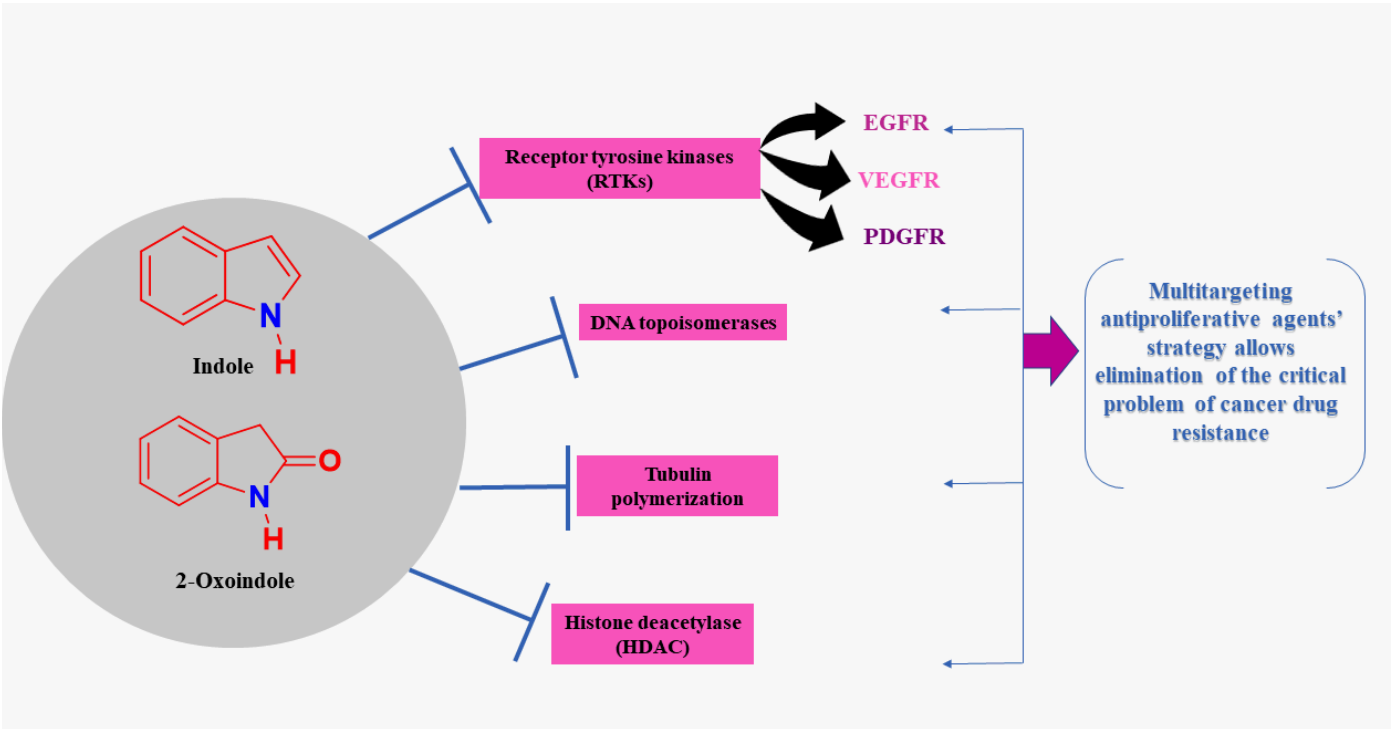
Abstract

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



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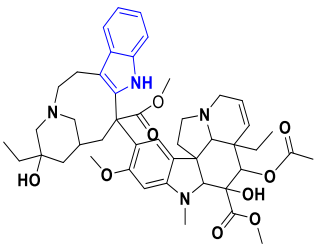
1.Introduction

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].

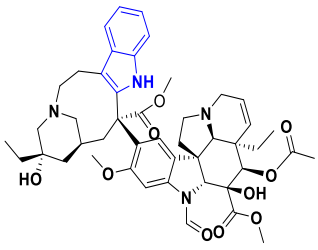
It is commonly comprehended that heterocyclic-based scaffolds represent a valuable source of bio-actives, which could be gained through organic synthesis or natural sources [8–10]. The existence of not less than one heteroatom, such as sulfur, oxygen, and nitrogen, in addition to one carbon atom in the 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-oxoindoles:

Among heterocyclic core scaffolds, indole-based scaffolds have exhibited significant potency in various biological activities as antimicrobial, anticancer, antiviral, antileishmanial, antitubercular, antioxidative, 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].

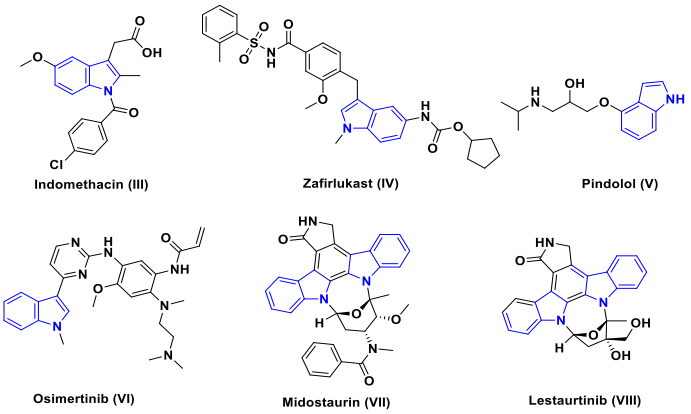


Vinblastine (I)



Vincristine (II)

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 diseases 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-oxoindole 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 C_8H_7NO (**Figure 1a**) [23, 24]. 2-Oxoindoles, named scientifically as 1,3-dihydro-2*H*-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-oxoindole-based compounds have acquired significant importance owing to their broad pharmacological activities such as antimicrobial, antiangiogenic, anticancer, antiviral, antileishmanial, antitubercular, antioxidative, 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-oxindoles (**Figure 1b**). Away from their biological valuably, 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.

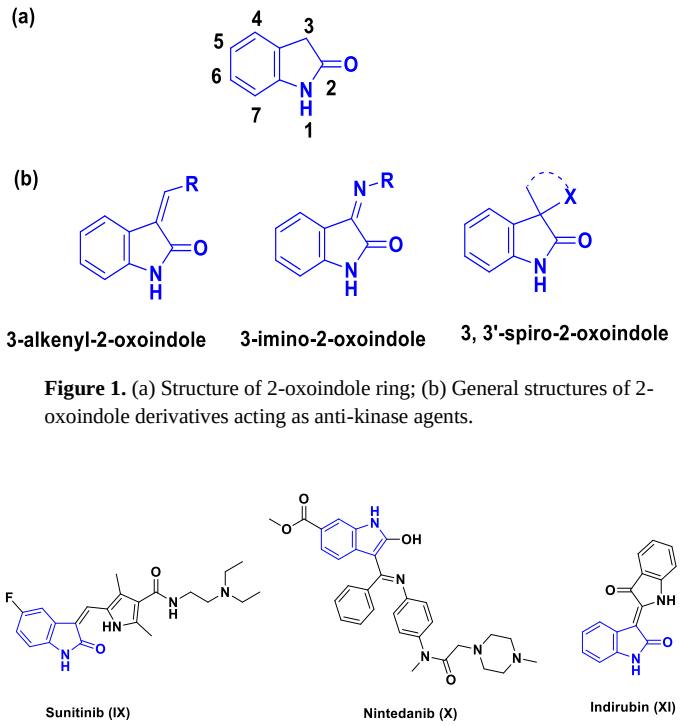


Figure 1. (a) Structure of 2-oxoindole ring; (b) General structures of 2-oxoindole derivatives acting as anti-kinase agents.

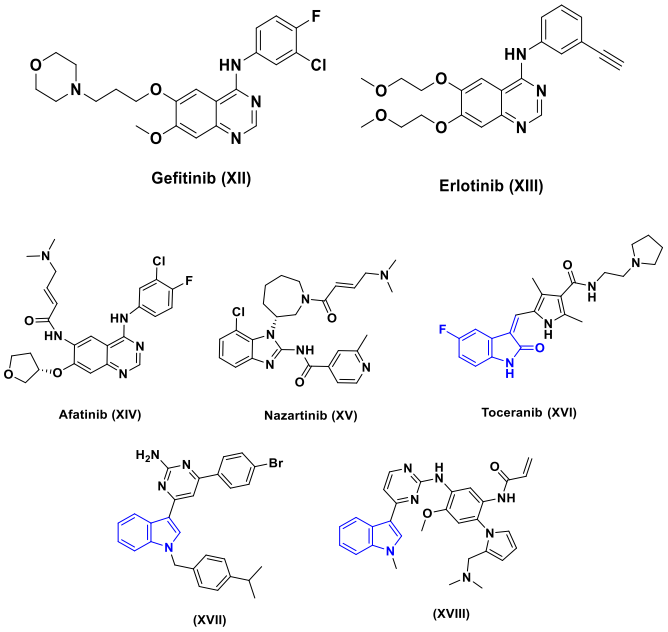
1.2. Antiproliferative bio-targets of the indole and 2-oxoindole-based anticancer agents:

1.2.1. 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].

1.2.1.1. Epidermal growth factor receptor (EGFR):

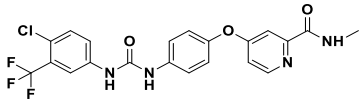
Briefly, there are four main members representing the ErbB subfamily, specifically epidermal growth factor receptor (EGFR) (HER1/ErbB1), HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4; all these members can act as heterodimers for signal cascades proliferation [36, 37]. Midst these factors, EGFR is the most 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 torceranib (**XVI**) [52]. In relation, indole-pyrimidine-based derivative **(XVII)** showed inhibitory activities with IC_{50} 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 $EGFR^{L858R/T790M}$ over $EGFR^{WT}$ kinase with IC_{50} 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 IC_{50} values of 4.17 µM and 0.052 µM, respectively, compared to the reference osimertinib with IC_{50} values of 2.91 µM and 0.064 µM, respectively [54].



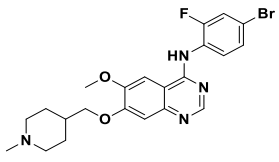
1.2.1.2. Vascular endothelial growth factor receptor (VEGFR):

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,

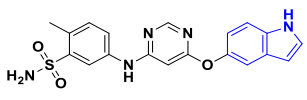
VEGFR-2 or KDR exemplifies a critical target to afford novel anticancer scaffolds owing to the essential role of VEGFR-2 in both traditional physiological and tumor pathophysiological angiogenesis [56, 57]. Angiogenesis is the proliferation of new blood vessels from the previous old ones. It is considered 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 VEGFR-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_{50} values of 18 nM and 45 nM, respectively [69]. Also, morpholino-indole-based hybrid **(XXII)** exhibited hampering activities versus both EGFR and VEGFR-2 with IC_{50} values of 0.007 µM and 1.2 µM, respectively [69].



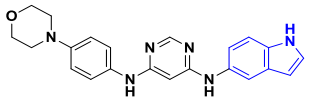
Sorafenib (XIX)



Vandetanib (XX)



(XXI)



(XXII)

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 (PDGFRα and PDGFRβ) 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 PDGFRα and/or PDGFRβ [74]. For instance, CP-673451 (**XXIII**) is a new, adenosine triphosphate (ATP)-competitive antiangiogenic agent, PDGFR circumventing agent that could act as a dual inhibitor for PDGFRα and PDGFRβ kinases, but it was ten folds more specific for PDGFRβ than PDGFRα**.** 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 factorβ (PDGFβ), 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, PDGFRβ, and FGFR-1 with IC_{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_{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_{50} values of 4.10 µM, 2.60 µM, 4.36 µM, and 1.10 µM, respectively and sorafenib with IC_{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 PDGFRβ with IC_{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_{50} values of 2.89 µM, 11.79 µM, 73.10 µM, and 8.90 µM, respectively compared

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].

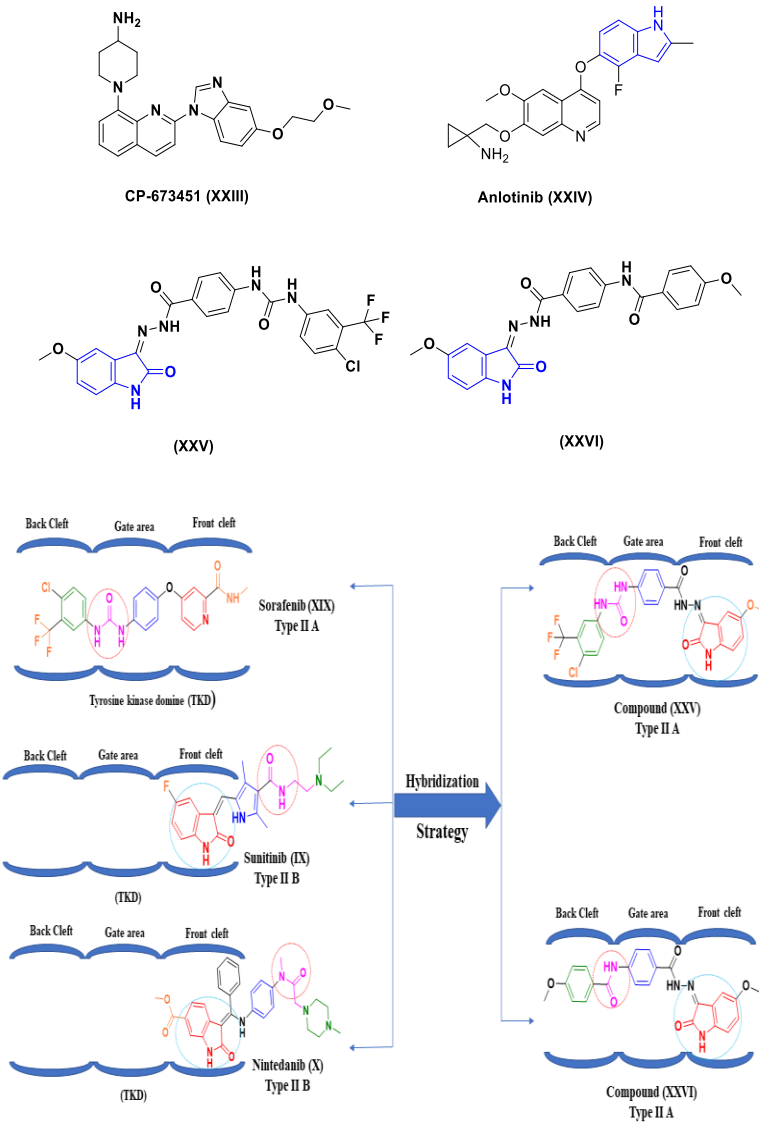
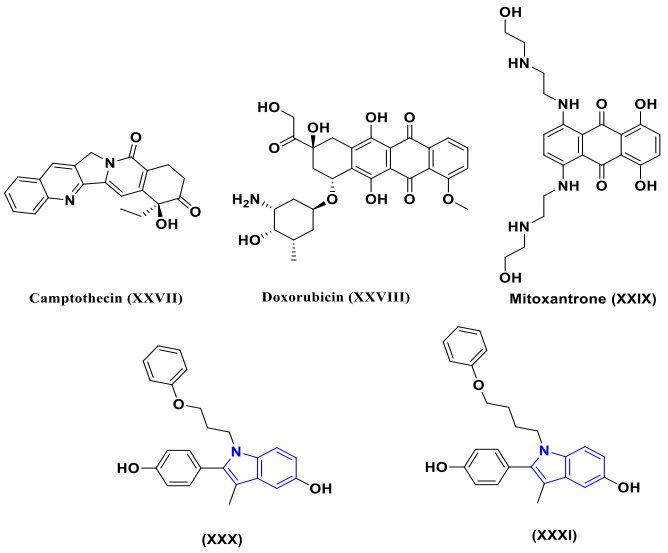


Figure 2. Rational design of the reported multiple TKIs (sorafenib, sunitinib, and nintedanib) and the strategy of the reconstruction of new multiple angiogenic TKIs as promising antiproliferative agents (**XXV** and **XXVI**) and their proposed binding mode within the VEGFR-2 tyrosine kinase domain.

1.2.2. DNA-Topoisomerases inhibitors:

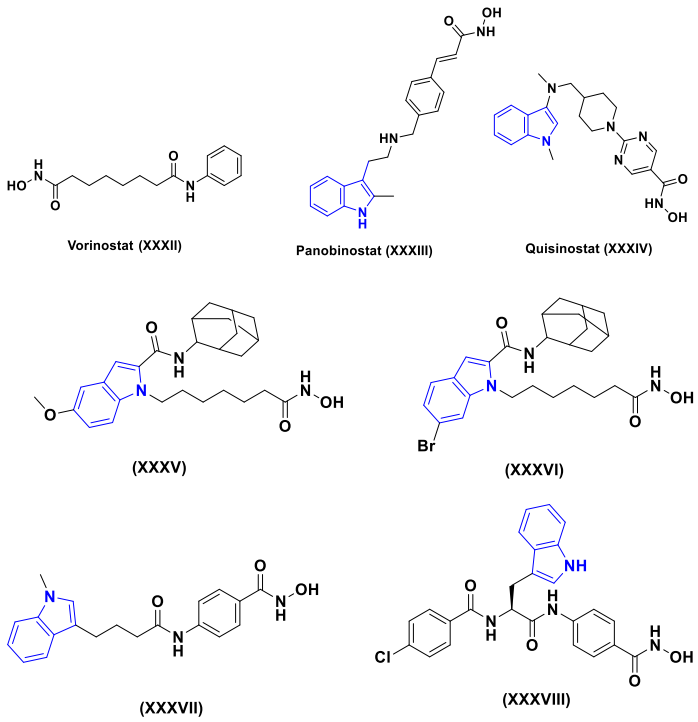
Mammalian topoisomerases are considered a critical target for numerous clinically useful anticancer drugs. DNA topoisomerases represent catalytic enzymes that may alter the topology of DNA as well; it contributes to processes such as DNA replication and transcription [81]. Topoisomerase I displays transition 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-1*H*-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 lastly 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 quisinostat (**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 (IC_{50}, $_{HDAC1}$ = 1.16 nM; IC_{50}, $_{HDAC6}$ = 2.30 nM), and displaying remarkable antiproliferative activity against the MDAMB-231 (IC_{50} =0.46 µM), A549 (IC_{50} = 0.96 µM), SGC7901 (IC_{50} = 0.04 µM), HL60 (IC_{50} = 0.02 µM), and HCT116 (IC_{50} = 0.14 µM) human cancer cell lines; relative to SAHA that exhibited IC_{50} 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 (IC_{50}, HDAC1 = 3.16 nM; IC_{50}, HDAC6 = 4.64 nM) and exhibited remarkable antiproliferative activity against the MDAMB-231 (IC_{50} = 1.77 µM), A549 (IC_{50} = 0.92 µM), SGC7901 (IC_{50} = 0.18 µM), HL60 (IC_{50} = 0.51 µM), and HCT116 (IC_{50} = 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* investigations. The IC_{50} 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 IC_{50} 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 IC_{50} values of 0.16 µM, 1.92 µM, and 1.85 µM, respectively, compared 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 IC_{50} values of 33.2 nM and 60.1 nM, respectively, compared to SAHA with IC_{50}s 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 IC_{50}s of 0.74 µM, 1.45 µM, 1.09 µM, 1.01 µM, and 1.67 µM, respectively; relative to SAHA (IC_{50}s = 5.36 µM, 6.15µM, 3.35 µM, 1.35 µM, 3.89 µM, respectively) [101].



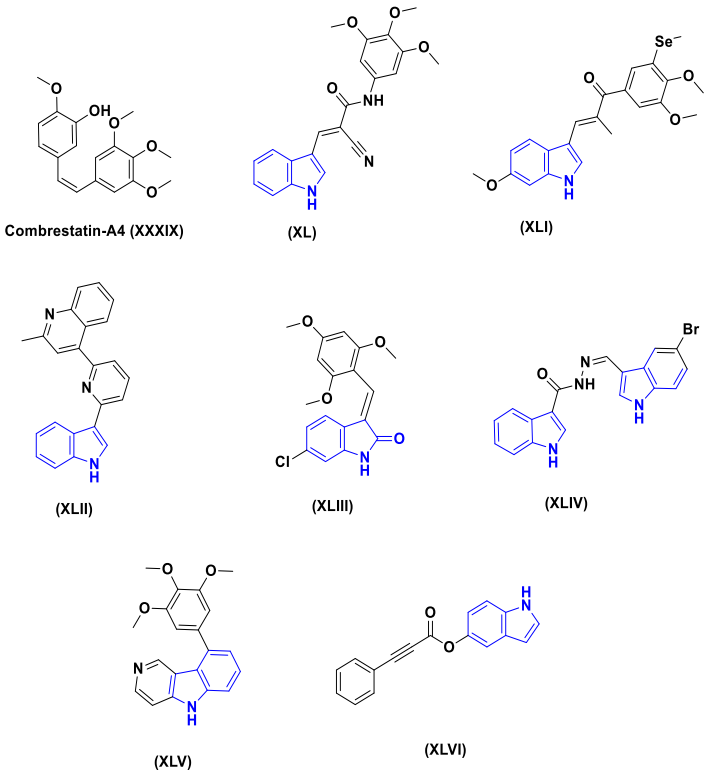
1.2.4. Tubulin polymerization inhibitors:

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 IC_{50} 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 IC_{50}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 IC_{50}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 IC_{50} 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 IC_{50} 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 IC_{50} value of the reference IC261 (IC_{50}= 0.2 µM) [120]. Additionally, compound **XLIII** was a potent inhibitor for EGFR compared to gefitinib with IC_{50} 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 IC_{50} values of 1.66 µM and 0.42 µM, respectively [120]. In 2020, Mukherjee et al. designed bis(indolyl)hydrazide-hydrazone derivative (**XLIV**) that displayed remarkable inhibitory activity versus HeLa cells, with IC_{50} value of 1.5 µM, besides it showed moderate cytotoxicity against MDA-MB-231, MCF-7, HepG2, and PA1 with IC_{50} 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 IC_{50} value of 13 µM [121]. In 2022, Shi et al. synthetized pyrido-indole hybrid (**XLV**) that exhibited highly potent antiproliferative activity against HeLa cells compared to the reference CA-4 with IC_{50} 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 IC_{50} values of 3.6 µM and 3.8 µM, respectively, relative to the reference drug vinblastine with IC_{50} 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-Oxoindoles, 1,3-dihydro-2*H*-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

[1]Jemal, A.; Bray, F.; Center, M. M.; Ferlay, J.; Ward, E.; Forman, D. Global Cancer Statistics. *CA. Cancer J. Clin.* **2011**, *61* [2], 69–90. https://doi.org/10.3322/caac.20107.

[2]Nemr, M. T. M.; AboulMagd, A. M.; Hassan, H. M.; Hamed, A. A.; Hamed, M. I. A.; Elsaadi, M. T. Design, Synthesis and Mechanistic Study of New Benzenesulfonamide Derivatives as Anticancer and Antimicrobial Agentsviacarbonic Anhydrase IX Inhibition. *RSC Adv.* **2021**, *11* [42], 26241–26257. https://doi.org/10.1039/d1ra05277b.

[3]Kassab, A. E.; Gedawy, E. M.; Hamed, M. I. A.; Doghish, A. S.; Hassan, R. A. Design, Synthesis, Anticancer Evaluation, and Molecular Modelling Studies of Novel Tolmetin Derivatives as Potential VEGFR-2 Inhibitors and Apoptosis Inducers. *J. Enzyme Inhib. Med. Chem.* **2021**, *36* [1], 922–939. https://doi.org/10.1080/14756366.2021.1901089.

[4]Rashid, H. ur; Xu, Y.; Muhammad, Y.; Wang, L.; Jiang, J. Research Advances

on Anticancer Activities of Matrine and Its Derivatives: An Updated Overview. *Eur. J. Med. Chem.* **2019**, *161*, 205–238. https://doi.org/10.1016/j.ejmech.2018.10.037.
[5]de Lera, A. R.; Ganesan, A. Epigenetic Polypharmacology: From Combination Therapy to Multitargeted Drugs. *Clin. Epigenetics* **2016**, *8* [1], 105. https://doi.org/10.1186/s13148-016-0271-9.
[6]Benedetti, R.; Conte, M.; Iside, C.; Altucci, L. Epigenetic-Based Therapy: From Single- to Multi-Target Approaches. *Int. J. Biochem. Cell Biol.* **2015**, *69*, 121–131. https://doi.org/10.1016/j.biocel.2015.10.016.
[7]Soltan, O. M.; Shoman, M. E.; Abdel-Aziz, S. A.; Narumi, A.; Konno, H.; Abdel-Aziz, M. Molecular Hybrids: A Five-Year Survey on Structures of Multiple Targeted Hybrids of Protein Kinase Inhibitors for Cancer Therapy. *Eur. J. Med. Chem.* **2021**, *225*, 113768. https://doi.org/10.1016/j.ejmech.2021.113768.
[8]Ahmad, S.; Alam, O.; Naim, M. J.; Shaquiquzzaman, M.; Alam, M. M.; Iqbal, M. *Pyrrole: An Insight into Recent Pharmacological Advances with Structure Activity Relationship*. *Eur. J. Med. Chem.* **2018**; 157, 527-561. https://doi.org/10.1016/j.ejmech.2018.08.002.
[9]Gholap, S. S. Pyrrole: An Emerging Scaffold for Construction of Valuable Therapeutic Agents. *Eur. J. Med. Chem.* **2016**, *110*, 13–31. https://doi.org/10.1016/j.ejmech.2015.12.017.
[10]Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. Review: Biologically Active Pyrazole Derivatives. *New J. Chem.* **2017**, *41* [1], 16–41. https://doi.org/10.1039/C6NJ03181A.
[11]Tantawy, M. A.; Nafie, M. S.; Elmegeed, G. A.; Ali, I. A. I. Auspicious Role of the Steroidal Heterocyclic Derivatives as a Platform for Anti-Cancer Drugs. *Bioorg. Chem.* **2017**, *73*, 128–146. https://doi.org/10.1016/j.bioorg.2017.06.006.
[12]Khetmalis, Y. M.; Shivani, M.; Murugesan, S.; Chandra Sekhar, K. V. G. Oxindole and Its Derivatives: A Review on Recent Progress in Biological Activities. *Biomed. Pharmacother.* **2021**, *141*, 111842. https://doi.org/10.1016/j.biopha.2021.111842.
[13]Sachdeva, H.; Mathur, J.; Guleria, A. INDOLE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS: A REVIEW. *J. Chil. Chem. Soc.* **2020**, *65* [3], 4900–4907. https://doi.org/10.4067/s0717-97072020000204900.
[14]Li, W.; Shao, Y.; Hu, L.; Zhang, X.; Chen, Y.; Tong, L.; Li, C.; Shen, X.; Ding, J. BM6, a New Semi-Synthetic Vinca Alkaloid, Exhibits Its Potent in Vivo Anti-Tumor Activities via Its High Binding Affinity for Tubulin and Improved Pharmacokinetic Profiles. *Cancer Biol. Ther.* **2007**, *6* [5], 787–794. https://doi.org/10.4161/cbt.6.5.4006.
[15]Mukhtar, E.; Adhami, V. M.; Mukhtar, H. Targeting Microtubules by Natural Agents for Cancer Therapy. *Mol. Cancer Ther.* **2014**, *13* [2], 275–284. https://doi.org/10.1158/1535-7163.MCT-13-0791.
[16]Föhr, K. J.; Knippschild, U.; Herkommer, A.; Fauler, M.; Peifer, C.; Georgieff, M.; Adolph, O. State-Dependent Block of Voltage-Gated Sodium Channels by the Casein-Kinase 1 Inhibitor IC261. *Invest. New Drugs* **2017**, *35* [3], 277–289. https://doi.org/10.1007/s10637-017-0429-0.
[17]Zidar, N.; Secci, D.; Tomašič, T.; Mašič, L. P.; Kikelj, D.; Passarella, D.; Argaez, A. N. G.; Hyeraci, M.; Dalla Via, L. Synthesis, Antiproliferative Effect, and Topoisomerase II Inhibitory Activity of 3-Methyl-2-Phenyl-1 H-Indoles. *ACS Med. Chem. Lett.* **2020**, *11* [5], 691–697. https://doi.org/10.1021/acsmedchemlett.9b00557.
[18]Zhao, B.; He, T. Chidamide, a Histone Deacetylase Inhibitor, Functions as a Tumor Inhibitor by Modulating the Ratio of Bax/Bcl-2 and P21 in Pancreatic Cancer. *Oncol. Rep.* **2015**, *33* [1], 304–310. https://doi.org/10.3892/or.2014.3595.
[19]FERREIRA, S. H.; MONCADA, S.; VANE, J. R. Indomethacin and Aspirin Abolish Prostaglandin Release from the Spleen. *Nat. New Biol.* **1971**, *231* [25], 237–239. https://doi.org/10.1038/newbio231237a0.
[20]Kelloway, J. S. Zafirlukast: The First Leukotreene-Receptor Antagonist Approved for the Treatment of Asthma. *Ann. Pharmacother.* **1997**, *31* [9], 1012–1021. https://doi.org/10.1177/106002809703100912.
[21]Blier, P.; Bergeron, R. The Use of Pindolol to Potentiate Antidepressant Medication. *J. Clin. Psychiatry* **1998**, *59* [suppl 5], 16–23; PMID:9635544.
[22]Wan, Y.; Li, Y.; Yan, C.; Yan, M.; Tang, Z. Indole: A Privileged Scaffold for the Design of Anti-Cancer Agents. *Eur. J. Med. Chem.* **2019**, *183*, 111691. https://doi.org/10.1016/j.ejmech.2019.111691.
[23]Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. Oxindole: A Chemical Prism Carrying Plethora of Therapeutic Benefits. *Eur. J. Med. Chem.* **2016**, *123*, 858–894. https://doi.org/10.1016/j.ejmech.2016.08.011.
[24]Dreifuss, A. A.; Bastos-Pereira, A. L.; Ávila, T. V.; Soley, B. da S.; Rivero, A. J.; Aguilar, J. L.; Acco, A. Antitumoral and Antioxidant Effects of a Hydroalcoholic Extract of Cat's Claw [Uncaria Tomentosa] [Willd. Ex Roem. & Schult] in an in Vivo Carcinosarcoma Model. *J. Ethnopharmacol.* **2010**, *130* [1], 127–133. https://doi.org/10.1016/j.jep.2010.04.029.
[25]Cerchiaro, G.; Ferreira, A. M. D. C. Oxindoles and Copper Complexes with Oxindole-Derivatives as Potential Pharmacological Agents. *J. Braz. Chem. Soc.* **2006**, *17* [8], 1473–1485. https://doi.org/10.1590/S0103-50532006000800003.
[26]Ziarani, G. M.; Gholamzadeh, P.; Lashgari, N.; Hajiabbasi, P. Oxindole as Starting Material in Organic Synthesis. *Arkivoc* **2013**, *2013* [1], 470–535. https://doi.org/10.3998/ark.5550190.p008.074.
[27]Dhokne, P.; Sakla, A. P.; Shankaraiah, N. Structural Insights of Oxindole Based Kinase Inhibitors as Anticancer Agents: Recent Advances. *Eur. J. Med. Chem.* **2021**, *216*, 113334. https://doi.org/10.1016/j.ejmech.2021.113334.
[28]Islam I, Bryant J, Chou YL, Arnaiz DO. Indolinone based phosphoinositide-dependent kinase-1 [PDK1] inhibitors. Part 1: design, synthesis and biological activity. *Bioorg Med Chem Lett.* **2007**, 17 [14], 3814-8. https://doi.org/10.1016/j.bmcl.2007.04.071. PMID: 17531483.
[29]Sestito, S.; Daniele, S.; Nesi, G.; Zappelli, E.; Di Maio, D.; Marinelli, L.; Digiacomo, M.; Lapucci, A.; Martini, C.; Novellino, E.; Rapposelli, S. Locking PDK1 in DFG-out Conformation through 2-Oxo-Indole Containing Molecules: Another Tools to Fight Glioblastoma. *Eur. J. Med. Chem.* **2016**, *118*, 47–63. https://doi.org/10.1016/j.ejmech.2016.04.003.
[30]Roth, G. J.; Binder, R.; Colbatzky, F.; Dallinger, C.; Schlenker-Herceg, R.; Hilberg, F.; Wollin, S.-L.; Kaiser, R. Nintedanib: From Discovery to the Clinic. *J. Med. Chem.* **2015**, *58* [3], 1053–1063. https://doi.org/10.1021/jm501562a.
[31]Moon, M. J.; Lee, S. K.; Lee, J.-W.; Song, W. K.; Kim, S. W.; Kim, J. Il; Cho, C.; Choi, S. J.; Kim, Y.-C. Synthesis and Structure–Activity Relationships of Novel Indirubin Derivatives as Potent Anti-Proliferative Agents with CDK2 Inhibitory Activities. *Bioorg. Med. Chem.* **2006**, *14* [1], 237–246. https://doi.org/10.1016/j.bmc.2005.08.008.
[32]Roskoski, R. Properties of FDA-Approved Small Molecule Protein Kinase Inhibitors. *Pharmacol. Res.* **2019**, *144*, 19–50. https://doi.org/10.1016/j.phrs.2019.03.006.
[33]Fujita KI, Ishida H, Kubota Y, Sasaki Y. Toxicities of Receptor Tyrosine Kinase Inhibitors in Cancer Pharmacotherapy: Management with Clinical Pharmacology. *Curr Drug Metab*. **2017**; 18 [3], 186-198. doi: 10.2174/1389200218666170105165832. PMID: 28059038.
[34]Paul MD, Hristova K. The RTK Interactome: Overview and Perspective on RTK Heterointeractions. *Chem Rev*. **2019**, 119 [9], 5881-5921. https://doi.org/10.1021/acs.chemrev.8b00467. PMID: 30589534.
[35]Spangle, J. M.; Roberts, T. M. Epigenetic Regulation of RTK Signaling. *J. Mol. Med.* **2017**, *95* [8], 791–798. https://doi.org/10.1007/s00109-017-1546-0.
[36]Pellat, A.; Vaquero, J.; Fouassier, L. Role of ErbB/HER Family of Receptor Tyrosine Kinases in Cholangiocyte Biology. *Hepatology* **2018**, *67* [2], 762–773. https://doi.org/10.1002/hep.29350.
[37]Choura M, Rebaï A. Receptor tyrosine kinases: from biology to pathology. *J Recept Signal Transduct Res*. **2011,** 31 [6], 387-94. https://doi.org/10.3109/10799893.2011.625425. PMID: 22040163.
[38]Yoshida, T.; Zhang, G.; Haura, E. B. Targeting Epidermal Growth Factor Receptor: Central Signaling Kinase in Lung Cancer. *Biochem. Pharmacol.* **2010**, *80* [5], 613–623. https://doi.org/10.1016/j.bcp.2010.05.014.
[39]Ismail, R. S. M.; Ismail, N. S. M.; Abuserii, S.; Abou El Ella, D. A. Recent Advances in 4-Aminoquinazoline Based Scaffold Derivatives Targeting EGFR Kinases as Anticancer Agents. *Futur. J. Pharm. Sci.* **2016**, *2* [1], 9–19. https://doi.org/10.1016/j.fjps.2016.02.001.
[40]Shah, R. R.; Shah, D. R. Safety and Tolerability of Epidermal Growth Factor Receptor [EGFR] Tyrosine Kinase Inhibitors in Oncology. *Drug Saf.* **2019**, *42* [2], 181–198. https://doi.org/10.1007/s40264-018-0772-x.
[41]Hynes, N. E.; Lane, H. A. ERBB Receptors and Cancer: The Complexity of Targeted Inhibitors. *Nat. Rev. Cancer* **2005**, *5* [5], 341–354. https://doi.org/10.1038/nrc1609.
[42]Pao, W.; Miller, V. A.; Kris, M. G. "Targeting" the Epidermal Growth Factor Receptor Tyrosine Kinase with Gefitinib [Iressa®] in Non-Small Cell Lung Cancer [NSCLC]. *Semin. Cancer Biol.* **2004**, *14* [1], 33–40. https://doi.org/10.1016/j.semcancer.2003.11.005.
[43]Li, L.; Fan, P.; Chou, H.; Li, J.; Wang, K.; Li, H. Herbacetin Suppressed MMP9 Mediated Angiogenesis of Malignant Melanoma through Blocking EGFR-ERK/AKT Signaling Pathway. *Biochimie* **2019**, *162*, 198–207. https://doi.org/10.1016/j.biochi.2019.05.003.
[44]Maemondo, M.; Inoue, A.; Kobayashi, K.; Sugawara, S.; Oizumi, S.; Isobe, H.; Gemma, A.; Harada, M.; Yoshizawa, H.; Kinoshita, I.; Fujita, Y.; Okinaga, S.; Hirano, H.; Yoshimori, K.; Harada, T.; Ogura, T.; Ando, M.; Miyazawa, H.; Tanaka, T.; Saijo, Y.; Hagiwara, K.; Morita, S.; Nukiwa, T. Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR. *N. Engl. J. Med.* **2010**, *362* [25], 2380–2388. https://doi.org/10.1056/NEJMoa0909530.
[45]Pao, W.; Chmielecki, J. Rational, Biologically Based Treatment of EGFR-Mutant Non-Small-Cell Lung Cancer. *Nat. Rev. Cancer* **2010**, *10* [11], 760–774. https://doi.org/10.1038/nrc2947.
[46]Kobayashi, S.; Boggon, T. J.; Dayaram, T.; Jänne, P. A.; Kocher, O.; Meyerson, M.; Johnson, B. E.; Eck, M. J.; Tenen, D. G.; Halmos, B. EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib. *N. Engl. J. Med.* **2005**, *352* [8], 786–792. https://doi.org/10.1056/NEJMoa044238.
[47]Ou, S.-H. I. Second-Generation Irreversible Epidermal Growth Factor Receptor [EGFR] Tyrosine Kinase Inhibitors [TKIs]: A Better Mousetrap? A Review of the Clinical Evidence. *Crit. Rev. Oncol. Hematol.* **2012**, *83* [3], 407–421. https://doi.org/10.1016/j.critrevonc.2011.11.010.
[48]Yap, T. A.; Vidal, L.; Adam, J.; Stephens, P.; Spicer, J.; Shaw, H.; Ang, J.; Temple, G.; Bell, S.; Shahidi, M.; Uttenreuther-Fischer, M.; Stopfer, P.; Futreal, A.; Calvert, H.; de Bono, J. S.; Plummer, R. Phase I Trial of the Irreversible EGFR and HER2 Kinase Inhibitor BIBW 2992 in Patients With Advanced Solid Tumors. *J. Clin. Oncol.* **2010**, *28* [25], 3965–3972.

https://doi.org/10.1200/JCO.2009.26.7278.
[49]Ward, R. A.; Anderton, M. J.; Ashton, S.; Bethel, P. A.; Box, M.; Butterworth, S.; Colclough, N.; Chorley, C. G.; Chuaqui, C.; Cross, D. A. E.; Dakin, L. A.; Debreczeni, J. É.; Eberlein, C.; Finlay, M. R. V.; Hill, G. B.; Grist, M.; Klinowska, T. C. M.; Lane, C.; Martin, S.; Orme, J. P.; Smith, P.; Wang, F.; Waring, M. J. Structure- and Reactivity-Based Development of Covalent Inhibitors of the Activating and Gatekeeper Mutant Forms of the Epidermal Growth Factor Receptor [EGFR]. *J. Med. Chem.* **2013**, *56* [17], 7025–7048. https://doi.org/10.1021/jm400822z.
[50]Sakata, Y.; Sakata, S.; Oya, Y..; Tsumura, S.; Morinaga, J.; Sakagami, T. Osimertinib as First-Line Treatment for Advanced Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer in a Real-World Setting [OSI-FACT]. *Eur. J. Cancer* **2021**, 159, 144–153. https://doi.org/10.1016/j.ejca.2021.09.041.
[51]Sullivan, I.; Planchard, D. Osimertinib in the Treatment of Patients with Epidermal Growth Factor Receptor T790M Mutation-Positive Metastatic Non-Small Cell Lung Cancer: Clinical Trial Evidence and Experience. *Ther. Adv. Respir. Dis.* **2016**, *10* [6], 549–565. https://doi.org/10.1177/1753465816670498.
[52]Roskoski, R. Classification of Small Molecule Protein Kinase Inhibitors Based upon the Structures of Their Drug-Enzyme Complexes. *Pharmacol. Res.* **2016**, *103*, 26–48. https://doi.org/10.1016/j.phrs.2015.10.021.
[53]Singh, P. K.; Silakari, O. Molecular Dynamics Guided Development of Indole Based Dual Inhibitors of EGFR [T790M] and c-MET. *Bioorg. Chem.* **2018**, *79*, 163–170. https://doi.org/10.1016/j.bioorg.2018.04.001.
[54]Ding, S.; Dong, X.; Gao, Z.; Chen, Y. Design, Synthesis and Biological Evaluation of Novel N-[3-Amino-4-Methoxyphenyl]Acrylamide Derivatives as Selective EGFRL858R/T790M Kinase Inhibitors. *Bioorg. Chem*. **2022**, 118, 105471. https://doi.org/10.1016/j.bioorg.2021.105471.
[55]Olsson, A. K.; Dimberg, A.; Kreuger, J.; Claesson-Welsh, L. VEGF Receptor Signalling - In Control of Vascular Function. *Nat. Rev. Mol. Cell Biol.* **2006**, *7* [5], 359–371. https://doi.org/10.1038/nrm1911.
[56]Alitalo, K.; Carmeliet, P. Molecular Mechanisms of Lymphangiogenesis in Health and Disease. *Cancer Cell* **2002**, *1* [3], 219–227. https://doi.org/10.1016/S1535-6108[02]00051-X.
[57]Shibuya, M. Vascular Endothelial Growth Factor [VEGF] and Its Receptor [VEGFR] Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes and Cancer* **2011**, *2* [12], 1097–1105. https://doi.org/10.1177/1947601911423031.
[58] Folkman, J.; D'Amore, P. A. Blood Vessel Formation: What Is Its Molecular Basis? *Cell* **1996**, *87* [7], 1153–1155. https://doi.org/10.1016/S0092-8674[00]81810-3.
[59]Modi, S. J.; Kulkarni, V. M. Vascular Endothelial Growth Factor Receptor [VEGFR-2]/KDR Inhibitors: Medicinal Chemistry Perspective. *Med. Drug Discov.* **2019**, *2*, 100009. https://doi.org/10.1016/j.medidd.2019.100009.
[60]Ghosh, S.; Sullivan, C. A. W.; Zerkowski, M. P.; Molinaro, A. M.; Rimm, D. L.; Camp, R. L.; Chung, G. G. High Levels of Vascular Endothelial Growth Factor and Its Receptors [VEGFR-1, VEGFR-2, Neuropilin-1] Are Associated with Worse Outcome in Breast Cancer. *Hum. Pathol.* **2008**, *39* [12], 1835–1843. https://doi.org/10.1016/j.humpath.2008.06.004.
[61]Amaya, H.; Tanigawa, N.; Lu, C.; Matsumura, M.; Shimomatsuya, T.; Horiuchi, T.; Muraoka, R. Association of Vascular Endothelial Growth Factor Expression with Tumor Angiogenesis, Survival and Thymidine Phosphorylase/Platelet-Derived Endothelial Cell Growth Factor Expression in Human Colorectal Cancer. *Cancer Lett.* **1997**, *119* [2], 227–235. https://doi.org/10.1016/S0304-3835[97]00280-2.
[62]Donnem, T.; Al-Shibli, K.; Andersen, S.; Al-Saad, S.; Busund, L. T.; Bremnes, R. M. Combination of Low Vascular Endothelial Growth Factor A [VEGF-A]/VEGF Receptor 2 Expression and High Lymphocyte Infiltration Is a Strong and Independent Favorable Prognostic Factor in Patients with Nonsmall Cell Lung Cancer. *Cancer* **2010**, *116* [18], 4318–4325. https://doi.org/10.1002/cncr.25333.
[63]Pakkala, S.; Ramalingam, S. S. Combined Inhibition of Vascular Endothelial Growth Factor and Epidermal Growth Factor Signaling in Non–Small-Cell Lung Cancer Therapy. *Clin. Lung Cancer* **2009**, *10*, S17–S23. https://doi.org/10.3816/CLC.2009.s.003.
[64]Jaseer, E. A.; Prasad, D. J. C.; Dandapat, A.; Sekar, G. An Efficient Copper[II]-Catalyzed Synthesis of Benzothiazoles through Intramolecular Coupling-Cyclization of N-[2-Chlorophenyl]Benzothioamides. *Tetrahedron Lett.* **2010**, *51* [38], 5009–5012. https://doi.org/10.1016/j.tetlet.2010.07.079.
[65]Traxler, P. Tyrosine Kinases as Targets in Cancer Therapy – Successes and Failures. *Expert Opin. Ther. Targets* **2003**, *7* [2], 215–234. https://doi.org/10.1517/14728222.7.2.215.
[66]Dhuguru, J.; Skouta, R. Role of Indole Scaffolds as Pharmacophores in the Development of Anti-Lung Cancer Agents. *Molecules* **2020**, *25* [7]. https://doi.org/10.3390/molecules25071615.
[67]Ciardiello, F.; Caputo, R.; Borriello, G.; Del Bufalo, D.; Biroccio, A.; Zupi, G.; Bianco, A. R.; Tortora, G. ZD1839 [Iressa], an EGFR-Selective Tyrosine Kinase Inhibitor, Enhances Taxane Activity in Bcl-2 Overexpressing, Multidrug-Resistant MCF-7 ADR Human Breast Cancer Cells. *Int. J. Cancer* **2002**, *98* [3], 463–469. https://doi.org/10.1002/ijc.10230.
[68]Wedge, S. R.; Ogilvie, D. J.; Hughes, G. D.; Thomas, A. P.; Stokes, E. S. E.; Curry, B.; Richmond, G. H. P.; Wadsworth, P. F.; Bigley, A. L.; Hennequin, L. F. ZD6474 Inhibits Vascular Endothelial Growth Factor Signaling, Angiogenesis, and Tumor Growth Following Oral Administration. *Cancer Res.* 2002, 62 [16], 4645–4655, PMID:12183421.
[69]Song, J.; Yoo, J.; Kwon, A.; Kim, D.; Nguyen, H. K.; Lee, B. Y.; Suh, W.; Min, K. H. Structure-Activity Relationship of Indole-Tethered Pyrimidine Derivatives That Concurrently Inhibit Epidermal Growth Factor Receptor and Other Angiokinases. *PLoS One* **2015**, *10* [9], 1–17. https://doi.org/10.1371/journal.pone.0138823.
[70]Thies, K. A.; Hammer, A. M.; Sizemore, S. T.; Sizemore, G. M. Stromal Platelet–Derived Growth Factor Receptor-β Signaling Promotes Breast Cancer Metastasis in the Brain. *Cancer Res.* **2021**, 81 [3], 606–618. https://doi.org/10.1158/0008-5472.CAN-19-3731.
[71]Kalra, K.; Eberhard, J.; Farbehi, N.; Chong, J. J.; Xaymardan, M. Role of PDGF-A/B Ligands in Cardiac Repair After Myocardial Infarction. *Front. Cell Dev. Biol.* **2021**, *9*, 1–13. https://doi.org/10.3389/fcell.2021.669188.
[72]Brahmi, M.; Lesluyes, T.; Dufresne, A.; Toulmonde, M.; Italiano, A.; Mir, O.; Le Cesne, A.; Valentin, T.; Chevreau, C.; Bonvalot, S.; Penel, N.; Coindre, J.-M.; Le Guellec, S.; Le Loarer, F.; Karanian, M.; Blay, J.-Y.; Chibon, F. Expression and Prognostic Significance of PDGF Ligands and Receptors across Soft Tissue Sarcomas. *ESMO Open* **2021**, *6* [1], 100037. https://doi.org/10.1016/j.esmoop.2020.100037.
[73]Cavalcanti, E.; Ignazzi, A.; De Michele, F.; Caruso, M. L. PDGFRα Expression as a Novel Therapeutic Marker in Well-Differentiated Neuroendocrine Tumors. *Cancer Biol. Ther.* **2019**, *20* [4], 423–430. https://doi.org/10.1080/15384047.2018.1529114.
[74]Zou, X.; Tang, X.; Qu, Z.; Sun, Z.; Ji, C.; Li, Y.; Guo, S.-D. Targeting the PDGF/PDGFR Signaling Pathway for Cancer Therapy: A Review. *Int. J. Biol. Macromol.* **2022**, *202*, 539–557. https://doi.org/10.1016/j.ijbiomac.2022.01.113.
[75]Roberts, W. G.; Whalen, P. M.; Ralston, S.; Szewc, R.; Kath, J. C.; Lin, J.; Soderstrom, C.; Hungerford, W.; Ung, E. Antiangiogenic and Antitumor Activity of a Selective PDGFR Tyrosine Kinase Inhibitor, CP-673,451. *Cancer Res.* **2005**, 65 [3], 957–966. PMID: 15705896.
[76]Yang, Y.; Deng, Y.; Chen, X.; Zhang, J.; Chen, Y.; Li, H.; Wu, Q.; Yang, Z.; Zhang, L.; Liu, B. Inhibition of PDGFR by CP-673451 Induces Apoptosis and Increases Cisplatin Cytotoxicity in NSCLC Cells via Inhibiting the Nrf2-Mediated Defense Mechanism. *Toxicol. Lett.* **2018**, *295*, 88–98. https://doi.org/10.1016/j.toxlet.2018.05.033.
[77]Roskoski, R. Vascular Endothelial Growth Factor [VEGF] Signaling in Tumor Progression. *Crit. Rev. Oncol. Hematol.* **2007**, *62* [3], 179–213. https://doi.org/10.1016/j.critrevonc.2007.01.006.
[78]Hilberg, F.; Roth, G. J.; Krssak, M.; Kautschitsch, S.; Sommergruber, W.; Tontsch-Grunt, U.; Garin-Chesa, P.; Bader, G.; Zoephel, A.; Quant, J.; Heckel, A.; Rettig, W. J. BIBF 1120: Triple Angiokinase Inhibitor with Sustained Receptor Blockade and Good Antitumor Efficacy. *Cancer Res.* **2008**, *68* [12], 4774–4782. https://doi.org/10.1158/0008-5472.CAN-07-6307.
[79]Lin, B.; Song, X.; Yang, D.; Bai, D.; Yao, Y.; Lu, N. Anlotinib Inhibits Angiogenesis via Suppressing the Activation of VEGFR2, PDGFRβ and FGFR1. *Gene* **2018**, *654*, 77–86. https://doi.org/10.1016/j.gene.2018.02.026.
[80]Eldehna, W. M.; El Kerdawy, A. M.; Al-Ansary, G. H.; Al-Rashood, S. T.; Ali, M. M.; Mahmoud, A. E. Type IIA - Type IIB Protein Tyrosine Kinase Inhibitors Hybridization as an Efficient Approach for Potent Multikinase Inhibitor Development: Design, Synthesis, Anti-Proliferative Activity, Multikinase Inhibitory Activity and Molecular Modeling of Novel Ind. *Eur. J. Med. Chem.* **2019**, *163*, 37–53. https://doi.org/10.1016/j.ejmech.2018.11.061.
[81]Nitiss, J. L. Targeting DNA Topoisomerase II in Cancer Chemotherapy. *Nat. Rev. Cancer* **2009**, *9* [5], 338–350. https://doi.org/10.1038/nrc2607.
[82]Parker, M. W.; Botchan, M. R.; Berger, J. M. Mechanisms and Regulation of DNA Replication Initiation in Eukaryotes. *Crit. Rev. Biochem. Mol. Biol.* **2017**, *52* [2], 107–144. https://doi.org/10.1080/10409238.2016.1274717.
[83]Champoux, J. J. DNA Topoisomerases: Structure, Function, and Mechanism. *Annu. Rev. Biochem.* **2001**, *70* [1], 369–413. https://doi.org/10.1146/annurev.biochem.70.1.369.
[84]Pommier, Y. DNA Topoisomerase I and II in Cancer Chemotherapy: Update and Perspectives. *Cancer Chemother. Pharmacol.* **1993**, *32* [2], 103–108. https://doi.org/10.1007/BF00685611.
[85]Schmidt, F.; Knobbe, C. B.; Frank, B.; Wolburg, H.; Weller, M. The Topoisomerase II Inhibitor, Genistein, Induces G2/M Arrest and Apoptosis in Human Malignant Glioma Cell Lines. *Oncol. Rep.* **2008**, *19* [4], 1061–1066. https://doi.org/10.3892/or.19.4.1061.
[86]Cea, M.; Soncini, D.; Fruscione, F.; Cagnetta, A.; Bergamaschi, M.; Casciaro, S.; Pierri, I.; Damonte, G.; Ansaldi, F.; Gobbi, M.; Pistoia, V.; Ballestrero, A.; Patrone, F.; Bruzzone, S.; Nencioni, A. Synergistic Interactions between HDAC and Sirtuin Inhibitors in Human Leukemia Cells. *PLoS One* **2011**, 6 [7], e22739. https://doi.org/10.1371/journal.pone.0022739.
[87]Gregoretti, I.; Lee, Y.-M.; Goodson, H. V. Molecular Evolution of the Histone Deacetylase Family: Functional Implications of Phylogenetic Analysis.

J. Mol. Biol. **2004**, *338* [1], 17–31. https://doi.org/10.1016/j.jmb.2004.02.006.
[88]Pulya, S.; Amin, S. A.; Adhikari, N.; Biswas, S.; Jha, T.; Ghosh, B. HDAC6 as Privileged Target in Drug Discovery: A Perspective. *Pharmacol. Res.* **2021**, *163*, 105274. https://doi.org/10.1016/j.phrs.2020.105274.
[89]Shetty, M. G.; Pai, P.; Deaver, R. E.; Satyamoorthy, K.; Babitha, K. S. Histone Deacetylase 2 Selective Inhibitors: A Versatile Therapeutic Strategy as next Generation Drug Target in Cancer Therapy. *Pharmacol. Res.* **2021**, *170*, 105695. https://doi.org/10.1016/j.phrs.2021.105695.
[90]Pazin, M. J.; Kadonaga, J. T. What's Up and Down with Histone Deacetylation and Transcription? *Cell* **1997**, *89* [3], 325–328. https://doi.org/10.1016/S0092-8674[00]80211-1.
[91]Seto, E.; Yoshida, M. Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. *Cold Spring Harb. Perspect. Biol.* **2014**, *6* [4], a018713–a018713. https://doi.org/10.1101/cshperspect.a018713.
[92]Li, X.; Hou, J.; Li, X.; Jiang, Y.; Liu, X.; Mu, W.; Jin, Y.; Zhang, Y.; Xu, W. Development of 3-Hydroxycinnamamide-Based HDAC Inhibitors with Potent in Vitro and in Vivo Anti-Tumor Activity. *Eur. J. Med. Chem.* **2015**, *89*, 628–637. https://doi.org/10.1016/j.ejmech.2014.10.077.
[93]Amin, S. A.; Trivedi, P.; Adhikari, N.; Routholla, G.; Vijayasarathi, D.; Das, S.; Ghosh, B.; Jha, T. Quantitative Activity–Activity Relationship [QAAR] Driven Design to Develop Hydroxamate Derivatives of Pentanoic Acids as Selective HDAC8 Inhibitors: Synthesis, Biological Evaluation and Binding Mode of Interaction Studies. *New J. Chem.* **2021**, *45* [37], 17149–17162. https://doi.org/10.1039/D1NJ02636D.
[94]Zhang, L.; Zhang, J.; Jiang, Q.; Zhang, L.; Song, W. Zinc Binding Groups for Histone Deacetylase Inhibitors. *J. Enzyme Inhib. Med. Chem.* **2018**, *33* [1], 714–721. https://doi.org/10.1080/14756366.2017.1417274.
[95]Jiang, B. E.; Hu, J.; Liu, H.; Liu, Z.; Wen, Y.; Liu, M.; Zhang, H. K.; Pang, X.; Yu, L. F. Design, Synthesis, and Biological Evaluation of Indole-Based Hydroxamic Acid Derivatives as Histone Deacetylase Inhibitors. *Eur. J. Med. Chem.* **2022**, *227*, 113893. https://doi.org/10.1016/j.ejmech.2021.113893.
[96]Garnock-Jones, K. P. Panobinostat: First Global Approval. *Drugs* **2015**, *75* [6], 695–704. https://doi.org/10.1007/s40265-015-0388-8.
[97]Fournel, M.; Bonfils, C.; Hou, Y.; Yan, P. T.; Rahil, J.; Lefebvre, S.; Moradei, O.; Delorme, D.; MacLeod, A. R.; Besterman, J. M.; Li, Z. MGCD0103, a Novel Isotype-Selective Histone Deacetylase Inhibitor, Has Broad Spectrum Antitumor Activity in Vitro and in Vivo. *Mol. Cancer Ther.* **2008**, 7 [4], 759–768. https://doi.org/10.1158/1535-7163.MCT-07-2026.
[98] Marks, P. A. Discovery and Development of SAHA as an Anticancer Agent. *Oncogene* **2007**, *26* [9], 1351–1356. https://doi.org/10.1038/sj.onc.1210204.
[99]Arts, J.; King, P.; Marin, A.; Talloen, W.; Goris, I.; Andries, L.; Du Jardin, M.; Janicot, M.; Page, M.; van Emelen, K.; Angibaud, P. JNJ-26481585, a Novel Second-Generation Oral Histone Deacetylase Inhibitor, Shows Broad-Spectrum Preclinical Antitumoral Activity. *Clin. Cancer Res.* **2009**, 15 [22], 6841–6851. https://doi.org/10.1158/1078-0432.CCR-09-0547.
[100]Chen, Y.; Zhang, L.; Zhang, L.; Jiang, Q.; Zhang, L. Discovery of Indole-3-Butyric Acid Derivatives as Potent Histone Deacetylase Inhibitors. *J. Enzyme Inhib. Med. Chem.* **2021**, *36* [1], 425–436. https://doi.org/10.1080/14756366.2020.1870457.
[101]Li, X.; Wu, J.; Li, X.; Mu, W.; Liu, X.; Jin, Y.; Xu, W.; Zhang, Y. Development of N-Hydroxybenzamide Derivatives with Indole-Containing Cap Group as Histone Deacetylases Inhibitors. *Bioorg. Med. Chem.* **2015**, *23* [19], 6258–6270. https://doi.org/10.1016/j.bmc.2015.08.040.
[102]Brouhard, G. J.; Rice, L. M. The Contribution of Aβ-Tubulin Curvature to Microtubule Dynamics. *J. Cell Biol.* **2014**, *207* [3], 323–334. https://doi.org/10.1083/jcb.201407095.
[103]Akhmanova, A.; Steinmetz, M. O. Control of Microtubule Organization and Dynamics: Two Ends in the Limelight. *Nat. Rev. Mol. Cell Biol.* **2015**, *16* [12], 711–726. https://doi.org/10.1038/nrm4084.
[104]Romagnoli, R.; Prencipe, F.; Oliva, P.; Baraldi, S.; Baraldi, P. G.; Schiaffino Ortega, S.; Chayah, M.; Kimatrai Salvador, M.; Lopez-Cara, L. C.; Brancale, A.; Ferla, S.; Hamel, E.; Ronca, R.; Bortolozzi, R.; Mariotto, E.; Mattiuzzo, E.; Viola, G. Design, Synthesis, and Biological Evaluation of 6-Substituted Thieno[3,2-d]Pyrimidine Analogues as Dual Epidermal Growth Factor Receptor Kinase and Microtubule Inhibitors. *J. Med. Chem.* **2019**, *62* [3], 1274–1290. https://doi.org/10.1021/acs.jmedchem.8b01391.
[105]Tang, S.; Zhou, Z.; Jiang, Z.; Zhu, W.; Qiao, D. Indole-Based Tubulin Inhibitors: Binding Modes and SARs Investigations. *Molecules* **2022**, *27* [5]. https://doi.org/10.3390/molecules27051587.
[106]Naaz, F.; Haider, M. R.; Shafi, S.; Yar, M. S. Anti-Tubulin Agents of Natural Origin: Targeting Taxol, Vinca, and Colchicine Binding Domains. *Eur. J. Med. Chem.* **2019**, *171*, 310–331. https://doi.org/10.1016/j.ejmech.2019.03.025.
[107]Jordan, M. A. Mechanism of Action of Antitumor Drugs That Interact with Microtubules and Tubulin. *Curr. Med. Chem. - Anti-Cancer Agents* **2002**, *2* [1], 1–17. https://doi.org/10.2174/1568011023354290.
[108]Tozer, G. M.; Prise, V. E.; Wilso, J.; Chaplin, D. J. Mechanisms Associated with Tumor Vascular Shut-down Induced by Combretastatin A-4 Phosphate: Intravital Microscopy and Measurement of Vascular Permeability. *Cancer Res.* **2001**, 61 [17], 6413–6422, PMID:11522635.
[109]Tozer, G. M.; Kanthou, C.; Baguley, B. C. Disrupting Tumour Blood Vessels. *Nat. Rev. Cancer* **2005**, *5* [6], 423–435. https://doi.org/10.1038/nrc1628.
[110]Kirwan, I. G.; Loadman, P. M.; Swaine, D. J.; Anthoney, D. A.; Pettit, G. R.; Lippert, J. W.; Shnyder, S. D.; Cooper, P. A.; Bibby, M. C. Comparative Preclinical Pharmacokinetic and Metabolic Studies of the Combretastatin Prodrugs Combretastatin A4 Phosphate and A1 Phosphate. *Clin. Cancer Res.* **2004**, *10* [4], 1446–1453. https://doi.org/10.1158/1078-0432.CCR-0518-03.
[111]Aprile, S.; Del Grosso, E.; Tron, G. C.; Grosa, G. In Vitro Metabolism Study of Combretastatin A-4 in Rat and Human Liver Microsomes. *Drug Metab. Dispos.* **2007**, *35* [12], 2252–2261. https://doi.org/10.1124/dmd.107.016998.
[112]Wang, G.; Liu, W.; Tang, J.; Ma, X.; Gong, Z.; Huang, Y.; Li, Y.; Peng, Z. Design, Synthesis, and Anticancer Evaluation of Benzophenone Derivatives Bearing Naphthalene Moiety as Novel Tubulin Polymerization Inhibitors. *Bioorg. Chem.* **2020**, *104*, 104265. https://doi.org/10.1016/j.bioorg.2020.104265.
[113]Shao, Y. Y.; Yin, Y.; Lian, B. P.; Leng, J. F.; Xia, Y. Z.; Kong, L. Y. Synthesis and Biological Evaluation of Novel Shikonin-Benzo[b]Furan Derivatives as Tubulin Polymerization Inhibitors Targeting the Colchicine Binding Site. *Eur. J. Med. Chem.* **2020**, *190*, 112105. https://doi.org/10.1016/j.ejmech.2020.112105.
[114]Beale, T. M.; Allwood, D. M.; Xian, J. A-Ring Dihalogenation Increases the Cellular Activity of Combretastatin-Templated Tetrazoles. *ACS Med. Chem. Lett.* **2012**, *3* [3], 177–181. https://doi.org/10.1021/ml200149g.
[115]Mustafa, M.; Abdelhamid, D.; Abdelhafez, E. S. M. N.; Ibrahim, M. A. A.; Gamal-Eldeen, A. M.; Aly, O. M. Synthesis, Antiproliferative, Anti-Tubulin Activity, and Docking Study of New 1,2,4-Triazoles as Potential Combretastatin Analogues. *Eur. J. Med. Chem.* **2017**, *141*, 293–305. https://doi.org/10.1016/j.ejmech.2017.09.063.
[116]Jin, Y.; Qi, P.; Wang, Z.; Shen, Q.; Wang, J.; Zhang, W.; Song, H. 3D-QSAR Study of Combretastatin a-4 Analogs Based on Molecular Docking. *Molecules* **2011**, *16* [8], 6684–6700. https://doi.org/10.3390/molecules16086684.
[117]Hawash, M.; Kahraman, D. C.; Olgac, A.; Ergun, S. G.; Hamel, E.; Cetin-Atalay, R.; Baytas, S. N. Design and Synthesis of Novel Substituted Indole-Acrylamide Derivatives and Evaluation of Their Anti-Cancer Activity as Potential Tubulin-Targeting Agents. *J. Mol. Struct.* **2022**, *1254*, 132345. https://doi.org/10.1016/j.molstruc.2022.132345.
[118]Yan, J.; Xu, Y.; Jin, X.; Zhang, Q.; Ouyang, F.; Han, L.; Zhan, M.; Li, X.; Liang, B.; Huang, X. Structure Modification and Biological Evaluation of Indole-Chalcone Derivatives as Anti-Tumor Agents through Dual Targeting Tubulin and TrxR. *Eur. J. Med. Chem.* **2022**, *227*, 113897. https://doi.org/10.1016/j.ejmech.2021.113897.
[119]Pecnard, S.; Provot, O.; Levaique, H.; Bignon, J.; Askenatzis, L.; Saller, F.; Borgel, D.; Michallet, S.; Laisne, M.-C.; Lafanechère, L.; Alami, M.; Hamze, A. Cyclic Bridged Analogs of IsoCA-4: Design, Synthesis and Biological Evaluation. *Eur. J. Med. Chem.* **2021**, *209*, 112873. https://doi.org/10.1016/j.ejmech.2020.112873.
[120]Fareed, M. R.; Shoman, M. E.; Hamed, M. I. A.; Badr, M.; Bogari, H. A.; Elhady, S. S.; Ibrahim, T. S.; Abuo-Rahma, G. E.-D. A.; Ali, T. F. S. New Multi-Targeted Antiproliferative Agents: Design and Synthesis of IC261-Based Oxindoles as Potential Tubulin, CK1 and EGFR Inhibitors. *Pharmaceuticals* **2021**, *14* [11], 1114. https://doi.org/10.3390/ph14111114.
[121]Das Mukherjee, D.; Kumar, N. M.; Tantak, M. P.; Datta, S.; Ghosh Dastidar, D.; Kumar, D.; Chakrabarti, G. NMK-BH2, a Novel Microtubule-Depolymerising Bis [Indolyl]-Hydrazide-Hydrazone, Induces Apoptotic and Autophagic Cell Death in Cervical Cancer Cells by Binding to Tubulin at Colchicine – Site. *Biochim. Biophys. Acta - Mol. Cell Res.* **2020**, *1867* [10], 118762. https://doi.org/10.1016/j.bbamcr.2020.118762.
[122]Shi, L.; Yang, S.; Chang, J.; Zhang, Y.; Liu, W.; Zeng, J.; Meng, J.; Zhang, R.; Wang, C.; Xing, D. Design, Synthesis and Biological Evaluation of 9-Aryl-5H-Pyrido[4,3-b]Indole Derivatives as Potential Tubulin Polymerization Inhibitors. *Front. Chem.* **2022**, *10*, 1–12. https://doi.org/10.3389/fchem.2022.1004835.
[123]Iacopetta, D.; Catalano, A.; Ceramella, J.; Barbarossa, A.; Carocci, A.; Fazio, A.; La Torre, C.; Caruso, A.; Ponassi, M.; Rosano, C.; Franchini, C.; Sinicropi, M. S. Synthesis, Anticancer and Antioxidant Properties of New Indole and Pyranoindole Derivatives. *Bioorg. Chem.* **2020**, *105* [September], 104440. https://doi.org/10.1016/j.bioorg.2020.104440.