


 Cite this: *RSC Adv.*, 2024, 14, 5690

Antineoplastic indole-containing compounds with potential VEGFR inhibitory properties†

 Dalia R. Aboshouk,^a M. Adel Youssef,^b Mohamed S. Bekheit,^a Ahmed R. Hamed^c and Adel S. Girgis^{*,a}

Cancer is one of the most significant health challenges worldwide. Various techniques, tools and therapeutics/materials have been developed in the last few decades for the treatment of cancer, together with great interest, funding and efforts from the scientific society. However, all the reported studies and efforts seem insufficient to combat the various types of cancer, especially the advanced ones. The overexpression of tyrosine kinases is associated with cancer proliferation and/or metastasis. VEGF, an important category of tyrosine kinases, and its receptors (VEGFR) are hyper-activated in different cancers. Accordingly, they are known as important factors in the angiogenesis of different tumors and are considered in the development of effective therapeutic approaches for controlling many types of cancer. In this case, targeted therapeutic approaches are preferable to the traditional non-selective approaches to minimize the side effects and drawbacks associated with treatment. Several indole-containing compounds have been identified as effective agents against VEGFR. Herein, we present a summary of the recent indolyl analogs reported within the last decade (2012–2023) with potential antineoplastic and VEGFR inhibitory properties. The most important drugs, natural products, synthesized potent compounds and promising hits/leads are highlighted. Indoles functionalized and conjugated with various heterocycles beside spiroindoles are also considered.

 Received 31st December 2023
 Accepted 29th January 2024

DOI: 10.1039/d3ra08962b

rsc.li/rsc-advances

1. Introduction

Cancer is one of the most significant health challenges worldwide. It is the second most fatal disease globally after cardiovascular disorders.¹ About 19–20 million people are diagnosed with different cancer types every year and many of them lose their life.² Although many techniques, tools and therapeutics/materials have been developed in the last few decades, none of them are effective in controlling the various types of cancer at different stages, especially the advanced ones.³ To date, this

^aDepartment of Pesticide Chemistry, National Research Centre, Dokki, Giza 12622, Egypt. E-mail: girgis10@yahoo.com; as.girgis@nrc.sci.eg

^bDepartment of Chemistry, Faculty of Science, Helwan University, Helwan, Egypt

^cChemistry of Medicinal Plants Department, National Research Centre, Dokki, Giza 12622, Egypt

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ra08962b>


Dalia R. Aboshouk

Dalia R. Aboshouk, Research Assistant in the National Research Centre, Egypt. Awarded BSc from the Faculty of Science, Alexandria University (Honors Degree, 2013) and MSc in Organic Chemistry from Helwan University (2022).


M. Adel Youssef

Prof. M. Adel Youssef, Prof. of Organic Chemistry, Faculty of Science, Helwan University, Egypt. He received his PhD from AL-Azhar University, Egypt in 1976 and became a Professor of Organic Chemistry in 1990. He supervised many MSc and PhD theses, contributing to different branches of chemistry.



challenge is still a significant task despite the great interest, funding and efforts from the entire scientific society (including research institutes and pharmaceutical companies).⁴ Recently, progress has been achieved in cancer chemotherapy due to the efforts devoted to developing selective molecular therapeutics. Although traditional non-selective therapeutics are still employed clinically, their drawbacks/side effects and poor survival rates are major problems, limiting their applications. Additionally, the early detection of this disease is challenging, although it is the most appropriate opportunity for curing it.^{5,6}

To date, 90 protein tyrosine kinases have been identified among the known 518 kinases.⁷ Tyrosine kinases are capable of many diverse cellular functions including growth, proliferation, differentiation and death.⁸ Tyrosine kinases can catalyze the phosphorylation of tyrosine utilizing the adenosine triphosphate (ATP) molecule, which can be classified into receptor and non-receptor types. The receptor category include transmembrane, extracellular and intracellular, whereas the non-

receptors are intracellular.⁹ The overexpression of tyrosine kinases is associated with cancer proliferation and/or metastasis, indicating their importance as cancer chemotherapeutics.^{10,11}

Angiogenesis is an essential biological process for the formation/extension of new blood capillaries from the vessels present in the vascular system. Thus, it is an essential process for growth, menstruation, embryonic development, wound healing, functional repair and many pathological disorders including cancer. Furthermore, it is one of the main functions for delivering vital supplies including nutrients and oxygen to cells and removal of waste. Angiogenesis is also a critical process for tumor progression and metastasis. Many growth factors (VEGF: vascular endothelial growth factor, EGF: epidermal growth factor, and FGF: fibroblast growth factor) can stimulate angiogenesis.^{12–15} VEGF can be categorized into different classes (VEGF-A, B, C, and D), which can bind to diverse tyrosine kinase receptors (VEGFR-1, 2, and 3). Notably, VEGF and its receptors are hyper-activated in different cancers, and thus considered an important target for combating this disease. VEGFR-2 is the most well-known factor for angiogenesis of various solid tumors (colon, breast, ovary, lung, skin, renal, head, neck, lymphoma, etc.). Several drugs with inhibitory VEGFR-2 activity have been recognized and clinically approved as anticancer drugs.^{12,13,16} Anti-angiogenic active agents reduce the vascular permeability and enhance the extravasation of the therapeutic small molecules.¹⁷ However, some adverse effects have been reported to be associated with anti-VEGFR therapeutics including dermatologic disorders (skin rash, depigmentation and mucositis), painful hand-foot skin reactions and pruritus.¹⁸

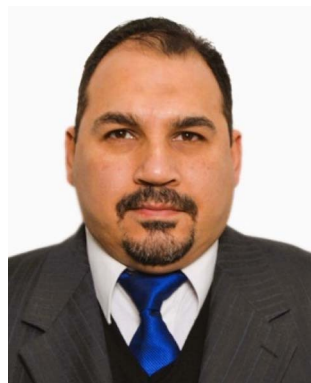
Accordingly, multi-targeted inhibitory drugs/candidates have become a recent trend in cancer chemotherapy, attracting significant attention and research interest. Interest in this strategy is attributed to the multifactorial nature of many cancer



Mohamed S. Bekheit

Mohamed S. Bekheit, Associate Professor in the National Research Center, Egypt since 2018. He received his PhD from Ain-Shams University, Egypt (2013). His research studies focus on design and synthesis of heterocyclic compounds of potential biological properties, together with interest in organophosphorus chemistry with special interest in computational chemistry techniques. He has participated in several national

and international research projects.



Ahmed R. Hamed

Ahmed Ragab Hamed, Professor of Therapeutic Biochemistry at the National Research Centre, Egypt. He was awarded his PhD in Biomedical Sciences from the University of Nottingham, UK (2005–2009). Subsequently, was granted two Postdoctoral Fellowships in Dundee (Scotland) and UT Health (Houston, Texas). His special interest is in the evaluation of compounds in various cell-based models such as cancer prevention, inflam-

mation inhibition and reversal of cancer multi-drug resistance. He also has experience in cancer cell biology and regulation of several members of the cytoprotective proteome using in vitro cell culture approaches, with experience in investigation the levels of expression of different mammalian proteins using western blotting.



Adel S. Girgis

Adel S. Girgis, Emeritus Professor at the National Research Centre (NRC), Egypt. He received his PhD from Cairo University, Egypt in 1997 and was promoted to Full Professor of Organic Chemistry at the National Research Centre, Egypt in 2009. He joined the research group of Prof. Alan R. Katritzky (Center of Heterocyclic Compounds, University of Florida, USA) in 2008 and 2013. He received many national and

international research funds. His research studies are focused on the design and synthesis of heterocyclic compounds with potential biological properties, with special interest in computational chemistry techniques.



types.⁷ Additionally, carcinoma cell initiation and proliferation involve various receptors and signaling pathways. Moreover, multi-target inhibitors can overcome cancer cell resistance, which is an advantage for multi-targeted treatment compared to single-targeted treatment or cocktail of multi-component drugs.^{7,19}

The indolyl scaffold occupies a unique position among the diverse alkaloids due to the wide range of bio-properties of its natural and synthesized analogs. Many natural alkaloids are well known, among which melatonin **1** is a natural hormone biosynthesized in the dark by the pineal gland²⁰ (Fig. 1). Recently, clinical trials supported its positive impact on the prevention or treatment COVID-19 infection upon being administered alone or in combination with other therapeutics.^{21–24} Serotonin **2** is a neurotransmitter that controls many human functions such as mood, appetite, sleep and social behavior.²⁵

Many indole-containing drugs have been approved and in clinical use for a long time, among which indomethacin **3** is a famous non-steroidal anti-inflammatory drug (approved by the FDA “Food and Drug Administration” since 1965)²⁶ with inhibitory properties against cyclooxygenase (COX), an enzyme controlling the formation of prostaglandin from arachidonic acid.²⁷ Delavirdine **4** (FDA approval in 1997) is an anti-HIV (human immunodeficiency virus) drug.^{28,29} Umifenovir **5** (approved in Russia and China) is an anti-influenza drug repurposed for the treatment of SARS-CoV-2.^{30–33} Pindolol **6** (antihypertensive drug, non-cardioselective β -blocker, FDA

approval in 1982)³⁴ and Maxalt 7 (antimigraine agent, FDA approval in 1998)³⁵ are also indole analogs. Cipargamin **8** exhibits high efficacy against protein synthesis in *Plasmodium falciparum*. In addition, it has entered pre-clinical trial investigations as a potential antimalarial drug.³⁶

The current study aims to describe and highlight the indole-containing compounds with potential anti-VEGFR properties. Specifically, the relevant keywords were input in different search engines such as Scopus, ScienceDirect and PubMed. The recent advances in this subject (last decade, 2023–2012) with the greatest diversification revealing promising bio-properties will be discussed.

2. Indole-containing drugs and potent agents

2.1. Sunitinib

Sunitinib (Sutent) **9** (Fig. 2) is an oral antitumor multi-targeted tyrosine kinase inhibitor (VEGFR-1,-2, -3; PDGFR- α , - β ; platelet-derived growth-factor receptor; and c-kit: stem cell factor receptor) against FLT3, which is an FMS-like tyrosine kinase inhibitor with potent anti-angiogenesis properties.^{16,37–39} It is clinically approved against advanced renal and imatinib-resistant gastrointestinal (FDA approval in 2006) and pancreatic cancers (FDA approval in 2011). It has also been given FDA approval (2017) for adult adjuvant treatment at high risk of

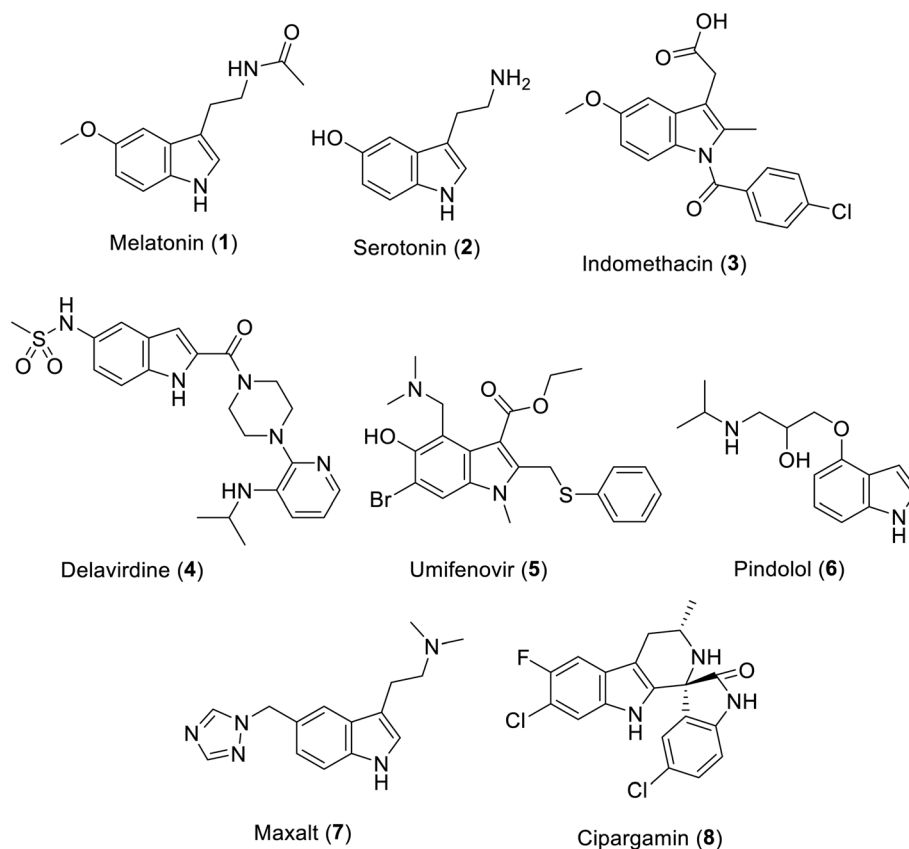


Fig. 1 Clinically approved indole-containing drugs (1–7) and cipargamin (8).



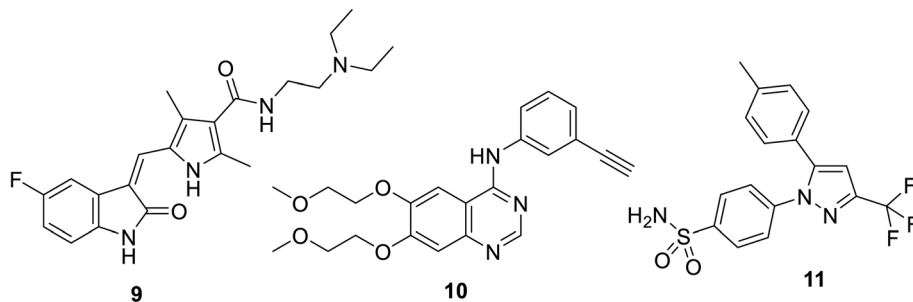


Fig. 2 Sunitinib (sutent) 9 multi-targeted tyrosine kinase inhibitor, erlotinib 10 (EGFR inhibitor) and celecoxib 11 (COX-inhibitor).

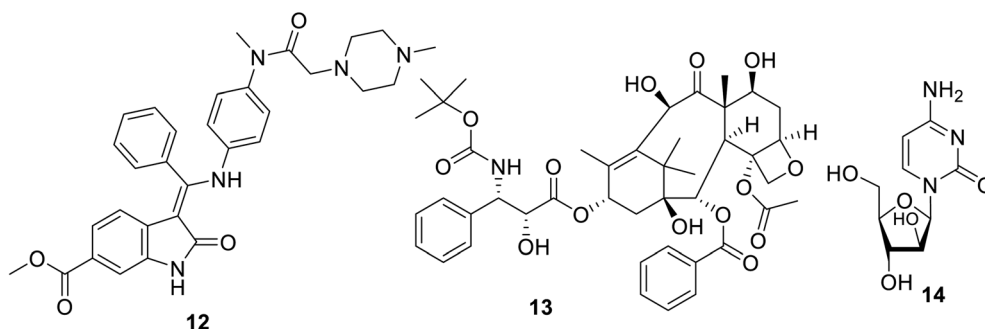


Fig. 3 Nintedanib 12 (multi-targeted) tyrosine kinase inhibitor, docetaxel 13 and cytarabine 14.

renal cancer.^{40,41} However, due to the side effects/drawbacks (diarrhea, fatigue, hypertension, hematologic toxicities, cardiotoxic effects and hand-foot syndrome)^{39,42–44} observed during clinical administration, many studies proposed the combination of sunitinib with another chemotherapeutic agent or radiation. This approach can reduce the unintended side effects and enhance the efficacy of the drug.⁴²

Also, sunitinib can be useful in the treatment of melanoma, which was supported by pre-clinical studies revealing the initiation of tumor hypoxia in melanoma xenografts.¹⁶ An obvious objective response by solid tumors to sunitinib including metastatic breast, colon, neuroendocrine and non-small cell lung cancers (NSCLC) was reported.^{39,42,45}

A synergistic effect was observed upon the combination of sunitinib with erlotinib 10 (EGFR: epidermal growth factor receptor, inhibitor) for the treatment of NSCLC A549 xenograft mice⁴⁶ (Fig. 2). Pre-clinical model studies supported that the combination of PRX177561 (CXC4, chemokine receptor type 4 antagonist) with sunitinib enhanced the therapeutic efficacy (reducing the tumor proliferation and extending the disease-free survival) against glioblastoma (brain cancer).^{47,48} *In vivo* studies supported that a COX-2 (cyclooxygenase-2) inhibitor (celecoxib 11) can enhance the activity of sunitinib in mice bearing human renal cancer xenografts *via* the observation of delay in tumor progression.⁴⁹

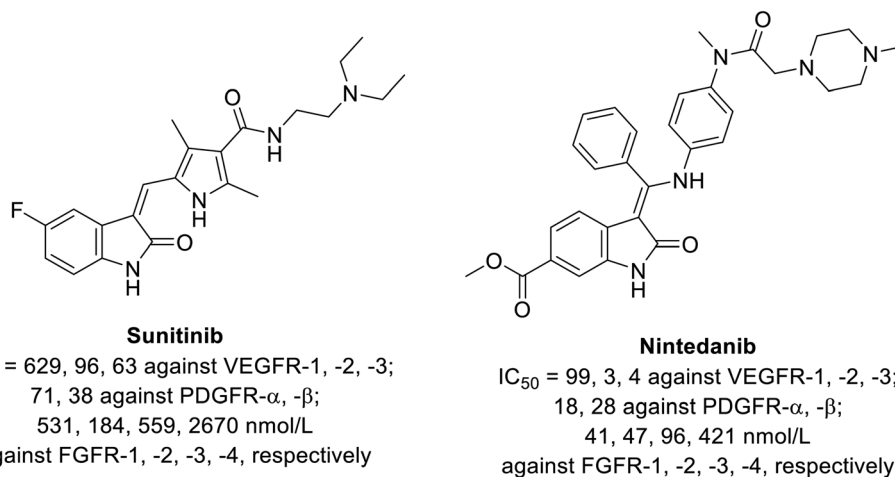


Fig. 4 Inhibitory properties of sunitinib and nintedanib against tyrosine kinases (VEGFR-1, -2, -3; PDGFR- α , - β and FGFR-1, -2, -3, -4).⁵²



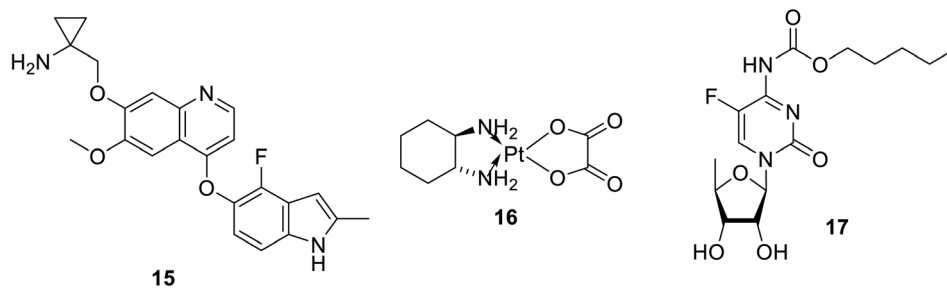


Fig. 5 Anlotinib 15 (a multi-targeted tyrosine kinase inhibitor), oxaliplatin 16 capecitabine 17.

2.2. Nintedanib

Nintedanib 12 (Ofev and Vargatef) is also an oral multi-targeted tyrosine kinase inhibitor (VEGFR-1, -2, -3; PDGFR- α , - β and

FGFR-1, -2, -3, -4: fibroblast growth-factor receptor)⁵⁰⁻⁵⁴ (Fig. 3 and 4). The FDA approved its use for the treatment of idiopathic lung fibrosis (2014), systemic sclerosis-associated interstitial

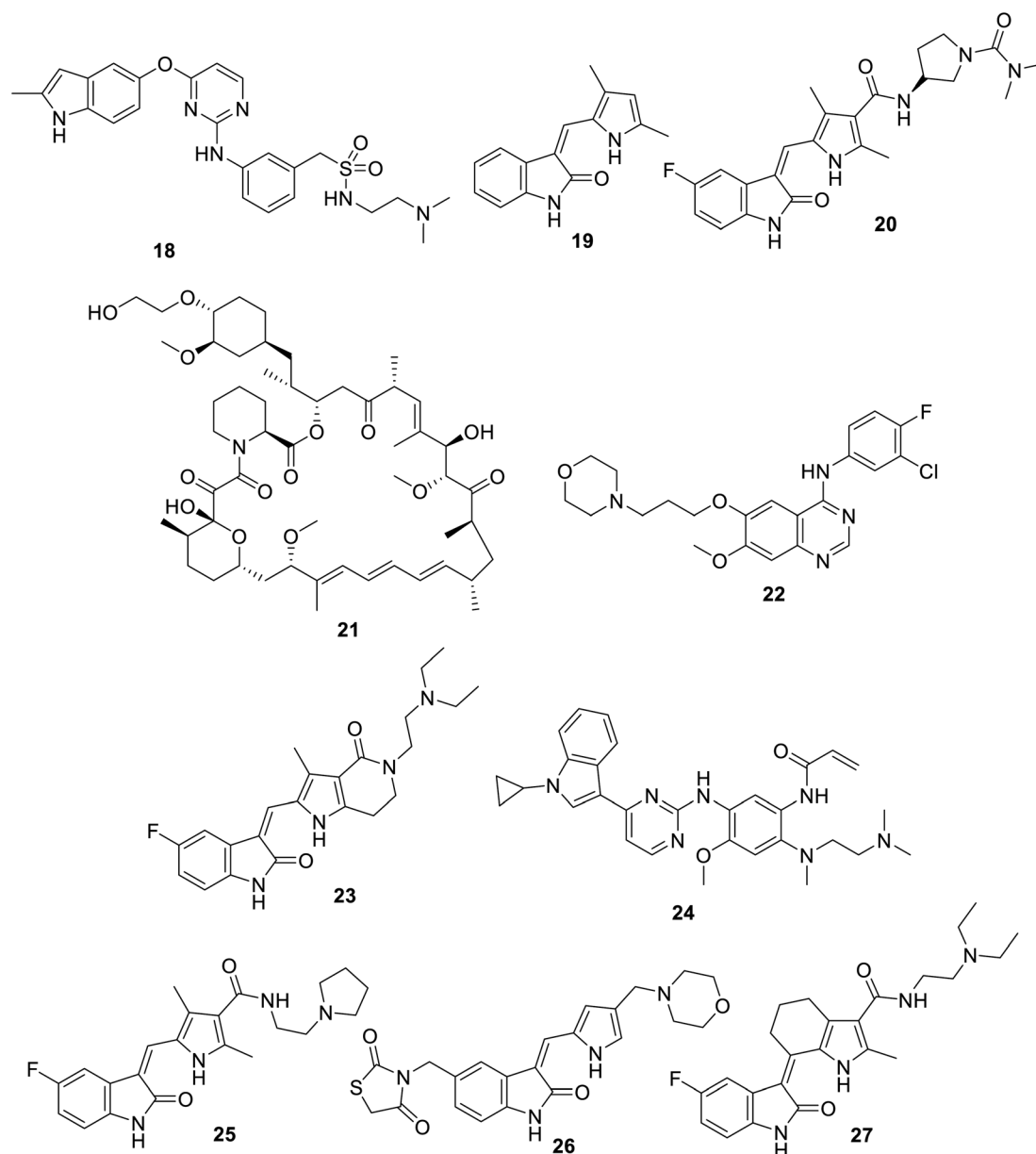
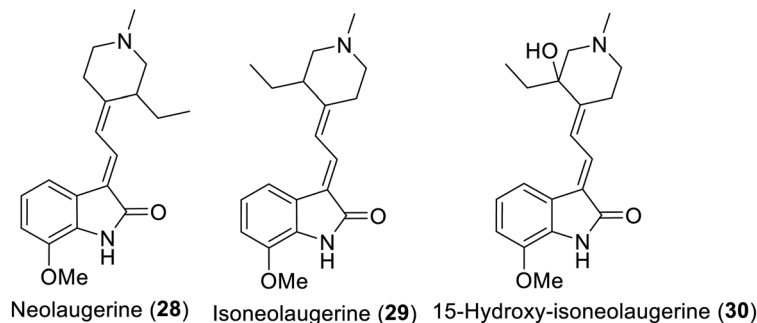
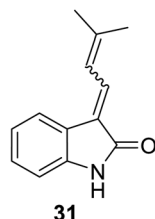


Fig. 6 Chemical structures of surufatinib 18, SU5416 (semaxanib) 19, vorolanib (CM082) 20, everolimus 21, gefitinib (Iressa) 22, famitinib 23, almonertinib (HS-10296) 24, toceranib (Palladia, Zoetis) 25, S49076 26 and SIM010603 27.

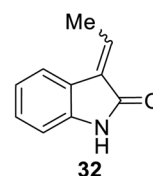




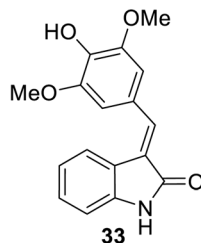
Three oxindole alkaloids were isolated from the root bark of *Neolaugeria resinosa*, a small evergreen tree distributed throughout the Bahamas and West Indies



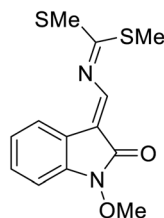
(*E*)- and (*Z*)-3-(3'-methyl-2'-butenylidene)-2-indolinones, these two yellow pigments were isolated from the rhizomes of *Cimicifuga dahurica*, a plant used in the Chinese traditional medicine and particularly known for its antipyretic properties



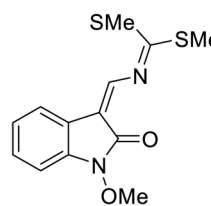
(*E*)- and (*Z*)-3-ethylidene-1,3-dihydroindol-2-ones were isolated from the fungus *Colletotrichum fragariae* and have been described as self-germination inhibitors



The oxindole alkaloid *E*-33 was isolated from the roots of *Isatis indigotica*, a constituent of the widely used traditional Chinese medicine mainly used for its antipyretic, antiviral and detoxifying properties

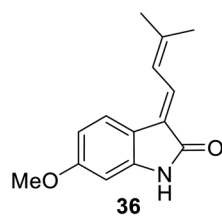


Wasalexin A (**34**)

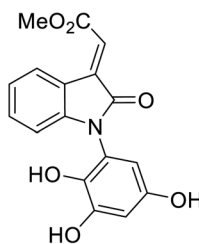


Wasalexin B (**35**)

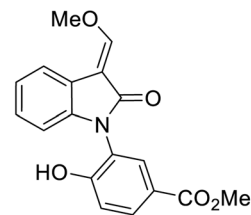
Two phytoalexins were isolated from the foliar tissue of wasabi (*Wasabia japonica*, *syn. Eutrema wasabi*) and wasalexin A exhibited antifungal activity against *Phoma lingam*



Soulieotine was isolated from the rhizomes of *Souliea vaginata*, a plant employed as an anti-inflammatory analgesic in traditional Chinese medicine.



Costinone A (**37**)



Costinone B (**38**)

Costinone A and costinone B were isolated from the Pakistani herb *Isatis costata* and found to inhibit lipoxygenases and butylcholinesterases

Fig. 7 Natural indole-containing compounds 28–38 with potential bio-properties.

lung disease (2019) and NSCLC (in combination with docetaxel **13**).^{50,52–56} However, the most notable side effects are diarrhea and increase in alanine and aspartate aminotransferase associated with the clinical administration of nintedanib.⁵⁴

Many studies explained the promising efficacy of nintedanib against different types of cancer. The delay of the proliferation and growth arrest of a mouse prostate (TRAMP: transgenic adenocarcinoma of the mouse prostate) model by nintedanib



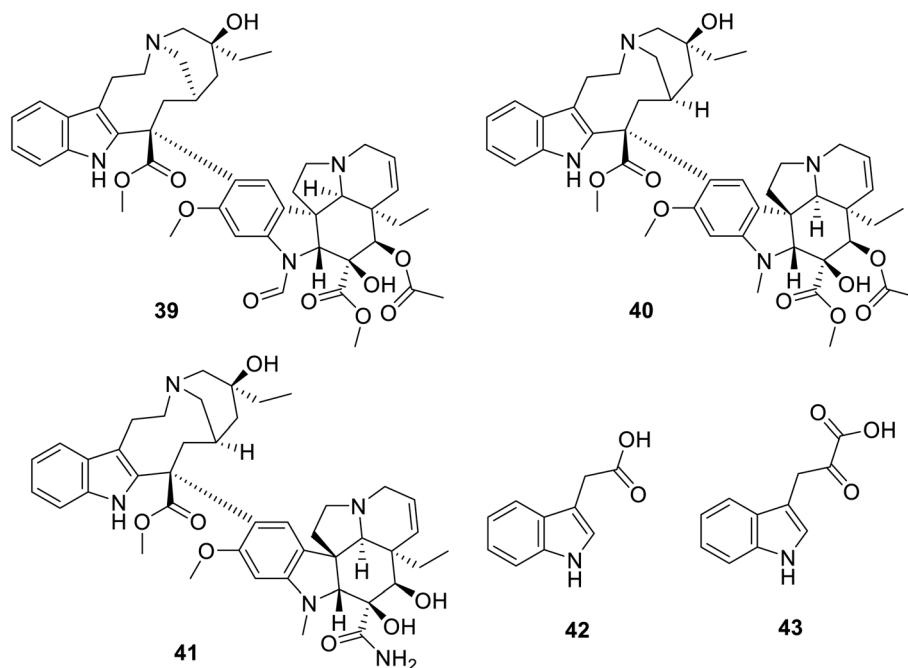
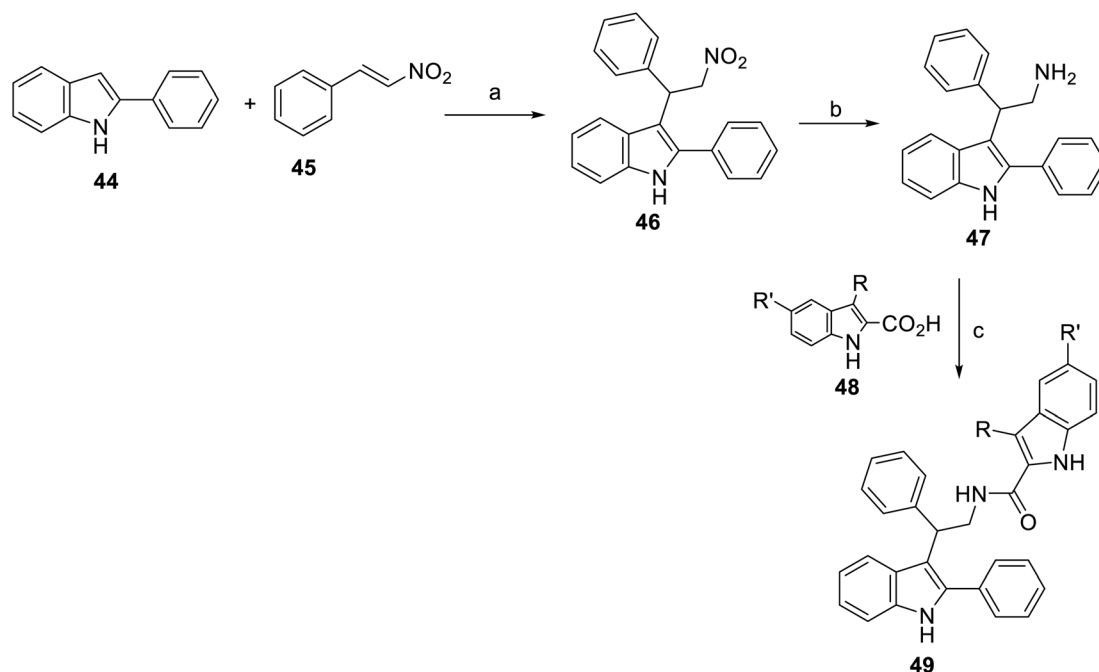


Fig. 8 Chemical structures of vincristine **39**, vinblastine **40**, vindesine **41**, 3-indole acetic acid **42** and 3-indole pyruvic acid **43**.

indicates its promising properties against prostate cancer.^{57,58} Its clinical trial (phase III) also support its promising properties against ovarian cancer.^{59,60} A compensatory role was reported for nintedanib towards metastatic colon cancer.⁶¹ Meanwhile, clinical trial observation (20 patients, 200 mg twice per day)

revealed that there was no considerable effect on salivary gland cancer except in controlling the rate of the disease.⁶² A phase I clinical study (13 elderly patients) also showed its efficacy towards myeloid leukemic cells, especially when used with cytarabine **14**.⁶³

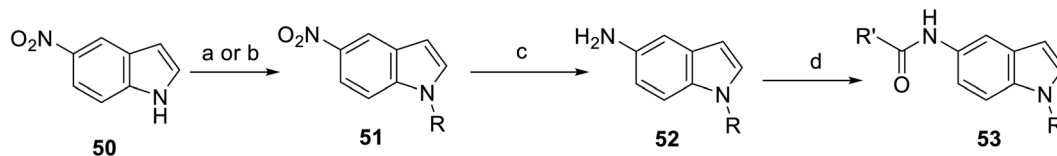


R = H, Me, Et, CH₂OH, Ph, CH=CH-OMe, CH₂OEt; R' = Cl, Br

a) sulfamic acid, MeOH, reflux, 12h; b) LiAlH₄, Et₂O, 0 °C to room temperature, overnight;
c) BOP, DIPEA, DCM, room temperature, overnight

Scheme 1 Synthesis of indole-2-carboxamides **49**.





R = Me, 4-FC₆H₄CH₂, 3-pyridinyl-CH₂, 3-FC₆H₄-CO; R' = 3-pyridinyl, 2-pyrazinyl, 4-pyridazinyl

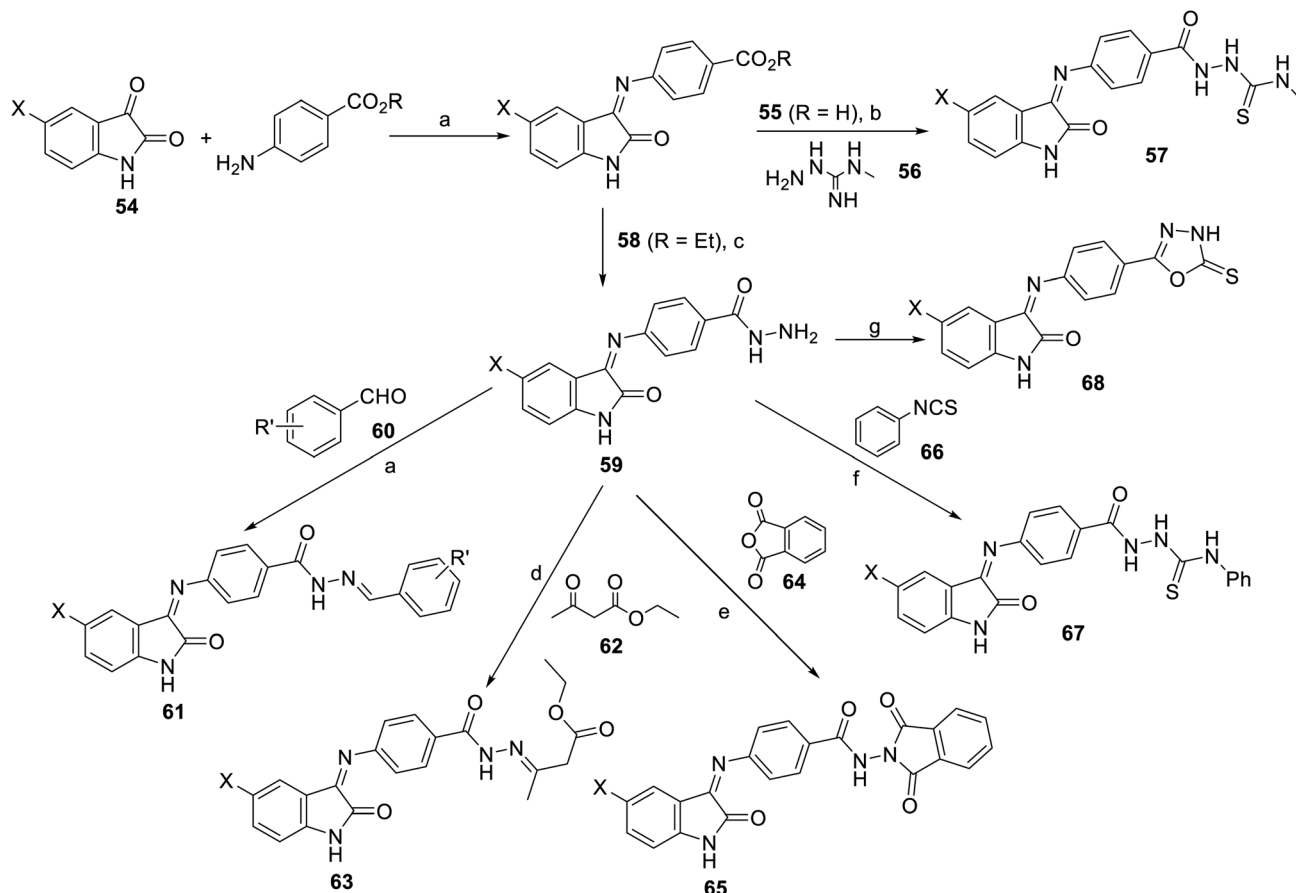
a) dimethyl carbonate, K₂CO₃, DMF, reflux 3h; b) aryl halide, NaH, DMF, 0–100 °C, 24h;
c) Fe, NH₄Cl, EtOH/H₂O, reflux, 1h; d) aryl carboxylic acid, HATU, DIPEA, DMF, mw, 116 °C, 45min.

Scheme 2 Synthesis of 5-indolecarboxamides 53.

2.3. Anlotinib

Anlotinib **15** (Fig. 5) is an oral multi-targeted tyrosine kinase inhibitor (VEGFR, PDGFR, FGFR and c-kit) approved in China for NSCLC.^{64–69} Hypertension and gastrointestinal problems are the most significant side effects associated with its administration.⁶⁵ Finger print loss for about two months was observed during a case study on its treatment of lung cancer.⁶⁵ It has also been

reported that anlotinib is capable of inhibiting lymphangiogenesis and lymphatic metastasis, which is probably due to the suppression of VEGFR-3 phosphorylation.⁷⁰ Antiproliferation properties were also observed against colon cancer cells (HCT-116 and LOVO).⁷¹ Moreover, anlotinib showed promising properties against thyroid and metastatic renal cell cancers.^{68,72} A phase II clinical study supported the possibility for the therapeutic

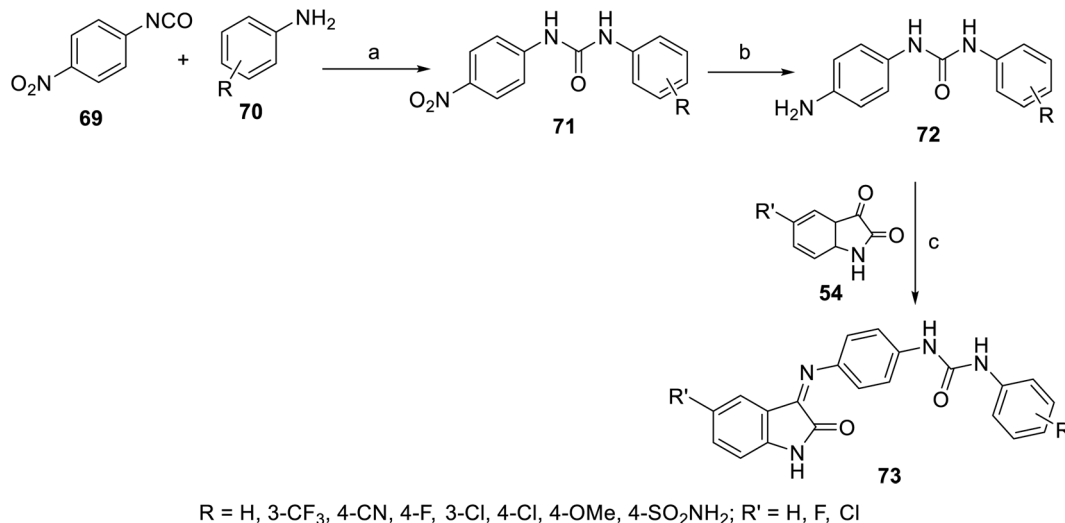


X = H, F; R = H, Et; R' = 4-NO₂, 4-Cl, 3-NO₂, 4-Me, 4-OMe, 4-NMe₂, 4-Br

a) EtOH, AcOH, reflux, 4–6 h; b) EDC, Et₃N, HOBt, DMF, 0 °C to room temperature, overnight; c) NH₂NH₂, EtOH, reflux, 2h; d) EtOH, AcOH, sonication, 50 °C, 4h;
e) AcOH, sonication, 50 °C, 4h; f) EtOH, reflux 8h, g) CS₂, KOH, EtOH, reflux, 12h then, 10% HCl

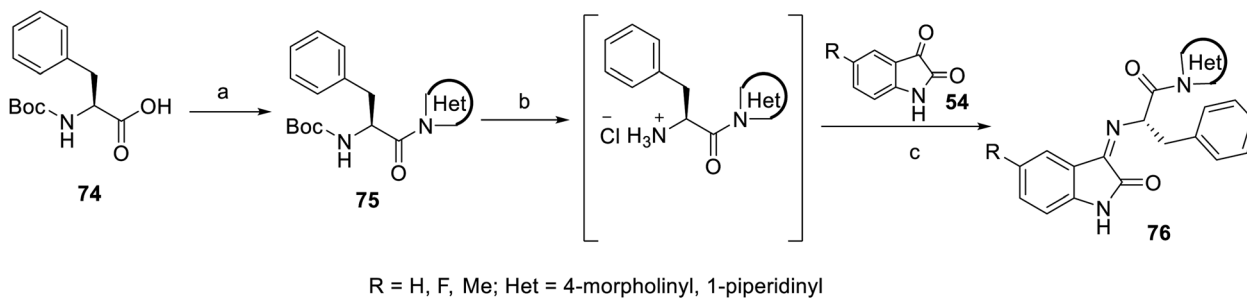
Scheme 3 Synthesis of indolyl Schiff bases 55, 57–59, 61, 63, 65, 67 and 68.





a) MeCN, reflux, 2h; b) H₂, Pd/C, MeOH, room temperature; c) EtOH, AcOH, reflux, 3h

Scheme 4 Synthesis of indolyl Schiff bases 73.



a) 2^o amine, THF, IBCF, NMM, room temperature, 6-8h; b) dioxane, HCl(g), room temperature, 2h;
c) EtOH, TEA, room temperature, 2h.

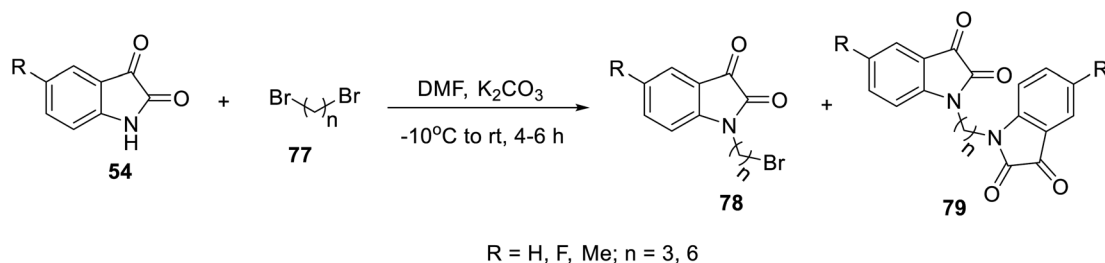
Scheme 5 Synthesis of indolyl Schiff bases 76.

utilization of anlotinib in combination with oxaliplatin **16** and capecitabine **17** to treat patients with metastatic colon cancer.⁷³

2.4. Surufatinib (HMPL-012, sulfatinib)

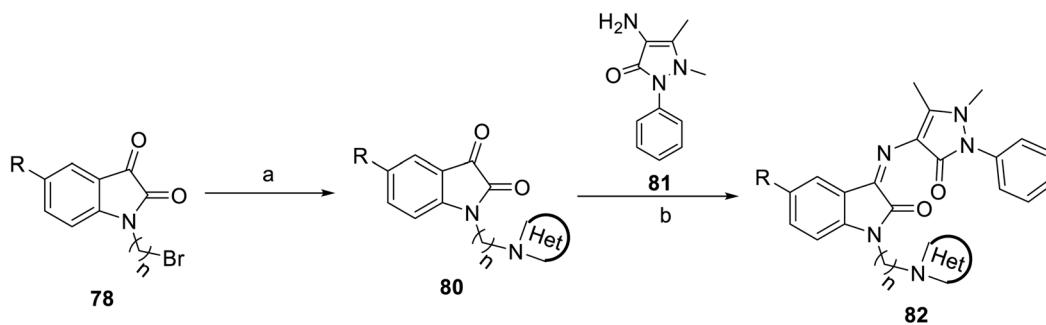
Surufatinib (Sulanda) **18** (Fig. 6) is an oral multi-kinase inhibitor with dual function against angiogenesis (VEGFR-1, -2, -3 and FGFR) and tumor immune evasion (CSF-1R: colony

stimulating factor-1 receptor). It is approved (in China, 2020) for the treatment of extrapancreatic neuroendocrine tumor (NET).⁷⁴ However, it has been filed with the FDA for approval for the treatment of advanced NET (2021).⁷⁵ Hypertension and proteinuria are the most severe adverse effects reported with the administration of Sulanda.⁷⁶ A phase II clinical study adopting 39 patients (300 mg, 28 day cycles, once daily) supported its possibility for moderate biliary tract cancer.⁷⁷



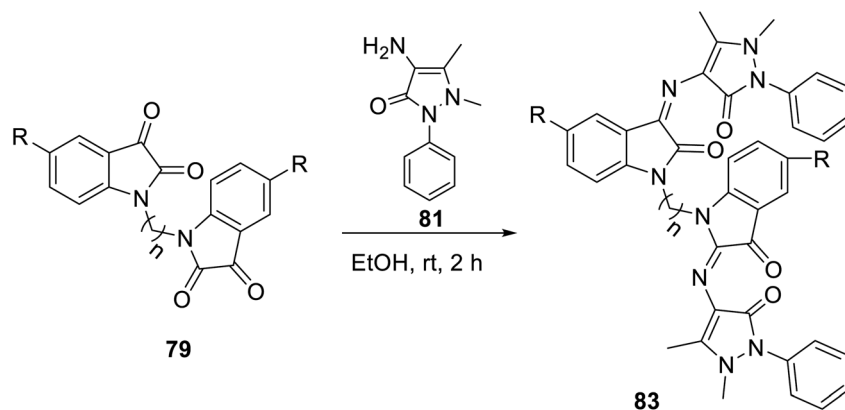
Scheme 6 Synthesis of mono- **78** and bis-alkylated isatins **79**.





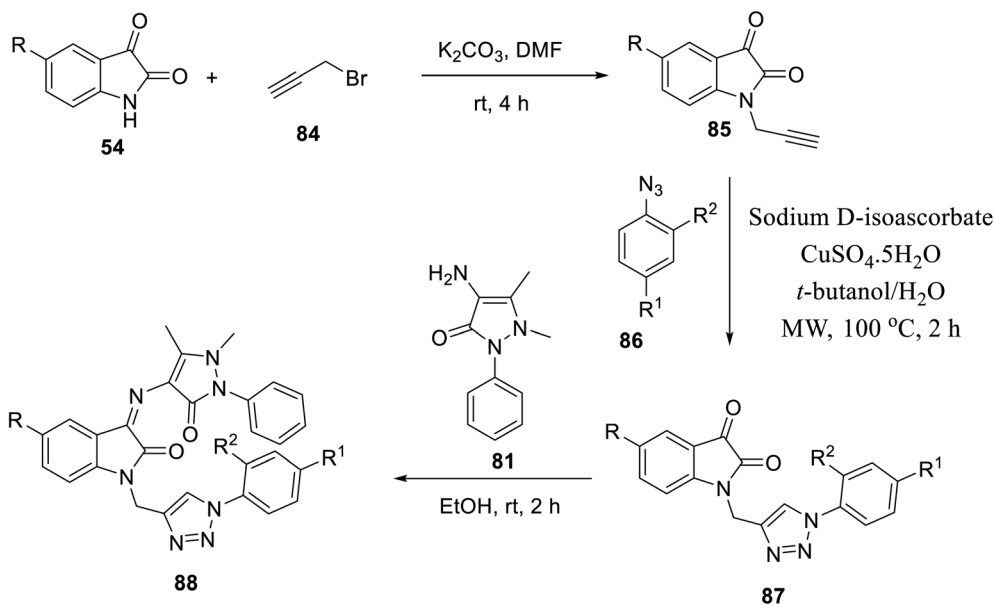
a) secondary amine, DMF, K_2CO_3 , room temperature, 4-6 h; b) EtOH, room temperature, 2h.

Scheme 7 Synthesis of indolyl Schiff bases 82.



$\text{R} = \text{H, F, Me}; n = 3, 6$

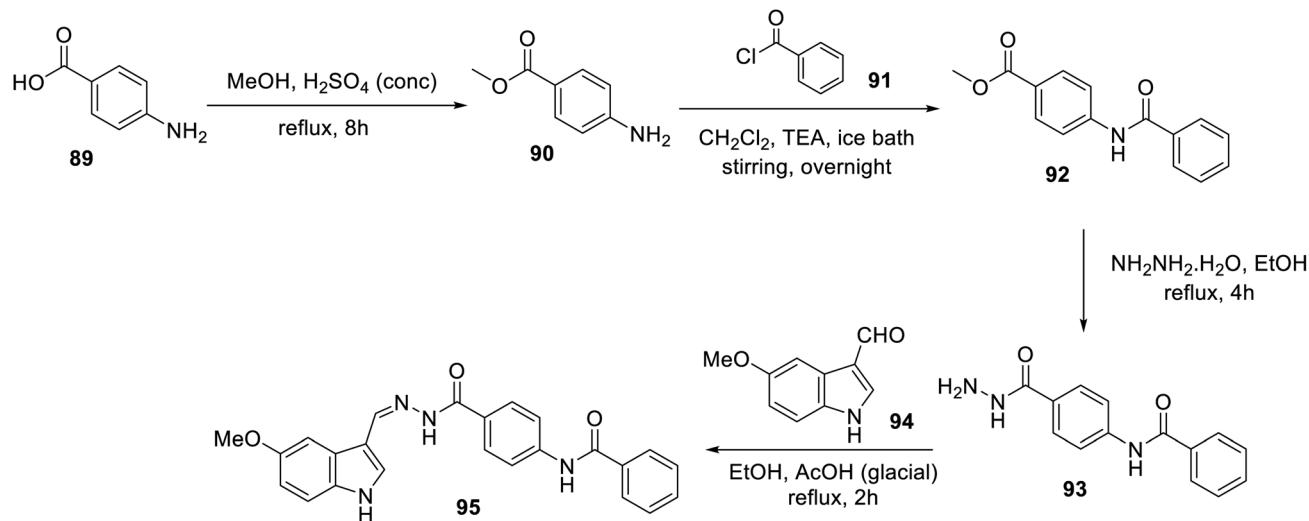
Scheme 8 Synthesis of indolyl Schiff bases 83.



$\text{R} = \text{H, Me}; \text{R}^1 = \text{H, Me, OMe}; \text{R}^2 = \text{H, Cl, OMe}$

Scheme 9 Synthesis of indolyl Schiff bases 88.





Scheme 10 Synthesis of hydrazone derivative 95.

2.5. SU5416 (semaxanib)

SU5416 (semaxanib) **19** (Fig. 6) is a human solid tumor anti-angiogenic VEGFR inhibitor under investigation.^{78–80} Its anti-proliferation of murine cardiac endothelial cells was reported.⁸⁰ Also, pathophysiological effects in respiratory disorders were mentioned, which was supported by the lipopolysaccharide-induced acute lung injury in mice *via* restrain/modulate vascular permeability.⁷⁹

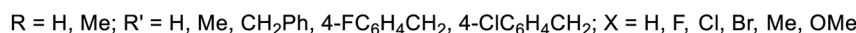
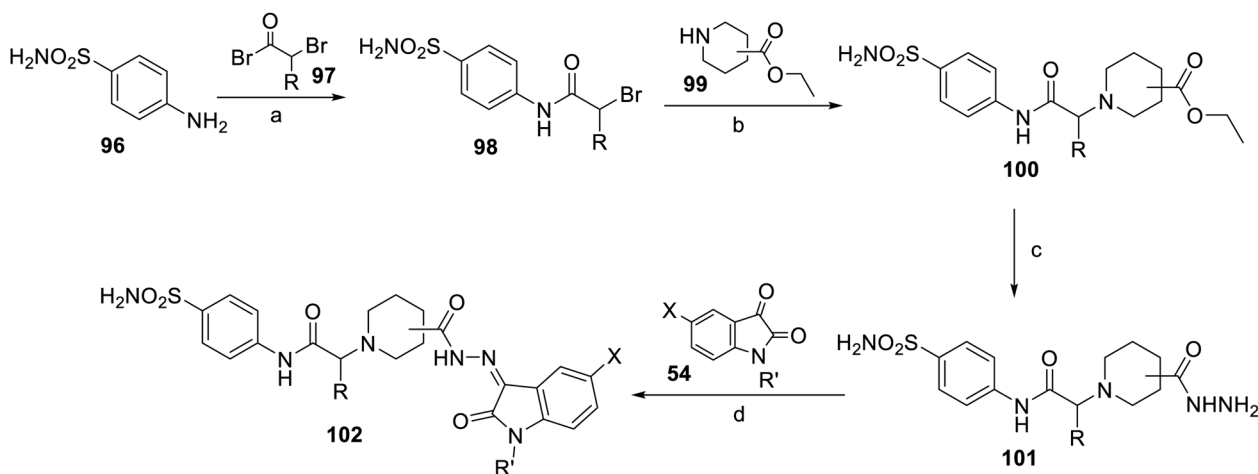
2.6. Vorolanib

Vorolanib (CM082) **20** (Fig. 6) is an oral VEGFR and PDGFR inhibitor.⁸¹ A phase I study (22 patients) exhibited promising results for the combination of vorolanib with everolimus **21**

towards renal and neuroendocrine cancers.⁸² It has also mentioned that vorolanib enhances the antiproliferation and apoptosis properties of gefitinib (Iressa) **22** (EGFR: epidermal growth factor receptor, inhibitor) towards NSCLC cell lines (HCC827 and H3255). This was explained by the strong inhibitory properties of the combined therapeutics on STAT3 phosphorylation compared to that of the mono-therapeutic.⁸³

2.7. Famitinib

Famitinib **23** (Fig. 6) is an oral VEGFR-2 and -3 inhibitor used in trial studies against colon and renal cancers.^{84,85} A promising synergistic effect was observed against NSCLC upon the combination of famitinib with almonertinib (HS-10296, EGFR inhibitor) **24**.⁸⁵



a) dioxane, TEA, room temperature, 20h; b) acetone, K₂CO₃, KI, room temperature, 2h; c) NH₂NH₂·H₂O, EtOH, reflux, 4h; d) EtOH, AcOH (glacial), reflux, 6h

Scheme 11 Synthesis of hydrazones 102.



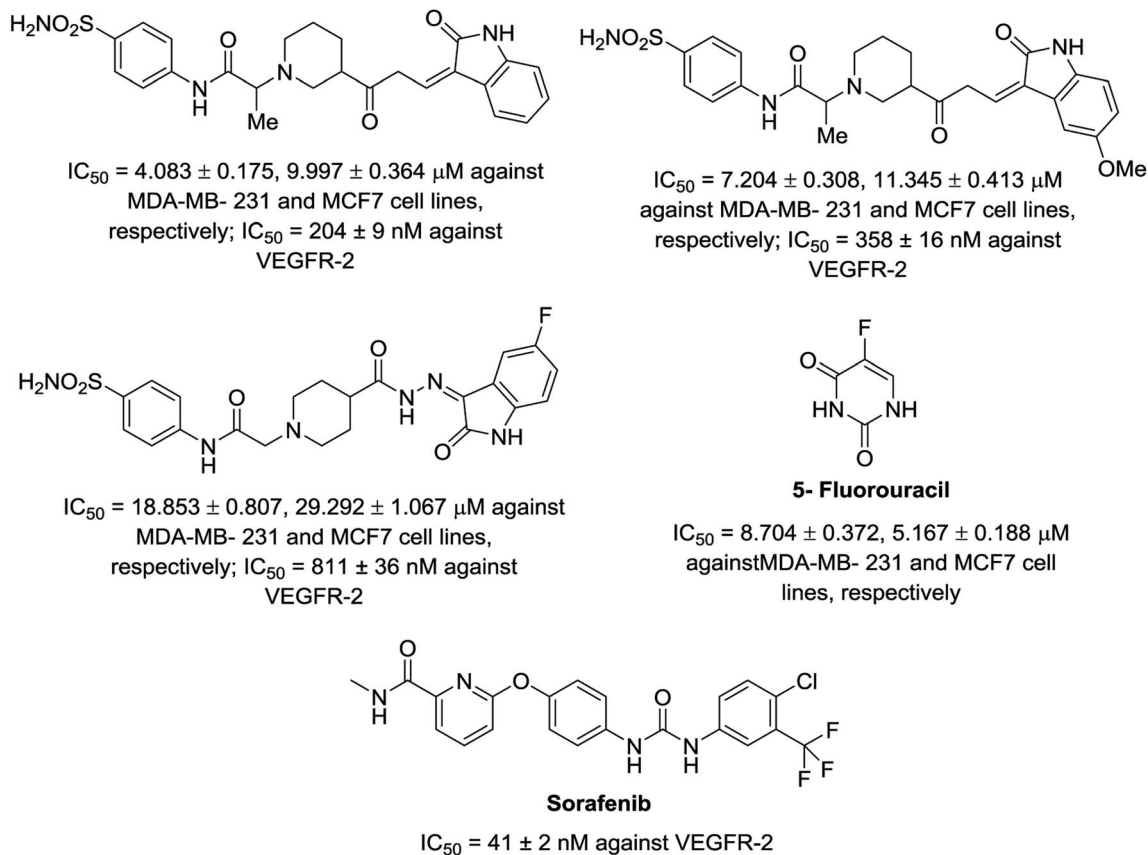
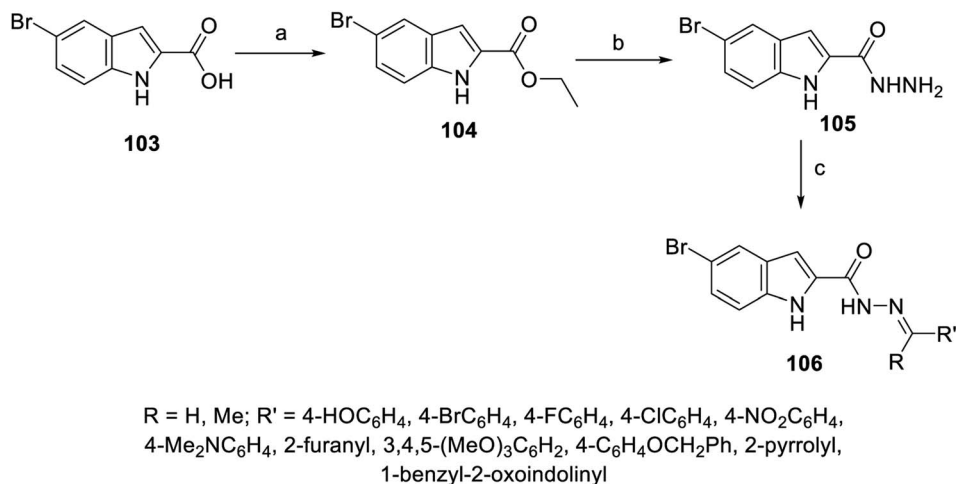


Fig. 9 Antiproliferation (in $\mu\text{M} \pm \text{SD}$) and inhibitory properties against VEGFR-2 (in $\mu\text{M} \pm \text{SD}$) of the tested hydrazones **102** and standard references (5-fluorouracil and sorafenib), respectively.

2.8. Toceranib

Toceranib (Palladia, Zoetis) **25** (Fig. 6) is a multi-targeted tyrosine kinase inhibitor (VEGFR-2, PDGFRs and c-Kit) used as a phosphate salt for the treatment of bone cancer (canine

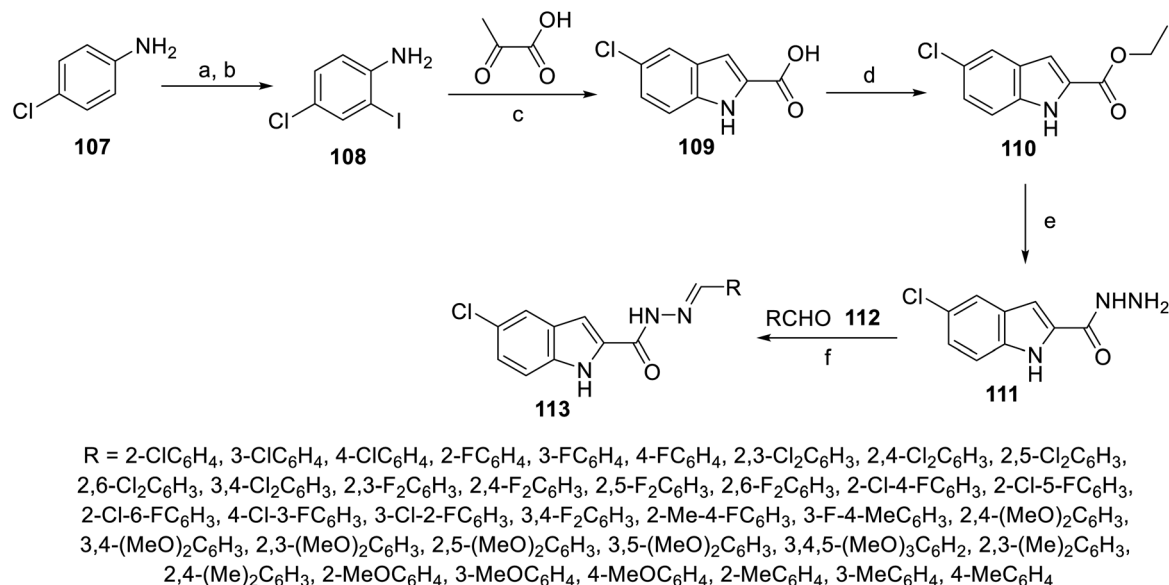
osteosarcoma) in veterinary medicine (dogs). Cell growth inhibition of toceranib phosphate on canine osteosarcoma (Penny and Wall) *in vitro* was reported.⁸⁶



a) EtOH, H_2SO_4 (5 °C), 80 °C, 9h; b) EtOH, $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, 80 °C, 9h; c) aldehyde/ketone/isatin, EtOH, $\text{AcOH}_{\text{glacial}}$, 80 °C, 6h.

Scheme 12 Synthesis of hydrazones **106**.





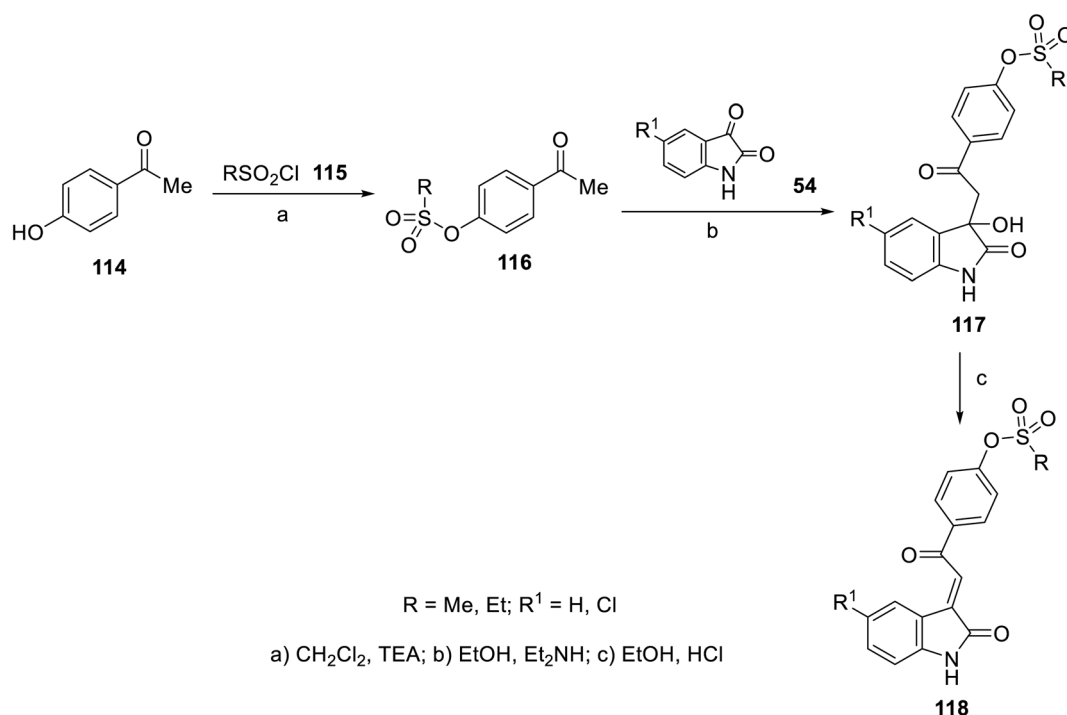
a) I₂, NaHCO₃, PhMe, 0.5 h, room temperature; b) HCl, H₂O, pH 6–7; c) DABCO, Pd(OAc)₂, DMF, reflux, 4h; d) thionyl chloride, EtOH, 0 °C; e) N₂H₄·H₂O, EtOH, reflux; f) EtOH, AcOH, reflux

Scheme 13 Synthesis of indolyl hydrazones 113.

2.9. S49076

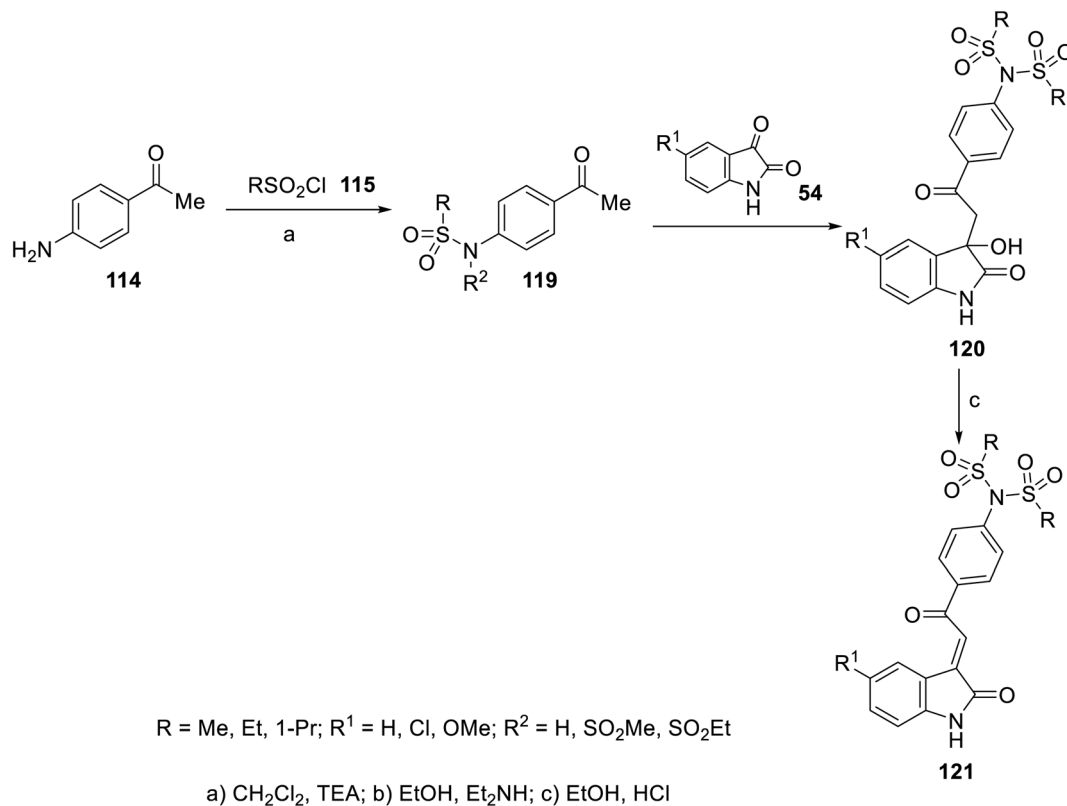
S49076 26 (Fig. 6) is a VEGF and HIF-1- α (hypoxia-inducible factor 1-alpha) inhibitor.⁸⁷ The inhibition of VEGF and HIF-1 expression can explain the mode of action of S49076 in ovarian cancer cells.⁸⁷ The administration of S49076 as a monotherapeutic resulted in the arrest of colon bevacizumab-

resistant tumor growth. Moreover, the combination of S49076 and bevacizumab (Avastin, anti-vascular endothelial growth factor antibody) showed total growth inhibition of colon cancer xenograft models.⁸⁸ A phase I study (103 patients) also revealed its effect on solid tumors (colon, lung, mesothelioma and uveal melanoma) upon oral administration.⁸⁹

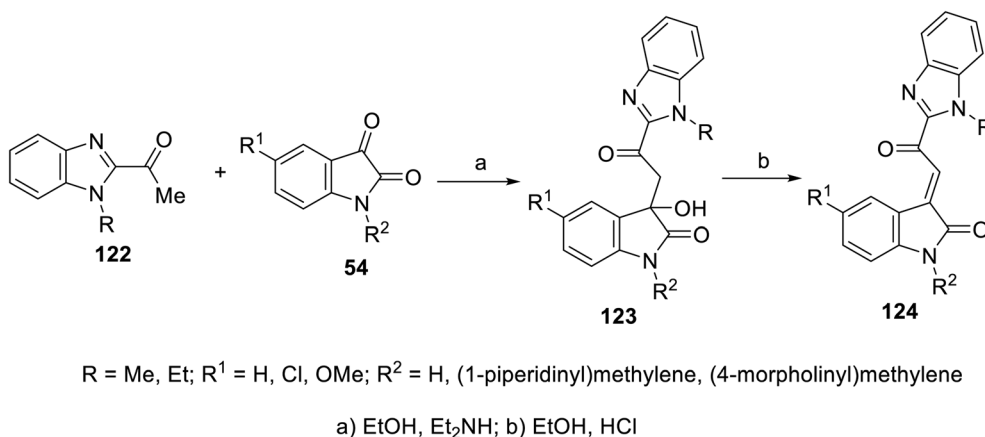


Scheme 14 Synthesis of 2-oxoindolin-3-ylidenes 118.





Scheme 15 Synthesis of 2-oxoindolin-3-ylidenes 121.



Scheme 16 Synthesis of 2-oxoindolin-3-ylidenes 124.

2.10. SIM010603

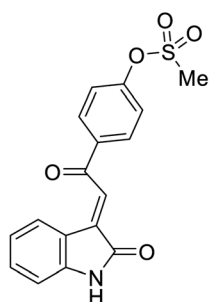
SIM010603 27 (Fig. 6) is an oral multi-targeted tyrosine kinase inhibitor (VEGFR-2, -3; PDGFR- β and stem cell factor receptor “c-kit”).⁹⁰ Antiproliferation properties were reported against NCI-H460 (human lung), LLC-SW44 (Lewis lung) and MDA-MB-435 (breast) cancer cells in addition to the inhibition of xenograft tumor growth models and angiogenesis in mice.⁹⁰ Adverse effects including gastrointestinal, pancreatic and skeletal toxicities, bronchopneumonia and cardiovascular dysfunction were mentioned in the toxicological studies of SIM010603 in rats and dogs (0–20 and 0–10 mg kg⁻¹ per day oral administration,

respectively, for 28 followed by 14 recovery days). However, no mortality rates were recorded for dogs receiving 10 mg kg⁻¹.⁹¹

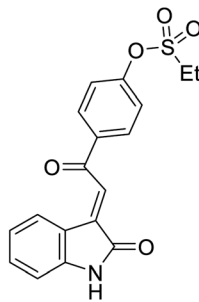
3. Natural indole-containing compounds

Many natural indolyl derivatives have been identified to possess considerable bio-properties including 28–38, as summarized in Fig. 7.⁹² Vincristine 39 (Fig. 8) was isolated from *Vinca rosea* and approved by the FDA (since 1963) for the treatment of Hodgkin's disease, non-Hodgkin's lymphoma and neuroblastoma.^{93–95}

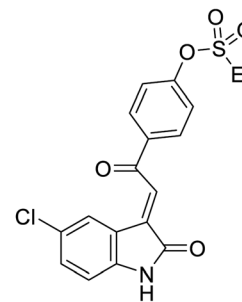


**118a**

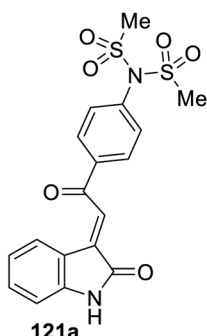
$IC_{50} = 8.30 \pm 0.44, 6.85 \pm 0.37, 16.38 \pm 0.70$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 54.03 \pm 5.4, 119.8 \pm 12.0$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**118b**

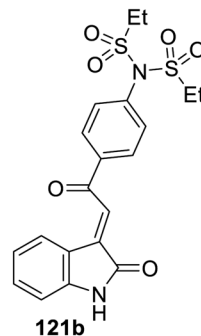
$IC_{50} = 5.60 \pm 0.57, 4.25 \pm 0.23, 12.77 \pm 1.41$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 98.95 \pm 9.9, 247.7 \pm 24.8$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**118c**

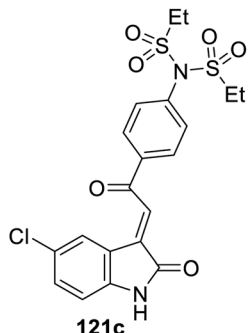
$IC_{50} = 4.99 \pm 0.29, 4.28 \pm 0.51, 5.33 \pm 0.46$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 36.86 \pm 3.7, 72.35 \pm 7.2$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**121a**

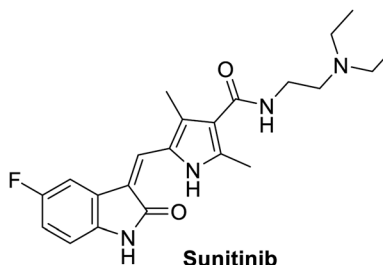
$IC_{50} = 6.91 \pm 0.89, 6.07 \pm 0.83, 20.96 \pm 1.75$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 102.2 \pm 10.2, 103.3 \pm 10.3$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**121b**

$IC_{50} = 5.08 \pm 0.57, 4.15 \pm 0.78, 13.83 \pm 1.06$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 74.06 \pm 7.4, 184.9 \pm 18.5$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**121c**

$IC_{50} = 6.18 \pm 0.32, 4.43 \pm 0.47, >50.00 \pm 0.84$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 53.36 \pm 5.3, 81.7 \pm 8.2$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

**Sunitinib**

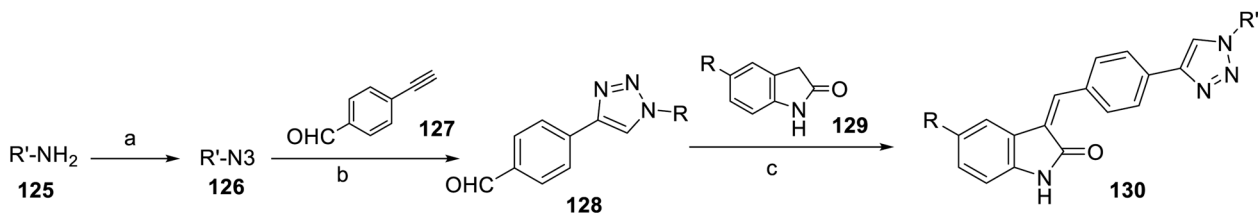
$IC_{50} = 16.91 \pm 0.95, 3.97 \pm 0.14, 5.03 \pm 0.30$ ($\mu\text{M} \pm \text{SD}$) against PaCa-2, MCF7 and HCT116, respectively; $IC_{50} = 47.54 \pm 4.8, 84.9 \pm 8.5$ (nM \pm SD) against VEGFR-2 and c-kit, respectively

Fig. 10 Antiproliferation and tyrosine kinase (VEGFR-2, c-kit) inhibitory properties of 118a–c, 121a–c and sunitinib.

Vinblastine (Velban) **40** is also a *Vinca* alkaloid approved by the FDA (since 1965) for the treatment of Hodgkin's disease, lymphoma, and testicular and breast cancers.^{95–97} Vindesine (Eldisine) **41** is a *Vinca* alkaloid with efficacy against acute

lymphocytic leukemia.^{95,98} 3-Indole acetic acid **42**, which is present in wine, and 3-indole pyruvic acid **43** (human metabolite) exhibited inhibitory properties against VEGFR-2 with $IC_{50} = 0.9704$ and 1.037 mM, respectively⁹⁹ (Fig. 8).

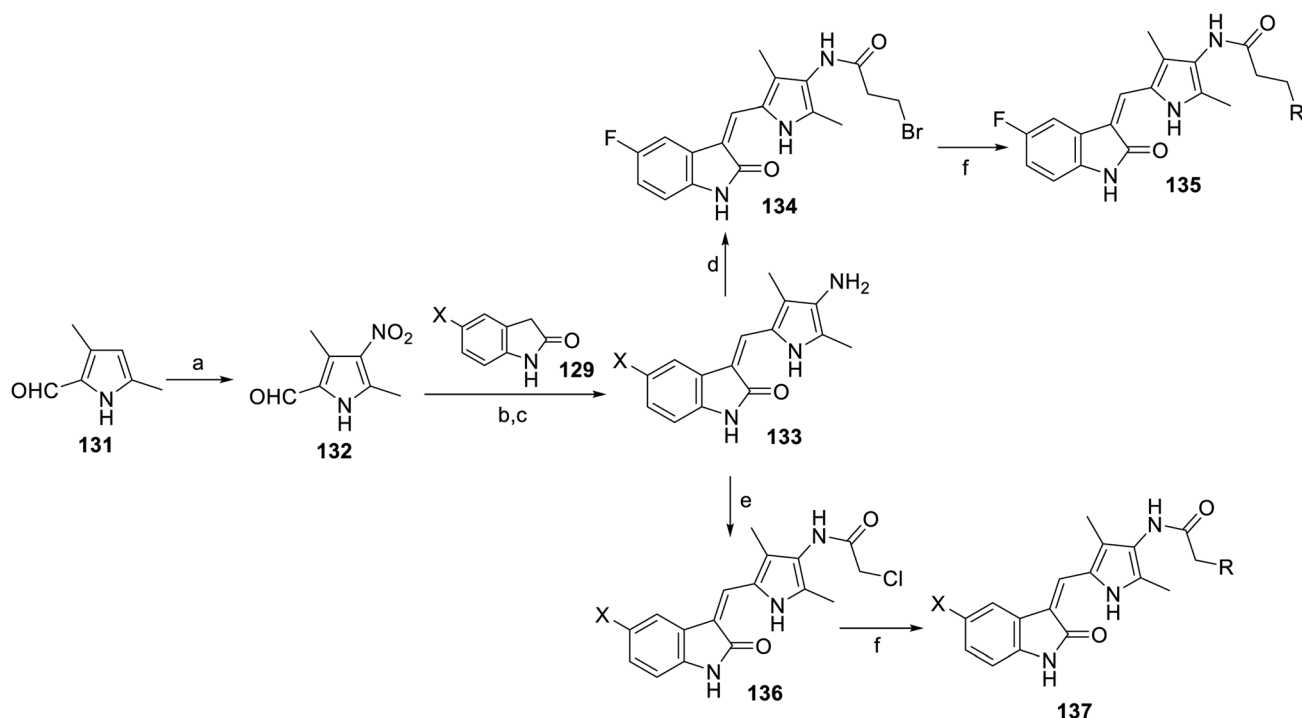




R = H, F; R' = Ph, 2-MeC₆H₄, 3-MeC₆H₄, 4-MeC₆H₄, 2-FC₆H₄, 3-FC₆H₄, 4-FC₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 2-NCC₆H₄, 3-NCC₆H₄, 4-NCC₆H₄, 3-Cl-4-CF₃C₆H₃

a) NaNO₂, HCl, NaN₃, CH₂Cl₂, H₂O, 0–5 °C, 3–5 h; b) CuSO₄·5 H₂O, ascorbic acid, KI, DMF, H₂O, 50 °C, 6–10 h; c) EtOH, piperidine, 80 °C, 4–8h

Scheme 17 Synthesis of 2-oxoindolin-3-ylidenes 130.



X = Cl, F, Br; R = (CH₂)₂NEt₂, CH=CHCH₂NMe₂, (CH₂)₃NMe₂, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-(1-methylpiperazinyl), 4-(1-ethylpiperazinyl)

a) KNO₃, H₂SO₄; b) pyrrolidine, EtOH, reflux; c) Zn, AcOH, EtOH/AcOEt; d) 3-bromopropionic acid, DMTMM, DMF; e) chloroacetyl chloride, TEA, THF; f) RH, DMF, 50–55 °C

Scheme 18 Synthesis of 2-oxoindolin-3-ylidenes 135 and 137.

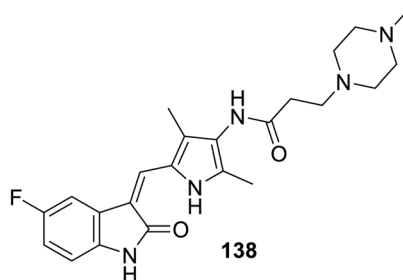
4. Synthesized indole-containing compounds

4.1. Indolecarboxamide

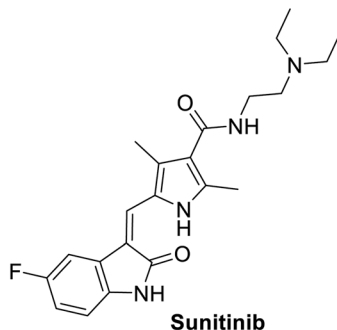
A variety of indole-2-carboxamides **49** was synthesized through the reaction of 2-(1*H*-indol-3-yl)ethan-1-amine **47** with 2-indolecarboxylic acids **48** in DCM (dichloromethane) containing

BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) and DIPEA (diisopropyl ethylamine). Compound **47** was obtained through the reduction of nitro analog **46** by LiAlH₄ in Et₂O (at 0 °C to room temperature) under an inert (nitrogen) atmosphere. The latter **46** was synthesized by the addition reaction of 2-phenylindole **44** to β-nitrostyrene **45** in refluxing MeOH containing sulfamic acid¹⁰⁰ (Scheme 1). Greater antiproliferation properties against a variety of human





IC_{50} = 0.008, 0.07, 6.11, 20.61, 17.08, 14.71, 6.85, 41.38 μ M against MV4-11, TT, NCI-H460, H526, H3122, Bel7402, HK-2, LO2, respectively; K_i = <0.0003, 0.0038, 0.019, 1.1, 0.2 μ M against FLT4 (VEGFR-3), KDR (VEGFR-2), PDGFR- β , VEGFR-1 and c-kit, respectively.



IC_{50} = 0.003, 0.04, 4.31, 1.01, 0.83, 2.67, 5.85, 19.93 μ M against MV4-11, TT, NCI-H460, H526, H3122, Bel7402, HK-2, LO2, respectively; K_i = 0.017, 0.009, 0.008, 0.002, 0.004 μ M against FLT4 (VEGFR-3), KDR (VEGFR-2), PDGFR- β , VEGFR-1 and c-kit, respectively.

Fig. 11 Antiproliferation and receptor inhibitory properties of **138** and sunitinib.

tumor cell lines [MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, Panc-1 (pancreatic), MCF7 (breast), HT-29 (colon) and A-549 (epithelial)] were revealed (IC_{50} , nM \pm SEM “standard error mean”) for some of the prepared 2-indolecarboxamides **49** compared to that of erlotinib. Also, mild VEGFR-2 inhibitory properties were observed by some of the derivatives of **49** relative to that of sorafenib. The most considerable agent was **49e** (R = CH_2OH , R' = Cl; IC_{50} = 44 ± 4 , 46 ± 4 , 45 ± 4 , and 42 ± 4 nM against Panc-1, MCF7, HT-29 and A-549, respectively; IC_{50} = 1.10 ± 0.08 nM against VEGFR-2) (ESI Fig. S1 \dagger). Based on the observed antiproliferation properties, it was concluded that the function/group at the 3-position of the indole-2-carboxamide is the dominant factor, with the bio-properties following the order of H > methoxyvinyl > ethoxymethyl > hydroxymethyl > phenyl.¹⁰⁰

A set of 5-indolecarboxamides **53** was obtained through the reaction of the corresponding amino analogs **52** with the appropriate carboxylic acid in the presence of Hünig's base (*N,N*-diisopropylethylamine “Hünig's base”, DIPEA) using HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium, coupling agent). 5-Aminoindoles **52** were prepared through the reduction of nitro analogs **51** (Fe, NH_4Cl , EtOH/ H_2O). The latter **51** was obtained through the alkylation of 5-nitroindole **50**^{101,102} (Scheme 2). Weak VEGFR-2, CDK-1/cyclin B (cyclin-dependent kinase 1), and HER-2 (human epidermal growth factor receptor 2) properties were exhibited by most of

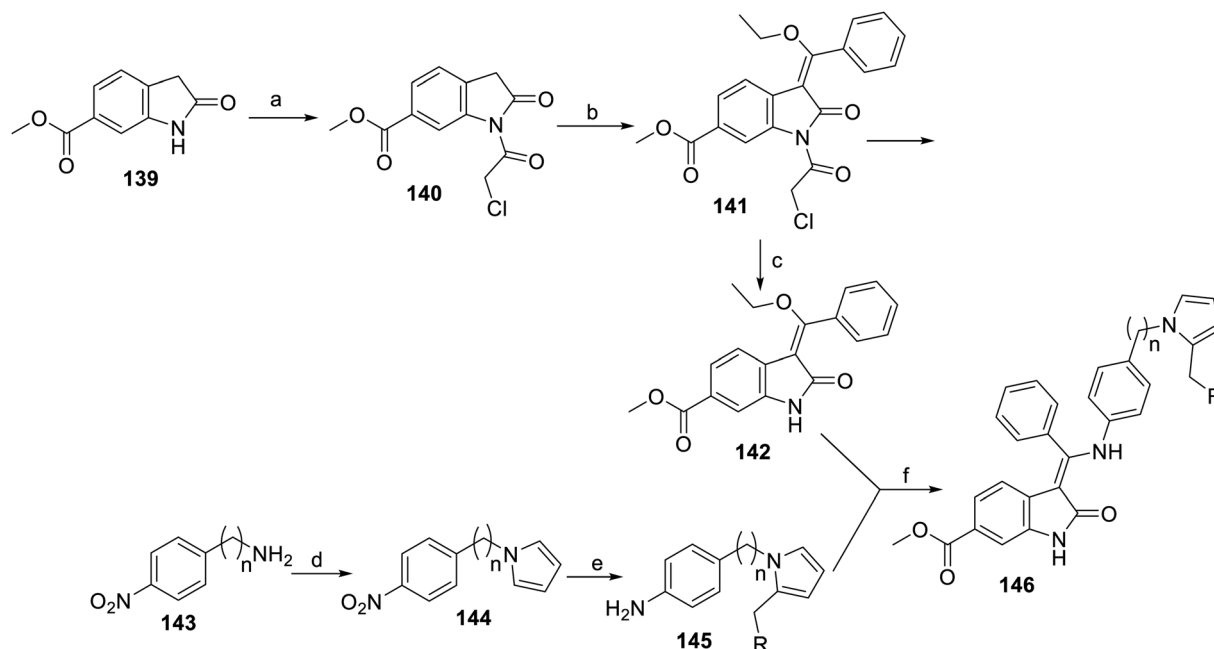
the synthesized agents **53** at 10 μ M. However, compound **53l** [R = CO(3- FC_6H_4), R' = 4-pyridazinyl] revealed promising kinase inhibitory activity against CDK-1/cyclin B and HER-2 (activity = 51% and 52%, respectively) at 10 μ M¹⁰¹ (ESI Fig. S2 \dagger).

4.2. Indolyl Schiff bases

Condensation of isatins **54** with *p*-aminobenzoic acid (in refluxing EtOH containing a catalytic amount of AcOH) resulted in the formation of Schiff bases **55**, which upon reaction with 4-methylthiosemicarbazide **56** afforded the corresponding semicarbazones **57**. Similarly, the reaction of isatins **54** with benzocaine (4-aminobenzoic acid ethyl ester) **58**, followed by reaction with hydrazine hydrate in refluxing ethanol gave the corresponding hydrazides **59**. The latter were subjected to reaction with aromatic aldehydes **60** (in refluxing EtOH containing a catalytic amount of AcOH), ethyl acetoacetate **62** (in EtOH/AcOH, under sonication at 50 $^{\circ}C$), phthalic anhydride **64** (in AcOH “glacial” under sonication at 50 $^{\circ}C$) or phenyl isothiocyanate **66** (in refluxing EtOH), yielding the corresponding hydrazone **61**, **63**, dioxoisindoline **65** and thiourea derivatives **67**, respectively. Reaction of **59** with carbon disulfide in refluxing ethanolic KOH followed by acidification with HCl (10%), afforded the corresponding oxadiazolyl derivatives **68** (Scheme 3).

Some of the synthesized agents exhibited promising antiproliferation properties against HepG2 (liver) and MCF7 (breast) cancer cell lines relative to that of sunitinib (MTT assay;





R = NMe₂, NEt₂, 1-pyrrolidinyl, 1-piperidinyl, 4-(1-methylpiperazinyl); n = 0, 1

a) chloroacetic anhydride, PhMe, reflux, 3 h; b) PhMe, Ac₂O, triethyl orthobenzoate, reflux, 5h; c) KOH, MeOH, 25 °C, 20 min; d) NaOAc, 2,5-dimethoxytetrahydrofuran, AcOH, 75 °C, 3–5 h; e) (i) paraformaldehyde, appropriate amine, AcOH, 35 °C, 6–8 h; (ii) Pd/C, EtOH, 25 °C, 4 h; f) MeOH, reflux, 5–8 h.

Scheme 19 Synthesis of 2-oxindolin-3-ylidenes 146.

IC₅₀, μM ± SD “standard division”) (ESI Fig. S3†). Some of the synthesized fluorinated analogs showed enhanced antitumor properties compared to other prepared derivatives, directing attention on the importance of this substituent in controlling the bio-properties. The VEGFR-2 inhibitory properties determined for the discovered promising agents were consistent with the observed antitumor properties. Compound 67a (X = H) revealed promising antiproliferation and enzymatic inhibitory properties (IC₅₀ = 1.13 ± 0.06, 1.44 ± 0.11 μM against HepG2 and MCF7, respectively; IC₅₀ = 0.078 ± 0.003 μM against VEGFR-2) relative to that of sunitinib (IC₅₀ = 2.23 ± 0.11, 4.77 ± 0.29 μM against HepG2 and MCF7, respectively; IC₅₀ = 0.139 ± 0.007 μM against VEGFR-2)¹⁰³ (ESI Fig. S3†).

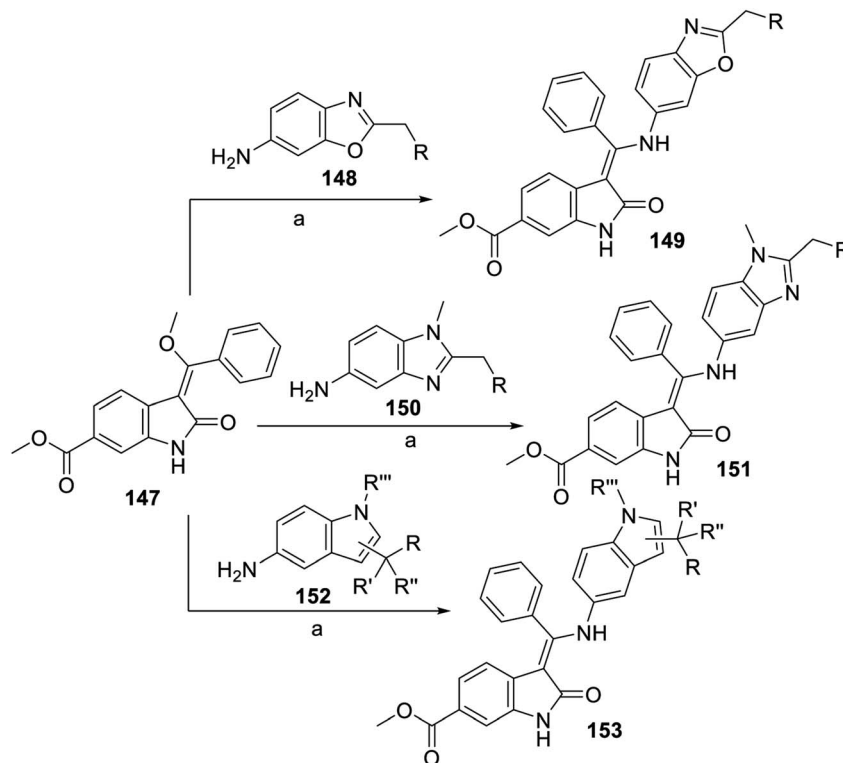
A set of indolyl Schiff bases incorporated in urea 73 was synthesized through the condensation reaction of the appropriate indoles 54 with the corresponding 1-(4-aminophenyl)-3-substituted urea 72. The latter was obtained through reduction (H₂, Pd/C, and MeOH) of the corresponding nitro analogs, which were prepared through reaction of 4-nitrophenylisocyanate 69 with the appropriate anilines 70 in refluxing acetonitrile¹⁰⁴ (Scheme 4). Some of the synthesized Schiff bases revealed promising antiproliferation properties (SRB “sulforhodamine B” technique) against the HepG2 (liver) cancer cell line relative to that of doxorubicin and sorafenib. The VEGFR-2 properties were determined for the discovered promising agents, which showed comparable observations to that of the antiproliferation efficacies. The efficacy observed for

most of the synthesized agents followed order of phenyl substitution of 4-Cl > 3-Cl > 3-CF₃. The most promising agent discovered was 73x (R = SO₂NH₂, R' = Cl; IC₅₀ = 3.15 ± 0.36 and 0.31 ± 0.04 μM for HepG2 cell line and VEGFR-2, respectively), which exhibited comparable activity to that of sorafenib (IC₅₀ = 3.40 ± 0.25, 0.10 ± 0.02 μM for the HepG2 cell line and VEGFR-2, respectively)¹⁰⁴ (ESI Fig. S4†).

The condensation reaction of isatins 54 with L-phenylalanine secondary amine conjugates (obtained from the reaction of Boc amino acid with secondary amines in THF (tetrahydrofuran) in the presence of IBCF (iso-butyl chloroformate) and NMM (N-methyl morpholine) at room temperature and inert atmosphere followed by removal of the Boc group (HCl_{gas} in dioxane)) in EtOH containing triethylamine (TEA) at room temperature gave the corresponding Schiff bases 76 (Scheme 5). Additionally, the reaction of isatins 79/80 with 4-amino antipyrine 81 in ethanolic solution at room temperature afforded the corresponding Schiff bases 83 and 82, respectively. Isatin derivatives 80 were obtained through alkylation with excess dibromoalkane (DMF/K₂CO₃), which gave monoalkylated derivatives 78 (major products) and bis-isatin derivatives 79 (minor products). The monoalkylated isatins were coupled with secondary amines (DMF/K₂CO₃ at room temperature) affording the corresponding isatin derivatives 80 (Schemes 6–8).

Similarly, Schiff bases 88 were obtained through the condensation of 4-amino antipyrine 81 with isatin triazol conjugates 87 (EtOH, room temperature). Isatin triazol





Scheme 20 Synthesis of 2-oxoindolin-3-ylidenes 149, 151 and 153.

conjugates **87** were synthesized through the click reaction of the appropriate aryl azides **86** with *N*-propargylated isatins **85** (*t*-butanol/H₂O, CuSO₅·5H₂O, sodium D-isoascorbate, microwave, 100 °C)¹⁵ (Scheme 9).

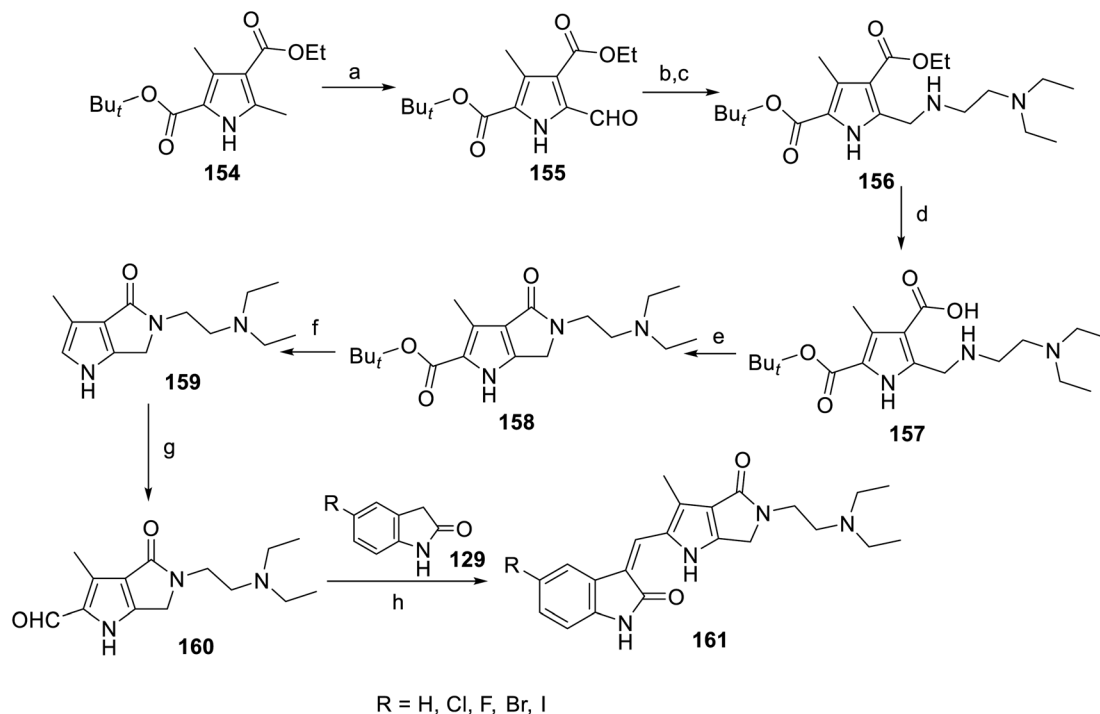
Some of the synthesized Schiff bases exhibited promising antiproliferation properties against MCF7 (breast), HCT116 (colon) and PaCa2 (pancreatic) cancer cell lines (MTT assay) compared to the reference standards (sunitinib and 5-fluorouracil) (ESI Fig. S5†). Compound **88f** ($R = \text{Me}$, $R^1 = \text{H}$, and $R^2 = \text{OMe}$) was the highest potent analog observed against MCF7 (2.1-times potency relative to the standard reference sunitinib). Additionally, some of the compounds prepared (**88b**, **88d** and **88f**) exhibited higher efficacies than that of the standard drug 5-fluorouracil (approved drug for colon cancer¹⁰⁵). The safe profile of all the tested analogs ($\text{IC}_{50} = >50.00 \mu\text{M}$) against the non-cancer RPE1 cell line is good support, especially for the high potent analogs towards more detailed studies for assigning promising hits. The CAM assay (chick chorioallantoic membrane) of fertilized chicken eggs in addition to VEGFR-2 inhibitory properties (% inhibition \pm SD utilizing the IC_{50} values observed against MCF7 cell line of the tested agents relative to that of sunitinib) (ESI Fig. S5†) support their capability towards antiangiogenesis.¹⁵

4.3. Indolyl hydrazones

An ethanolic solution of 3-indolecarbaldehyde derivative **94** and hydrazide analog **93** in the presence of a catalytic amount of acetic acid under reflux afforded hydrazone **95** (Scheme 10). Hydrazone **95** exhibited considerably higher antiproliferation properties (MTT assay) against the MCF-7 and HCT116 cell lines ($\text{IC}_{50} = 12.93 \pm 0.54$ and $11.52 \pm 0.70 \mu\text{M}$, respectively) compared to that of sorafenib ($\text{IC}_{50} = 4.32 \pm 0.33$ and $7.28 \pm 0.53 \mu\text{M}$, respectively) with a safety profile against the W138 (non-cancer) cell line. Furthermore, the VEGFR-2 inhibitory properties of **95** ($\text{IC}_{50} = 25 \pm 1.29 \text{ nM}$) were comparable to that of the standard reference sorafenib ($\text{IC}_{50} = 35 \pm 1.34 \text{ nM}$). This study was supported by diverse computational studies (molecular docking “PDB: 2OH4, MOE2014 software”; MD “molecular dynamics, CHARMM-GUI web server, GROMACS 2021 engine”; DFT “density functional theory, Gaussian 09” and ADMET “absorption, distribution, metabolism, excretion and toxicity; Discovery Studio 4.0”).¹⁰⁶

A series of indolyl hydrazones incorporating benzenesulfonamides **102** was synthesized through the condensation of the appropriate isatins **54** with hydrazides **101** in refluxing ethanol containing a catalytic amount of acetic acid. Hydrazides **101** were obtained through the reaction of hydrazine hydrate with the corresponding ethyl esters **100** in refluxing ethanol





- a) ceric ammonium nitrate (CAN), THF, AcOH, H₂O, 1 h; b) *N,N*-diethylethylenediamine, EtOH, room temperature, 4 h; c) NaBH₄, *p*-toluenesulfonic acid (TsOH H₂O), EtOH, 6 h; d) 1N NaOH_(aq), MeOH, 65 °C, 6 h; e) 1,1'-carbonyldiimidazole (CDI), THF (dry), 6 h; f) H₂SO₄, MeOH, reflux, 4.5 h; g) Vilsmeier reagent, CH₂Cl₂, room temperature, 5 h; h) piperidine, EtOH, room temperature, 5h.

Scheme 21 Synthesis of 2-oxoindolin-3-ylidenes **161**.

(Scheme 11). Some of the synthesized hydrazones **102** revealed considerable antiproliferation activities against MDA-MB-231 and MCF7 (breast cancer cell lines) compared to that of 5-fluorouracil, and VEGFR-2 inhibitory properties compared to that of sorafenib (Fig. 9). Inhibitory properties against carbonic anhydrase (CA) *h*CAI, II, IX, XII were also observed by hydrazones **102** compared to the standard reference acetazolamide.¹⁰⁷

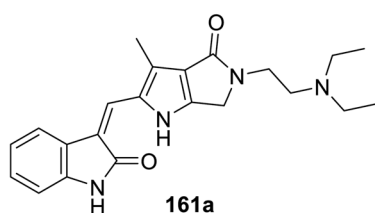
A set of hydrazones **106a–k** was prepared through the condensation reaction of 5-bromo-2-indolecarbohydrazide **105** (obtained from the reaction of hydrazine hydrate with ethyl ester of indole derivative **104** in refluxing EtOH) with the appropriate aldehyde, ketone or isatin derivative in refluxing EtOH containing a few drops of glacial AcOH (catalytic amount) (Scheme 12). Mild antiproliferation properties were exhibited by the synthesized hydrazones **106a–k** against HepG2 (liver), HeLa (cervical) and PC3 (prostate) cancer cell lines (MTT assay) with modest VEGFR-2 inhibitory activity compared to the standard reference (sorafenib; IC₅₀ = 6.2 ± 1.1, 11.7 ± 1.3, 19.0 ± 1.2, and 15.3 ± 1.8 μM against HepG2, HeLa, PC3 and WI-38 respectively; EC₅₀ = 57.1 ± 3.0 nM ± SEM against VEGFR-2). Furthermore, the most promising agent **106e** (R=4-Me₂NC₆H₄, R'=H; IC₅₀ = 14.3 ± 2.0, 22.2 ± 2.3, 36.2 ± 3.1, and 25.9 ± 2.1 μM against HepG2, HeLa, PC3 and WI-38, respectively) was screened against WI-38 (normal lung fibroblasts; EC₅₀ = 102.6 ± 3.1 nM ± SEM against VEGFR-2) to confirm its safety index¹⁰⁸ (ESI Fig. S6†).

Similarly, 5-chloroindolyl hydrazones **113** were obtained through the reaction of the corresponding hydrazide **111** and aromatic aldehydes **112** in refluxing ethanol containing AcOH as a catalyst (Scheme 13). Considerable antiproliferation properties against HCT116 and SW489 (colon) cancer in addition to MRC-5 (non-cancer human) cell lines were exhibited by some of the synthesized hydrazones compared to the standard references (cisplatin “GI₅₀ = 7.67 ± 3.4, 4.43 ± 2.1, and 3.82 ± 1.9 μM against HCT116, SW480 and MRC-5, respectively”, sorafenib “GI₅₀ = 4.17 ± 2.5, 2.02 ± 1.2, and 30.81 ± 10.6 μM against HCT116, SW480 and MRC-5, respectively” and sunitinib “GI₅₀ = 15.84 ± 1.7, 1.09 ± 0.9, > 100 μM against HCT116, SW480 and MRC-5, respectively”) (ESI Fig. S7†). Compound **113x** (R = 2,4-(MeO)₂C₆H₃; GI₅₀ = 8.10 ± 1.8, 7.90 ± 1.3, and >100 μM against HCT116, SW480 and MRC-5, respectively) was the most promising agent synthesized. Its anti-angiogenesis effect was supported by CAM proliferation and HUVEC (human umbilical vein endothelial cell) migration.¹⁰⁹

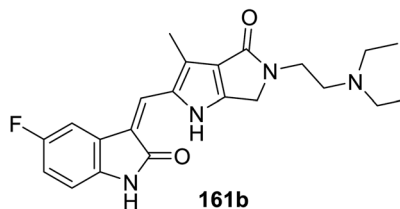
4.4. 2-Oxoindolin-3-ylidenes

The FDA approval for the use of sunitinib and nintedanib as potent multi-targeted tyrosine kinase inhibitors against many cancer types^{40,41,55,56} has inspired many researchers to utilize the 2-oxoindolin-3-ylidene scaffold for optimizing novel antitumor active agents. A variety of 2-oxoindolin-3-ylidenes bearing

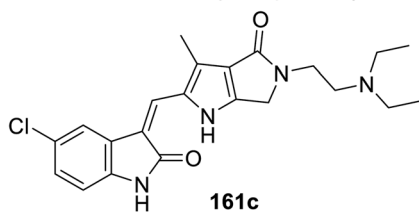




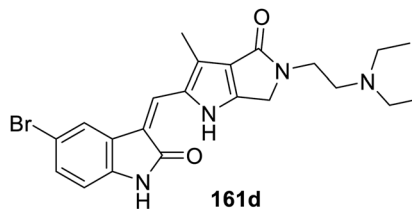
$IC_{50} = 4.25 \pm 1.88, >10, >10, >10 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 30.2, 22.4 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively



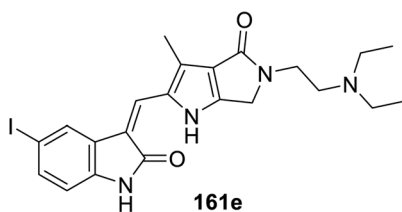
$IC_{50} = 2.94 \pm 0.66, >10, >10, >10 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 110.7, 97.5 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively



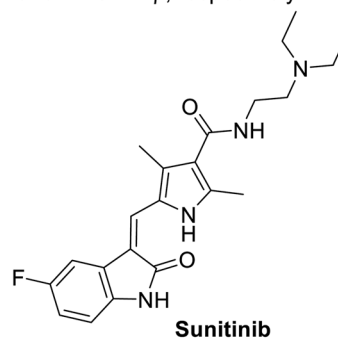
$IC_{50} = 3.09 \pm 0.70, >10, 7.30 \pm 1.20, >10 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 35.0, 24.9 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively



$IC_{50} = 1.05 \pm 0.18, 6.57 \pm 1.64, 7.06 \pm 0.30, >10 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 24.7, 16.1 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively



$IC_{50} = 0.42 \pm 0.16, 2.95 \pm 0.83, 7.76 \pm 0.29, 9.21 \pm 1.61 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 35.1, 29.3 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively



$IC_{50} = 3.42 \pm 0.57, 6.23 \pm 0.57, 6.27 \pm 0.67, 9.48 \pm 0.18 \mu\text{M}$ against HCT116, NCT-H460, 786-O and Detroit 551 cell lines, respectively; $IC_{50} = 140.0, 61.4 \text{ nM}$ against VEGFR-2 and PDGFR- β , respectively

Fig. 12 Antiproliferation and enzymatic inhibitory properties of **161a–e** and sunitinib.

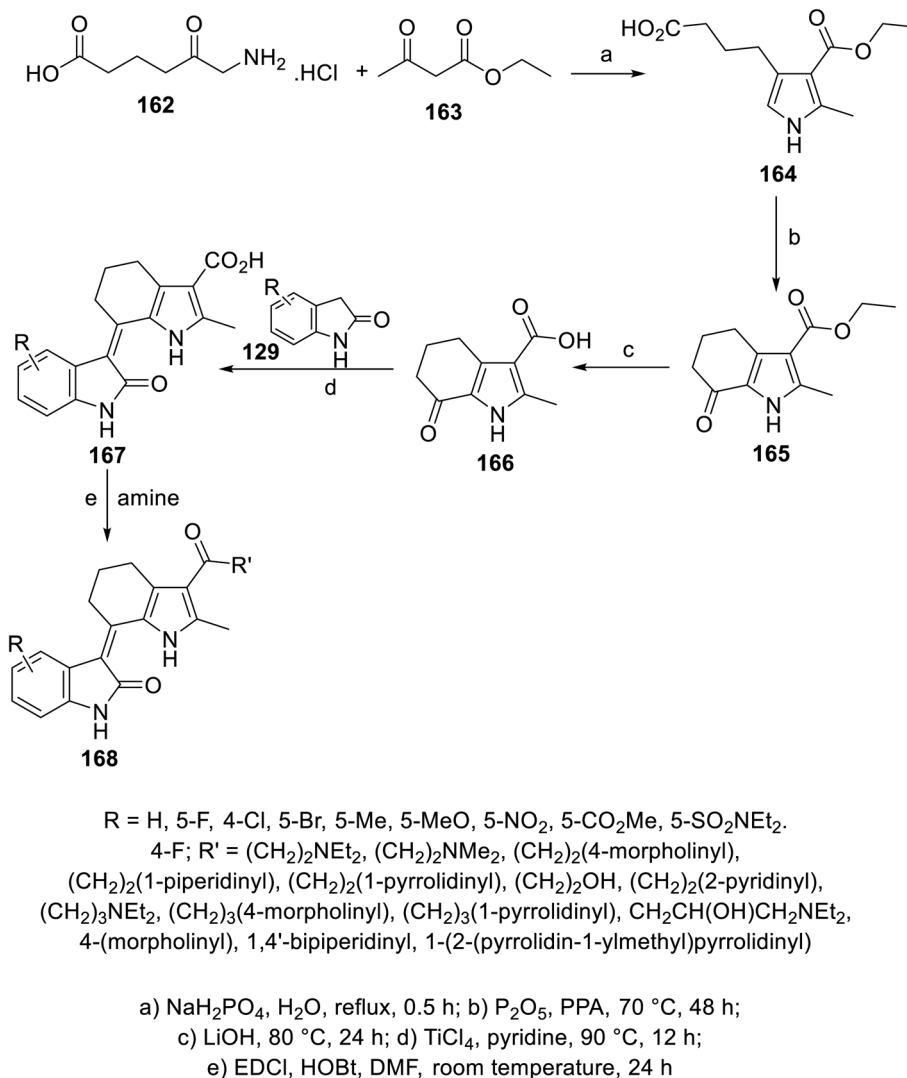
alkanesulfonate **118** was synthesized in a two-step reaction in excellent yields. The reaction of isatins **54** in EtOH containing a quantitative amount of Et₂NH gave the corresponding 3-hydroxy-2-oxoindole derivatives **117**. Acidic dehydration (EtOH and HCl) of **117** gave the corresponding **118**⁹² (Scheme 14).

2-Oxoindolin-3-ylidenes incorporating alkanesulfonamide **121** were formed starting from the corresponding alkanesulfonamide derivatives **119** utilizing a similar reaction sequence. It was mentioned that the reaction of isatins **54** with **119** bearing a mono-propanesulfonamide function gave the corresponding **120**. This is presumably *via* the elimination of propylsulfonate from **119** under the applied basic condition⁹² (Scheme 15). Similarly, 2-oxoindolin-3-ylidenes connected to

benzimidazolyl heterocycle **124** were prepared following the same reaction sequence utilizing 2-acetylbenimidazoles **122**⁹² (Scheme 16).

Some of the synthesized agents **118** and **121** exhibited antiproliferation properties (MTT assay) against PaCa-2 (pancreatic), MCF7 (breast) and HCT116 (colon) cancer cell lines with potency comparable to that of sunitinib. The safety index of the tested agents was established through screening against the RPE1 (retinal pigment epithelium) normal cell line. The inhibitory properties of the tested agents against VEGFR-2 and c-kit were comparable to that of the antiproliferation results (Fig. 10). Their anti-angiogenesis properties were also supported by the CAM assay.⁹²





Scheme 22 Synthesis of 2-oxoindolin-3-ylidenes 168.

Condensation of 2-indolinones **129** with aryl aldehydes substituted with 1,2,3-triazolyl heterocycle **128** in refluxing ethanol containing a catalytic amount of piperidine gave the corresponding 2-oxoindolin-3-ylidenes **130**. The aryl aldehydes bearing 1,2,3-triazolyl heterocycle **128** were obtained through the click reaction of 4-ethynylbenzaldehyde **127** and azidobenzene **126** in DMF containing aqueous CuSO₄·5H₂O, ascorbic acid and a catalytic amount of KI¹⁰⁰ (Scheme 17). Based on the VEGFR-2 inhibitory properties of the tested **130**, it was observed that the substituent of the phenyl ring attached to the triazolyl nitrogen possesses a significant effect on the observed bio-properties. The potency against VEGFR-2 followed the order of 4-CH₃ > 3-CH₃ > 2-CH₃ > H. The antiproliferation properties (CCK-8 assay) were studied against HT-29 (colon), MKN-45 (gastric) and HUVEC (umbilical vein endothelial) cancer cells. Compound **130d** (R = H, R' = 4-MeCH₃; IC₅₀ = 1.61 ± 0.45, 1.92 ± 0.37, and 7.94 ± 0.36 μM against HT-29, MKN-45 and HUVEC, respectively; IC₅₀ = 26.38 ± 1.09 nM against VEGFR-2) was the most promising agent synthesized with anti-proliferation and anti-VEGFR-2 properties comparable to that of sunitinib (IC₅₀ = 10.34 ± 0.96, 9.25 ± 0.77, and 6.37 ± 0.59 μM

against HT-29, MKN-45 and HUVEC, respectively; IC₅₀ = 83.20 ± 1.36 nM against VEGFR-2) (ESI Fig. S8†). Also, its angiogenesis properties were supported by a zebrafish labeling model assay.¹¹⁰

A series of 2-oxoindolin-3-ylidenes connected to pyrrole heterocycle **135** and **137** with high structural resemblance to sunitinib was synthesized *via* the condensation of 2-indolinones **129** with 2-pyrrolicarbaldehyde **132**, followed by the reduction of the nitro group (Zn/AcOH). Subsequently, the reaction of **133** with chloroacetyl chloride (TEA, THF) or 3-bromopropionic acid (DMTMM: 4-(4,6-dimethoxytriazine) chlorinated-4-methylmorpholine, DMF) with various amines finally furnished **135** and **137** (Scheme 18). Based on their physicochemical properties and rat aortic ring assay, a few of the synthesized analogs was selected for *in vitro* testing (MTT assay) considering HT-29 (colon) and NCI-H460 (non-small cell lung) cancer cell lines, and compound **138** was selected for more sophisticated cell line and targeted receptor assays (Fig. 11) Compound **138** was nominated as a promising drug candidate based on its observed bio-properties compared to that of sunitinib.³⁹



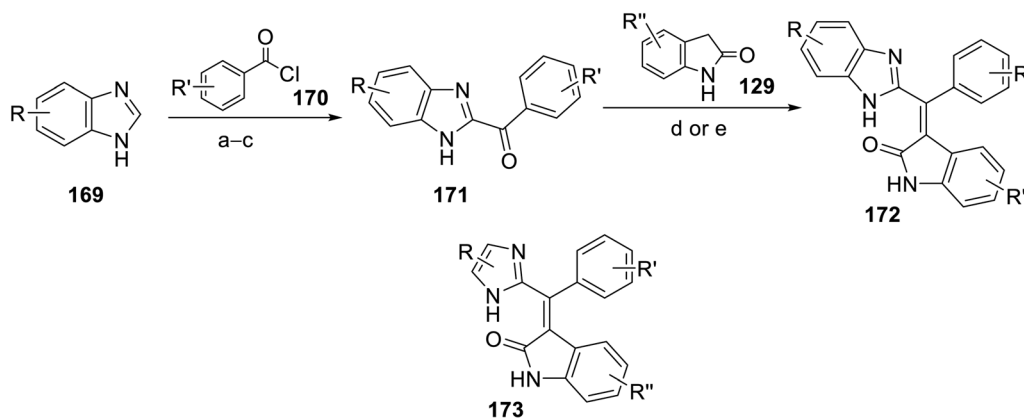
2-Oxoindolin-3-ylidene **141** was obtained through the condensation of 2-indolinone **140** with triethyl orthobenzoate in boiling toluene (110 °C) in the presence of acetic anhydride. The removal of the chloroacetyl group (KOH, MeOH, room temperature), followed by reaction with 4-(1*H*-pyrrol-1-yl)aniline derivatives **145** gave 2-oxoindolin-3-ylidene **146** (Scheme 19). Some of the synthesized agents **146a** (R=NMe₂) and **146e** (R = 1-methyl-4-piperazinyl) exhibited considerable VEGFR-2 and PDGFR-β inhibitory properties compared to that of nintedanib. The most promising agents observed were screened for antiproliferation properties (MTT assay) against HT-29 (colon), SK-OV-3 (ovarian) and HeLa (cervical) cancer cells, exhibiting promising activities (**146a**; IC₅₀ = 51.7, 14.3 nM against VEGFR-2 and PDGFR-β, respectively; IC₅₀ = 0.98 ± 0.11, 5.22 ± 0.36, 53.25 ± 1.20 μM against HT-29, SK-OV-3 and HeLa cells, respectively and **146e**; IC₅₀ = 38.0, 83.17 nM against VEGFR-2 and PDGFR-β, respectively; IC₅₀ = 3.12 ± 0.27, 25.87 ± 1.32, 30.42 ± 1.98 μM against HT-29, SK-OV-3 and HeLa cells, respectively) compared to that of nintedanib (IC₅₀ = 3.3, 3.7 nM against VEGFR-2 and PDGFR-β, respectively; IC₅₀ = 4.90 ± 0.65, 28.76 ± 2.13, 51.65 ± 2.68 μM against HT-29, SK-OV-3 and HeLa cells, respectively)¹¹⁴ (ESI Fig. S9†).

Similarly, the reaction of 2-oxoindolin-3-ylidene **147** with various amine-containing heterocycles (benzoxazole **148**, benzimidazole **150** and indole **152**) in refluxing methanol yielded the corresponding 2-oxoindolin-3-ylidenes **149**, **151** and **153**, respectively (Scheme 20). Some of the synthesized agents revealed promising antiproliferation activity (MTT assay) against the A549 (NSCLC), MCF7 (breast) and HT-29 (colon) cancer cell lines with enzymatic inhibitory properties against VEGFR-2 and PDGFR-β (ESI Fig. S10†). It was noticed that the prepared benzoxazolyl

analogs were not tolerated due to either their weak or complete inactivity towards the tested enzymes. Meanwhile, the synthesized compounds with indolyl heterocycle **153** exhibited considerable antiproliferation properties against the MCF7 and/or HT-29 cell lines. Compound **153c** (CR'R''R''' = 2-[4-methylpiperazin-1-yl]carbonyl) was the most effective agent synthesized with promising inhibitory properties against VEGFR-2, -3 and PDGFR-α, PDGFR-β (IC₅₀ = 69.1, 18.2, 4.4 and 22.0 nM, respectively) compared to nintedanib (IC₅₀ = 8.5, 3.2, 2.3 and 3.5 nM, respectively). Furthermore, the safe proliferation behavior of **153c** against the HEK293T (human embryonic kidney) normal cell line supports its use as a promising candidate.¹¹²

2-Oxoindolin-3-ylidenes linked to pyrrolo[3,4-*b*]pyrrol-2-yl **161** were synthesized through the condensation of 2-indolinones **129** with pyrrolo[3,4-*b*]pyrrole-2-carbaldehyde **160** (Scheme 21). The synthesized agents were screened for their antiproliferation properties (MTT assay) against HCT116 (colon), NCT-H460 (NSCLC), and 786-O (renal) cancer in addition to Detroit 551 (fibroblast) normal cell line. Iodoindolinone analog **161e** (R = I) exhibited promising properties against HCT116 and NCT-H460 with potency higher than that of sunitinib (IC₅₀ = 0.42 ± 0.16, 2.95 ± 0.83; 3.42 ± 0.57, 6.23 ± 0.57 μM for **161e** and sunitinib, respectively). Bromo- **161d** and iodoindolinones **161e** showed considerable inhibitory properties against VEGFR-2 and PDGFR-β compared to that of sunitinib (IC₅₀ = 24.7, 16.1; 35.1, 29.3; and 140.0, 61.4 nM against VEGFR-2 and PDGFR-β for **161d** and **161e** and sunitinib, respectively)¹¹³ (Fig. 12).

A series of 2-oxoindolin-3-ylidenes connected to pyrrolo[*b*]cyclohexyl heterocycle **168** was prepared *via* the condensation

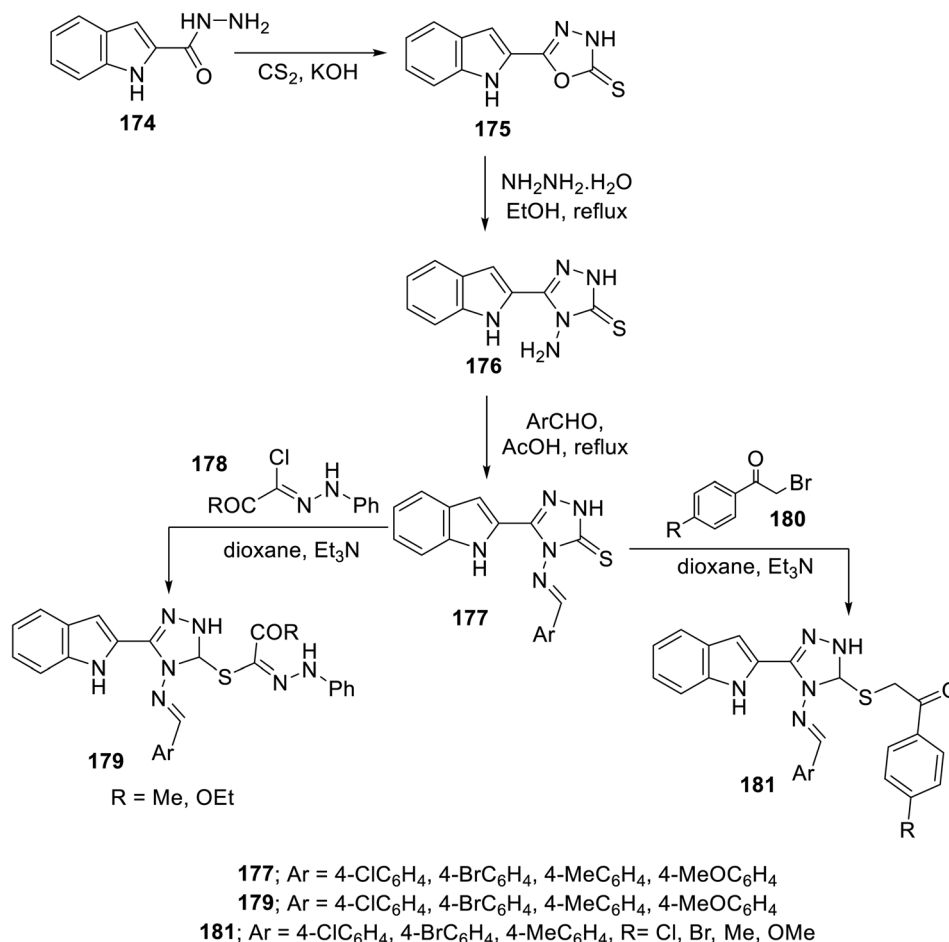


172; R = H, 5-OMe; R' = 2-Me, 3-Me, 4-Me, 3-F, 4-F, 3,5-difluoro, 2,4-difluoro, 4-CF₃, 2,4-dichloro, 4-OMe, 4-OEt, 4-NH₂; R'' = H, 5-Br, 6-Br, 7-Br, 5-CO₂H, 6-CO₂H, 7-CO₂H, 5-NH₂, 5-CONH(CH₂)₃CH₃, 5-CONH(CH₂)₂OMe, 5-CO-4-(1-methylpiperazinyl), 5-SO₂NH(CH₂)₃CH₃, 5-SO₂NH(CH₂)₂OMe, 5-SO₂-4-(1-methylpiperazinyl), 5-[(1-ethylpiperidin-4-yl)oxy], 5-[(1-ethylpiperidin-3-yl)amino], 5-[(1-ethylpiperidin-4-yl)amino], 5-[(1-(2-methoxyethyl)piperidin-4-yl)amino], **173**; R = H, 4-Me; R' = H, 2-F, 3-F, 4-Cl, 3,5-difluoro; R'' = 5-[(1-ethylpiperidin-4-yl)amino]

a) Et₃N, CH₃CN, 135 °C, 2 h; b) 7% HCl, acetone, charcoal, reflux, 0.5 h; c) NH₄OH; d) NH₃, EtOH, 90 °C; e) *N,N*-dimethylethylene diamine, EtOH, 90 °C

Scheme 23 Synthesis of 2-oxoindolin-3-ylidenes **172** and **173**.





Scheme 24 Synthesis of indole triazole conjugates 179 and 181.

(pyridine containing TiCl₄ “catalyst”) of the ketonic function of 1*H*-indole-3-carboxylate **166** with 2-indolinones **129**, followed by reaction with either primary or secondary amines (in DMF containing EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and HOBt: hydroxybenzotriazole at room temperature) (Scheme 22). Some of the synthesized agents **168** showed promising inhibitory properties against different/multi-targeted tyrosine kinases (VEGFR-2, PDGFR-β and c-kit) compared to that of sunitinib. Furthermore, some of the promising agents were tested for their antiproliferation properties (MTT assay) against BXP-3 (pancreatic), T24 (bladder), BGC (gastric), HEPG2 (liver) and HT29 (colon) cancer cell lines. Among them, compound **168c** (R = 5-Cl, R' = NH(CH₂)₂NEt₂) was one of the most promising candidates discovered with antiproliferation (IC₅₀ = 1.95, 1.83, 2.03, 3.14, and 6.48 μM against BXP-3, T24, BGC, HEPG2 and HT29, respectively) and enzymatic inhibitory properties (IC₅₀ = 2.6, 12.1, and 2.7 nM against VEGFR-2, PDGFR-β and c-kit, respectively) comparable to that of sunitinib (IC₅₀ = 3.63, 2.44, 4.78, 5.61 and 1.47 μM against BXP-3, T24, BGC, HEPG2 and HT29; IC₅₀ = 4.0, 10.6, and 8.9 nM against VEGFR-2, PDGFR-β and c-kit, respectively)¹¹⁴ (ESI Fig. S11†).

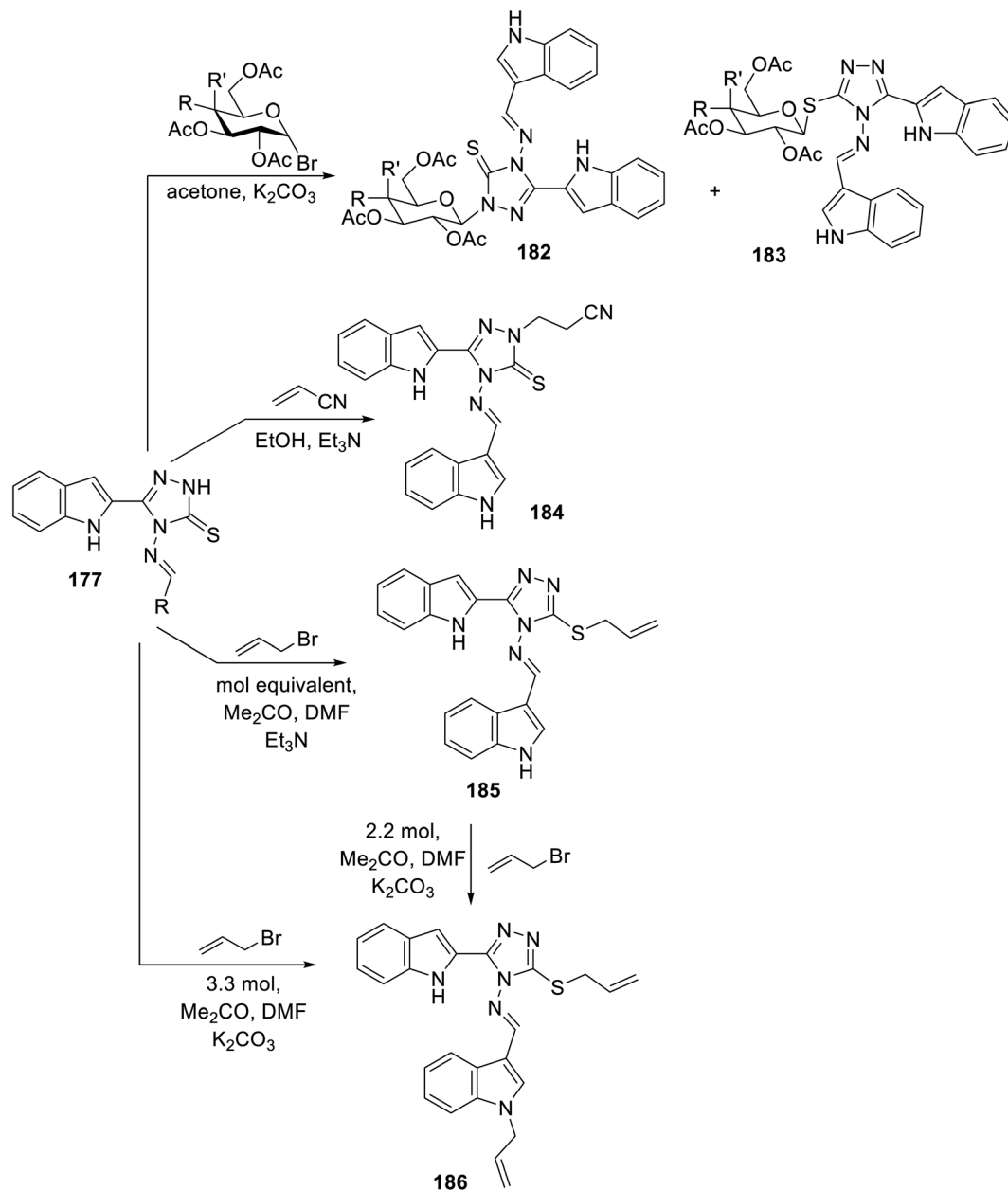
The reaction of benzimidazoles **169** with benzoyl chlorides **170** at 135 °C in the presence of TEA led to the formation of *N*- and *C*-

diacylated benzimidazoles. The *N*-acyl function was removed upon refluxing with 7% aqueous HCl. Condensation of the formed benzimidazolyl ketones **171** with 2-indolinones **129** in a sealed tube (90 °C) in EtOH/NH₃ gave the targeted 2-oxoindolin-3-ylidenes **172**. Similarly imidazolyl connected to 2-oxoindolin-3-ylidenes **173** were obtained (Scheme 23).¹¹⁵ Some of the synthesized 2-oxoindolin-3-ylidenes **172/173** revealed promising enzymatic inhibitory properties against VEGFR-1 (Flt-1), VEGFR-2 (KDR), FGFR-1 and PDGFR-α compared to sunitinib and SU6668 (standard references). Compounds **172p** (R = R' = H, R'' = 5-CO₂H), **172t** (R = H, R' = 4-Me, R'' = 5-CO₂H) and **172v** (R = 5-OMe, R' = H, R'' = 5-CO₂H) exhibited considerable potencies against VEGFR-2 compared to the standard references used (IC₅₀ = 4, 5, and 3 nM, respectively). Additionally, compounds **172af** {R = 5-OMe, R' = H, R'' = 5-NH[4-(*N*-ethylpiperidinyl)]} and **173c** {R = H, R' = 4-Cl, R'' = 5-NH[4-(*N*-ethylpiperidinyl)]} (IC₅₀ = 10, 4 nM, respectively) showed promising enzymatic inhibitory, ADME properties and cellular potencies¹¹⁵ (ESI Fig. S12†).

5. Indole heterocycle conjugates

Bio-conjugation is one of the most powerful and attractive rational drug design strategies used for the development of new drug candidates by connecting two or more therapeutic





Scheme 25 Synthesis of indole triazole conjugates 182–186.

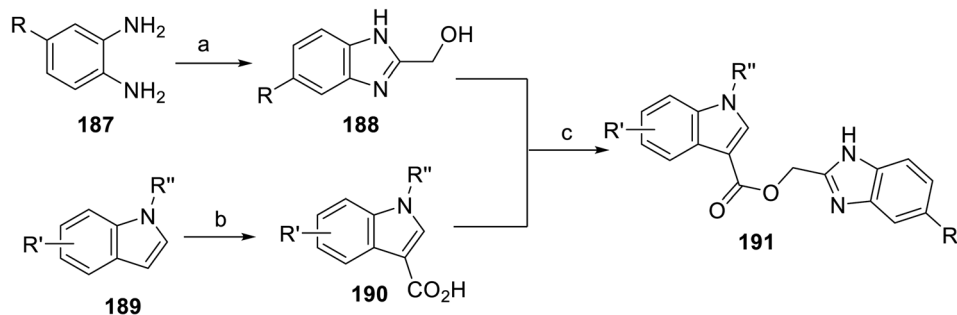
pharmacophoric functions/fragments/agents.^{116,117} Many conjugates have been reported to possess diverse potential bio-properties, among which vasodilation is useful for smooth muscle relaxation,^{118,119} anti-inflammatory, analgesic,^{120–123} antibacterial,^{124–126} antimycobacterial,¹²⁷ antimalarial,¹²⁸ antiviral including anti-SARS-CoV-2,^{129–133} HCV “hepatitis C viruses” and chikungunya,¹³⁴ anti-parasitic¹³⁵ and antitumor.^{136,137}

5.1. Indole triazole conjugates

The condensation reaction (in refluxing acetic acid) of the appropriate aromatic aldehyde with indole triazole conjugate

bearing an amino function **176** (obtained through reaction of 2-indolecarbohydrazide **174** with CS_2/KOH followed by hydrazinolysis ($\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ in refluxing EtOH)) afforded the corresponding Schiff base **177**. The reaction of **177** with hydrazonoyl chlorides **178** or phenacyl bromides **180** (in dioxane, Et_3N) afforded the corresponding conjugates **179** and **181**¹³⁸ (Scheme 24). Some of the synthesized agents were observed to exhibit considerable VEGFR-2 inhibitory and antiproliferation properties (MTT assay, against human renal cancer cell lines CAKI-1 and A498). The most promising agents discovered were **179c** (Ar = 4- $\text{H}_3\text{CC}_6\text{H}_4$; $\text{IC}_{50} = 0.075 \pm 0.002 \mu\text{M}$ against VEGFR-2;

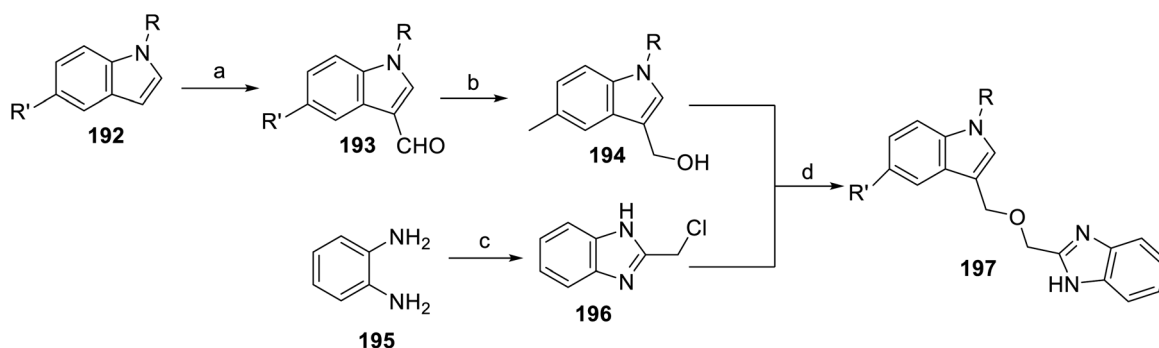




R = H, Me, NO₂; R' = H, 5-OMe, 5-Br, 1-Me, 2-Me, R'' = H, Me

a) HOCH₂CO₂H, H₃PO₄ (conc.), 130 °C, 3 h; b) (CF₃CO)₂O, 0 °C, DMF, room temperature, 3.5 h then, NaOH solution (20 %), 55 °C, 6h; c) DCC, DMAP, THF, room temperature, 7–9 h.

Scheme 26 Synthesis of indole benzimidazole conjugates 191.



R = H, Et, CH₂Ph; R' = H, OMe

a) POCl₃, DMF, 0 °C, 55 °C, 2 h; b) NaBH₄, EtOH, THF, room temperature; c) ClCH₂CO₂H, 4N HCl, reflux, 3 h; d) Me₂CO, K₂CO₃, reflux, 8–20 h

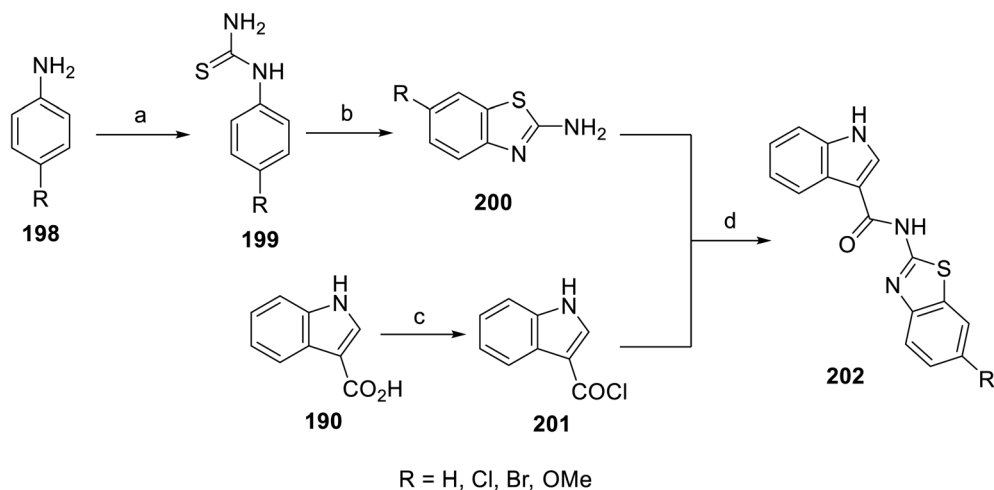
Scheme 27 Synthesis of indole benzimidazole conjugates 197.

IC₅₀ = 3.23 ± 0.15 and 2.05 ± 0.09 μM against CAKI-1 and A498 cell lines, respectively) and **181g** (Ar = 4-MeOC₆H₄, R = Cl; IC₅₀ = 0.071 ± 0.002 μM against VEGFR-2; IC₅₀ = 0.89 ± 0.04 and 2.2 ± 0.1 μM against CAKI-1 and A498 cell lines, respectively) compared to sunitinib (IC₅₀ = 0.075 ± 0.002 μM against VEGFR-2; IC₅₀ = 4.93 ± 0.16, 1.25 ± 0.04 μM against CAKI-1 and A498 cell lines, respectively) with a safety profile upon testing against the RPTEC/TERT1 non-cancer cell line¹³⁸ (ESI Fig. S13†).

Glycosylation of Schiff base **177** with either acetobromoglucose or acetobromogalactose (K₂CO₃, acetone at room temperature) gave a mixture of *N*-glycosylated **182** and *S*-analog **183**. However, the reaction of **177** with acrylonitrile (Michael acceptor) in refluxing ethanol containing Et₃N afforded the corresponding *N*-substituted Michael adduct **184**. Meanwhile, the reaction of **177** with allyl bromide (equimolar values) in acetone/DMF (1 : 1 v/v) containing Et₃N at room temperature as a basic catalyst gave the *S*-allylated analog **185**. Meanwhile, utilizing K₂CO₃ in the

same reaction (using 3.3 molar value equivalent of allyl bromide relative to **177**), the allylation of both the indolyl nitrogen and *S*-function of triazolyl heterocycle **186** was achieved. The same product was obtained upon reacting *S*-allylated analog **185** under the same conditions (2.2 molar equivalent value) (Scheme 25). The antiproliferation properties of the synthesized conjugates **182–186** were studied against the MCF7 (breast) and HepG2 (liver) cancer cell lines (MTT assay) utilizing 5-fluorouracil and sorafenib as reference standards. Also, the VEGFR-2 inhibitory properties were studied for the most effective antiproliferative agent observed, supporting that compound **185** is a promising conjugate (IC₅₀ = 1.18 ± 0.15 and 7.09 ± 0.67 μM against MCF7 and HepG2 cell lines; IC₅₀ = 19.8 ± 1.58 nM against VEGFR-2, respectively) compared to sorafenib (IC₅₀ = 2.13 ± 0.24 and 3.24 ± 0.23 μM against MCF7 and HepG2 cell lines; IC₅₀ = 30.0 nM against VEGFR-2, respectively). The safe profile of compound **185** was supported through antiproliferation studies against the MDA-MB-





a) $C_6H_5NH_2$, NH_4SCN , AcOH, 4 h; b) Br_2 , 0 °C, 15 °C, 2 h; c) $SOCl_2$, reflux, 5 h; d) CH_2Cl_2 , Et_3N , 30 °C, 18 h

Scheme 28 Synthesis of indole benzothiazole conjugates 202.

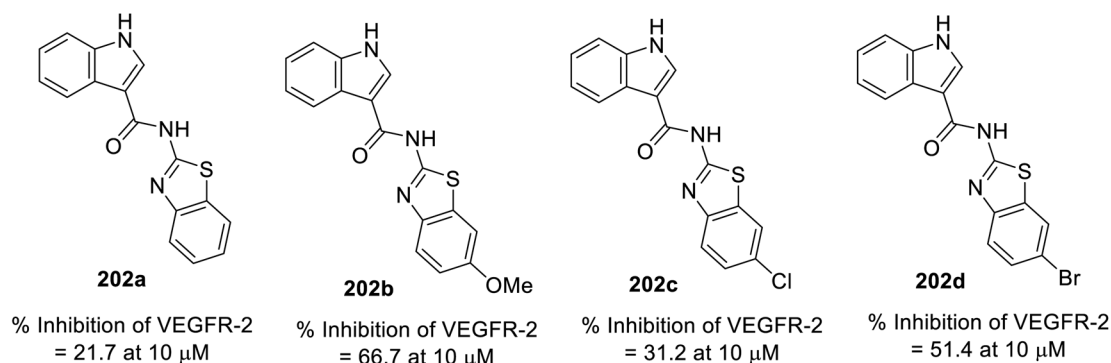


Fig. 13 % Inhibitory properties of VEGFR-2 by indole benzothiazole conjugates 202 at 10 μ M.

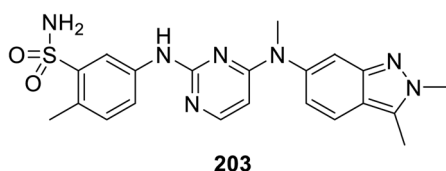


Fig. 14 Pazopanib VEGFR-2 inhibitor FDA approved for treatment of advanced renal cell cancer and soft tissue sarcoma.

231 non-cancer cell line (triple-negative breast cancer) and normal breast cells (MCF-10A) (IC_{50} = 10.49, 24.76 μ M, against MDA-MB-231 and MCF-10A, respectively)¹³⁹ (ESI Fig. S14[†]).

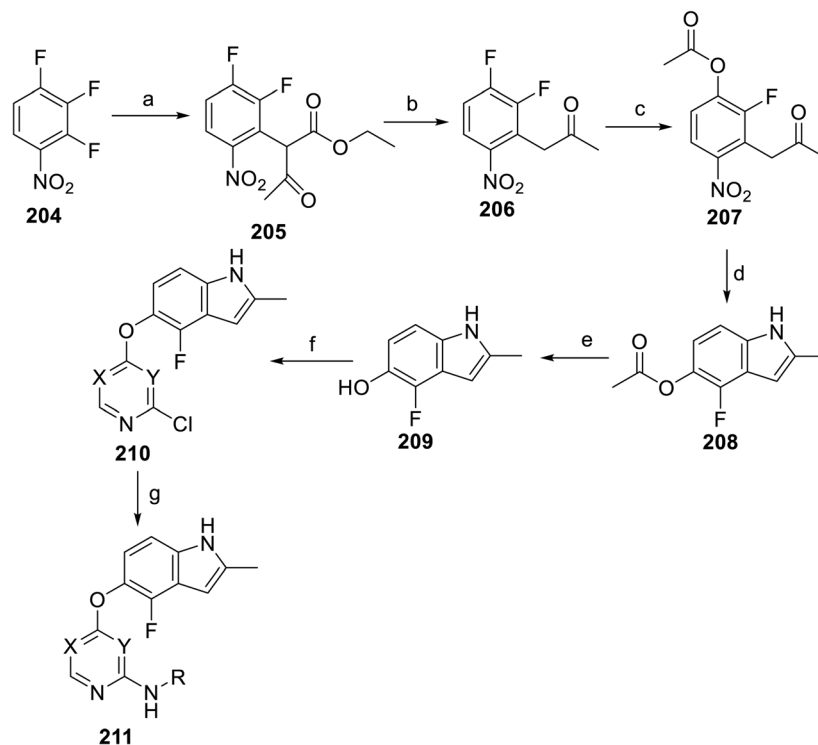
5.2. Indole benzimidazole conjugates

The esterification reaction of 3-indolecarboxylic acid **190** (obtained through the reaction of indole analogs **189** with $(CF_3CO)_2O$ in DMF followed by treatment with 20% NaOH solution at 55 °C) with 2-hydroxymethyl benzimidazole **188** (synthesized through the reaction of the appropriate *o*-phenylenediamine **187** with hydroxyacetic acid in conc. H_3PO_4 at 130 °C) in THF containing DMAP (dimethylaminopyridine) and (DCC) (dicyclohexylcarbodiimide) at room temperature afforded indole benzimidazole conjugates **191** (Scheme 26). Additionally, indole benzimidazole conjugates **197** were obtained *via* the reaction of 2-chloromethyl-1*H*-benzimidazoles **196** (prepared by refluxing the appropriate *o*-phenylenediamine **195** with chloroacetic acid in 4 N HCl) with the appropriate (1*H*-indol-3-yl)methanol **194** (obtained through the formylation of the appropriate indolyl analogs “ $POCl_3$, DMF, 55 °C” followed by $NaBH_4$ reduction) in refluxing acetone containing anhydrous K_2CO_3 (Scheme 27). Some of the synthesized conjugates exhibited considerable VEGFR-2 inhibitory properties (ESI Fig. S15[†]). Among them, the most promising was **191j** ($R = R' = H$, $R'' = Me$; % inhibition of VEGFR-2 at 10 μ M = 6.0) relative to sunitinib/SU11248 (% inhibition of VEGFR-2 at 10 μ M = 98.1).¹⁴⁰

5.3. Indole benzothiazole conjugates

A variety of indole benzothiazole conjugates **202** was obtained through the reaction of 3-indole carbonyl chloride **201** (obtained by refluxing 3-indolecarboxylic acid **190** with thionyl chloride)





X, Y = C, N; R = Ph, 3-SO₂NH₂-4-MeC₆H₃, 3-SO₂NH₂C₆H₄, 4-SO₂NH₂C₆H₄,
3-SO₂NH₂-2-MeC₆H₃, 5-SO₂NH₂-2-MeOC₆H₃, 3-NHSO₂MeC₆H₄,
3-CH₂SO₂MeC₆H₄, 4-CH₂SO₂MeC₆H₄, 2-Me-5-CH₂SO₂MeC₆H₃,
3,4,5-(MeO)₃C₆H₂, 3-SO₂MeC₆H₄, 2-Me-5-SO₂MeC₆H₃, 3-SO₂EtC₆H₄,
2-Me-5-SO₂EtC₆H₃, 3-MeCOC₆H₄, 3-NO₂C₆H₄, 3-MeOC₆H₄, 4-MeOC₆H₄,
3,4-(MeO)₂C₆H₃

a) NaH, MeCOCH₂CO₂Et, THF, 5 °C – room temperature, 12 h; b) HCl, AcOH, reflux,
12 h; c) NaOAc, DMF, 100 °C, 10 h; d) H₂, Pd/C, EtOH-DMF, 40 °C, 10 h;
e) aq. NaHCO₃, MeOH, room temperature, 10 h; f) 2,4-dichloropyrimidine or
4,6-dichloropyrimidine, aq. NaOH, Me₂CO, 0–80 °C; g) primary amine,
36% HCl, *i*-PrOH, sealed tube, 100 °C.

Scheme 29 Synthesis of indole-pyrimidine conjugates **211**.

with 2-aminobenzothiazoles **200** (in CH₂Cl₂ containing Et₃N at room temperature) (Scheme 28). The synthesized conjugates exhibited considerable inhibitory properties (Fig. 13) compared to that of sunitinib (% inhibition of VEGFR-2 at 10 μM = 98.1).¹⁴⁰

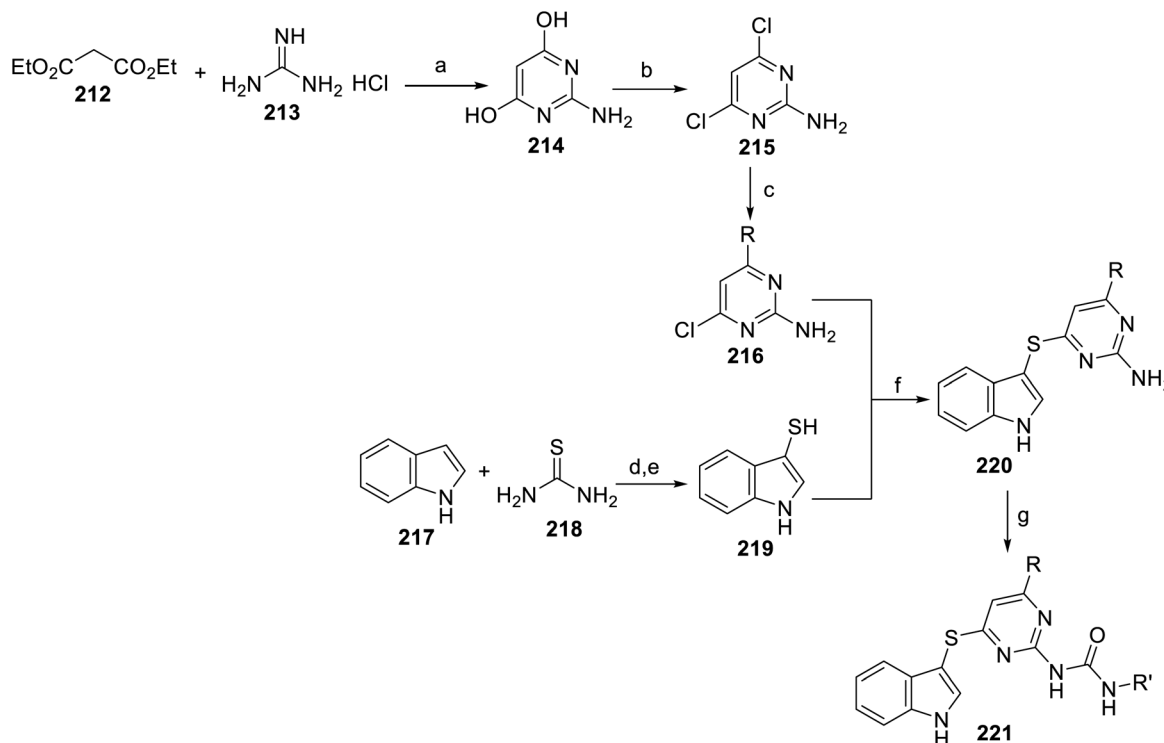
5.4. Indole-pyrimidine conjugates

Pazopanib **203** (Fig. 14) is an FDA approved VEGFR-2 inhibitor for the treatment of advanced renal cell cancer (2009) and soft tissue sarcoma.^{141,142} In this molecule, the pyrimidinyl pharmacophoric heterocycle is attached to an indazole heterocycle. This inspired the design, construction and VEGFR-2 inhibitory properties investigation of indole pyrimidine conjugates linked through an ether linkage.¹⁴³ A set of indole pyrimidine conjugates **211** was synthesized through the coupling of 5-hydroxyindole derivative **209** with 2,4-dichloropyrimidine or 4,6-dichloropyrimidine in Me₂CO containing aq. NaOH, followed by reaction with various primary amines (HCl “36%”, *i*-PrOH, sealed tube, 100 °C) (Scheme 29). Some of the synthesized

conjugates **211** were observed to exhibit considerable VEGFR-2 inhibitory properties. Among them, the most promising was **211k** [R = 3-(MeSO₂C₆H₄)CH₂] compared to sunitinib (IC₅₀ = 0.0038 ± 0.0033, 0.0022 ± 0.0005 μM, respectively) (ESI Fig. S16[†]). Additionally, compound **211k** exhibited inhibitory properties against VEGFR-1, VEGFR-3, PDGFR-α and PDGFR-β (IC₅₀ = 40.4, 515.8, 24.1 and 33.6 nM, respectively) and can be nominated as multi-targeted tyrosine kinase inhibitor.¹⁴³

Indole pyrimidine conjugates **221** connected through a thioether linkage were also reported. The reaction of indole-3-thiol **219** with 6-chloro-2,4-diaminopyrimidines **216** (obtained from condensation of diethylmalonate **212** and guanidine hydrochloride **213** under basic condition, followed by chlorination with POCl₃, and then reaction with either primary or secondary amine) in refluxing ethanol containing Et₃N and KI gave **220**, which was reacted with isocyanate in refluxing 1,4-dioxane, finally giving **221**¹⁴⁴ (Scheme 30). Some of the synthesized agents exhibited promising antiproliferation properties (MTT

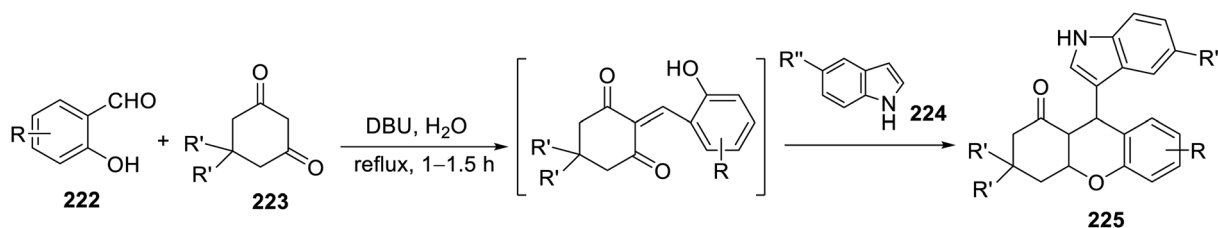




R = 4-morpholinyl, 1-piperidiny, 1-pyrrolidiny, PhNH, 1-(2-pyridiny)-4-piperaziny, 1-benzyl-4-piperaziny, (cyclopropyl)NH, 3,5-(MeO)₂C₆H₃NH, 4-ClC₆H₄NH; R' = Ph, 4-MeOC₆H₄, 2-Me-4-ClC₆H₃, 2,5-Me₂C₆H₃, 4-ClC₆H₄, 3,5-(MeO)₂C₆H₃, 3-(CF₃)-4-ClC₆H₃

a) NaOMe, MeOH, 70 °C, 5 h; b) POCl₃, *N,N*-dimethyl aniline, 60 °C, 1 h; c) primary amine (1M HCl, 1,4-dioxane, 80 °C, 6–8 h) or secondary amine (DIPEA, *n*-BuOH, 50–100 °C, 5h; d) I₂, KI, MeOH, room temperature, 2 h; e) 4M NaOH, 80 °C, 0.5 h; f) KI, Et₃N, EtOH, reflux, 12–16 h; g) R'NCO, 1,4-dioxane, 100 °C, 3–8 h

Scheme 30 Synthesis of indole-pyrimidine conjugates 221.



Scheme 31 Synthesis of indole chromene conjugates 225.

assay) against A549 (lung), PC-3 (prostate), MDAMB-231 (breast) and HepG2 (liver) human cancer cell lines with promising VEGFR-2 properties compared to that of sorafenib. The most promising was **221k** (R = 1-pyrrolidiny, R' = 4-ClC₆H₄; IC₅₀ = 6.41 ± 0.81, 10.42 ± 0.78, 5.85 ± 0.71, and 7.87 ± 1.18 μM against A549, PC-3, MDAMB-231 and HepG2, respectively with % inhibition = 0.33% ± 0.04% of VEGFR-2 at 10 μM) compared to that of Sorafenib (IC₅₀ = 7.43 ± 0.81, 9.77 ± 1.12, 11.84 ± 1.25, 5.78 ± 0.41 μM against A549, PC-3, MDAMB-231 and

HepG2, respectively with % inhibition = 1.21% ± 0.02% of VEGFR-2 at 10 μM)¹⁴⁴ (ESI Fig. S17†).

5.5. Indole chromene conjugates

A multi-component eco-friendly synthetic procedure was employed for the preparation of indole chromene conjugates **225** via the one-pot reaction of salicylaldehydes **222**, with the appropriate 1,3-cyclohexanones **223** and indole derivative **224** in refluxing water containing DBU (1,8-diazabicyclo[5.4.0]undec-7-



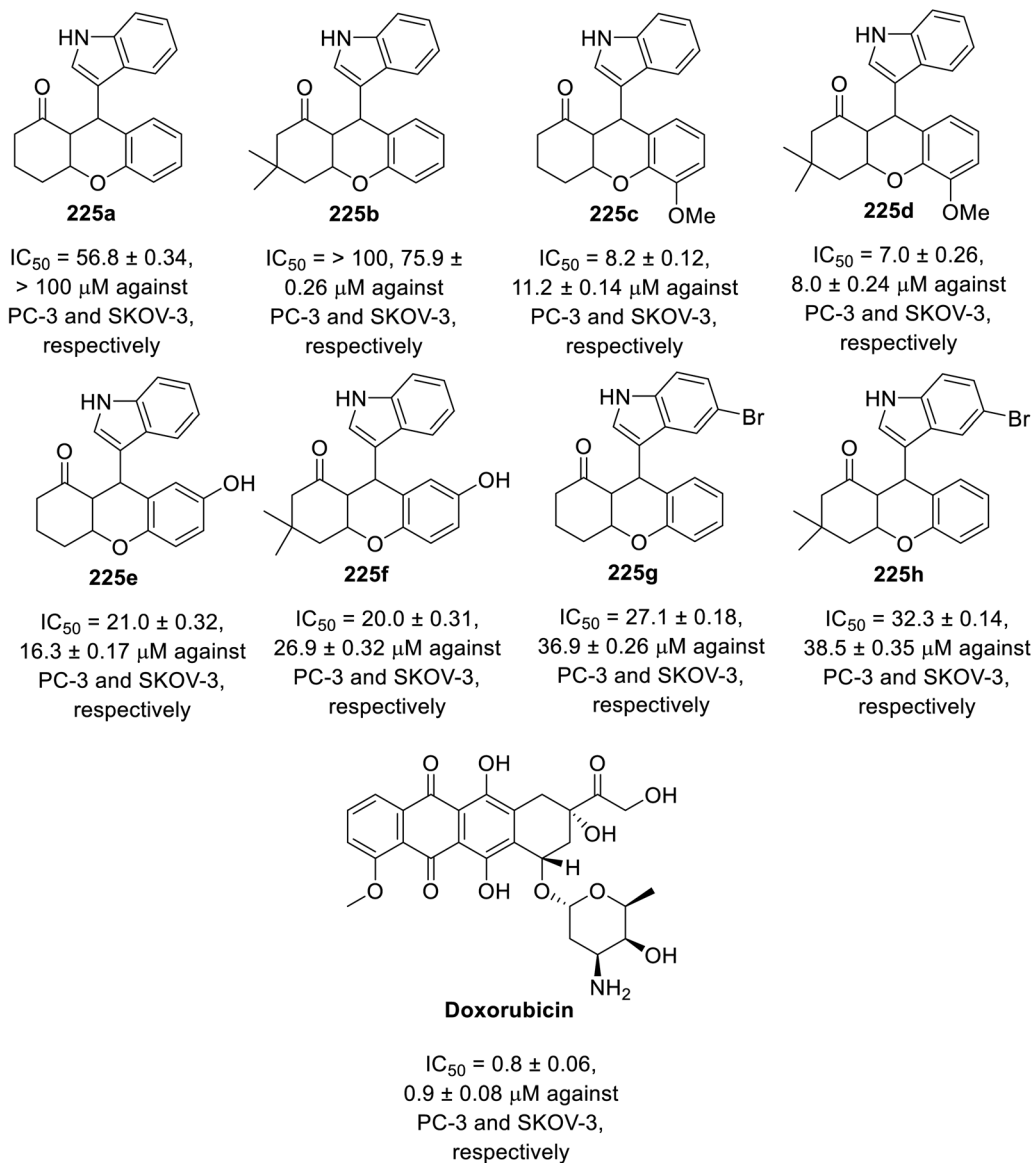
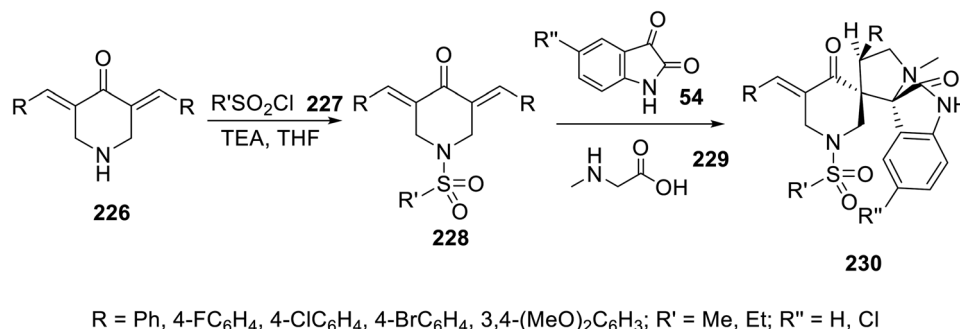


Fig. 15 Antiproliferation properties of indole chromene conjugates 225 and doxorubicin (standard reference).

ene). The reaction was assumed to take place *via* the base-catalyzed Michael addition of indole to the Knoevenagel adduct formed from the condensation of the salicylaldehyde with 1,3-cyclohexanone assisted by the basic catalysis of DBU¹⁴⁵ (Scheme

31). The synthesized conjugates 225 exhibited mild antitumor properties (MTT assay) against the PC-3 (prostate) and SKOV-3 (ovarian) cancer cell lines compared to that of doxorubicin (Fig. 15). Their VEGFR-2 inhibitory properties were reported based



Scheme 32 Synthesis of spiroindoles 230.



on the molecular modeling technique (PDB ID: 4ASD, AutoDock Tools 4.2).¹⁴⁵ However, theoretical (molecular modeling) studies are insufficient supporting evidence for assigning the mode of action, and thus experimental data is required.

6. Spiroindoles

Spiroindoles occupy a unique place in heterocyclic chemistry due to the versatile bio-properties of their natural and synthetic analogs¹⁴⁶ (exemplified by antibacterial, antifungal,^{147–151} antimycobacterial,^{152–154} antiviral,^{19,155} anticancer,^{156–160} antimalarial,^{161,162} anti-inflammatory¹⁶³ and antihyperglycemic^{164,165}). [3 + 2]-Dipolar cycloaddition of azomethine ylides derived from isatin derivatives with α -amino acids to the exocyclic olefinic linkage derived from alicycles or heterocycles is an accessible synthetic approach successfully used for the construction of various spiroindoles with regio- and stereoselectivity.^{146,166–168} Many antitumor active agents against various human tumor cell lines were optimized *via* the above-mentioned synthetic approach; however, the VEGFR mode of action was only assigned for a few analogs.^{169,170}

Spiroindoles **230** were regioselectively synthesized through the one-pot three-component reaction of 3,5-diylidene-4-piperidones **228** and azomethine, which were formed by the condensation of isatins **54** and sarcosine **229** in refluxing ethanol (Scheme 32). The stereochemical structure of **230** was established by single crystal X-ray studies. Promising anti-proliferation properties were exhibited by some of the synthesized spiroindoles **230** against the MCF7 (breast), HCT116 (colon), A431 (skin squamous) and PaCa2 (pancreatic) cancer cell lines (MTT assay) compared to the standard references (sunitinib and 5-fluorouracil). Safe behaviors against the non-cancer RPE1 cell line were revealed by the synthesized agents. Considerable multi-targeted inhibitory properties (western blotting technique) were exhibited by the synthesized agents against VEGFR-2 and EGFR. The SAR (structure–activity relationship) study indicated that the chloro-substituted indolyl heterocycle can optimize efficient agents against the tested cancer cell lines. Compound **231n** (R = 4-BrC₆H₄, R' = Me, R'' = H) was the most promising agent observed (IC₅₀ = 3.597 ± 0.19, 3.236 ± 0.27, 2.434 ± 0.18, 12.500 ± 0.67, and 14.894 ± 1.61 μ M against the MCF7, HCT116, A431, PaCa-2 and RPE1 cell lines, respectively; % inhibition = 61.3% and 65.6% against VEGFR-2 and EGFR at the IC₅₀ value observed against MCF7, respectively) compared to sunitinib (IC₅₀ = 3.97 ± 0.32, 9.67 ± 0.22, and 16.91 ± 0.95 μ M against MCF7, HCT116, and PaCa-2 cell lines, respectively; % inhibition = 74.7% and 81.4% against VEGFR-2 and EGFR at IC₅₀ value observed against MCF7, respectively)¹⁹ (ESI Fig. S18†).

7. Conclusion

Tyrosine kinases are capable of many diverse cellular functions including growth, proliferation, differentiation and death. VEGFR is one of the targeted therapeutic approaches that is preferable to the classical non-selective therapies to minimize the associated side effects or drawbacks. VEGF is an important

category of tyrosine kinases, which can stimulate angiogenesis. VEGFR-2 is the most well-known factor in the angiogenesis of different solid tumors (colon, breast, ovary, lung, skin, renal, head, neck, lymphoma, *etc.*). Indolyl therapeutics have been approved against some serious types of cancer. Additionally, research efforts identified natural and synthesized antitumor indole-containing compounds with promising anti-VEGFR properties. Computational/theoretical studies can assist in designing and identifying novel hits/leads of anti-VEGFR agents; however, without experimental supporting their enzymatic properties, the predictions cannot be considered for further investigations or utilization.

Abbreviations

ADMET	Absorption, distribution, metabolism, excretion and toxicity
AMD	Age-related macular degeneration
ATP	Adenosine triphosphate
BOP	Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
CA	Carbonic anhydrase
CAM	Chick chorioallantoic membrane
CDK-1	Cyclin-dependent kinase 1
c-kit	Stem cell factor receptor
COX	Cyclooxygenase
COX-2	Cyclooxygenase-2
CSF-1R	Colony stimulating factor-1 receptor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DFT	Density function theory
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMTMM	4-(4,6-Dimethoxytriazine)chlorinated 4-methylmorpholine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
FDA	Food and drug administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth-factor receptor
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HCV	Hepatitis C viruses
HER-2	Human epidermal growth factor receptor 2
HIF-1- α	Hypoxia-inducible factor-1- α
HIV	Human immunodeficiency virus
HOBt	Hydroxybenzotriazole
HUVEC	Human umbilical vein endothelial cell
IBCF	Iso-butyl chloroformate
MD	Molecular dynamic
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NET	Neuroendocrine tumor
NSCLC	Non-small cell lung cancer
NT	Not tested
PDGFR	Platelet-derived growth-factor receptor
SAR	Structure–activity relationship



Review

SD	Standard division
SEM	Standard error mean
SRB	Sulforhodamine B
TEA	Triethylamine
THF	Tetrahydrofuran
TRAMP	Transgenic adenocarcinoma of the mouse prostate
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Author contributions

Conceptualization, A. S. G.; methodology, A. S. G. and D. R. A.; data analyses, A. S. G.; writing – original draft preparation, A. S. G. and D. R. A.; review and editing, A. S. G., D. R. A., M. S. B. and A. R. H.; supervision, A. S. G. and M. A. Y. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There is no conflict to declare.

Acknowledgements

This work was supported financially by National Research Centre, Egypt, project ID: 13060103.

References

- G.-F. Zha, H.-L. Qin, B. G. M. Youssif, M. W. Amjad, M. A. G. Raja, A. H. Abdelazeem and S. N. A. Bukhari, Discovery of potential anticancer multi-targeted ligustrazine based cyclohexanone and oxime analogs overcoming the cancer multidrug resistance, *Eur. J. Med. Chem.*, 2017, **135**, 34–48, DOI: [10.1016/j.ejmech.2017.04.025](https://doi.org/10.1016/j.ejmech.2017.04.025).
- B. S. Chhikara and K. Parang, Global cancer statistics 2022: the trends projection analysis, *Chem. Biol. Lett.*, 2023, **10**, 451.
- R. L. Siegel, K. D. Miller, N. S. Wagle and A. Jemal, Cancer statistics, 2023, *Ca-Cancer J. Clin.*, 2023, **73**, 17–48, DOI: [10.3322/caac.21763](https://doi.org/10.3322/caac.21763).
- J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman and F. Bray, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, *Int. J. Cancer*, 2015, **136**, 359–386, DOI: [10.1002/ijc.29210](https://doi.org/10.1002/ijc.29210).
- L. K. Penny and H. M. Wallace, The challenges for cancer chemoprevention, *Chem. Soc. Rev.*, 2015, **44**, 8836–8847, DOI: [10.1039/c5cs00705d](https://doi.org/10.1039/c5cs00705d).
- K. T. Jha, A. Shome, Chahat and P. A. Chawla, Recent advances in nitrogen-containing heterocyclic compounds as receptor tyrosine kinase inhibitors for the treatment of cancer: biological activity and structural activity relationship, *Bioorg. Chem.*, 2023, **138**, 106680, DOI: [10.1016/j.bioorg.2023.106680](https://doi.org/10.1016/j.bioorg.2023.106680).
- O. M. Soltan, M. E. Shoman, S. A. Abdel-Aziz, A. Narumi, H. Konno and M. Abdel-Aziz, 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, DOI: [10.1016/j.ejmech.2021.113768](https://doi.org/10.1016/j.ejmech.2021.113768).
- D. R. Robinson, Y.-M. Wu and S.-F. Lin, The protein tyrosine kinase family of the human genome, *Oncogene*, 2000, **19**, 5548–5557, DOI: [10.1038/sj.onc.1203957](https://doi.org/10.1038/sj.onc.1203957).
- D. Mondal, S. Abdul Amin, M. Moinul, K. Das, T. Jha and S. Gayen, How the structural properties of the indole derivatives are important in kinase targeted drug design?: a case study on tyrosine kinase inhibitors, *Bioorg. Med. Chem.*, 2022, **53**, 116534, DOI: [10.1016/j.bmc.2021.116534](https://doi.org/10.1016/j.bmc.2021.116534).
- A. M. Srour, S. S. Panda, A. Mostafa, W. Fayad, M. A. El-Manawaty, A. A. F. Soliman, Y. Moatasim, A. El Taweel, M. F. Abdelhameed, M. S. Bekheit, M. A. Ali and A. S. Girgis, Synthesis of aspirin-curcumin mimic conjugates of potential antitumor and anti-SARS-CoV-2 properties, *Bioorg. Chem.*, 2021, **117**, 105466, DOI: [10.1016/j.bioorg.2021.105466](https://doi.org/10.1016/j.bioorg.2021.105466).
- X. Liang, Q. Yang, P. Wu, C. He, L. Yin, F. Xu, Z. Yin, G. Yue, Y. Zou, L. Li, X. Song, C. Lv, W. Zhang and B. Jing, The synthesis review of the approved Tyrosine kinase inhibitors for anticancer therapy in 2015–2020, *Bioorg. Chem.*, 2021, **113**, 105011, DOI: [10.1016/j.bioorg.2021.105011](https://doi.org/10.1016/j.bioorg.2021.105011).
- A. M. Abuzenadah, F. Al-Sayes, S. S. M. Alam, M. Hoque, S. Karim, I. M. R. Hussain and S. Tabrez, Elucidating antiangiogenic potential of *Rauwolfia serpentina*: VEGFR-2 targeting-based molecular docking study, *Evidence-Based Complementary Altern. Med.*, 2022, 6224666, DOI: [10.1155/2022/6224666](https://doi.org/10.1155/2022/6224666).
- T. A. Farghaly, W. A. Al-Hasani and H. G. Abdulwahab, An updated patent review of VEGFR-2 inhibitors (2017-present), *Expert Opin. Ther. Pat.*, 2021, **31**, 989–1007, DOI: [10.1080/13543776.2021.1935872](https://doi.org/10.1080/13543776.2021.1935872).
- S. Török and B. Döme, Possibilities for inhibiting tumor-induced angiogenesis: results with multi-target tyrosine kinase inhibitors, *Magy. Onkol.*, 2012, **56**, 3–15.
- I. A. Seliem, S. S. Panda, A. S. Girgis, Q. L. Tran, M. F. Said, M. S. Bekheit, A. Abdelnaser, S. Nasr, W. Fayad, A. A. F. Soliman, R. Sakhuja, T. S. Ibrahim, Z. K. M. Abdel-Samii and A. M. M. Al-Mahmoudy, Development of isatin-based Schiff bases targeting VEGFR-2 inhibition: synthesis, characterization, antiproliferative properties, and QSAR studies, *ChemMedChem*, 2022, **17**, e202200164, DOI: [10.1002/cmdc.202200164](https://doi.org/10.1002/cmdc.202200164).
- M. Sabbah, A. Najem, M. Krayem, A. Awada, F. Journe and G. E. Ghanem, RTK inhibitors in melanoma: from bench to bedside, *Cancers*, 2021, **13**, 1685, DOI: [10.3390/cancers13071685](https://doi.org/10.3390/cancers13071685).
- A. Weiss, D. Bonvin, R. H. Berndsen, E. Scherrer, T. J. Wong, P. J. Dyson, A. W. Griffioen and P. Nowak-Sliwinska, Angiostatic treatment prior to chemo- or photodynamic therapy improves anti-tumor efficacy, *Sci. Rep.*, 2015, **5**, 8990, DOI: [10.1038/srep08990](https://doi.org/10.1038/srep08990).
- P. R. Massey, J. S. Okman, J. Wilkerson and E. W. Cowen, Tyrosine kinase inhibitors directed against the vascular



- endothelial growth factor receptor (VEGFR) have distinct cutaneous toxicity profiles: a meta-analysis and review of the literature, *Support. Care Cancer*, 2015, **23**, 1827–1835, DOI: [10.1007/s00520-014-2520-9](https://doi.org/10.1007/s00520-014-2520-9).
- 19 N. G. Fawazy, S. S. Panda, A. Mostafa, B. M. Kariuki, M. S. Bekheit, Y. Moatasim, O. Kutkat, W. Fayad, M. A. El-Manawaty, A. A. F. Soliman, R. A. El-Shiekh, A. M. Srour, R. F. Barghash and A. S. Girgis, Development of spiro-3-indolin-2-one containing compounds of antiproliferative and anti-SARS-CoV-2 properties, *Sci. Rep.*, 2022, **12**, 13880, DOI: [10.1038/s41598-022-17883-9](https://doi.org/10.1038/s41598-022-17883-9).
- 20 R. Begum, A. N. M. Mamun-Or-Rashid, T. T. Lucy, K. Pramanik, B. K. Sil, N. Mukerjee, P. Tagde, M. Yagi and Y. Yonei, Potential therapeutic approach of melatonin against omicron and some other variants of SARS-CoV-2, *Molecules*, 2022, **27**, 6934, DOI: [10.3390/molecules27206934](https://doi.org/10.3390/molecules27206934).
- 21 A. S. Girgis, S. S. Panda, B. M. Kariuki, M. S. Bekheit, R. F. Barghash and D. R. Aboshouk, Indole-Based Compounds as Potential Drug Candidates for SARS-CoV-2, *Molecules*, 2023, **28**, 6603, DOI: [10.3390/molecules28186603](https://doi.org/10.3390/molecules28186603).
- 22 R. J. Reiter, R. Sharma, F. Simko, A. Dominguez-Rodriguez, J. Tesarik, R. L. Neel, A. T. Slominski, K. Kleszczynski, V. M. Martin-Gimenez, W. Manucha and D. P. Cardinali, Melatonin: highlighting its use as a potential treatment for SARS-CoV-2 infection, *Cell. Mol. Life Sci.*, 2022, **79**, 143, DOI: [10.1007/s00018-021-04102-3](https://doi.org/10.1007/s00018-021-04102-3).
- 23 G. García, M. Rodríguez-Rubio, A. R. Mariblanca, L. M. de Soto, L. D. García, J. M. Villatoro, J. Q. Parada, E. S. Meseguer, M. J. Rosales, J. González, J. R. Arribas, A. J. Carcas, P. de la Oliva and A. M. Borobia, A randomized multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts (MeCOVID Trial): a structured summary of a study protocol for a randomised controlled trial, *Trials*, 2020, **21**, 466, DOI: [10.1186/s13063-020-04436-6](https://doi.org/10.1186/s13063-020-04436-6).
- 24 Z. T. Hasan, M. Q. Y. M. A. Al Atrakji and A. K. Mehuaiden, The effect of Melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients, *Int. J. Infect. Dis.*, 2022, **114**, 79–84, DOI: [10.1016/j.ijid.2021.10.012](https://doi.org/10.1016/j.ijid.2021.10.012).
- 25 <https://go.drugbank.com/drugs/DB08839>, (accessed on Dec. 11, 2023).
- 26 <https://www.drugs.com/history/tivorbex.html>, (accessed on Dec. 11, 2023).
- 27 R. M. Bokhtia, S. S. Panda, A. S. Girgis, N. Samir, M. F. Said, A. Abdelnaser, S. Nasr, M. S. Bekheit, A. S. Dawood, H. Sharma, M. Wade, S. K. Sharma and A. M. Ghanim, New NSAID conjugates as potent and selective COX-2 inhibitors: synthesis, molecular modeling and biological investigation, *Molecules*, 2023, **28**, 1945, DOI: [10.3390/molecules28041945](https://doi.org/10.3390/molecules28041945).
- 28 <https://www.drugs.com/dosage/delavirdine.html>, (accessed on Dec. 11, 2023).
- 29 G. Li, Y. Wang and E. De Clercq, Approved HIV reverse transcriptase inhibitors in the past decade, *Acta Pharm. Sin. B*, 2022, **12**, 1567–1590, DOI: [10.1016/j.apsb.2021.11.009](https://doi.org/10.1016/j.apsb.2021.11.009).
- 30 <https://go.drugbank.com/drugs/DB13609>, (accessed on Dec. 11, 2023).
- 31 <https://www.drugs.com/international/umifenovir.html>, (accessed on Dec. 11, 2023).
- 32 A. Shuster, D. Pechalrieu, C. B. Jackson, D. Abegg, H. Choe and A. Adibekian, Clinical antiviral drug arbidol inhibits infection by SARS-CoV-2 and variants through direct binding to the spike protein, *ACS Chem. Biol.*, 2021, **16**, 2845–2851, DOI: [10.1021/acscchembio.1c00756](https://doi.org/10.1021/acscchembio.1c00756).
- 33 X. Wang, R. Cao, H. Zhang, J. Liu, M. Xu, H. Hu, Y. Li, L. Zhao, W. Li, X. Sun, X. Yang, Z. Shi, F. Deng, Z. Hu, W. Zhong and M. Wang, The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro, *Cell Discovery*, 2020, **6**, 28, DOI: [10.1038/s41421-020-0169-8](https://doi.org/10.1038/s41421-020-0169-8).
- 34 <https://www.drugs.com/mtm/pindolol.html>, (accessed on Dec. 11, 2023).
- 35 <https://www.drugs.com/maxalt.html>, (accessed on Dec. 11, 2023).
- 36 B. Yu, D.-Q. Yu and H.-M. Liu, Spirooxindoles: promising scaffolds for anticancer agents, *Eur. J. Med. Chem.*, 2015, **97**, 673–698, DOI: [10.1016/j.ejmech.2014.06.056](https://doi.org/10.1016/j.ejmech.2014.06.056).
- 37 J. Jin, Y. Xie, J.-S. Zhang, J.-Q. Wang, S.-J. Dai, W.-f. He, S.-Y. Li, C. R. Ashby Jr., Z.-S. Chen and Q. He, Sunitinib resistance in renal cell carcinoma: from molecular mechanisms to predictive biomarkers, *Drug Resistance Updates*, 2023, **67**, 100929, DOI: [10.1016/j.drug.2023.100929](https://doi.org/10.1016/j.drug.2023.100929).
- 38 F. M. Guida, M. Santoni, A. Conti, L. Burattini, A. Savini, T. Zeppola, M. Caricato, S. Cascinu, G. Tonini and D. Santini, Alternative dosing schedules for sunitinib as a treatment of patients with metastatic renal cell carcinoma, *Crit. Rev. Oncol. Hematol.*, 2014, **92**, 208–217, DOI: [10.1016/j.critrevonc.2014.07.006](https://doi.org/10.1016/j.critrevonc.2014.07.006).
- 39 L. Zhang, Q. Zheng, Y. Yang, H. Zhou, X. Gong, S. Zhao and C. Fan, Synthesis and in vivo SAR study of indolin-2-one-based multi-targeted inhibitors as potential anticancer agents, *Eur. J. Med. Chem.*, 2014, **82**, 139–151, DOI: [10.1016/j.ejmech.2014.05.051](https://doi.org/10.1016/j.ejmech.2014.05.051).
- 40 <https://go.drugbank.com/drugs/DB01268>, (accessed on Dec. 11, 2023).
- 41 <https://www.drugs.com/history/sutent.html>, (accessed on Dec. 11, 2023).
- 42 X. Zheng, Y. Zhang, L. Zhang, W. Xu, W. Ma, R. Sun and H. Zeng, Synergistic inhibition of sunitinib and ethaselen against human colorectal cancer cells proliferation, *Biomed. Pharmacother.*, 2016, **83**, 212–220, DOI: [10.1016/j.biopha.2016.06.040](https://doi.org/10.1016/j.biopha.2016.06.040).
- 43 L. A. Leon and L. M. Antón-Aparicio, Treatment of sunitinib-induced hypertension in solid tumors by nitric oxid donors, *Redox Biol.*, 2015, **5**, 413–423, DOI: [10.1016/j.redox.2015.09.036](https://doi.org/10.1016/j.redox.2015.09.036).
- 44 A. M. J. Thijs, C. M. L. van Herpen, V. Verweij, J. Pertijs, P. H. H. van den Broek, W. T. A. van der Graaf and G. A. Rongen, Impaired endothelium-dependent vasodilation does not initiate the development of



- sunitinib-associated hypertension, *J. Hypertens.*, 2015, **33**, 2075–2082, DOI: [10.1097/HJH.0000000000000662](https://doi.org/10.1097/HJH.0000000000000662).
- 45 L. Q. Chow and S. G. Eckhardt, Sunitinib: from rational design to clinical efficacy, *J. Clin. Oncol.*, 2007, **25**, 884–896, DOI: [10.1200/JCO.2006.06.3602](https://doi.org/10.1200/JCO.2006.06.3602).
- 46 J.-Y. Li, Y.-P. Ren, Y. Yuan, S.-M. Ji, S.-P. Zhou, L.-J. Wang, Z.-Z. Mou, L. Li, W. Lu and T.-Y. Zhou, Preclinical PK/PD model for combined administration of erlotinib and sunitinib in the treatment of A549 human NSCLC xenograft mice, *Acta Pharmacol. Sin.*, 2016, **37**, 930–940, DOI: [10.1038/aps.2016.55](https://doi.org/10.1038/aps.2016.55).
- 47 G. L. Gravina, A. Mancini, F. Marampon, A. Colapietro, S. D. Monache, R. Sferra, F. Vitale, P. J. Richardson, L. Patient, S. Burbidge and C. Festuccia, The brain-penetrating CXCR4 antagonist, PRX177561, increases the antitumor effects of bevacizumab and sunitinib in preclinical models of human glioblastoma, *J. Hematol. Oncol.*, 2017, **10**, 5, DOI: [10.1186/s13045-016-0377-8](https://doi.org/10.1186/s13045-016-0377-8).
- 48 G. L. Gravina, A. Mancini, A. Colapietro, F. Vitale, A. Vetuschi, S. Pompili, G. Rossi, F. Marampon, P. J. Richardson, L. Patient, L. Patient, S. Burbidge and C. Festuccia, The novel CXCR4 antagonist, PRX177561, reduces tumor cell proliferation and accelerates cancer stem cell differentiation in glioblastoma preclinical models, *Tumour Biol.*, 2017, **39**, DOI: [10.1177/1010428317695528](https://doi.org/10.1177/1010428317695528).
- 49 X. Wang, L. Zhang, A. O'Neill, B. Bahamon, D. C. Alsop, J. W. Mier, S. N. Goldberg, S. Signoretti, M. B. Atkins, C. G. Wood and R. S. Bhatt, Cox-2 inhibition enhances the activity of sunitinib in human renal cell carcinoma xenografts, *Br. J. Cancer*, 2013, **108**, 319–326, DOI: [10.1038/bjc.2012.591](https://doi.org/10.1038/bjc.2012.591).
- 50 A. Jamadar, S. M. Suma, S. Mathew, T. A. Fields, D. P. Wallace, J. P. Calvet and R. Rao, The tyrosine-kinase inhibitor Nintedanib ameliorates autosomal-dominant polycystic kidney disease, *Cell Death Dis.*, 2021, **12**, 947, DOI: [10.1038/s41419-021-04248-9](https://doi.org/10.1038/s41419-021-04248-9).
- 51 C. Landi, L. Bergantini, P. Cameli, M. d'Alessandro, A. Carleo, E. Shaba, P. Rottoli, L. Bini and E. Bargagli, Idiopathic pulmonary fibrosis serum proteomic analysis before and after nintedanib therapy, *Sci. Rep.*, 2020, **10**, 9378, DOI: [10.1038/s41598-020-66296-z](https://doi.org/10.1038/s41598-020-66296-z).
- 52 F. Hilberg, U. Tontsch-Grunt, A. Baum, A. T. Le, R. C. Doebele, S. Lieb, D. Gianni, T. Voss, P. Garin-Chesa, C. Haslinger and N. Kraut, Triple angiokinase inhibitor Nintedanib directly inhibits tumor cell growth and induces tumor shrinkage via blocking oncogenic receptor tyrosine kinases, *J. Pharmacol. Exp. Ther.*, 2018, **364**, 494–503, DOI: [10.1124/jpet.117.244129](https://doi.org/10.1124/jpet.117.244129).
- 53 M. C. Riesco-Martinez, A. S. Torre and R. García-Carbonero, Safety and efficacy of nintedanib for the treatment of metastatic colorectal cancer, *Expert Opin. Invest. Drugs*, 2017, **26**, 1295–1305, DOI: [10.1080/13543784.2017.1385762](https://doi.org/10.1080/13543784.2017.1385762).
- 54 R. Kurzrock and D. J. Stewart, Exploring the benefit/risk associated with antiangiogenic agents for the treatment of non-small cell lung cancer patients, *Clin. Cancer Res.*, 2017, **23**, 1137–1148, DOI: [10.1158/1078-0432.CCR-16-1968](https://doi.org/10.1158/1078-0432.CCR-16-1968).
- 55 <https://go.drugbank.com/drugs/DB09079>, (accessed on Dec. 11, 2023).
- 56 <https://www.drugs.com/history/ofev.html>, (accessed on Dec. 11, 2023).
- 57 R. F. da Silva, T. P. Banzato, L. F. Alves, J. E. Carvalho, R. Agarwal and V. H. A. Cagnon, Antiangiogenic therapy with Nintedanib affects hypoxia, angiogenesis and apoptosis in the ventral prostate of TRAMP animals, *Cell Tissue Res.*, 2020, **379**, 407–420, DOI: [10.1007/s00441-019-03091-x](https://doi.org/10.1007/s00441-019-03091-x).
- 58 R. F. da Silva, E. Nogueira-Pangrazi, L. A. Kido, F. Montico, S. Arana, D. Kumar, K. Raina, R. Agarwal and V. H. A. Cagnon, Nintedanib antiangiogenic inhibitor effectiveness in delaying adenocarcinoma progression in Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP), *J. Biomed. Sci.*, 2017, **24**, 31, DOI: [10.1186/s12929-017-0334-z](https://doi.org/10.1186/s12929-017-0334-z).
- 59 S. Khalique and S. Banerjee, Nintedanib in ovarian cancer, *Expert Opin. Invest. Drugs*, 2017, **26**, 1073–1081, DOI: [10.1080/13543784.2017.1353599](https://doi.org/10.1080/13543784.2017.1353599).
- 60 G. J. Roth, R. Binder, F. Colbatzky, C. Dallinger, R. Schlenker-Herceg, F. Hilberg, S.-L. Wollin and R. Kaiser, Nintedanib: from discovery to the clinic, *J. Med. Chem.*, 2015, **58**, 1053–1063, DOI: [10.1021/jm501562a](https://doi.org/10.1021/jm501562a).
- 61 A. Rossi, T. P. Latiano, P. Parente, C. Chiarazzo, F. Limosani, G. Di Maggio and E. Maiello, The potential role of Nintedanid in treating colorectal cancer, *Expert Opin. Pharmacother.*, 2017, **18**, 1153–1162, DOI: [10.1080/14656566.2017.1346086](https://doi.org/10.1080/14656566.2017.1346086).
- 62 Y. Kim, S. J. Lee, J. Y. Lee, S.-H. Lee, J.-M. Sun, K. Park, H. J. An, J. Y. Cho, E. J. Kang, H.-Y. Lee, J. Kim, B. Keam, H. R. Kim, K. E. Lee, M. Y. Choi, K. H. Lee and M.-J. Ahn, Clinical trial of Nintedanib in patients with recurrent or metastatic salivary gland cancer of the head and neck: a multicenter phase 2 study (Korean Cancer Study Group HN14-01), *Cancer*, 2017, **123**, 1958–1964, DOI: [10.1002/ncr.30537](https://doi.org/10.1002/ncr.30537).
- 63 C. Schliemann, J. Gerss, S. Wiebe, J.-H. Mikesch, N. Knoblauch, T. Sauer, L. Angenendt, T. Kewitz, M. Urban, T. Butterfass-Bahloul, S. Edemir, K. Vehring, C. Müller-Tidow, W. E. Berdel and U. Krug, A phase I dose escalation study of the triple angiokinase inhibitor Nintedanib combined with low-dose cytarabine in elderly patients with acute myeloid leukemia, *PLoS One*, 2016, **11**, e0164499, DOI: [10.1371/journal.pone.0164499](https://doi.org/10.1371/journal.pone.0164499).
- 64 <https://go.drugbank.com/drugs/DB11885>, (accessed on Dec. 11, 2023).
- 65 L. Xie, Y. Feng and J. Sun, Fingerprint loss during combination therapy using osimertinib and anlotinib: a case report, *J. Clin. Pharm. Ther.*, 2022, **47**, 248–250, DOI: [10.1111/jcpt.13480](https://doi.org/10.1111/jcpt.13480).
- 66 J. Liang, Z. Jin, J. Kuang, H. Feng, Q. Zhao, Z. Yang, L. Zhan, B. Shen, J. Yan, W. Cai, X. Cheng and W. Qiu, The role of anlotinib-mediated EGFR blockade in a positive feedback loop of CXCL11-EGF-EGFR signalling in anaplastic thyroid cancer angiogenesis, *Br. J. Cancer*, 2021, **125**, 390–401, DOI: [10.1038/s41416-021-01340-x](https://doi.org/10.1038/s41416-021-01340-x).



- 67 S. Li, Anlotinib: a novel targeted drug for bone and soft tissue sarcoma, *Front. Oncol.*, 2021, **11**, 664853, DOI: [10.3389/fonc.2021.664853](https://doi.org/10.3389/fonc.2021.664853).
- 68 G. Shen, F. Zheng, D. Ren, F. Du, Q. Dong, Z. Wang, F. Zhao, R. Ahmad and J. Zhao, Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development, *J. Hematol. Oncol.*, 2018, **11**, 120, DOI: [10.1186/s13045-018-0664-7](https://doi.org/10.1186/s13045-018-0664-7).
- 69 Y. Y. Syed, Anlotinib: first global approval, *Drugs*, 2018, **78**, 1057–1062, DOI: [10.1007/s40265-018-0939-x](https://doi.org/10.1007/s40265-018-0939-x).
- 70 T. Qin, Z. Liu, J. Wang, J. Xia, S. Liu, Y. Jia, H. Liu and K. Li, Anlotinib suppresses lymphangiogenesis and lymphatic metastasis in lung adenocarcinoma through a process potentially involving VEGFR-3 signaling, *Cancer Biol. Med.*, 2020, **17**, 753–767, DOI: [10.20892/j.issn.2095-3941.2020.0024](https://doi.org/10.20892/j.issn.2095-3941.2020.0024).
- 71 Z.-X. Jia, Z. Zhang, Z. Li, A. Li, Y.-N. Xie, H.-J. Wu, Z.-B. Yang, H.-M. Zhang and X.-M. Zhang, Anlotinib inhibits the progress of colorectal cancer cells by antagonizing VEGFR/JAK2/STAT3 axis, *Eur. Rev. Med. Pharmacol. Sci.*, 2021, **25**, 2331–2343, DOI: [10.26355/eurev_202103_25272](https://doi.org/10.26355/eurev_202103_25272).
- 72 D. Li, Y. Chi, X. Chen, M. Ge, Y. Zhang, Z. Guo, J. Wang, J. Chen, J. Zhang, Y. Cheng, Z. Li, H. Liu, J. Qin, J. Zhu, R. Cheng, Z. Xu, X. Zheng, P. Tang and M. Gao, Anlotinib in locally advanced or metastatic medullary thyroid carcinoma: a randomized, double-blind phase IIB trial, *Clin. Cancer Res.*, 2021, **27**, 3567–3575, DOI: [10.1158/1078-0432.CCR-20-2950](https://doi.org/10.1158/1078-0432.CCR-20-2950).
- 73 Y. Liu, Q. Xiao, J. He, H. Hu, J. Du, Y. Zhu, J. Chen, Z. Liu, J. Wang, L. Sun, D. Xu, J. Li, X. Liao, J. Wang, Y. Cai, C. Cai, Z. Jin, L. Wang, Y. Yuan and K. Ding, Phase II study of anlotinib in combination with oxaliplatin and capecitabine for patients with RAS/BRAF wild-type metastatic colorectal adenocarcinoma as the first-line therapy, *BMC Med.*, 2022, **20**, 155, DOI: [10.1186/s12916-022-02357-6](https://doi.org/10.1186/s12916-022-02357-6).
- 74 Y. Y. Syed, Surufatinib: first approval, *Drugs*, 2021, **81**, 727–732, DOI: [10.1007/s40265-021-01489-y](https://doi.org/10.1007/s40265-021-01489-y).
- 75 <https://www.drugs.com/history/surufatinib.html>, (accessed on Dec. 11, 2023).
- 76 X. Lu, S. Yan, K. A. Koral and Z. Chen, Surufatinib for the treatment of advanced extrapancreatic neuroendocrine tumors, *Expert Rev. Anticancer Ther.*, 2021, **21**, 917–926, DOI: [10.1080/14737140.2021.1944110](https://doi.org/10.1080/14737140.2021.1944110).
- 77 J. Xu, Y. Bai, H. Sun, C. Bai, R. Jia, Y. Li, W. Zhang, L. Liu, C. Huang, M. Guan, J. Zhou and W. Su, A single-arm, multicenter, open-label phase 2 trial of Surufatinib in patients with unresectable or metastatic biliary tract cancer, *Cancer*, 2021, **127**, 3975–3984, DOI: [10.1002/cncr.33803](https://doi.org/10.1002/cncr.33803).
- 78 <https://go.drugbank.com/articles/A24188>, (accessed on Dec. 11, 2023).
- 79 X. Huang, J. Zhu, Y. Jiang, C. Xu, Q. Lv, D. Yu, K. Shi, Z. Ruan and Y. Wang, SU5416 attenuated lipopolysaccharide-induced acute lung injury in mice by modulating properties of vascular endothelial cells, *Drug Des., Dev. Ther.*, 2019, **13**, 1763–1772, DOI: [10.2147/DDDT.S188858](https://doi.org/10.2147/DDDT.S188858).
- 80 G. L. Peloquin, L. Johnston, M. Damarla, R. L. Damico, P. M. Hassoun and T. M. Kolb, SU5416 does not attenuate early RV angiogenesis in the murine chronic hypoxia PH model, *Respir. Res.*, 2019, **20**, 123, DOI: [10.1186/s12931-019-1079-x](https://doi.org/10.1186/s12931-019-1079-x).
- 81 <https://go.drugbank.com/drugs/DB15247>, (accessed on Dec. 11, 2023).
- 82 K. S. Pedersen, P. M. Grierson, J. Picus, A. C. Lockhart, B. J. Roth, J. Liu, A. Morton, E. Chan, J. Huffman, C. Liang, A. Wang-Gillam and B. Tan, Vorolanib (X-82), an oral anti-VEGFR/PDGFR/CSF1R tyrosine kinase inhibitor, with everolimus in solid tumors: results of a phase I study, *Invest. New Drugs*, 2021, **39**, 1298–1305, DOI: [10.1007/s10637-021-01093-7](https://doi.org/10.1007/s10637-021-01093-7).
- 83 K. Zhang, L. Wang, A. Wei, X. Jia and X. Liu, CM082, a novel angiogenesis inhibitor, enhances the antitumor activity of gefitinib on epidermal growth factor receptor mutant non-small cell lung cancer in vitro and in vivo, *Thorac. Cancer*, 2020, **11**, 1566–1577, DOI: [10.1111/1759-7714.13430](https://doi.org/10.1111/1759-7714.13430).
- 84 <https://go.drugbank.com/drugs/DB11741>, (accessed on Dec. 11, 2023).
- 85 M. Zhang, H. Quan, L. Fu, Y. Li, H. Fu and L. Lou, Third-generation EGFR inhibitor HS-10296 in combination with famitinib, a multi-targeted tyrosine kinase inhibitor, exerts synergistic antitumor effects through enhanced inhibition of downstream signaling in EGFR-mutant non-small cell lung cancer cells, *Thorac. Cancer*, 2021, **12**, 1210–1218, DOI: [10.1111/1759-7714.13902](https://doi.org/10.1111/1759-7714.13902).
- 86 R. Sánchez-Céspedes, P. Accornero, S. Miretti, E. Martignani, F. Gattino, L. Maniscalco, C. Gola, S. Iussich, M. Martano, E. Morello, P. Buracco, L. Aresu and R. De Maria, In vitro and in vivo effects of toceranib phosphate on canine osteosarcoma cell lines and xenograft orthotopic models, *Vet. Comp. Oncol.*, 2020, **18**, 117–127, DOI: [10.1111/vco.12562](https://doi.org/10.1111/vco.12562).
- 87 <https://go.drugbank.com/drugs/DB16821>, (accessed on Dec. 11, 2023).
- 88 M. F. Burbridge, C. J. Bossard, C. Saunier, I. Fejes, A. Bruno, S. Léonce, G. Ferry, G. Da Violante, F. Bouzom, V. Cattan, A. Jacquet-Bescond, P. M. Comoglio, B. P. Lockhart, J. A. Boutin, A. Cordi, J.-C. Ortuno, A. Pierré, J. A. Hickman, F. H. Cruzalegui and S. Depil, S49076 is a novel kinase inhibitor of MET, AXL, and FGFR with strong preclinical activity alone and in association with bevacizumab, *Mol. Cancer Ther.*, 2013, **12**, 1749–1762, DOI: [10.1158/1535-7163.MCT-13-0075](https://doi.org/10.1158/1535-7163.MCT-13-0075).
- 89 J. Rodon, S. Postel-Vinay, A. Hollebecque, P. Nuciforo, A. Azaro, V. Cattan, L. Marfai, I. Sudey, K. Brendel, A. Delmas, S. Malasse and J.-C. Soria, First-in-human phase I study of oral S49076, a unique MET/AXL/FGFR inhibitor, in advanced solid tumours, *Eur. J. Cancer*, 2017, **81**, 142–150, DOI: [10.1016/j.ejca.2017.05.007](https://doi.org/10.1016/j.ejca.2017.05.007).
- 90 D. Wang, F. Tang, S. Wang, Z. Jiang and L. Zhang, Preclinical anti-angiogenesis and anti-tumor activity of



- SIM010603, an oral, multi-targets receptor tyrosine kinases inhibitor, *Cancer Chemother. Pharmacol.*, 2012, **69**, 173–183, DOI: [10.1007/s00280-011-1681-1](https://doi.org/10.1007/s00280-011-1681-1).
- 91 Y. Mao, Z. Xia, X. Zhang, Y. Zong, L. Zhu, B. Yuan and G. Lu, Evaluation of subchronic toxicity of SIM010603, a potent inhibitor of receptor tyrosine kinase, after 28-day repeated oral administration in SD rats and beagle dogs, *Food Chem. Toxicol.*, 2012, **50**, 1256–1270, DOI: [10.1016/j.fct.2012.02.007](https://doi.org/10.1016/j.fct.2012.02.007).
- 92 A. S. Girgis, S. S. Panda, A. M. Srour, A. Abdelnaser, S. Nasr, Y. Moatasim, O. Kutkat, A. El Taweel, A. Kandeil, A. Mostafa, M. A. Ali, N. G. Fawzy, M. S. Bekheit, E. M. Shalaby, L. Gigli, W. Fayad and A. A. F. Soliman, 3-Alkenyl-2-oxindoles: synthesis, antiproliferative and antiviral properties against SARS-CoV-2, *Bioorg. Chem.*, 2021, **114**, 105131, DOI: [10.1016/j.bioorg.2021.105131](https://doi.org/10.1016/j.bioorg.2021.105131).
- 93 <https://www.drugs.com/mtm/vincristine.html>, (accessed on Dec. 11, 2023).
- 94 <https://go.drugbank.com/drugs/DB00541>, (accessed on Dec. 11, 2023).
- 95 D. Mondal, S. Abdul Amin, M. Moinul, K. Das, T. Jha and S. Gayen, How the structural properties of the indole derivatives are important in kinase targeted drug design?: a case study on tyrosine kinase inhibitors, *Bioorg. Med. Chem.*, 2022, **53**, 116534, DOI: [10.1016/j.bmc.2021.116534](https://doi.org/10.1016/j.bmc.2021.116534).
- 96 <https://www.drugs.com/mtm/vinblastine.html>, (accessed on Dec. 11, 2023).
- 97 <https://go.drugbank.com/drugs/DB00570>, (accessed on Dec. 11, 2023).
- 98 <https://go.drugbank.com/drugs/DB00309>, (accessed on Dec. 11, 2023).
- 99 M. Gallardo-Fernández, A. B. Cerezo, R. Hornedo-Ortega, A. M. Troncoso and M. C. Garcia-Parrilla, Anti-VEGF effect of bioactive indolic compounds and hydroxytyrosol metabolites, *Foods*, 2022, **11**, 526, DOI: [10.3390/foods11040526](https://doi.org/10.3390/foods11040526).
- 100 L. H. Al-Wahaibi, A. F. Mohammed, M. H. Abdelrahman, L. Trembleau and B. G. M. Youssif, Design, synthesis, and biological evaluation of indole-2-carboxamides as potential multi-target antiproliferative agents, *Pharmaceuticals*, 2023, **16**, 1039, DOI: [10.3390/ph16071039](https://doi.org/10.3390/ph16071039).
- 101 A. Elkamhaw, U. M. Ammar, S. Paik, M. H. Abdellattif, M. H. Elsherbeny, K. Lee and E. J. Roh, Scaffold repurposing of in-house small molecule candidates leads to discovery of first-in-class CDK-1/HER-2 dual inhibitors: in vitro and in silico screening, *Molecules*, 2021, **26**, 5324, DOI: [10.3390/molecules26175324](https://doi.org/10.3390/molecules26175324).
- 102 A. Elkamhaw, S. Paik, H. J. Kim, J.-H. Park, A. M. Londhe, K. Lee, A. N. Pae, K. D. Park and E. J. Roh, Discovery of *N*-(1-(3-fluorobenzoyl)-1*H*-indol-5-yl)pyrazine-2-carboxamide: a novel, selective, and competitive indole-based lead inhibitor for human monoamine oxidase B, *J. Enzyme Inhib. Med. Chem.*, 2020, **35**, 1568–1580, DOI: [10.1080/14756366.2020.1800666](https://doi.org/10.1080/14756366.2020.1800666).
- 103 M. A. Abdelgawad, A. M. Hayallah, S. N. A. Bukhari, A. Musa, M. Elmowafy, H. M. Abdel-Rahman and M. K. Abd El-Gaber, Design, synthesis, molecular modeling, and anticancer evaluation of new VEGFR-2 inhibitors based on the indolin-2-One scaffold, *Pharmaceuticals*, 2022, **15**, 1416, DOI: [10.3390/ph15111416](https://doi.org/10.3390/ph15111416).
- 104 W. M. Eldehna, M. Fares, H. S. Ibrahim, M. H. Aly, S. Zada, M. M. Ali, S. M. Abou-Seri, H. A. Abdel-Aziz and D. A. Abou El Ella, Indoline ureas as potential anti-hepatocellular carcinoma agents targeting VEGFR-2: synthesis, *in vitro* biological evaluation and molecular docking, *Eur. J. Med. Chem.*, 2015, **100**, 89–97, DOI: [10.1016/j.ejmech.2015.05.040](https://doi.org/10.1016/j.ejmech.2015.05.040).
- 105 <https://www.cancer.gov/about-cancer/treatment/drugs/fluorouracil>, (accessed on Dec. 11, 2023).
- 106 E. B. Elkaeed, R. G. Yousef, H. Elkady, I. M. M. Gobaara, A. A. Alsouk, D. Z. Husein, I. M. Ibrahim, A. M. Metwaly and I. H. Eissa, The assessment of anticancer and VEGFR-2 inhibitory activities of a new 1*H*-indole derivative: in silico and in vitro approaches, *Processes*, 2022, **10**, 1391, DOI: [10.3390/pr10071391](https://doi.org/10.3390/pr10071391).
- 107 S. Saied, M. Shaldam, M. M. Elbadawi, S. Giovannuzzi, A. Nocentini, H. Almahli, R. Salem, T. M. Ibrahim, C. T. Supuran and W. M. Eldehna, Discovery of indolinone-bearing benzenesulfonamides as new dual carbonic anhydrase and VEGFR-2 inhibitors possessing anticancer and pro-apoptotic properties, *Eur. J. Med. Chem.*, 2023, **259**, 115707, DOI: [10.1016/j.ejmech.2023.115707](https://doi.org/10.1016/j.ejmech.2023.115707).
- 108 O. M. Hassan, A. A. R. Mahmood, A. H. Hamzah and L. H. Tahtamouni, Design, synthesis, and molecular docking studies of 5-bromoindole-2-carboxylic acid hydrazone derivatives: in vitro anticancer and VEGFR-2 inhibitory effects, *ChemistrySelect*, 2022, **7**, e202203726, DOI: [10.1002/slct.202203726](https://doi.org/10.1002/slct.202203726).
- 109 J. Zhang, T. Liu, M. Chen, F. Liu, X. Liu, J. Zhang, J. Lin and Y. Jin, Synthesis and biological evaluation of indole-2-carbohydrazide derivatives as anticancer agents with anti-angiogenic and antiproliferative activities, *ChemMedChem*, 2018, **13**, 1181–1192, DOI: [10.1002/cmdc.201800033](https://doi.org/10.1002/cmdc.201800033).
- 110 D.-P. Wang, K.-L. Liu, X.-Y. Li, G.-Q. Lu, W.-H. Xue, X.-H. Qian, K. Mohamed and F.-H. Meng, Design, synthesis, and in vitro and in vivo anti-angiogenesis study of a novel vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor based on 1,2,3-triazole scaffold, *Eur. J. Med. Chem.*, 2021, **211**, 113083, DOI: [10.1016/j.ejmech.2020.113083](https://doi.org/10.1016/j.ejmech.2020.113083).
- 111 M. Qin, S. Yan, L. Wang, H. Zhang, Y. Tian, Y. Zhao and P. Gong, Novel 6-methoxycarbonyl indolinones bearing a pyrrole Mannich base moiety as angiokinase inhibitors, *Bioorg. Med. Chem.*, 2017, **25**, 1778–1786, DOI: [10.1016/j.bmc.2017.01.039](https://doi.org/10.1016/j.bmc.2017.01.039).
- 112 M. Qin, Y. Tian, X. Sun, S. Yu, J. Xia, P. Gong, H. Zhang and Y. Zhao, Novel methyl indolinone-6-carboxylates containing an indole moiety as angiokinase inhibitors, *Eur. J. Med. Chem.*, 2017, **139**, 492–502, DOI: [10.1016/j.ejmech.2017.08.031](https://doi.org/10.1016/j.ejmech.2017.08.031).
- 113 T.-H. Yang, C.-I. Lee, W.-H. Huang and A.-R. Lee, Synthesis and evaluation of novel 2-pyrrolidone-fused (2-oxoindolin-



- 3-ylidene)methylpyrrole derivatives as potential multi-target tyrosine kinase receptor inhibitors, *Molecules*, 2017, **22**, 913, DOI: [10.3390/molecules22060913](https://doi.org/10.3390/molecules22060913).
- 114 L. Ding, F. Tang, W. Huang, Q. Jin, H. Shen and P. Wei, Design, synthesis, and biological evaluation of novel 3-pyrrolo[b]cyclohexylene-2-dihydroindolinone derivatives as potent receptor tyrosine kinase inhibitors, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5630–5633, DOI: [10.1016/j.bmcl.2013.08.037](https://doi.org/10.1016/j.bmcl.2013.08.037).
- 115 M. H. Kim, A. L. Tshako, E. W. Co, D. T. Aftab, F. Bentzien, J. Chen, W. Cheng, S. Engst, L. Goon, R. R. Klein, D. T. Le, M. Mac, J. J. Parks, F. Qian, M. Rodriguez, T. J. Stout, J. H. Till, K.-A. Won, X. Wu, F. M. Yakes, P. Yu, W. Zhang, Y. Zhao, P. Lamb, J. M. Nuss and W. Xu, The design, synthesis, and biological evaluation of potent receptor tyrosine kinase inhibitors, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4979–4985, DOI: [10.1016/j.bmcl.2012.06.029](https://doi.org/10.1016/j.bmcl.2012.06.029).
- 116 S. Patel, N. Challagundla, R. A. Rajput and S. Mishra, Design, synthesis, characterization and anticancer activity evaluation of deoxycholic acid-chalcone conjugates, *Bioorg. Chem.*, 2022, **127**, 106036, DOI: [10.1016/j.bioorg.2022.106036](https://doi.org/10.1016/j.bioorg.2022.106036).
- 117 R. Dudchak, M. Podolak, S. Holota, O. Szewczyk-Roszczenko, P. Roszczenko, A. Bielawska, R. Lesyk and K. Bielawski, Click chemistry in the synthesis of antibody-drug conjugates, *Bioorg. Chem.*, 2024, **143**, 106982, DOI: [10.1016/j.bioorg.2023.106982](https://doi.org/10.1016/j.bioorg.2023.106982).
- 118 Z. M. Nofal, A. M. Srour, W. I. El-Eraky, D. O. Saleh and A. S. Girgis, Rational design, synthesis and QSAR study of vasorelaxant active 3-pyridinecarbonitriles incorporating 1*H*-benzimidazol-2-yl function, *Eur. J. Med. Chem.*, 2013, **63**, 14–21, DOI: [10.1016/j.ejmech.2013.01.042](https://doi.org/10.1016/j.ejmech.2013.01.042).
- 119 A. S. Girgis, A. Kalmouch and M. Ellithy, Synthesis of novel vasodilatory active nicotinate esters with amino acid function, *Bioorg. Med. Chem.*, 2006, **14**, 8488–8494, DOI: [10.1016/j.bmc.2006.08.041](https://doi.org/10.1016/j.bmc.2006.08.041).
- 120 A. M. Ghanim, A. S. Girgis, B. M. Kariuki, N. Samir, M. F. Said, A. Abdelnaser, S. Nasr, M. S. Bekheit, M. F. Abdelhameed, A. J. Almalki, T. S. Ibrahim and S. S. Panda, Design and synthesis of ibuprofen-quinoline conjugates as potential anti-inflammatory and analgesic drug candidates, *Bioorg. Chem.*, 2022, **119**, 105557, DOI: [10.1016/j.bioorg.2021.105557](https://doi.org/10.1016/j.bioorg.2021.105557).
- 121 S. S. Panda, A. S. Girgis, S. J. Thomas, J. E. Capito, R. F. George, A. Salman, M. A. El-Manawaty and A. Samir, Synthesis, pharmacological profile and 2D-QSAR studies of curcumin-amino acid conjugates as potential drug candidates, *Eur. J. Med. Chem.*, 2020, **196**, 112293, DOI: [10.1016/j.ejmech.2020.112293](https://doi.org/10.1016/j.ejmech.2020.112293).
- 122 S. S. Panda, A. S. Girgis, H. H. Honkanadavar, R. F. George and A. M. Srour, Synthesis of new ibuprofen hybrid conjugates as potential anti-inflammatory and analgesic agents, *Future Med. Chem.*, 2020, **12**, 1369–1386, DOI: [10.4155/fmc-2020-0109](https://doi.org/10.4155/fmc-2020-0109).
- 123 A. D. Tiwari, S. S. Panda, A. S. Girgis, S. Sahu, R. F. George, A. M. Srour, B. La Starza, A. M. Asiri, C. D. Hall and A. R. Katritzky, Microwave assisted synthesis and QSAR study of novel NSAID acetaminophen conjugates with amino acid linkers, *Org. Biomol. Chem.*, 2014, **12**, 7238–7249, DOI: [10.1039/c4ob01281j](https://doi.org/10.1039/c4ob01281j).
- 124 I. A. Seliem, S. S. Panda, A. S. Girgis, Y. I. Nagy, R. F. George, W. Fayad, N. G. Fawzy, T. S. Ibrahim, A. M. M. Al-Mahmoudy, R. Sakhuja and Z. K. M. Abdel-samii, Design, synthesis, antimicrobial and DNA gyrase inhibitory properties of fluoroquinolone-dichloroacetic acid hybrids, *Chem. Biol. Drug Des.*, 2020, **95**, 248–259, DOI: [10.1111/cbdd.13638](https://doi.org/10.1111/cbdd.13638).
- 125 H. M. Faidallah, A. S. Girgis, A. D. Tiwari, H. H. Honkanadavar, S. J. Thomas, A. Samir, A. Kalmouch, K. A. Alamry, K. A. Khan, T. S. Ibrahim, A. M. M. EL-Mahmoudy, A. M. Asiri and S. S. Pand, Synthesis, antibacterial properties and 2D-QSAR studies of quinolone-triazole conjugates, *Eur. J. Med. Chem.*, 2018, **143**, 1524–1534, DOI: [10.1016/j.ejmech.2017.10.042](https://doi.org/10.1016/j.ejmech.2017.10.042).
- 126 S. S. Panda, O. S. Detistov, A. S. Girgis, P. P. Mohapatra, A. Samir and A. R. Katritzky, Synthesis and molecular modeling of antimicrobial active fluoroquinolone-pyrazine conjugates with amino acid linkers, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 2198–2205, DOI: [10.1016/j.bmcl.2016.03.062](https://doi.org/10.1016/j.bmcl.2016.03.062).
- 127 S. S. Panda, A. S. Girgis, B. B. Mishra, M. Elagawany, V. Devarapalli, W. F. Littlefield, A. Samir, W. Fayad, N. G. Fawzy, A. M. Srour and R. M. Bokhtia, Synthesis, computational studies, antimycobacterial and antibacterial properties of pyrazinoic acid-isoniazid hybrid conjugates, *RSC Adv.*, 2019, **9**, 20450–20462, DOI: [10.1039/c9ra03380g](https://doi.org/10.1039/c9ra03380g).
- 128 H. M. Faidallah, S. S. Panda, J. C. Serrano, A. S. Girgis, K. A. Khan, K. A. Alamry, T. Therathanakorn, M. J. Meyers, F. M. Sverdrup, C. S. Eikhoff, S. G. Getchell and A. R. Katritzky, Synthesis, antimalarial properties and 2D-QSAR studies of novel triazole-quinine conjugates, *Bioorg. Med. Chem.*, 2016, **24**, 3527–3539, DOI: [10.1016/j.bmc.2016.05.060](https://doi.org/10.1016/j.bmc.2016.05.060).
- 129 Q. Zhou, Y. Luo, Y. Zhu, Q. Chen, J. Qiu, F. Cong, Y. Li and X. Zhang, Nonsteroidal anti-inflammatory drugs (NSAIDs) and nucleotide analog GS-441524 conjugates with potent *in vivo* efficacy against coronaviruses, *Eur. J. Med. Chem.*, 2023, **249**, 115113, DOI: [10.1016/j.ejmech.2023.115113](https://doi.org/10.1016/j.ejmech.2023.115113).
- 130 N. S. El-Sayed, A. S. Jureka, M. R. Edwards, S. Lohan, C. G. Williams, P. T. Keiser, R. A. Davey, J. Totonchy, R. K. Tiwari, C. F. Basler and K. Parang, Synthesis and antiviral activity of fatty acyl conjugates of remdesivir against severe acute respiratory syndrome coronavirus 2 and Ebola virus, *Eur. J. Med. Chem.*, 2021, **226**, 113862, DOI: [10.1016/j.ejmech.2021.113862](https://doi.org/10.1016/j.ejmech.2021.113862).
- 131 I. A. Seliem, S. S. Panda, A. S. Girgis, Y. Moatasim, A. Kandeil, A. Mostafa, M. A. Ali, E. S. Nossier, F. Rasslan, A. M. Srour, R. Sakhuja, T. S. Ibrahim, Z. K. M. Abdel-samii and A. M. M. Al-Mahmoudy, New quinoline-triazole conjugates: synthesis, and antiviral properties against SARS-CoV-2, *Bioorg. Chem.*, 2021, **114**, 105117, DOI: [10.1016/j.bioorg.2021.105117](https://doi.org/10.1016/j.bioorg.2021.105117).



- 132 I. A. Seliem, A. S. Girgis, Y. Moatasim, A. Kandeil, A. Mostafa, M. A. Ali, M. S. Bekheit and S. S. Panda, New pyrazine conjugates: synthesis, computational studies, and antiviral properties against SARS-CoV-2, *ChemMedChem*, 2021, **16**, 3418–3427, DOI: [10.1002/cmdc.202100476](https://doi.org/10.1002/cmdc.202100476).
- 133 K. A. Wyman, A. S. Girgis, P. S. Surapaneni, J. M. Moore, N. M. Abo Shama, S. H. Mahmoud, A. Mostafa, R. F. Barghash, Z. Juan, R. D. Dobarra, A. J. Almalki, T. S. Ibrahim and S. S. Panda, Synthesis of potential antiviral agents for SARS-CoV-2 using molecular hybridization approach, *Molecules*, 2022, **27**, 5923, DOI: [10.3390/molecules27185923](https://doi.org/10.3390/molecules27185923).
- 134 J. R. Hwu, M. Kapoor, N. K. Gupta, S.-C. Tsay, W.-C. Huang, K.-T. Tan, Y.-C. Hu, P. Lyssen and J. Neyts, Synthesis and antiviral activities of quinazolinamine–coumarin conjugates toward chikungunya and hepatitis C viruses, *Eur. J. Med. Chem.*, 2022, **232**, 114164, DOI: [10.1016/j.ejmech.2022.114164](https://doi.org/10.1016/j.ejmech.2022.114164).
- 135 N. Mishriky, F. M. Asaad, Y. A. Ibrahim and A. S. Girgis, New 2-pyrazolines of anticipated molluscicidal activity, *Pharmazie*, 1996, **51**, 544–548.
- 136 M. Chen, L. Cai, Y. Xiang, L. Zhong and J. Shi, Advances in non-radioactive PSMA-targeted small molecule-drug conjugates in the treatment of prostate cancer, *Bioorg. Chem.*, 2023, **141**, 106889, DOI: [10.1016/j.bioorg.2023.106889](https://doi.org/10.1016/j.bioorg.2023.106889).
- 137 M. A. Youssef, S. S. Panda, D. R. Aboshouk, M. F. Said, A. El Taweel, M. GabAllah, W. Fayad, A. A. F. Soliman, A. Mostafa, N. G. Fawzy and A. S. Girgis, Novel curcumin mimics: design, synthesis, biological properties and computational studies of piperidone–piperazine conjugates, *ChemistrySelect*, 2022, **7**, e202201406, DOI: [10.1002/slct.202201406](https://doi.org/10.1002/slct.202201406).
- 138 S. A. Al-Hussain, T. A. Farghaly, M. E. A. Zaki, H. G. Abdulwahab, N. T. Al-Qurashi and Z. A. Muhammad, Discovery of novel indolyl-1,2,4-triazole hybrids as potent vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors with potential anti-renal cancer activity, *Bioorg. Chem.*, 2020, **105**, 104330, DOI: [10.1016/j.bioorg.2020.104330](https://doi.org/10.1016/j.bioorg.2020.104330).
- 139 M. S. Nafie and A. T. A. Boraie, Exploration of novel VEGFR2 tyrosine kinase inhibitors *via* design and synthesis of new alkylated indolyl-triazole Schiff bases for targeting breast cancer, *Bioorg. Chem.*, 2022, **122**, 105708, DOI: [10.1016/j.bioorg.2022.105708](https://doi.org/10.1016/j.bioorg.2022.105708).
- 140 C. Zhang, D. Xu, J. Wang and C. Kang, Efficient synthesis and biological activity of novel indole derivatives as VEGFR-2 tyrosine kinase inhibitors, *Russ. J. Gen. Chem.*, 2017, **87**, 3006–3016, DOI: [10.1134/S1070363217120465](https://doi.org/10.1134/S1070363217120465).
- 141 <https://www.drugs.com/history/votrient.html>, (accessed on Dec. 11, 2023).
- 142 <https://go.drugbank.com/drugs/DB06589>, (accessed on Dec. 11, 2023).
- 143 G.-R. Gao, M.-Y. Li, L.-J. Tong, L.-X. Wei, J. Ding, H. Xie and W.-H. Duan, Design, synthesis and biological evaluation of O-linked indoles as VEGFR-2 kinase inhibitors (I), *Chin. Chem. Lett.*, 2015, **26**, 1165–1168, DOI: [10.1016/j.cclet.2015.07.016](https://doi.org/10.1016/j.cclet.2015.07.016).
- 144 S. Sana, V. G. Reddy, S. Bhandari, T. S. Reddy, R. Tokala, A. P. Sakla, S. K. Bhargava and N. Shankaraiah, Exploration of carbamide derived pyrimidine-thioindole conjugates as potential VEGFR-2 inhibitors with anti-angiogenesis effect, *Eur. J. Med. Chem.*, 2020, **200**, 112457, DOI: [10.1016/j.ejmech.2020.112457](https://doi.org/10.1016/j.ejmech.2020.112457).
- 145 K. Ravi, B. N. Dhoddi and J. Pochampally, DBU-mediated efficient synthesis of indole-conjugated chromene derivatives and their anticancer evaluation and molecular modeling study, *Russ. J. Org. Chem.*, 2023, **59**, 907–914, DOI: [10.1134/S1070428023050214](https://doi.org/10.1134/S1070428023050214).
- 146 S. S. Panda, A. S. Girgis, M. N. Aziz and M. S. Bekheit, Spirooxindole: a versatile biologically active heterocyclic scaffold, *Molecules*, 2023, **28**, 618, DOI: [10.3390/molecules2802061](https://doi.org/10.3390/molecules2802061).
- 147 A. Pandey, A. Pandey, R. Dubey, R. Kant and J. Pandey, Synthesis and computational studies of potent antimicrobial and anticancer indolone scaffolds with spiro cyclopropyl moiety as a novel design element, *J. Indian Chem. Soc.*, 2022, **99**, 100539, DOI: [10.1016/j.jics.2022.100539](https://doi.org/10.1016/j.jics.2022.100539).
- 148 M. A. Salem, A. Ragab, A. A. Askar, A. El-Khalafawy and A. H. Makhlof, One-pot synthesis and molecular docking of some new spiro pyranindol-2-one derivatives as immunomodulatory agents and in vitro antimicrobial potential with DNA gyrase inhibitor, *Eur. J. Med. Chem.*, 2020, **188**, 111977, DOI: [10.1016/j.ejmech.2019.111977](https://doi.org/10.1016/j.ejmech.2019.111977).
- 149 A. Jarrahpour, Z. Jowkar, Z. Haghighijoo, R. Heiran, J. A. Rad, V. Sinou, F. Rouvier, C. Latour, J. M. Brunel and N. Özdemir, Synthesis, in-vitro biological evaluation, and molecular docking study of novel spiro-β-lactam-isatin hybrids, *Med. Chem. Res.*, 2022, **31**, 1026–1034, DOI: [10.1007/s00044-022-02898-8](https://doi.org/10.1007/s00044-022-02898-8).
- 150 M. Bolous, N. Arumugam, A. I. Almansour, R. S. Kumar, K. Maruoka, V. C. Antharam and S. Thangamani, Broad-spectrum antifungal activity of spirooxindolo-pyrrolidine tethered indole/imidazole hybrid heterocycles against fungal pathogens, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 2059–2063, DOI: [10.1016/j.bmcl.2019.07.022](https://doi.org/10.1016/j.bmcl.2019.07.022).
- 151 M. Moghaddam-Manesh, E. Sheikhhosseini, D. Ghazanfari and M. Akhgar, Synthesis of novel 2-oxospiro[indoline-3,4'-[1,3]dithiine]-5'-carbonitrile derivatives by new spiro [indoline-3,4'-[1,3]dithiine]@Cu(NO₃)₂ supported on Fe₃O₄@gly@CE MNPs as efficient catalyst and evaluation of biological activity, *Bioorg. Chem.*, 2020, **98**, 103751, DOI: [10.1016/j.bioorg.2020.103751](https://doi.org/10.1016/j.bioorg.2020.103751).
- 152 V. V. Vintonyak, K. Warburg, B. Over, K. Hübel, D. Rauh and H. Waldmann, Identification and further development of thiazolidinones spiro-fused to indolin-2-ones as potent and selective inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B, *Tetrahedron*, 2011, **67**, 6713–6729, DOI: [10.1016/j.tet.2011.04.026](https://doi.org/10.1016/j.tet.2011.04.026).
- 153 M. A. Borad, M. N. Bhoi, S. K. Rathwa, M. S. Vasava, H. D. Patel, C. N. Patel, H. A. Pandya, E. A. Pithawala and J. J. Georrg, Microwave-assisted ZrSiO₂ catalysed



- synthesis, characterization and computational study of novel spiro[indole-thiazolidines] derivatives as anti-tubercular agents, *Interdiscip. Sci.: Comput. Life Sci.*, 2018, **10**, 411–418, DOI: [10.1007/s12539-016-0195-2](https://doi.org/10.1007/s12539-016-0195-2).
- 154 M. A. Borad, D. J. Jethava, M. N. Bhoi, C. N. Patel, H. A. Pandya and H. D. Patel, Novel isoniazid-spirooxindole derivatives: design, synthesis, biological evaluation, *in silico* ADMET prediction and computational studies, *J. Mol. Struct.*, 2020, **1222**, 128881, DOI: [10.1016/j.molstruc.2020.128881](https://doi.org/10.1016/j.molstruc.2020.128881).
- 155 J. Xu, X. Xie, N. Ye, J. Zou, H. Chen, M. A. White, P.-Y. Shi and J. Zhou, Design, synthesis, and biological evaluation of substituted 4,6-dihydrospiro[[1,2,3]triazolo[4,5-*b*]pyridine-7,3'-indoline]-2',5(3H)-dione analogues as potent NS4B inhibitors for the treatment of dengue virus infection, *J. Med. Chem.*, 2019, **62**, 7941–7960, DOI: [10.1021/acs.jmedchem.9b00698](https://doi.org/10.1021/acs.jmedchem.9b00698).
- 156 A. Gollner, H. Weinstabl, J. E. Fuchs, D. Rudolph, G. Garavel, K. S. Hofbauer, J. Karolyi-Oezguer, G. Gmaschitz, W. H. Hela, N. Kerres, E. Grondal, P. Werni, J. Ramharter, J. Broecker and D. B. McConnell, Targeted synthesis of complex spiro [3H-indole-3,2'-pyrrolidin]-2(1H)-ones by intramolecular cyclization of azomethine ylides: highly potent MDM2-p53 inhibitors, *ChemMedChem*, 2019, **14**, 88–93, DOI: [10.1002/cmdc.201800617](https://doi.org/10.1002/cmdc.201800617).
- 157 M. Espadinha, E. A. Lopes, V. Marques, J. D. Amaral, D. J. V. A. dos Santos, M. Mori, S. Daniele, R. Piccarducci, E. Zappelli, C. Martini, C. M. P. Rodrigues and M. M. M. Santos, Discovery of MDM2-p53 and MDM4-p53 protein-protein interactions small molecule dual inhibitors, *Eur. J. Med. Chem.*, 2022, **241**, 114637, DOI: [10.1016/j.ejmech.2022.114637](https://doi.org/10.1016/j.ejmech.2022.114637).
- 158 K. Murali, H. A. Sparkes and K. J. R. Prasad, Regio- and stereoselective synthesis of dispirooxindolepyrrolocarbazole hybrids via 1,3-dipolar cycloaddition reactions: cytotoxic activity and SAR studies, *Eur. J. Med. Chem.*, 2018, **143**, 292–305, DOI: [10.1016/j.ejmech.2017.11.039](https://doi.org/10.1016/j.ejmech.2017.11.039).
- 159 R. F. George, N. S. M. Ismail, J. Stawinski and A. S. Girgis, Design, synthesis and QSAR studies of dispiroindole derivatives as new antiproliferative agents, *Eur. J. Med. Chem.*, 2013, **68**, 339–351, DOI: [10.1016/j.ejmech.2013.07.035](https://doi.org/10.1016/j.ejmech.2013.07.035).
- 160 A. S. Girgis, A. F. Mabied, J. Stawinski, L. Hegazy, R. F. George, H. Farag, E. M. Shalaby and I. S. Ahmed Farag, Synthesis and DFT studies of an antitumor active spiro-oxindole, *New J. Chem.*, 2015, **39**, 8017, DOI: [10.1039/c5nj01109d](https://doi.org/10.1039/c5nj01109d).
- 161 E. A. Lopes, R. Mestre, D. Fontinha, J. Legac, J. V. Pei, M. Sanches-Vaz, M. Mori, A. M. Lehané, P. J. Rosenthal, M. Prudêncio and M. M. M. Santos, Discovery of spirooxadiazoline oxindoles with dual-stage antimalarial activity, *Eur. J. Med. Chem.*, 2022, **236**, 114324, DOI: [10.1016/j.ejmech.2022.114324](https://doi.org/10.1016/j.ejmech.2022.114324).
- 162 B. Mathebula, K. R. Butsi, R. L. van Zyl, N. C. J. van Vuuren, H. C. Hoppe, J. P. Michael, C. B. de Koning and A. L. Rousseau, Preparation and antiplasmodial activity of 3',4'-dihydro-1'*H*-spiro(indoline-3,2'-quinolin)-2-ones, *Chem. Biol. Drug Des.*, 2019, **94**, 1849–1858, DOI: [10.1111/cbdd.13598](https://doi.org/10.1111/cbdd.13598).
- 163 R. S. Kumar, P. Antonisamy, A. I. Almansour, N. Arumugam, G. Periyasami, M. Altaf, H.-R. Kim and K.-B. Kwon, Functionalized spirooxindole-indolizine hybrids: stereoselective green synthesis and evaluation of anti-inflammatory effect involving TNF- α and nitrite inhibition, *Eur. J. Med. Chem.*, 2018, **152**, 417–423, DOI: [10.1016/j.ejmech.2018.04.060](https://doi.org/10.1016/j.ejmech.2018.04.060).
- 164 M. B. Hammouda, S. Boudriga, K. Hamden, M. Askri, M. Knorr, C. Strohmman, L. Brieger, A. Krupp, E. Anouar, M. Snoussi, K. Aouadi and A. Kadri, New spiropyrrolothiazole derivatives bearing an oxazolone moiety as potential antidiabetic agent: design, synthesis, crystal structure, Hirshfeld surface analysis, ADME and molecular docking studies, *J. Mol. Struct.*, 2022, **1254**, 132398, DOI: [10.1016/j.molstruc.2022.132398](https://doi.org/10.1016/j.molstruc.2022.132398).
- 165 A. Kaur, B. Singh, B. Vyas and O. Silakari, Synthesis and biological activity of 4-aryl-3-benzoyl-5-phenylspiro [pyrrolidine-2.3'-indolin]-2'-one derivatives as novel potent inhibitors of advanced glycation end product, *Eur. J. Med. Chem.*, 2014, **79**, 282–289, DOI: [10.1016/j.ejmech.2014.04.022](https://doi.org/10.1016/j.ejmech.2014.04.022).
- 166 S. S. Panda, M. N. Aziz, J. Stawinski and A. S. Girgis, Azomethine ylides–Versatile synthons for pyrrolidinyl-heterocyclic compounds, *Molecules*, 2023, **28**, 668, DOI: [10.3390/molecules28020668](https://doi.org/10.3390/molecules28020668).
- 167 A. S. Girgis, S. S. Panda, I. S. Ahmed Farag, A. M. El-Shabiny, A. M. Moustafa, N. S. M. Ismail, G. G. Pillai, C. S. Panda, C. D. Hall and A. R. Katritzky, Synthesis, and QSAR analysis of anti-oncological active spiro-alkaloids, *Org. Biomol. Chem.*, 2015, **13**, 1741–1753, DOI: [10.1039/c4ob02149e](https://doi.org/10.1039/c4ob02149e).
- 168 A. S. Girgis, S. S. Panda, A. M. Srour, H. Farag, N. S. M. Ismail, M. Elgendy, A. K. Abdel-Aziz and A. R. Katritzky, Rational design, synthesis and molecular modeling studies of novel anti-oncological alkaloids against melanoma, *Org. Biomol. Chem.*, 2015, **13**, 6619–6633, DOI: [10.1039/c5ob00410a](https://doi.org/10.1039/c5ob00410a).
- 169 A. S. Girgis, S. S. Panda, E. M. Shalaby, A. F. Mabied, P. J. Steel, C. D. Hall and A. R. Katritzky, Regioselective synthesis and theoretical studies of an anti-neoplastic fluoro-substituted dispirooxindole, *RSC Adv.*, 2015, **5**, 14780–14787, DOI: [10.1039/c4ra13433h](https://doi.org/10.1039/c4ra13433h).
- 170 A. S. Girgis, S. S. Panda, M. N. Aziz, P. J. Steel, C. D. Hall and A. R. Katritzky, Rational design, synthesis, and 2D-QSAR study of anti-oncological alkaloids against hepatoma and cervical carcinoma, *RSC Adv.*, 2015, **5**, 28554–28569, DOI: [10.1039/c4ra16663a](https://doi.org/10.1039/c4ra16663a).

