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An overview on 2-indolinone derivatives as anticancer agents

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A B S T R A C T

2-Indolinone nucleus is considered one of a promising heterocyclic core in medicinal chemistry that showed numerous range of activity among which antimicrobial, antioxidant, antiviral, antitubercular and anticancer activities. Cancer targeting is still an issue so there is a need for developing new agents that inhibit cancer growth without or low effect on normal body cells. Some derivatives of indolin-2-one are known to be a critical structure in some inhibitors of receptor tyrosine kinases (RTKs); a cancer target therapy, for example, Sunitinib. Herein in this review we focus on 2-indolinone derivatives as RTKs inhibitors as cancer targeting therapy.

1. Introduction

2-Indolinone is considered an indole derivative. Indole is a heterocyclic organic compound that consists of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. It is a ubiquitous compound in nature and is found in various biological systems, including tryptophan, a common amino acid. The unique structure of indole has garnered significant interest in the scientific community, leading to extensive research on its derivatives and biological activities.[1-4] Indole derivatives have shown to exhibit diverse biological activities, including antimicrobial, anti-inflammatory, and antitumor properties. They have been utilized as starting materials for the synthesis of various pharmaceuticals and agrochemicals, making them an essential class of compounds in synthetic organic chemistry. Moreover, indole derivatives have also shown promise in drug discovery, with several compounds undergoing clinical trials for the treatment of various diseases.[5-7]

Cancer epidemic is a global health problem that causes one death for each six cases worldwide. According to estimates, 19.3 million cancer cases were diagnosed, and 10 million cancer deaths occurred worldwide in 2020.[8] In addition to their uncontrolled proliferation, cancer cells invade healthy tissues, causing them to suffer destruction. Surgical, chemotherapy, and radiation treatments for cancer have significantly improved patient prognosis and survival rates. New approaches to cancer treatment are being developed, including targeted therapy. A few advantages over traditional methods are that it is specific and has few side effects. Tyrosine kinase inhibitors, which target intracellular molecules in tumor cells, c-Met and apoptosis-inducing drugs are ideal candidates for targeted cancer therapy. Recently, US Food and Drug Administration (FDA) has been approved 28 molecules as tyrosine kinase inhibitor.[8]

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Heterocyclic compounds, including the widely distributed indole derevatives, have been found to be a significant source of pharmacologically active compounds, particularly anti-cancer agents. Due to its unique physical, chemical, and biological properties, the indole compounds have been used as a privileged scaffold in the design of anti-cancer agents. Many natural and synthetic indole componds have been discovered as promising anti-cancer agents and have been used in clinical evaluations, such as 2-indolinones, indicating the significant role of indole derivatives in the development of anti-cancer drugs.[9-11] This review aimed to provide an overview on some 2-indolinone derevatives as anti-cancer agents.

2. Cancer Development and control

Cancer proliferation, survival, and angiogenesis are regulated by protein kinases. Protein kinases are fundamental for phosphorylation of proteins/enzymes which in turn control signal transduction within the cell in response to internal or external signals. Additionally, epidermal growth factors (EGFs), angiopoietin-2, vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs), and platelet-derived growth factors (PDGFs) stimulated tumor angiogenesis. So targeting of VEGFs, PDGFs and their RTKs by using SMKIs (i.e. small molecule kinase inhibitors) can block signal transduction and induce cancer death (**Fig. 1**). Tyrosine kinase inhibitors (TKIs) is considered one of the most promising cancer targeted therapy causing less damage to normal cell.[12]

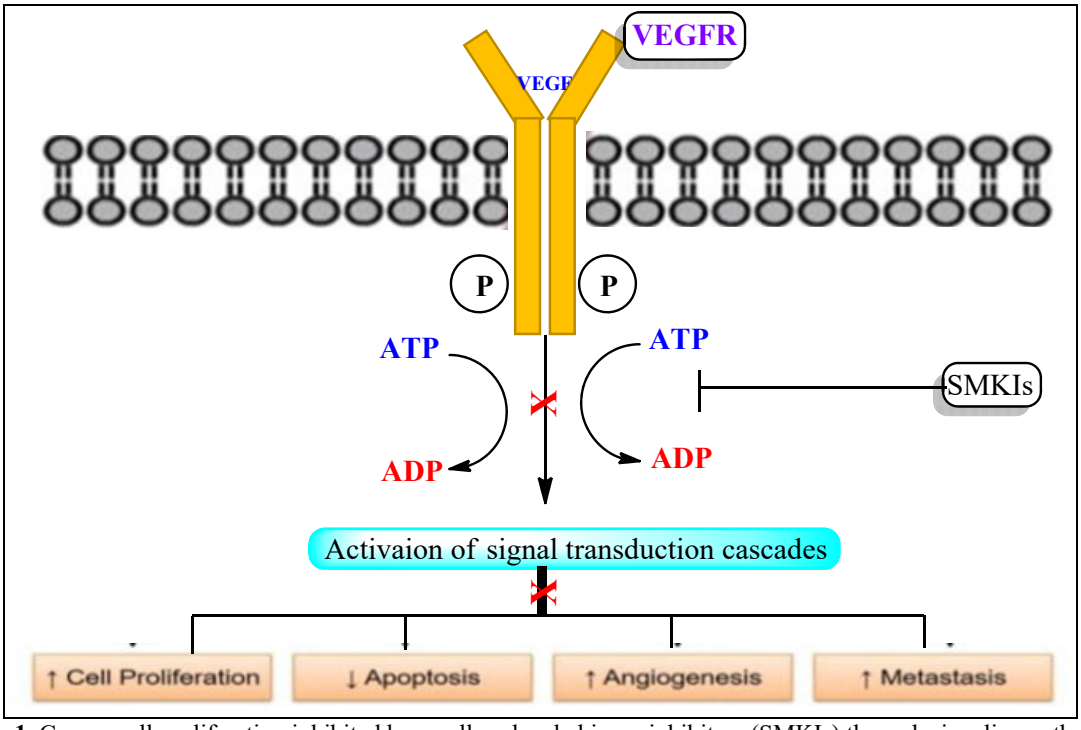


Fig. 1. Cancer cell proliferation inhibited by small molecule kinase inhibitors (SMKIs) through singaling pathway blockage.

3. 2-Indolinone chemistry

2-Indolinone (oxindole) has an indole analog structure with carbonyl group at C-2 position (**Fig. 2**).[13]

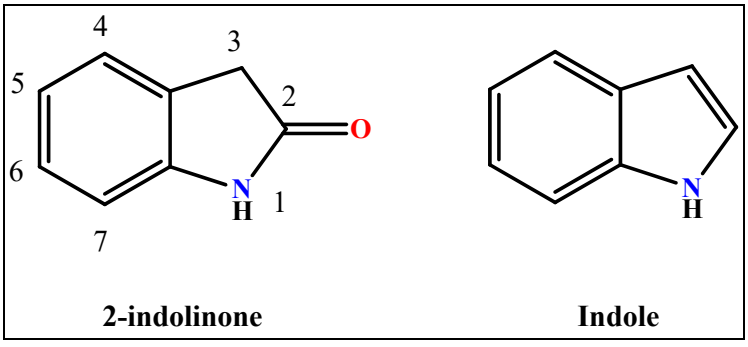


Fig 2. 2-indolinone and indole structures.

This scaffold has many biological properties that are relevant to medicinal chemistry, making it a pharmacologically advantageous scaffold. From the bark of the tropical climber, Cat claw's plant (**Fig. 3**) (Uncaria Tomentosa), the first known oxindole derivative was naturally obtained in the form of alkaloids. It originated in the Amazon rainforests and other tropical zones of central and southern South America. Traditionally, it has been used to treat infections, cancer, gastric ulcers, arthritis, and other mild physical inflammations.[13]

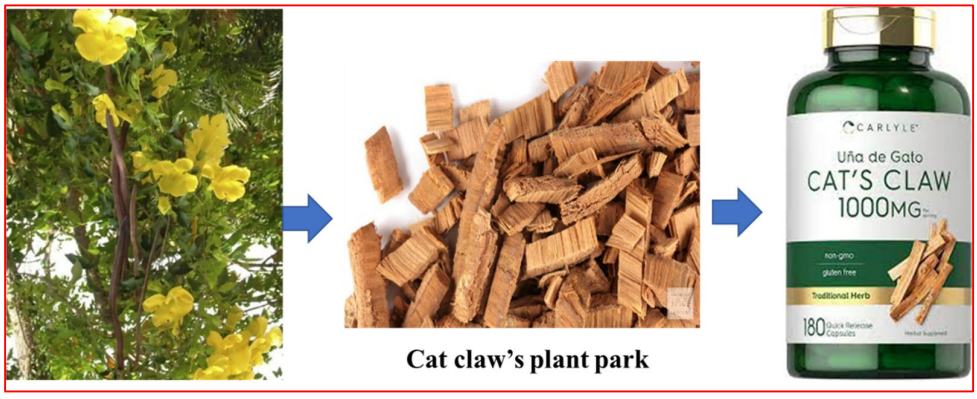
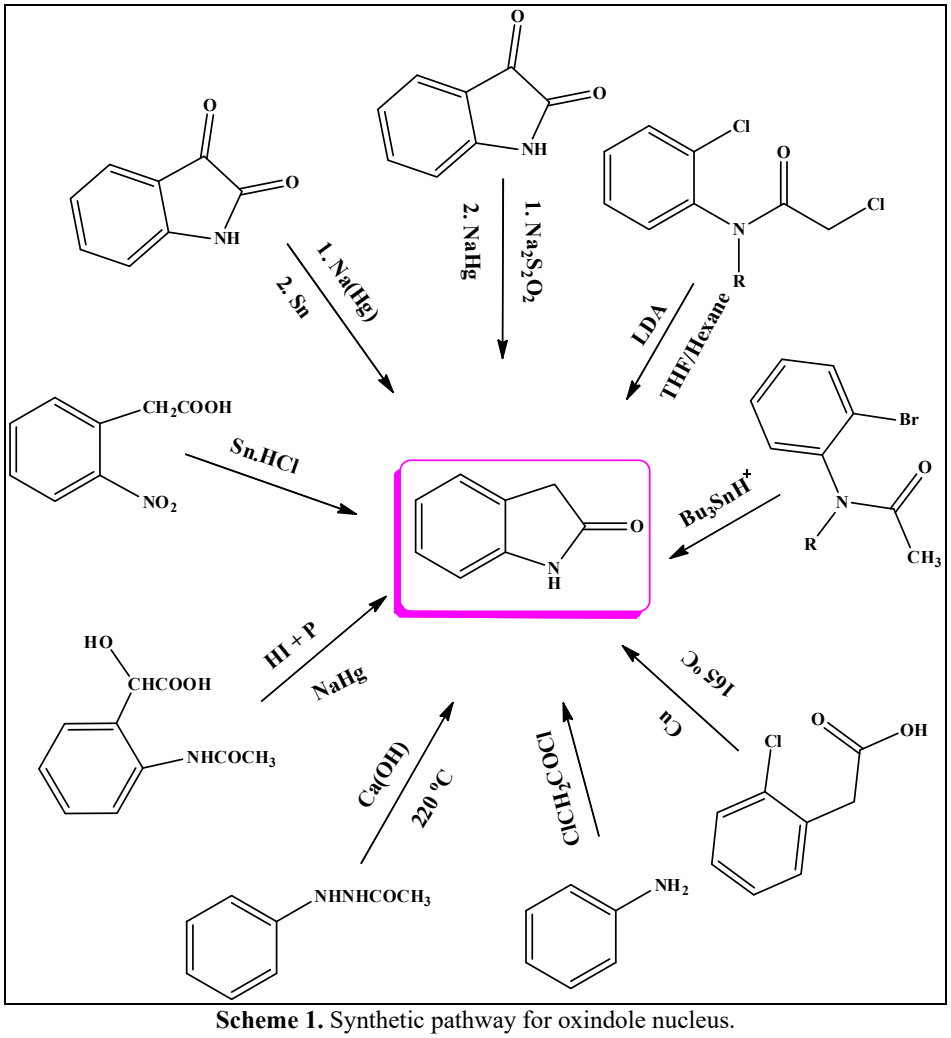
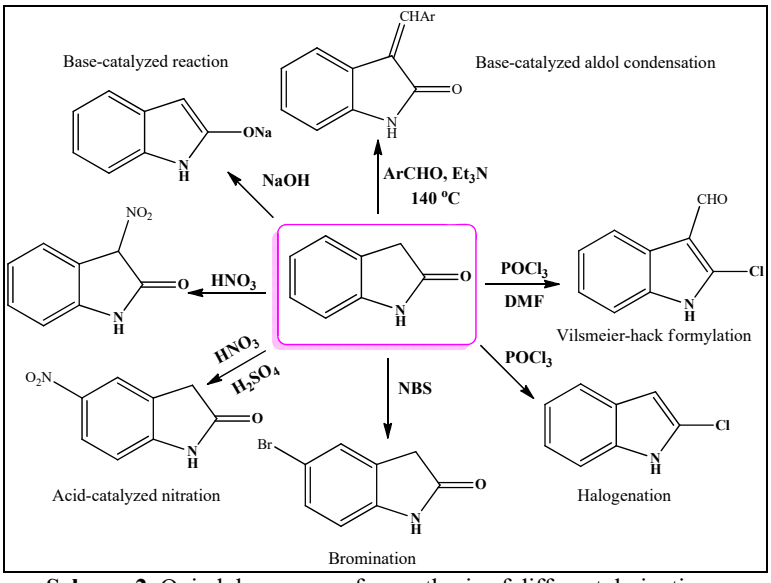


Fig. 3. Naturally occurring oxindole alkaloid isolated from Cat claw's plant.

As previously reported oxindole core structure can be obtained by following synthetic routes demonstrated in **Scheme 1**.[13] Moreover, oxindole can be used as lead structure for developing various derivatives as shown in **Scheme 2**.[13]



Scheme 1. Synthetic pathway for oxindole nucleus.



Scheme 2. Oxindole as a core for synthesis of different derivatives.

4. Pharmacological activity

Researchers have designed, synthesized, and tested oxindole derivatives for countless biological activities, such as the ability to treat cancer, microbes, rheumatoid arthritis, glucosidase inhibition, reducing intraocular pressure, tyrosinase inhibition, PAK-4 (Serine/threonine-protein kinase), antileishmanial, antimycobacterial, antioxidant, and antiviral.[13]

4.1 Oxindole as anticancer

Pyrrole indolin-2-One derivatives; Semaxanib, Sunitinib, Nintedanib (**Fig. 4**)[12] and benzyl Sulfoxide 2-indolinone derivatives; PHA665752 and SU11274 (**Fig. 4**)[14] will be handled in details.

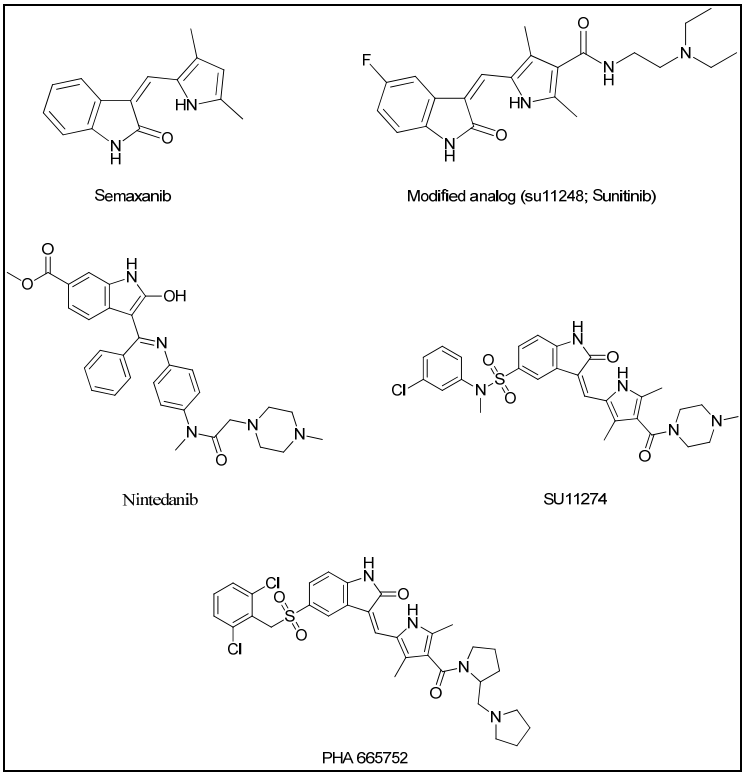
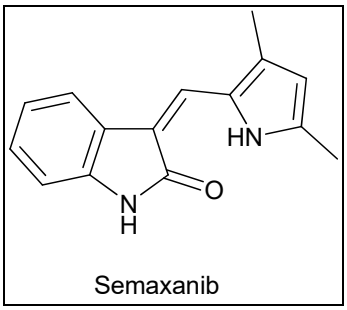
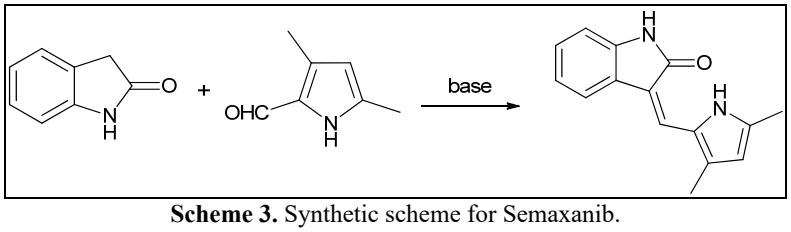


Fig 4. Chemical structures of Semaxanib, Sunitinib, Nintedanib, SU11274 and PHA 665752.

4.1.1 Semaxanib (SU5416) ((Z)-3-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)indolin-2-one)

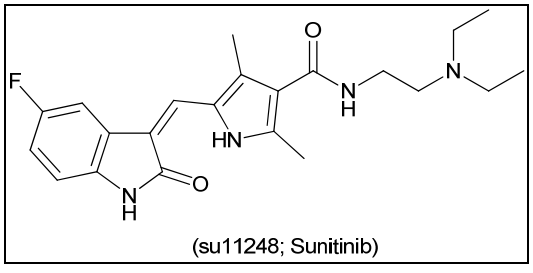


Semaxanib is a potent and selective synthetic inhibitor of the Flk-1/KDR vascular endothelial growth factor (VEGF) receptor tyrosine kinase designed by SUGEN, as a strategy to control malignancy, targeting angiogenesis is highly attractive.[15] In 2002, Phase III clinical trial of semaxinib was prematurely ended due to discouraging results.[16] Additionally, studies at earlier stages have been carried out.[17,18] This drug inhibits tumor growth and metastasis and decreases tumor microvessel density in preclinical models. Patients with acute myeloid leukemia and colorectal cancer have shown activity with semaxanib in clinical trials. According to the structure activity relationship, for VEGFR inhibition, the indolin-2-one core is essential for activity. However, their antiangiogenic and anticancer properties are also enhanced by pyrrol-2-yl substitutions at C-3 of the oxindole ring, water solubility and high protein binding properties, making it less desirable in clinical trials. The inefficacy of semaxanib in clinical trials and the prospect of next-generation tyrosine kinase inhibitors, the drug's development has been discontinued.[19] As of January 2006, Sugen and Pfizer developed SU11248 for renal carcinoma, and the FDA approved it as sunitinib. It was prepared following the synthetic pathway in **Scheme 3**.

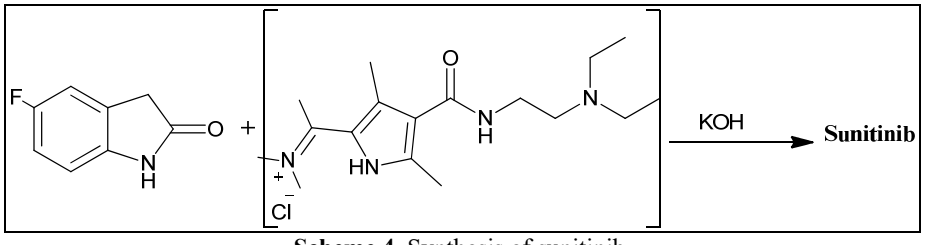


Scheme 3. Synthetic scheme for Semaxanib.

4.1.2 Sunitinib ((Z)-N-(2-(diethylamino)ethyl)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide)

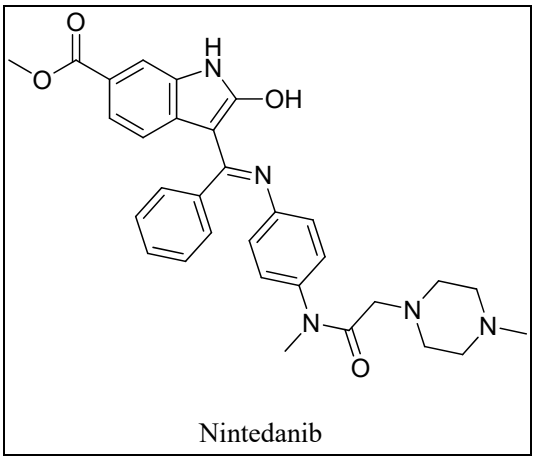


During the screening of indolin-2-one analogs, sunitinib was discovered as having potential and selective inhibition properties for four RTKs, including VEGFR-2, PDGFRs, FGFR-1, and EGFRs. However, modifications at C4′ position of SU-5416 were made through the introduction of the side chain. This renders sunitinib high water solubility compared to its prototype Semaxanib.[20] Sunitinib competition with ATP for the VEGFR ATP-binding pocket were located in the cytoplasm. Sunitinib inhibits further downstream cell signaling by preventing the activated VEGFR from activating its intracellular kinase domain.[21] It can be clinically used for treatment of renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST).[22] It can be obtained by reaction of 5-fluorooxindole and from Vilsmeier adduct **(Scheme 4)**.[14,23]

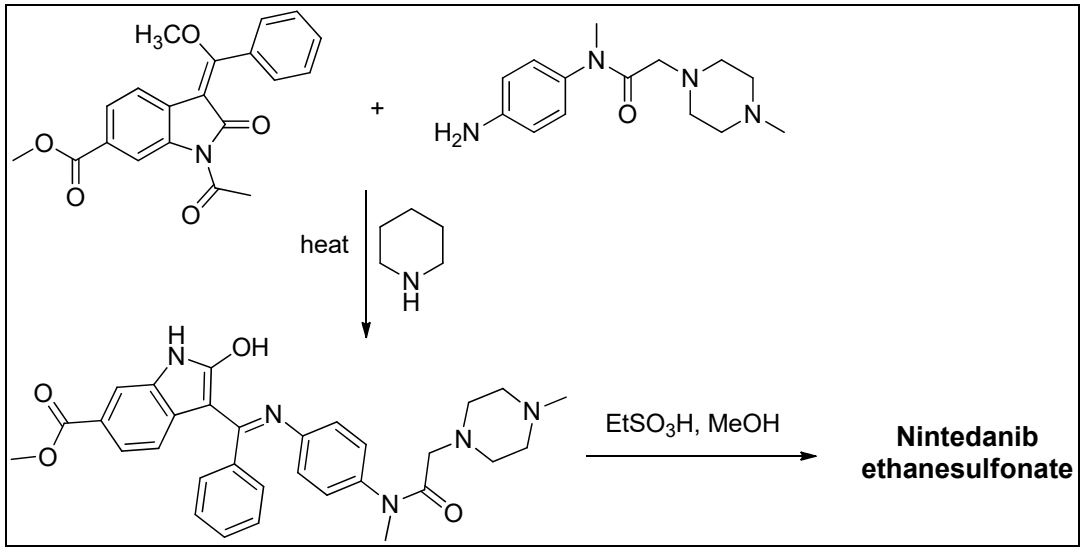


Scheme 4. Synthesis of sunitinib.

4.1.3 Nintedanib (BIBF1120) ((E)-methyl 2-hydroxy-3-((((4-(N-methyl-2-(4-methylpiperazin-1-yl)acetamido)phenyl)imino)(phenyl)methyl)-1H-indole-6-carboxylate)



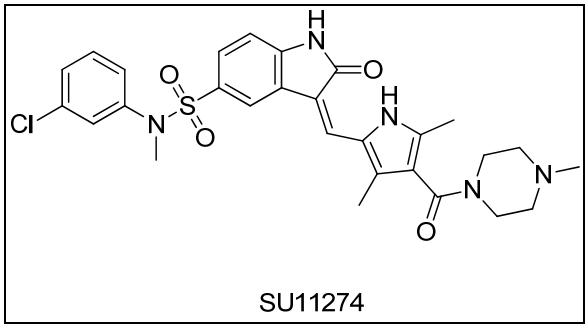
Vascular endothelial growth factor2 (VEGFR-2) inhibitors, endothelial cell proliferation and good oral bioavailability were targeted as lead optimization by Boehringer Ingelheim during developing angiogenesis inhibitors in 1998. As a result of that program, nintedanib has been identified and is currently in phase III clinical trials.[24] Nintedanib exerts its action through inhibition of autophosphorylation of growth factor receptors by binding to its intracellular adenosine triphosphate (ATP) binding site. Furthermore, it inhibits fibroblast proliferation and migration, preventing complications like pulmonary hypertension by reducing angiogenesis in the lungs.[25] In 2014, the FDA approved nintedanib for the treatment of idiopathic pulmonary fibrosis (IPF). A fascinating finding was that it reduced rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and systemic sclerosis-associated interstitial lung disease (SSc-ILD). Accordingly, in 2020 the FDA approved nintedanib for progressive fibrosing ILD and SSc-ILD. Patients with COVID-19-related pulmonary fibrosis and bleomycin-induced fibrosis also saw improvements in lung volume.[26] It is prepared according to literature procedure summarized in **Scheme 5**.[24]



Scheme 5. Synthesis of nintedanib ethanesulfonate.

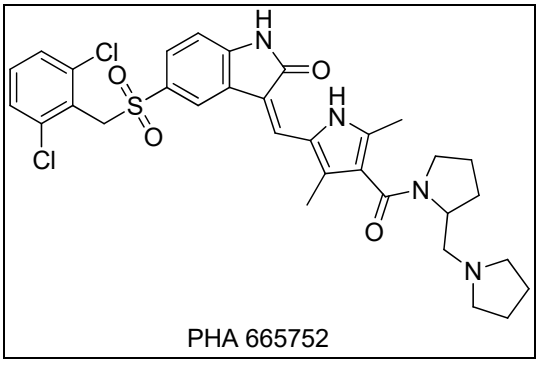
Nintedanib dose is 100 mg and 150 mg soft capsules recommended to be taken with food and fluids twice daily.[27] Besides hepatic impairment and gastrointestinal side effects, fatigue, dermal ulcer and upper respiratory tract infection can also appeared.[27] The drug is contraindicated during pregnancy and should be taken with caution in female patients over 65 with low body mass index (BMI), as well as those who have coronary artery disease, thromboembolism, anticoagulation, recent abdominal surgery, and gastrointestinal perforation in their past. There is no evidence that nintedanib therapy is safe for adolescents, children, or infants.[28]

4.1.4 C-Met inhibitor (SU11274) ((Z)-N-(3-chlorophenyl)-3-((3,5-dimethyl-4-(4-methylpiperazine-1-carbonyl)-1H-pyrrol-2-yl)methylene)-N-methyl-2-oxoindoline-5-sulfonamide)



As reported in literature, SU11274, a class I c-Met inhibitor, fluoresces when excited with 488 nm laser light and accumulates rapidly in subcellular compartments. The newly identified spectral properties of SU11274 were used to determine its intracellular distribution and accumulation in human pancreatic cancer cells. Researchers identified organelles to which SU11274 traffic. SU11274 accumulates primarily in the endoplasmic reticulum.[29] The intracellular kinase domain of c-MET is dimerized and transphosphorylated by hepatocyte growth factor (HGF), followed by the C-terminal multifunctional docking site (also known as the MET binding domain) phosphorylation of tyrosine residues). Apoptosis, migration, differentiation, and cell growth can all be modified by downstream signal transduction initiated by TKs. The dysregulation of signal cascades caused by constitutive activation or inhibition can result in malignancy and other diseases.[30] Cancer proliferation and motility can be affected by c-Met which can play a role in colorectal tumorigenesis, pancreatic cancer and non-small cell lung cancer (NSCLC) cells. SU11274 was found to have antitumorigenic and antimetastatic effect in melanoma and might be effective for inhibition of pancreatic and non-small lung cancer growth.[31] It can be synthesized as reported procedure by Leiser D *et al*.[32]

4.1.5 PHA-665752 ((Z)-5-((2,6-dichlorobenzyl)sulfonyl)-3-((3,5-dimethyl-4-(2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carbonyl)-1H-pyrrol-2-yl)methylene)indolin-2-one)



PHA-665752; has evolved from SU-11274 by substituting the 5-position of the indolinone and adding a 3,5-dimethylpyrrole group. Many publications have assigned c-Met as a suitable target for cancer therapy and also, numerous crystal structures were isolated with or without c-Met inhibitors.[33] In many tissues, c-Met and its ligand are expressed, respectively, as receptors for hepatocyte growth factor/scatter factor (HGF/SF). During embryogenesis, organogenesis, and tissue regeneration, C-Met/HGF/SF signaling is essential. It has been shown that abnormal c-Met/HGF/SF signaling leads to aggressive and metastatic tumor phenotypes in different types of tumors. Small-molecule inhibitor PHA665752 inhibits c-Met/HGF/SF signaling in vitro and in vivo. PHA665752 was tested on growth and motility of two neuroblastoma (NBL) cell lines and tumor tissue from patients with NBL.[34] Tumor cells treated with PHA665752 were also evaluated for their ability to migrate and proliferate in response to the tumor suppressor protein PTEN.[35] It is an anti-tumor agent capable of inhibiting tumorigenicity and angiogenesis, as well as being selective and ATP competitive against met kinase.[36] Clinically, it is used to treat mant types of leukemia including chronic myeloid leukemia, hairy cell leukemia acute and chronic lymphoblastic leukemia.[37] By the end of this literature review, we would like to emphasize that we continue in our current project to provide an updated reviews on diseases and drugs chemistry that help the humanity all over the world, and also we would like to emphasize on the importance of applied sciences in different fields as shown in this work and the other scientific papers published before.[38-136]

5. Conclusion

From the previous data, it was concluded that 2-indolinone is incorporated in many derivatives which were used clinically in treatment of different types of cancer. It was proved that 2- indolinone derivatives like Sunitinib, Semaxinib, Nintedanib, SU11274 and PHA-665752 were used successfully in treatment of acute myeloid leukemia, colorectal carcinoma, renal cell carcinoma, gastrointestinal stromal tumors, non-small cell lung cancer, chronic lymphocytic leukemia and hairy cell leukemia. Also, the 2-indolinone derivatives that were proved in treatment of cancer lack the substitutions in annular nitrogen. This literature review prompted the scientists in the medicinal field to create numerous 2-indolinone derivatives which simulate that in the literature with the hope that these compounds will be used in the field of cancer treatment.

Author Contributions

Samy M. Ibrahim, Ahmed S. Abdelkhalek, & Mahmoud M. Sebaiy: designed the study. Samy M. Ibrahim, Ahmed S. Abdelkhalek, Nada E. Freah, Nada H. El Hady, Nada K. Aidia, Nada A. Tawfeq, Nora I. Gomaa, Nora M. Fouad, Hager A. Salem, Hager M. Ibrahim & Mahmoud M. Sebaiy: paper preparation and writing original draft. Ahmed S. Abdelkhalek, Mahmoud M. Sebaiy, & Shaban A. A. Abdel-Raheem: adjusting the paper linguistically and spelling, and adjusting the paper according to the style of the journal.

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