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RECENT ADVANCES IN INDAZOLE-BASED DERIVATIVES OF VEGFR-2 KINASE INHIBITORS AS AN ANTI-CANCER AGENT

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ABSTRACT

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Cancer continues increasing a serious threat to a people health. Cancer is the uncontrolled growth of abnormal cells in the body; cancer develops when the body's normal control mechanism stops working. Many anti-cancer agents have been developed in recent year but survival rate does not satisfy. Therefore, through many efforts to develop novel anti-cancer agents to cover up for deficiency. Indazole is class of heterocyclic bioactive compounds, making structural modification on active indazole derivatives giving a variety of biological activities such as anti-depressant and antitumor anti-bacterial, anti-inflammatory, anti- hypertensive. These study through various literature focus on recent research of indazole derivatives as an anti-cancer will be useful for further development of Indazole base derivatives with new scaffold and high potency as anti-cancer agent. Recently many efforts have been taken for the development of indazole derivatives as vascular endothelial growth factor-2 (VEGFR-2) kinase inhibitors give good anti-tumor activities. Vascular endothelial growth factor-2 plays a role in tumor angiogenesis. Newly synthesized 2-(4-(1H-indazol-6-yl)-1H-pyrazol-1-yl) acetamide derivatives were designed as VEGFR-2 inhibitors based on scaffold hopping strategy. These compounds exhibited the excellent inhibitory in both vegfr-2 and tumor cells proliferation. A novel vegfr2 inhibitor CHMFL-VEGFR2-002 showed high selectivity among structurally closed kinases including PDGFRs, FGFRs, CSF1R etc. CHMFL-VEGFR2-002 given potent inhibitory activity against VEGFR2 kinase. CHMFL-VEGRF2-002 as a research tool for developing new function of VEGFR2 kinase as well as a potential antiangiogenetic agent for the cancer therapy.

Keywords: Anti-cancer, Angiogenesis, bioactive compounds, biological activities, Cancer, indazole, VEGFR2 kinase inhibitor.

1. INTRODUCTION

Cancer is one of the leading causesof human mortality globally thus, the word has been paying close attention to its treatment. Compared with radiotherapy and biological therapy, chemotherapy remains the backbone of current treatment. Never the fewer arrays of these drugs is limited by narrow therapeutic index and frequently require resistance. Consequently the development of novel anticancer drug with high efficiency and low toxicity still urgently needed, nitrogen containing heterocycles are pharmacologically important scoffolds, and they are widely present commercially available drug. As a crucial family of nitrogen containing hetrocycle, the structurally diverse indazole analogue have receive enormous attention in the past , as well as in recent year because of their variety of biological property, such as anti-inflammatory, antimicrobial, anti-HIV, antihypertensive activity. More importantly indazole best therapeutic agent like pazopanib, axitinib and nerapariv has been approved for treat cancer. Structurally, indazole, also called benzopyrazole are isoindazole, is an aromatic heterocyclic molecule in which benzene ring is fused with pyrazole ring. It exists in three tautomericform: 1H-indazole, 2H indazole 3H indazole (figure1). 1H indazole and its derivatives are usually thermodynamically, more stable than the corresponding 2H or 3H forms and therefore the predominant tautomer. There evidence that 6the indazole tautomer identify has an influence on biological properties.

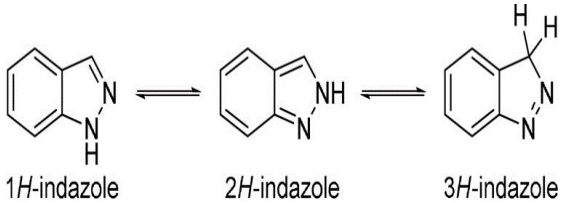


Figure- tautomerism of indazoles

Pharmacologically and structurally diverse indazoles analogues have been the subject of new publications. Correspondingly, there are several reviews focused primarily on the synthetics method to build the indazole skeleton and the broad range of bioactivity of indazole derivatives that can be found in literature. This work has contributed significantly to the general scientifically understanding of these compounds. However, vast numbers of novel indazole containing molecules endowed with antineoplastic activity have been reported recently, and some are currently progressing into clinical trials. This reflect the importance, as well as research

intensity of this field, and an up to date revive has been highly merited. Here in we attempt to describe the design strategy and progress made from 2013 to the beginning of 2018 in the development of indazole –based anticancer agents. The indazole derivatives discussed in this minireview are grouped on the basis of their biomolecular targets. We hope this work will provide useful clues for rational design of indazole containing derivatives as more potent antitumor candidates.

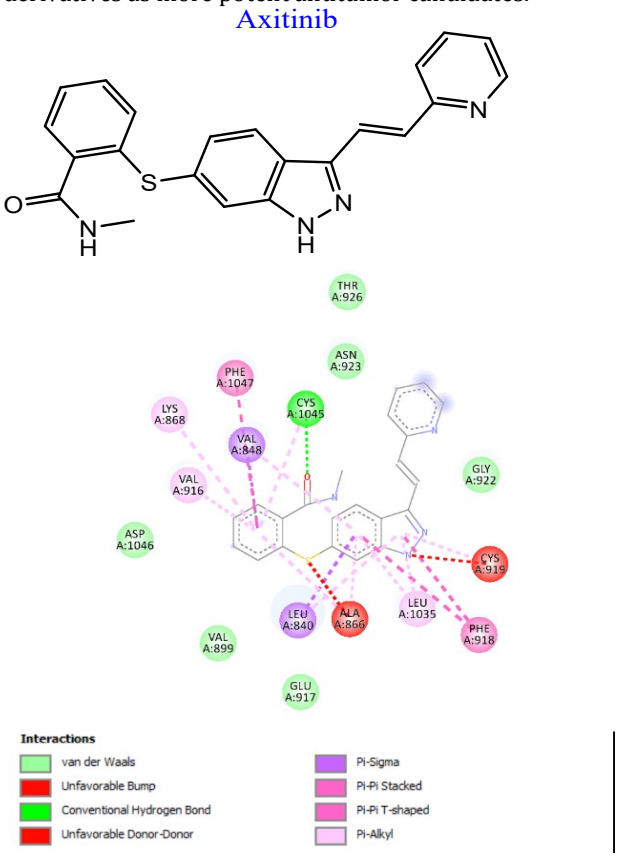


Figure: Indazole derivativeAxitinib and its molecular docking 2D structure

receptor (EGFR), fibroblast growth factor receptors (FGFRs), and vascular endothelial growth factor receptors (VEGFRs) has been widely reported angiogenesis is associated not only with physiological conditions, such as embryonic development, pregnancy, and menstruation, but also with several pathologic conditions, including cancer, eye disease, and inflammatory disorder. Angiogenesis is modulated by a plethora of pro-and anti-angiogenic factors. VEGFRs (VEGFR-1,2, and 3, especially VEGFR-2) are involved in the angiogenesis pathway. Pazopanib, a drug for the treatment of metastatic renal cell carcinoma and soft tissue sarcoma, is a multi-targeted RTK inhibitor that shows potent inhibitory activity not only against VEGFRs, but also toward platelet –derived growth factor receptor (PDGFR-a and –b), and stem cell factor receptor (c-KIT). However, itsbroad spectrumant malignant potency result in many adverse effect, such as hypertension, nausea, anorexia, and lever trans alivation. As consequence greater attention has been drawn to the derivatisation of pazopanib as aVEGFR -2inhibitor. 2H indazole moiety in this structure project in to the black lipophilic pocket of VEGFR -2 and directly interact with Lys868 through p-cation interaction it all optimized pazopanib by modification terminal in aniline moiety with the aim of improving binding to lipophilic residue of VEGFR-2.

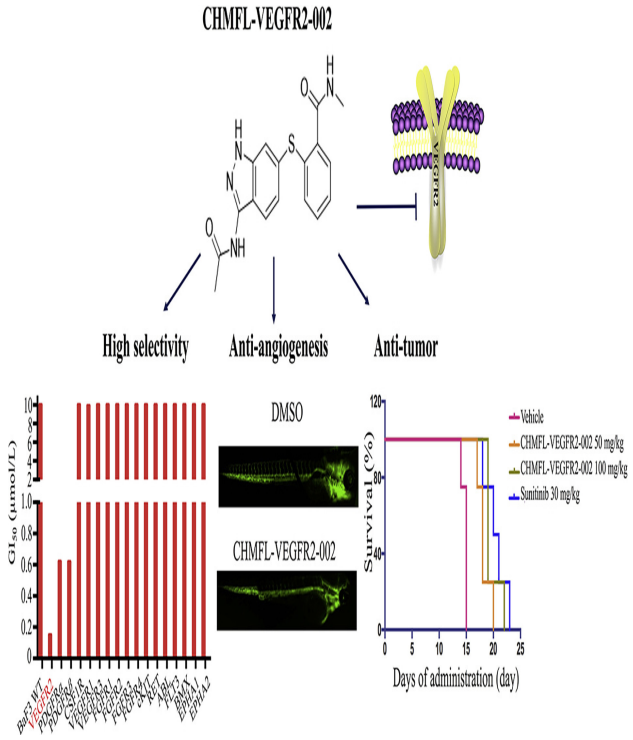


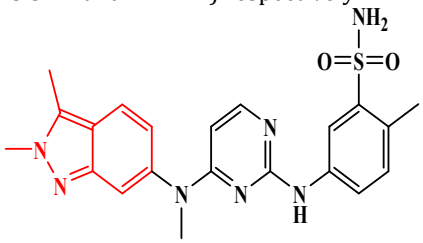
Figure: VEGFR2 inhibitor (CHMFL-VEGFR2-002)

2. ANTI-CANCER ACTIVITIES

2.1 FGFR Inhibitors

The FGFR family is composed of four receptor tyrosinekinases (RTKs), that is FGFR ½/3/4, which plays a prominent role in many biological events, such as embryogenesis, tissue homeostasis, tissue repair, wound healing and inflammation in cancer cells, FGFR signalling could be activated by gene amplification, point mutation, or chromosomal translocation/rearrangements, which are associated with cell growth, angiogenesis, cell migration invasion, and metastasis. Considerable evidence demonstrate the aberrant amplification of FGFR-1 inhibitor .it inhibited FGFR -1 activity with an IC50 value of 15.0 nM andexhibitedsub micromolar cellular activity against SNU-16 cell line (IC50=642.1 nM). The obtained crystal of FGFR -1 bound to compound 1 showed that additional halogen substituents in are position might be beneficial to enhance cellular potencies. As a result, a novel indazole derivative 2 displayed the most FGFR 1 inhibitory activity (IC50=40.5nM). in order to further improve tyghe cellular activity 2 the group synthesized a new series of indazole derivatives harnessing fluorine substituent in 2017. In addition, they also explode the piperazine region which extended out to the ATP binding pocket toward solvent. Pleasingly, compound 3 bearing 2,6 –difluoro-3 methoxyphenyl moiety had most inhibitory activities against FGFR 1 (IC50<4.1nM_) and FGFR 2 (IC50=2.0nM). as expected, it markedly

improved the anti- proliferative activity against KG 1 and SNU 16cell lines (2: IC50=283.9nM and 590.8nM:3: IC5=25.3nM and 77.4nM) respectively.



5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-benzenesulfonamid

2.2. IDO1 Inhibitors

IDO1 is a monomeric enzyme containing heme, which could degrade essential amino acid tryptophan into kynurenine [17]. Theconsumption of tryptophan culminates to the inactivation of T-cells, important immune-suppressive regulators [18]. In general, IDO1 issilent in most tissues but active in an array of clinical cancers [19]The degradation of tryptophan catalysed by IDO1 is considered asan important immune pathway to escape the immune response inthe tumour cells. The reported studies demonstrated that thehigh expressed IDO1 was related to the poor patient prognosis [23].This has aroused the passions of researchers to develop IDO1 inhibitorsto restore the anti-cancer immune in cancer patients [24-27]. In 2016, Qian et al. reported a new series of 1H-indazole derivativesas IDO1 inhibitors via molecular docking and pharmacophoremodels [28]. The biological studies showed that compound4 had the most potent activity against IDO1 (IC50 = 5.3 μM). Additionally, they also explored the structure–activity relationships(SARs) of these compounds containing 1H-indazole scaffold asIDO1 inhibitors. The halogen atom on 6-position of the 1Hindazolescaffold is essential for the IDO1 inhibitory activity. Thecompounds containing a nitrogen (-NH) atom at the 4-position aremore potent than these containing an oxygen (-O) atom, respectively,which may be related to the different bond angles between –NH and –O. The location of the polar group at the 4-position of the1H-indazole scaffold is of great importance for the IDO1 inhibition. In addition, the carboxyl or hydroxyl group at the para-position ofbenzene ring is helpful to improve the inhibitory potency.

2.3. Pim Kinase Inhibitors

The Pim family consists of three active serine/threonine kinases (Pim-1, Pim-2, and Pim-3) which phosphorylate a variety of substrates substrate involved in gene transcription, protein translation, cell cycleprogression, and apoptosis [29]. Many mutagenic and transgenicmice models demonstrated that Pim kinases were helpful to tumorigenesiseither alone or combined with other oncogenes, such as Myc and Bcl-2 [30, 31]. Some recent studies showed that Pimkinases were in favour of the growth of solid tumours, such as prostatecancer, gastric and liver carcinomas [31, 32]. Significantly, over expression of Pims was associated with the poor patient prognosis inmany cancers [33]. Therefore, Pim kinase inhibitors are potentialfor the cancer therapy. In 2013, Gavara et al. synthesized andevaluated a new series of dihydropyrrole[2,3-g] indazoles as Pimkinases inhibitors. Among these compounds, compounds 5 and6 had promising inhibitory activities against Pim-1 and Pim-3. Importantly,compound 6 displayed a nanomolar activity against Pim-3 (IC50 = 33 nM), which could be a tool to study the biological roleof Pim-3. In addition, they also proposed a binding mode of these twocompounds in Pim-3 ATP-binding pocket by molecular dockingtheir compounds and undertook some hit optimization efforts toidentify a promising scaffold for Pim kinase inhibitors, 5-(1Hindol-5-yl)-1,3,4-thiadiazol-2-amine, such as compound 7 [35]. Inspite that the series of compounds displayed an excellent potency against Pim kinases, the instability of metabolism in both rats' andhuman liver microsomes limited their further development. Pleasingly, similar structure of compound 8 had moderate inhibitory activities against Pim kinases and promising metabolic stability, which could be used as an attractive hit for further modification. Therefore, they systematically optimized piperidine and 6-difluorophenyl parts of compound 8 to discover a new series of **potent** Pim kinases inhibitors. Among these compounds, compound9 exhibited sub nanomolar to nanomolar inhibitory activities against Pim kinases (Pim-1: IC50 = 0.1 nM; Pim-2: IC50 = 1.1 nM). In addition,it inhibited the BAD phosphorylation with an IC50 value of 1.4 μMin KMS-12 BM cell assays [36].

2.4. Aurora Kinases Inhibitors

The Aurora kinases are important members of serine/threoninekinases family, which are closely associated with the regulation ofmitosis [37]. Three human paralogues are identified, which arelabelled Aurora A, Aurora B and Aurora C. In mitosis, they are involvedin some important events such as spindle assembly checkpoint, alignment of metaphase chromosomes and chromosomal disorientation. Overexpression of Aurora kinases could be observedin many cancers, such as glioma, breast, ovarian and thyroidcancers [39, 40]. Thus, they have become intriguing targets forresearchers to suppress cancers. Song et al. reported a novel seriesof 3-(pyrrolopyridin-2-yl) indazole derivatives as Aurora A inhibitors. Three representative compounds 10-12 showed goodinhibitory activities against Aurora A (IC50 = 32 nM, 46 nM and519 nM, respectively), but almost no efficacy for other kinases. Tobetter understand the interactions between these compounds andAurora A, compounds 10 and 12 were chosen to undertake moleculardocking utilizing Discovery Studio 2.5. The results showed thatboth compounds 10 and 12 took up the ATP binding site via manyhydrophobic interactions with various hydrophobic residues.Moreover, they formed three hydrogen bonds to stabilize the bindingaffinity for Aurora A with Ala213 and Glu211. In addition, anadditional hydrogen bonding was observed between compound 10and Arg220, which may be a reason that compound 10 was betterpotent than compound 12 in inhibitory activities against Aurora A.In addition, most compounds had good anti-proliferative activities against five cancer cell lines (HL60, KB, SMMC-7721, HCT116and A549). Particularly, compound 12 displayed nanomolar IC50values against HL60 (IC50 = 8.3 nM) and

HCT116 (IC50 = 1.3 nM).Furthermore, it induced HCT116 cells at G2/M phase and apoptosisby flow cytometry [41].NCOIn2016, Chang et al. screened their internal library to obtain anindazole compound 13 with moderate inhibitory activity againstAurora A (IC50 = 13.56 μM) by sub-structure screening [42]. After docking studies of compound 13 to Aurora A, a total 225 fragmentswere suggested to replace the amino group of the aniline with insilico fragment-based drug design (FBDD) approach. Compared to
initial hit 13, compound 14 showed a 10-fold potency improvementfor Aurora A (IC50 = 1.66 μM). To further improve the bindingaffinity, they identified two new pharmacophores by knowledge-baseddrug design, that is the carboxylic acid group extending fromthe C-3 position of the aniline and substituted groups at the C-5position of the indazole core. As a result, compound 15, the mostdistinguished one, had a nanomolar IC50 value of 26 nM agaAurora A. In addition, it also could effectively inhibit Aurora B(IC50 = 15 nM), which could be as a dual Aurora A and B inhibitor.

2.5. Bcr-Abl Inhibitors

Chronic myelogenous leukaemia (CML) is a type of haematologicalcancer that is characterized by the Philadelphia chromosomaltranslocation [43]. The occurrence of mutation forms a fusiongene encoding tyrosine kinase, Bcr-Abl, which is involved in celldifferentiation, migration and signaling transduction [44]. The activationof Bcr-Abl is closely related to the pathology of CML. Accordingly,Bcr-Abl is a potential therapeutic target for CML to developsmall molecule inhibitors. So far, the big challenge of Bcr-Abl inhibitors is to overcome imatinib resistance. In 2015, Shan etal. reported a new series ofN,N'-dibenzoyl piperazine derivatives bearing 1H-indazol-3-amine as Bcr-Abl inhibitors [45]. Some representativecompounds had potent inhibitory activity against both Bcr-Abl wild type and T315I mutant, such as compound 16 and 17.Especially, compound 16 displayed similar inhibitory activity toimatinib. It strongly suppressed both Bcr-Abl wild type and T315Imutant with IC50 values of 0.014 μM and 0.45 μM, respectively.Moreover; it exhibited good anti-proliferative activity against K562leukaemia cancer cells with an IC50 value of 6.50 μM. Thus, it isattractive to be as a lead compound for developing more potent Bcr-Abl wild type and T315I mutant inhibitors.

2.6. HIF-1 Inhibitors

Most solid tumours are in a hypoxia environment owing to theinefficient microvascular systems. During these hypoxia regions, tumour cells display the resistance to both chemotherapy and radiotherapyand also contribute to the poor prognosis of tumourpatients. HIF-1 is a key transcription factor which mediates adaptiveresponses to reduced O2 availability in tumour cells by manycellular responses, such as angiogenesis, glycolysis, pH adaptation,cell proliferation and migration. Overexpression of HIF-1could be observed in many types of cancers, such as brain, lung,breast and prostate cancers, which is associated with rapid tumourgrowth, therapeutic resistance and poor tumour prognosis [49].Therefore, it is considered as a promising target for anti-cancer.Chun et al. reported an indazole-furan derivative YC-1 as an attractivelead compound inhibiting HIF-1α both in vitro and in vivo . Additionally, YC-1 was identified to inhibit tumour invasionand metastasiseffectively, which could develop to be a multipurposeanticancer drug in the future [52]. Inspired by YC-1, Sheng etal. designed an indazole-1,2,4-oxadiazole derivative 18 based onthe bio isostere theory, which displayed the comparable HIF-1 inhibitoryactivity (IC50 = 5.72 μM) to that of YC-1 (IC50 = 3.97 μM)[53]. To obtain more potent HIF-1 inhibitor, they modified YC-1from four parts, that is hydroxyethyl moiety of 1,2,4-oxadiazole, indazole scaffold, chlorobenzyl moiety of the indazole and thetautomerism possibilities of the indazole scaffold. The resultsshowed that compounds 19 and 20 had the most potent HIF-1 inhibitoryactivities with IC50 values of 0.62 and 0.55 μM in vitro, respectively. Furthermore, they inhibited HIF-1 more efficientlythan YC-1 in xenograft tumours. Besides, they significantly blockedthe migration of SKOV3 cells stimulated by hypoxia and tumourmetastasis in vivo. The action mechanism demonstrated thatthey achieved anti-cancer activity by downregulating HIF-1α andVEGF expression.

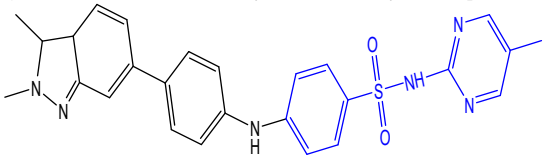
2.7. CA Inhibitors

Hypoxia-triggered oncogenic metabolism often contributes tothe acidic microenvironment in tumours, which results in the accumulationof lactate, protons and carbon dioxide. The regulationof pH homeostasis in tumour depends on many complex molecularmechanisms involving a number of proteins and buffer systems tokeep a moderately base environment which the cellular environmentdisplays significantly acidic. Among them, the familyof carbonic anhydrases (Cas) is a class of key proteins in the pHregulatorysystem. They could catalyse the reversible reactionof carbon dioxide to the bicarbonate ion and protons. In theaspect of tumours, two specific members, CA IX and XII, are involvedin the cancer progression, metastasis and response to therapy. Therefore, these two isoforms are regarded as potentialtargets for hypoxic tumours and metastatic tumours. So far,most reported CA inhibitors are isoform nonspecific, resulting insome unexpected side effects by targeting other CA isoforms, suchas CA I and II. Thus, it is urgent to develop new lead compoundswith novel aromatic/heterocyclic scaffolds. In 2017, Angapellyet al. described some sulfocoumarin/coumarin/4-sulfamoylphenyl
bearingindazole-3-carboxamide derivatives as selective inhibitors CA IXand XII. The bioactivity studies on isoform selectivity demonstratedthat indazole derivatives with none sulphonamide, such ascompounds 21-35 did not inhibit CA I and II. Compounds 36-41with sulphonamide moiety had a low nanomolar range of CA II inhibitory activities (Ki: 6.1-8.4 nM) and the substitutions on indazolenitrogen had no effects on the potency of inhibition. However, thesesubstitutions remarkably influenced the activity against CA I (Ki: 7.2-9304.7 nM). Methyl or ethyl moiety on indazole scaffold exhibitedalmost 3 and 23-folds inhibitory activities, compared to nosubstituted compound. Indazole derivatives with sulfocoumarin and coumarin ring had a high nanomolar to micromolarrange of CA IX inhibitory

activity. Sulfocoumarinswith isopropyl and methyl substituted in indazole scaffold wereidentified to be the best moieties for the activity. Sulphonamide hybridsshowed more potent inhibitory activities against CAIX than other compounds with Ki values of 1.8-19.4 nM. Anothertumour-associated isoform, CA XII, was inhibited by these indazolederivatives in low/medium nanomolar range (Ki: 8.5-73.5 nM) except some compounds in high nanomolar range. Most of the indazole derivatives with sulfocoumarin and coumarin moieties hadhigh binding affinities for this isoform. Determined by X-ray crystallography, these two classes of derivatives are mechanism-basedCA inhibitors, while the main class of CA inhibitors derivativeswith sulphonamide and its bio isosteres substituted (sulfamates, sulfamides,etc) did not show this phenomenon [61-65]. Compounds21-35 could bind at the entrance of active site cavity regarded as themost variable region among CA isoforms, which could be the probablereasons for their selectivelyinhibitory activities against CA IXand XII. Thus, they could be further developed as valuable candidatesfor the treatment of hypoxic tumors.

2.8. Others

In 2012, Abbasi et al. reported a series of indazole derivativesbearing a sulphonamide moiety as potential anti-cancer agent. Compound displayed the lowest IC50 values against three tumour celllines: A2780 (human ovarian carcinoma, IC50 = 0.86 μM), A549(human lung adenocarcinoma, IC50 = 1.83 μM) and P388 (murineleukaemia, IC50 = 0.50 μM). Moreover, it induced apoptosis through up regulating p53 and Bax via western blot analysis, two typicalapoptosis markers. To further investigate the effects of substitutionsof indazole at different positions on the anti-proliferativeand apoptotic potential, the group synthesized new indazole derivatives.The bioactivity studies showed that compound and hadexcellent anti-proliferative activities against A2780 and A549 celllines with IC50 values from 4.21 to 18.6 μM and resulted in apoptosisin a dose-dependent manner. Furthermore, both two compoundscould induce A2780 cells arrest in the G2/M phase of the cell cycle. In order to decrease the cardiotoxic side effects of Mitoxantrone,Shahabi et al. synthesized a series of indazolo is quinolinones derivatives. The anti-proliferative activities showedthat compounds and had a two-fold improvement againstNCI-H460 cell lines compared to Mitoxantrone (EC50: 0.062 and0.071 μM vs 0.122 μM, respectively).



VEGFR Inhibitor

CONCLUSION

Cancer is a severe disease that threatens human health. Developingnew anti-cancer agents with new scaffolds and high efficiencyis a big challenge for researchers. Indazole derivatives are class ofimportant bioactive compounds. Making structural modifications onactive indazole derivatives is of benefit to obtain more potent anticancerleads or clinical drugs. This review introduces the recentadvances of various indazole derivatives based on the anti-cancertargets including FGFR, IDO1, Pim kinase, aurora kinases, Bcr-Abl, HIF-1 and CA. In addition, we also explore the correspondingstructure-activity relationships of these derivatives. We hope thisreview will be useful for further development of new indazole based derivatives as anti-cancer agents.

LIST OF ABBREVIATIONS

CA = Carbonic anhydrase, CML = Chronic myelogenous leukaemia, FBDD = Fragment-based drug design, FGFR = Fibroblast growth factor receptor, HIF-1 = Hypoxia inducible factor-1, IDO1 = Indoleamine-2,3-dioxygenase 1, Pim = Proviral integration site MuLV , RTKs = receptor tyrosine kinases, SARs = Structure, activity relationships

REFERENCES

1. Tantawy, M.A.; Nafie, M.S.; Elmegeed, G.A.; Ali, I.A.I. Auspiciousrole of the steroidal heterocyclic derivatives as a platform foranti-cancer drugs. Bioorg. Chem., 2017, 73, 128-146.
2. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics. CA. CancerJ. Clin., 2017, 67(1),7-30.
3. MacDonald, V. Chemotherapy: managing side effects and safehandling. Can. Vet. J., 2009, 50(6), 665-668.
4. Zhou, B.B.; Zhang, H.; Damelin, M.; Geles, K.G.; Grindley, J.C.;Dirks, P.B. Tumour-initiating cells: challenges and opportunitiesfor anticancer drug discovery. Nat. Rev. Drug. Discov., 2009,8(10), 806-823.
5. Gholap, S.S. Pyrrole: An emerging scaffold for construction ofvaluable therapeutic agents. Eur. J. Med. Chem., 2016, 110, 13-31.
6. Katoh, M. FGFR inhibitors: Effects on cancer cells, tumor microenvironmentand whole-body homeostasis (Review). Int. J. Mol.Med., 2016, 38(1), 3-15.
7. Tiong, K.H.; Mah, L.Y.; Leong, C.O. Functional roles of fibroblastgrowth factor receptors (FGFRs) signaling in human cancers.Apoptosis, 2013, 18(12), 1447-1468.
8. Ahmad, I.; Iwata, T.; Leung, H.Y. Mechanisms of FGFR-mediatedcarcinogenesis. Biochim. Biophys. Acta., 2012, 1823(4), 850-860..Carneiro, B.A.; Meeks, J.J.; Kuzel, T.M.; Scaranti, M.; Abdulkadir,S.A.; Giles, F.J. Emerging therapeutic targets in bladder cancer.Cancer Treat. Rev., 2015, 41(2), 170-178.
9. Helsten, T.; Elkin, S.; Arthur, E.; Tomson, B.N.; Carter, J.;Kurzrock, R. The FGFR Landscape in Cancer: Analysis of 4,853Tumors by Next-Generation Sequencing. Clin. Cancer Res., 2016,22(1), 259-267.
10. Touat, M.; Ileana, E.; Postel-Vinay, S.; Andre, F.; Soria, J.C. TargetingFGFR Signaling in Cancer. Clin. Cancer Res., 2015, 21(12),2684-2694.
11. Giacomini, A.; Chiodelli, P.; Matarazzo, S.; Rusnati, M.; Presta,M.; Ronca, R. Blocking the FGF/FGFR system as a "twocompartment"antiangiogenic/antitumor approach in cancer therapy.Pharmacol. Res., 2016, 107, 172-185.
12. Zhou, W.Y.; Zheng, H.; Du, X.L.; Yang, J.L. Characterization ofFGFR signaling pathway as

therapeutic targets for sarcoma patients.Cancer Biol. Med., 2016, 13(2), 260-268.
13. Helsten, T.; Schwaederle, M.; Kurz rock, R. Fibroblast growthfactor receptor signalling in hereditary and neoplastic disease: biologic and clinical implications. Cancer Metastasis Rev., 2015,34(3), 479-496.
14. Liu, J.; Peng, X.; Dai, Y.; Zhang, W.; Ren, S.; Ai, J.; Geng, M.; Li,Y. Design, synthesis and biological evaluation of novel FGFR inhibitorsbearing an indazole scaffold. Org. Biomol. Chem., 2015,13(28), 7643-7654.
15. Cui, J.; Peng, X.; Gao, D.; Dai, Y.; Ai, J.; Li, Y. Optimization of1H-indazol-3-amine derivatives as potent fibroblast growth factorreceptor inhibitors. Bioorg. Med. Chem. Lett., 2017, 27(16), 3782-3786.
16. Sono, M.; Roach, M.P.; Coulter, E.D.; Dawson, J.H. Heme-Containing Oxygenase. Chem. Rev., 1996, 96(7), 2841-2888. Int. J.Cancer Suppl., 1989, 4, 22-25.
17. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2020.
18. Blackadar CB: Historical review of the cause of cancer. World J Clin Oncol 2016; 7(1): 54-86.
19. Guidry JJ, Aday LA and Zhang D: Transportation as a barrier to cancer treatment. Can Pract 1997; 5: 361-66.
20. Zugazagoitia J, Guedes C, Ponce S,Ferrer I, Molina-Pinelo S and Paz-Ares L: Current challenges in cancer treatments. Clinical Therapeutics 2016; 7: 1551-66.
21. Jiang, Z., Wang, L., Liu, X., Chen, C., Wang, B., Wang, W., … Liu, Q. (2019). Discovery of a Highly Selective VEGFR2 Kinase Inhibitor CHMFL-VEGFR2-002 as a Novel Anti-angiogenesis Agent. Acta Pharmaceutica Sinica B. doi: 10.1016/j.apsb.2019.10.004
22. Elsayed, N. M. Y., Serya, R. A. T., Tolba, M. F., Ahmed, M., Barakat, K., Abou El Ella, D. A., &Abouzid, K. A. M. (2018). Design, synthesis, biological evaluation and dynamics simulation of indazole derivatives with antiangiogenic and antiproliferative anticancer activity. Bioorganic Chemistry. doi: 10.1016/j.bioorg.2018.10.071
23. Ahmed, M. F., & Santali, E. Y. (2021). Discovery of pyridine- sulfonamide hybrids as a new scaffold for the development of potential VEGFR-2 inhibitors and apoptosis inducers. Bioorganic Chemistry, 111, 104842. doi: 10.1016/j.bioorg.2021.104842.
24. Ghorab, M. M., Alsaid, M. S., Nissan, Y. M., Ashour, A. E., Al-Mishari, A. A., Kumar, A., & Ahmed, S. F. (2016). Novel Sulfonamide Derivatives Carrying a Biologically Active 3,4-Dimethoxyphenyl Moiety as VEGFR-2 Inhibitors. Chemical & pharmaceutical bulletin, 64(12), 1747–1754. doi:10.1248/cpb.c16-
25. Yáñez-Alarid R, Santos-Santos E, Lejarazo-Gómez EF. Amide Synthesis through Selective Partial Hydrolysis of Nitriles in Alkaline Media. J. Chem. Chem. Eng. 2020; 14:53-65.
26. Wang, X.-R., Wang, S., Li, W.-B., Xu, K.-Y., Qiao, X.-P., Jing, X.-L., Chen, S.-W. (2021). Design, synthesis and biological evaluation of novel 2-(4-(1H-indazol-6-yl)-1H-pyrazol-1-yl) acetamide derivatives as potent VEGFR-2 inhibitors. European JournalofMedicinal Chemistry113192. https://doi.org/10.1016/j.ejmech.2021.113192
27. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000; 407:249-57.
28. Gotink KJ, Verheul HMW. Anti-angiogenic tyrosine kinase inhibitors: what istheir mechanism of action?. Angiogenesis 2010;13:1–14.
29. Benjamin LE, Bergers G. Tumorigenesis and the angiogenic switch. Nat RevCancer 2003;3:401–10.
30. Kerbel RS. Tumor angiogenesis: past, present and the near future.Carcinogenesis 2000;21:505–15.
31. Kerbel R, Folkman J. Clinical translation of angiogenesis inhibitors. Nat RevCancer 2002;2;727–39.
32. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology2005; 69:4
33. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005; 23:1011–27.
34. Otrock ZK, Makarem JA, Shamseddine AI. Vascular endothelial growth factorfamily of ligands and receptors: review. Blood Cell Mol Dis 2007; 38:258–68.
35. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development ofbevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discovery 2004;3:391–400.
36. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signaling—in control of vascular function. Nat Rev Mol Cell Biol2006; 7:359–71.
37. Yu Y, Cai W, Pei C, Shao Y. Rhamnazin, a novel inhibitor of VEGFR2 signaling with potent antiangiogenic activity and antitumor efficacy. Biochem Biophys ResCommun2015; 458:913–9.
38. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005; 23:1011–27