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# G-Quadruplex DNA Recognition with Various Novel Moieties Binding At Minor Groove

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## ABSTRACT:

G-4 (Guanine containing-Quadruplex) is highly specialized non-canonical motif related to Genetic material (DNA). G-4, clearly recognize that its involvement into replication of many cancerous cells, apart from whole central dogma process in cancer-related genes. Hence, targeting G-4 has become a new promising area for anti-cancer drug development. Targeting G4 through low molecular weight molecules targeting the G-4 have been designed, synthesized, verified to immense use against tumor cells, it involves that molecule directly stack to the G-4 non canonical motif. The significance of the G-Quadruplex motif acting as an anti-cancer drug, especially in metastatic cancer, Indeed helicase is an enzymatic protein, which is more specific towards G-4 scaffold, emerging target like helicase in case of G-4 motif is big deal to design specific small scaffold that helps in hacking cancer problem since Elizabeth discovery of G-4.

## INTRODUCTION:

**G-Quadruplex scaffold-** DNA is the genetic material having the specialized double-helical structure it found in eukaryotic as well as in somatic cells [1]. The fundamental function of telomerase is to protect the genomic end by maintaining length [2]. During replication of the cells leads to erosion of telomeres approximately50-200 base pair loss during every single round of somatic cell division [3]. The secondary scaffold of G-Quadruplex classified into unimolecular, bimolecular, tri-molecular and tetra-molecular it formed by DNA and RNA based upon the sequence. However it shows the various morphological strands by orienting themselves, it shows variation in their number G strand number of stack central part and length also shows type variation. In the corresponding to G Quadruplex, it includes four parallel or antiparallel direction and its related to the conformational changes and glycosidic torsion angle, in case of parallel G Quadruplex all legs in contrary route it has both syn and anti- guanine. G-Quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice- versa, also known as hybrid mixed G- tetrad core

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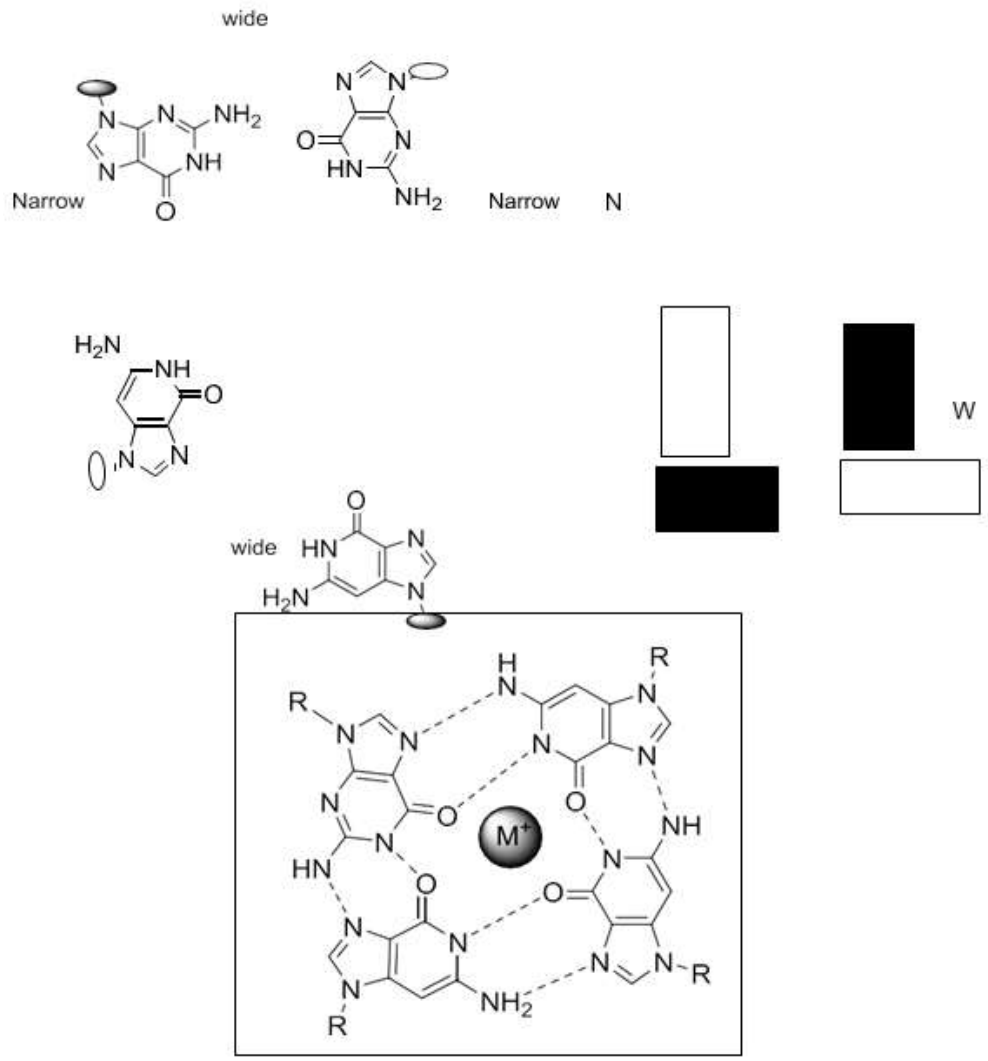


Figure 1: Representation of G-Quadruplex core groove.

The secondary scaffold categorizes into unimolecular, bimolecular, trimolecular and tetra-molecular it formed by DNA and RNA relies upon the sequence. However it shows the various morphological strands by orienting themselves, its shows variation in their number G strand number of stack central part and length also shows type variation. In the corresponding to G Quadruplex, it includes four parallel or antiparallel directions and it's related to the conformational changes and glycosidic torsion angle, in case of parallel G Quadruplex all legs in contrary route it has both syn and anti-guanine. G-Quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice-versa, also known as hybrid mixed G- tetrad core [4].

**Unimolecular G-Quadruplex**

G-Quadruplex can implement the various kind of the significant turns like, the diagonal type loop, lateral side loop and last is the external loop. It can crease into a parallel tetrad with

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three G-Quadruplex loops [5]. For Instance, human telomeres sequences form crystal structure through the reappearance of the [AG3 (T2AG3)3]. It is also called a hybrid G-Quadruplex, by orient themselves in the same and one is a conflicting path, that further agrees to anti-anti-anti-syn confirmation. It also surrounds one narrow and wide external loop. The adaptability of the confirmation depends on their situation and cationic environment. The Quadruplex has Watson- crick duplex in a long loop that may a crucial part of the novel target. The identification of that the c-Myc2345, oncogene promoter sequence contains 22 nucleotides and c-Myc 1245, 5'-TGAG3TG4AG3TG4A2-3' these two sequences are formed by intra-molecular G-4 scaffold similar to the human telomeres genome. The extend beyond of telomeric gene segment made of mono duplicate of the TTAGGG unit of something like 100-200 base pair in biological system.

**Tetrad G-Quadruplex**

The G-Quadruplex family it fashioned from single frequent guanine containing sequences. In G- Quadruplex type four, it showed their crystal structure that each and every one of four legs is corresponding and anti-affirmation has no loop [18]. However, it contains four groove and its RNA parts. The explication of the G-Quadruplex type four by NMR and UV spectroscopy has (GGGT), G-Quadruplex [19].The further G tetrads at the boundary in between two were accomplished by the free guanine at 5'-end of G4 monomer [2+2 type] [20]. The subsistence and determination of the G- Quadruplex construction have been established by the anthropological genome. in the region of 370000 DNA bp are found in the anthropological genome [21]. The G-Quadruplex DNA created from the telomeric region and inhibits the telomeres activity. Polymorphism of this configuration mainly results from their direction of the strand length DNA and position. There are some challenges at the morphological intensity, G-Quadruplex fashioned structure through the assortment of the long double helical strand. An additional is it formed at from three guanine-rich stands. The consequence of the natural role of G-Quadruplex occupies and they are great probable, for stabilization G-Quadruplex small molecules have crucial drug- like properties. The current innovation walk around the conspirator molecules may correspond to a new class of drugs that stack the guanine-rich workstation. Apart from the natural meaning there so many challenges like to start on with to fussiness intended for G-4 over double helical DNA but giving to the subclass of the G-4 scaffold [22].

In the vivo G4 scaffold adopt the human gene sequences below bio-physi significant circumstance is still indecisive therefore, some of reports have not compulsory crossed link structure to be the major alteration inside biological circumstance [6]. The telomeric length is completed by enzyme telomerase which is overexpressed in 85-90% of oncogenic cells but not normal body cells. There are an abundance of reports recitation their antitumor, anticancer and antioxidant properties. The prime responsibility of flavonoids as effective G-4 binding agents. Earlier, it has been mentioned through different optical spectral techniques

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that Quercetin, a naturally occurring flavonoid, interacts with single and double polymeric forms of the G-4 motif from end to end amassing and hollow binding mode, respectively [7].

Another oncogene supporter gene contains the 23-nt bcl-2 promoter sequence 5'-G3CGCG3AG2A2T2G3 CG3- 3' also formed the intramolecular G-Quadruplex, it's quite analogous to the [3+1] G-4 scaffold [8, 9]. It has likewise the capability to temper the gene copy process. HIV-1 integrase, in which they produce a small molecular ligand. These are confirmed by means of the CD, NMR, and molecular docking techniques. The interface monomer especially two must be an anti-anti-anti-syn alignment that held guanine both sides from another monomer [3+1type] [10, 11]. The various different locked interface interlocked dimeric forms of G-Quadruplex are more stable, this is the reason that acts as the biological application, it serves as molecular target canyon of the multimedia protein. The various different locked interface interlocked dimeric forms of G-Quadruplex are more stable, this is the reason that acts as the biological application, and it serves as molecular target canyon of the multimedia protein [12]. Double stuck G-Quadruplex. Usually, supplementary about one form of G-4 hardly ever reported double-stranded G-Quadruplex twisted by the repeating unit of guanine territory. The oblique loop of the G-Quadruplex can be fashioned in the Oxyctrica nova telomeric (G4T4G4) [13] arrangement these in sequence about key assembly and crystal assembly acquired by the x-ray crystallography and NMR spectroscopy [14]. The two T4 sequences that formed the in this G-quadruplexes these loops operation as a connector as anti- anti-syn-syn G scaffold these obliquely cross it maximum and bottommost faced about the G-Quadruplex. In the twofold stuck G-Quadruplex has one extensive one slender and two intermediate hollows [15].

**Tetrad G-Quadruplex**

The G-Quadruplex family it fashioned from single frequent guanine containing sequences. In G- Quadruplex type four, it showed their crystal structure that each and every one of four legs is corresponding and anti-affirmation has no loop [18]. However, it contains four groove and its RNA parts. The explication of the G-Quadruplex type four by NMR, UV spectroscopy having d(GGGT), G- Quadruplex [19]. The further G tetrads at the boundary in between two were accomplished by the free guanine at 5'-end of G4 monomer [2+2 type] [20]. The subsistence and determination of the G- Quadruplex construction have been established by the anthropological genome. in the region of 370000 DNA bp are found in the anthropological genome [21]. The G Quadruplex DNA created from the telomeric region and inhibits the telomeres activity. Polymorphism of this configuration mainly results from their direction of the strand length DNA and position. There is some challenges at the morphological intensity, G Quadruplex fashioned structure through the assortment of the long double helical strand. An additional is it formed at from three guanine-rich stands. The consequence of the natural role of G Quadruplex occupies and they are great probable, for stabilization G-Quadruplex small molecules have crucial drug- like properties. The current innovation walk around the conspirator molecules may correspond to a new class of drugs

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that stack the guanine-rich workstation. Apart from the natural meaning there so many challenges like to start on with to fussiness intended for G-4 over double helical DNA but giving to the subclass of the G-4 scaffold [22].

**Indazole**

Indazole nucleus is most profound, contains numerous biological activity, its nitrogen-containing heterocyclic moiety [23]. It formed by the fusion of two rings one is benzene and pyrazole. Indazole nucleus having the ability to convert in their tautomerized form; its mentioned below 1H-indazole, 2H- indazole and last is 3H-indazole [24]. The stability is the more prominent towards the 1H-indazole rest of the two are not as stable as the first one. Recently, being a heterocyclic nucleus it pays considerable focus to deal with these scaffolds. Indazole derivatives do not occur in nature, having a wide range pharmacological activity such as anti-tumor, anti-inflammatory, anti-fungal, etc. Indazoles nucleus is a planar heterocyclic ring, so its substituted derivatives have numerous bioactivities. In several drug molecules such as niraparib have indazole core exhibit potential towards the treatment of cancer (epithelial ovarian, fallopian tube and breast cancer also in protest of cancer)

**Synthesis scheme of 1*H*- indazole**

A reported method that used in synthesis of indazole from aminohydrazones by intra-molecular ligand free catalyzed by palladium C-H amination reaction [25].

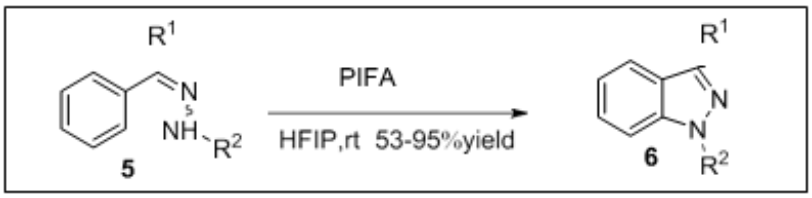


Figure 2: synthetic scheme of indazole.

**Synthetic scheme of 2*H* -indazole**

The synthesis of another tautomer 2H- indazole reveal by Nazare at al.[26] an organophosphorus mediated reductive cyclization further coming N,N dimethyl substituted benzamidines that lead to the formation of 3-amino-2H-indazole and this

Moiety derived from the 2-nitrobenzonitril.

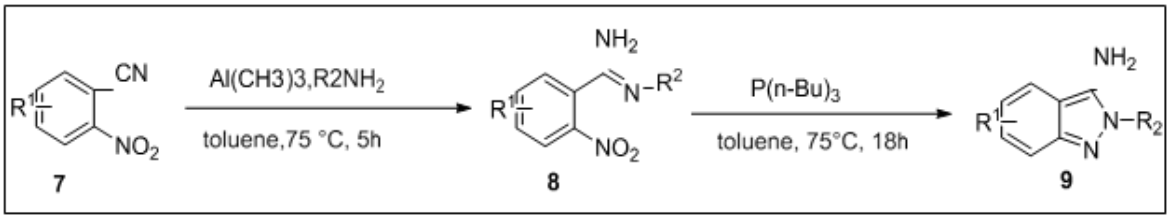


Figure 3: synthetic scheme of 2H- indazole

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In corresponding to reaction synthesis of the N-aryl-2H-indazoles by Cp*Co (iii) leads to C-H bond functionalization, treated the azobenzene with aldehyde [27] within presence reagents in reaction [28].

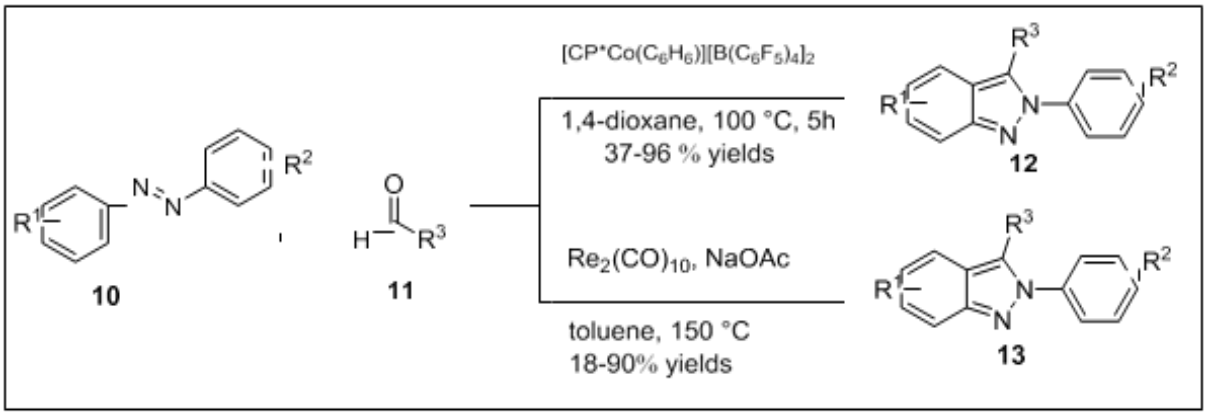


Figure 4: synthetic scheme of 2*H*- indazole.

The researcher further realized that cyclization of azobenzene with α- ketoaldehydes is also possible by this method synthesis of 3-acetylated 2H- indazole more efficiently done [30]

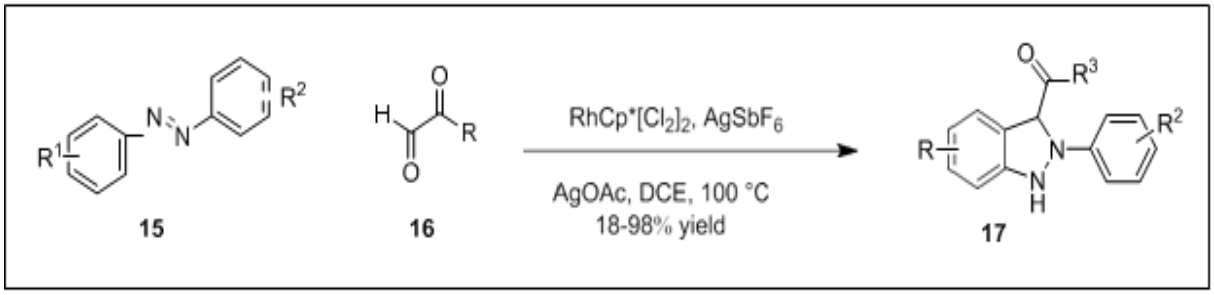


Figure 5: synthetic scheme of 2H- indazole by rhodium catalyzed from azobenzene and α keto.

## 1. Blockade of EGFR

The epidermal growth factor receptor involved the prime family of Tyrosine kinase receptor or erbB family. This large receptor family contain four different subfamily EGFR (ErbB1/HER1), (erbB2/HER3), (erbB3/HER3) and (erbB4/HER4) [31]. These all tyrosine kinase receptors play a crucial role in down-regulation, it consists of multilayer networks that permit the horizontal interaction and show the multiple responses. Disturbance in their normal signaling networks provokes several types of malignancy such as breast, prostate, ovarian and stomach cancer. The cell membrane has an extracellular-ligand binding domain that is a trans-membrane segment consist of intracellular tyrosine kinase contain carboxyl terminal [32].

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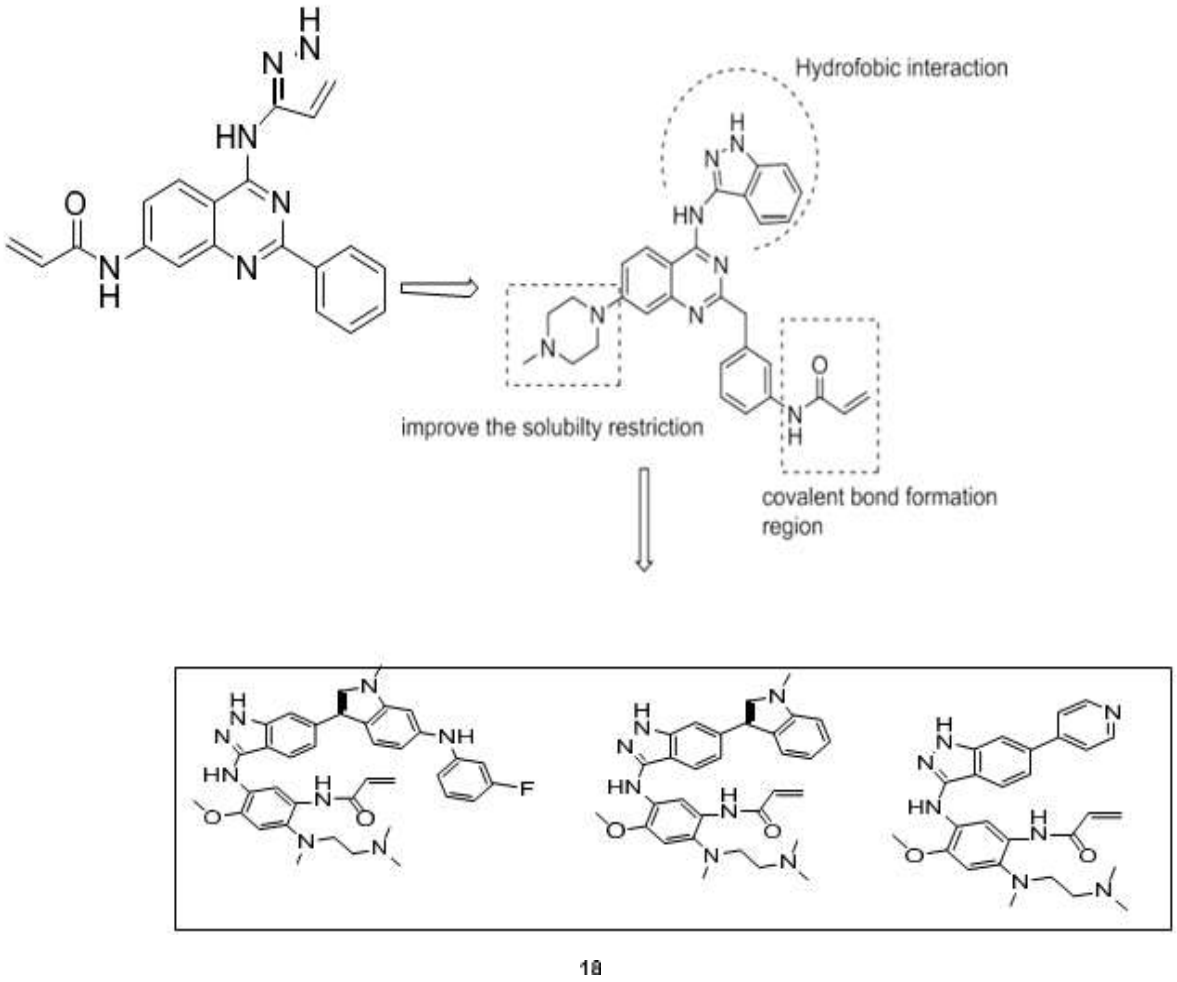


Figure: 6 EGRF inhibitors.

The inhibition of these deregulated signalling pathways by small molecules is quite effective and forms an inactive homodimer of the receptor through the competition with the ATP-binding site, where EGFR (erbB/HER) forms a dimer complex.

## 2. Inhibition of FGFRs

The fibroblast growth factor receptor is incorporate in several physiological functions such as growth, proliferation and the importantly plays a key role in neoplastic behavior [33]. The FGF/FGFRs trans- membrane receptor exposed to single point mutation, especially (FGFR3) create orthopedic disorders further initiates dwarfism, and craniofacial disorder. Some of these expressed in human also that leads to several types of cancer [34]. In the human bio-signaling (especially FGF/FGFRs) abruption provokes the change in their functional behavior, causing malignancies such as breast squamous lung carcinomas (Head and neck). The molecular-based targeted therapy that involved the better downfall in NSCLC due to the effective EGFR-TKIs gets mutated or not responds well by alteration in gatekeeper or

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enlargement of the EGFR. Other consequences are it bypasses the mutation in HGF-MET and PI3KCA mutation through changing their normal singling pathways.

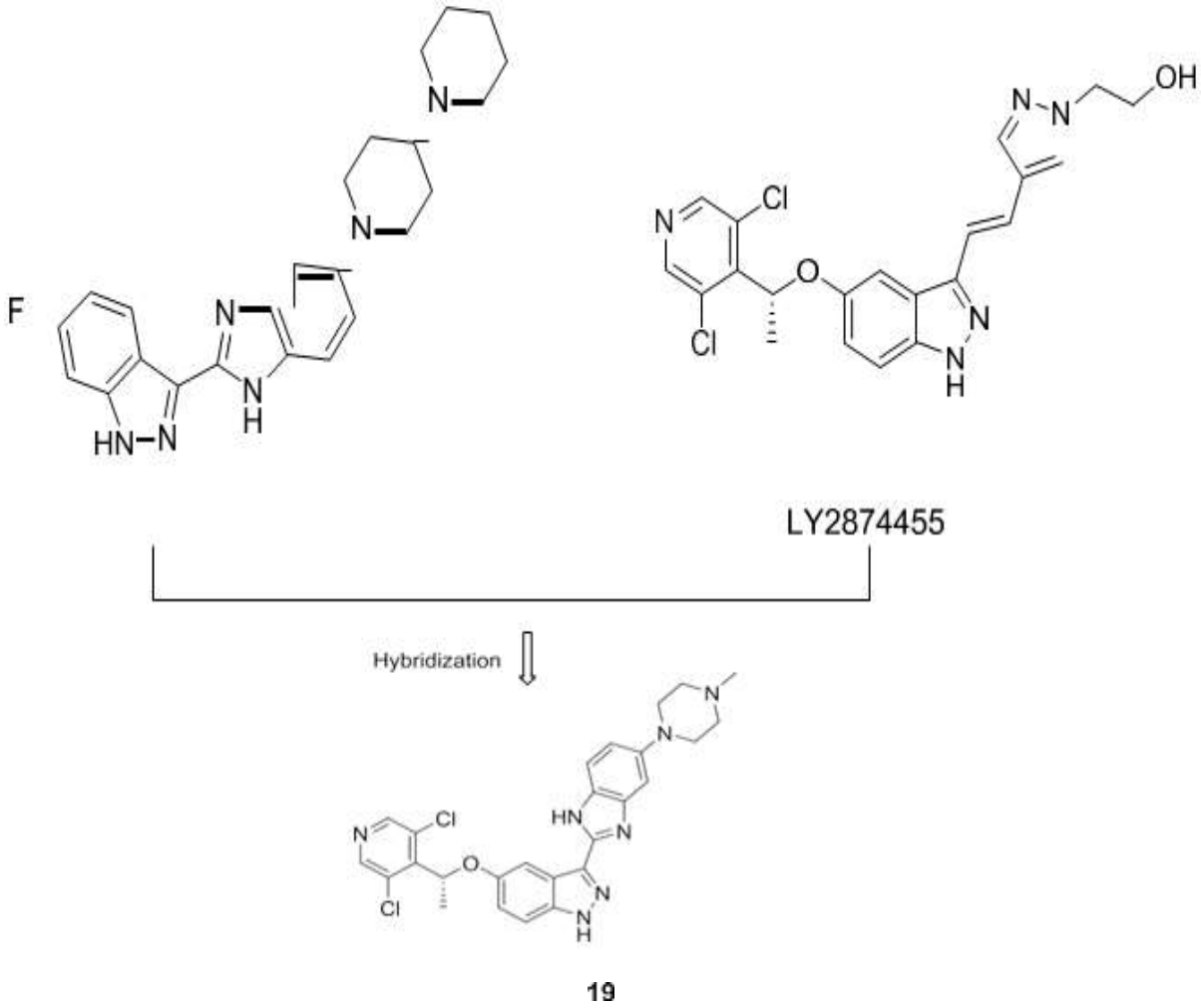


Figure: 7 Design of FGFR blocker.

The reported data suggested that the available selective inhibitors like AZD4547, NVP-BGJ 398 and PD173074 blocks the ATP binding site due to 3, 5-dimethoxydiphenyl moiety [35].

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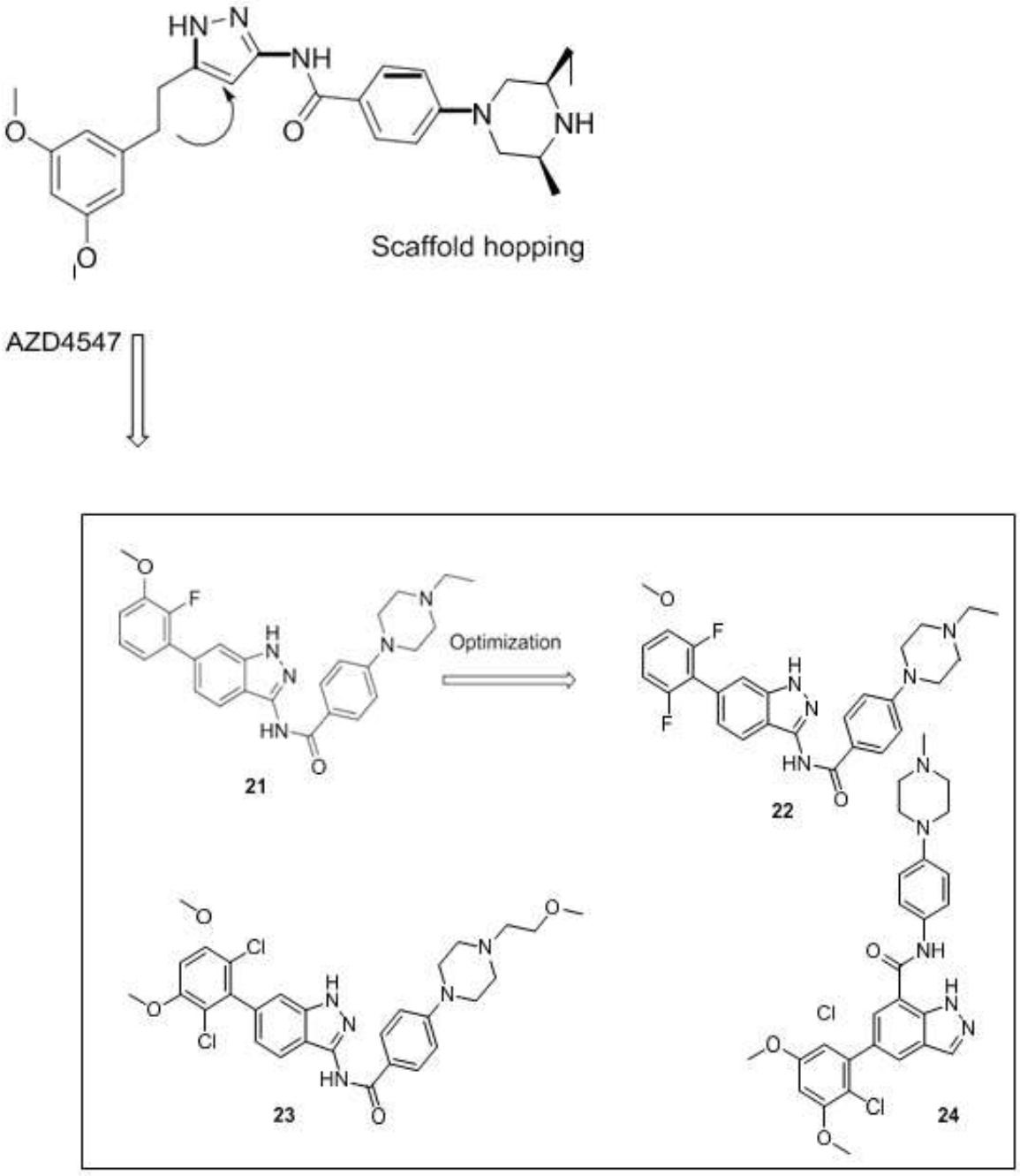


Figure:8 Indazole derivatives as FGFR blockers.

## 3. Blockade of VEGFRs

Angiogenesis term describes the extensive spread network of the blood vessels that helps out to nurtures, the tissues by supplying that proper oxygen and nutrition. The endothelial cell line provides supportive growth for inner development for the blood vessels [36]. Their abnormal function provokes many consequences like ischemia and inflammatory disease, and the continuous abnormal growth of blood vessels is the hallmark of cancer.

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The VEGFRs and notch co-operating acts as branching and differentiating by integrated feedback. VEGF stimulates the cell tip induction via VEGFR2 and VEGFR3 expressed in the embryonic vasculature but it convert moderate to lymphocyte [37].

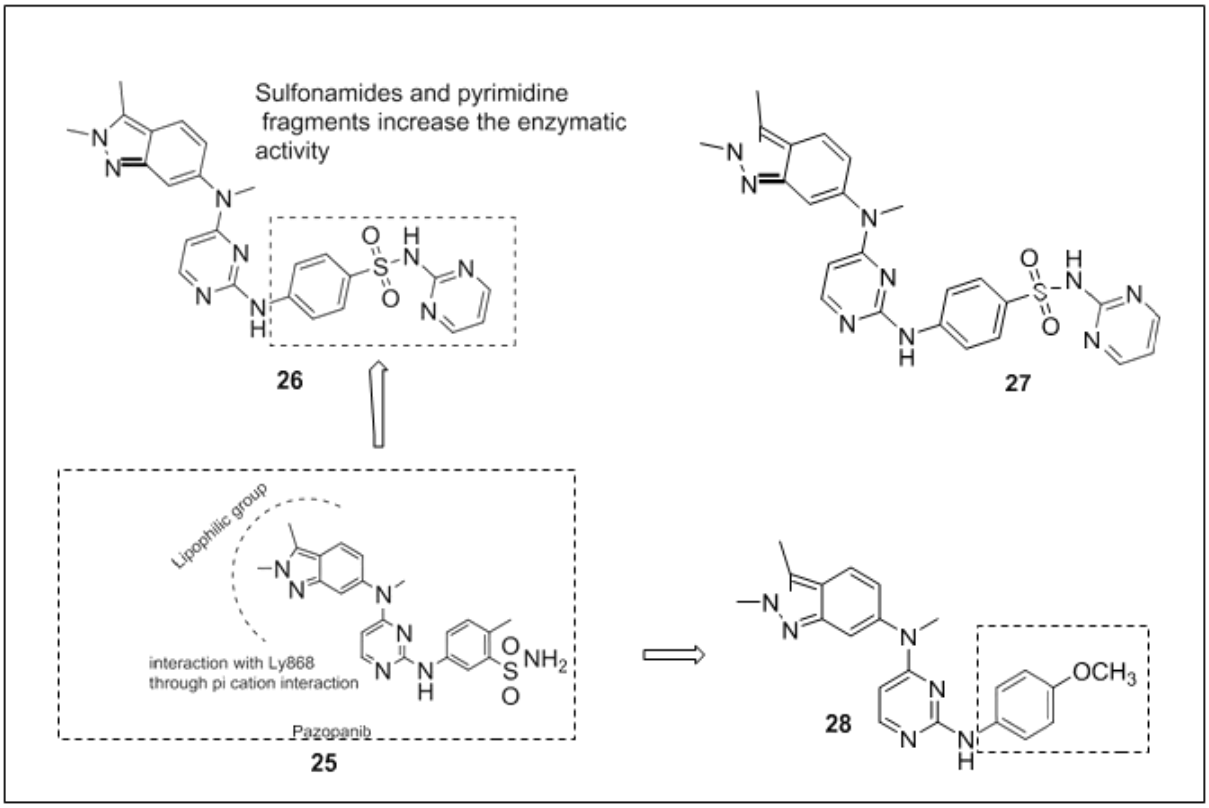


Figure: 9 Indazole derivatives as VEGFRs blocker.

In the pazopanib the activity against VEGFR2 displayed by the substituted sulfonamide and pyrimidine fragments, its activity also noticed against the platelets derived growth factor (PDGFR-α and β ) c-kit stem cell receptor[38]. The anti-angiogenic drugs are not feasible for the children or pregnant lady in case of inflammatory disorder like arthritis; however, it is used only in case of nonsolid tumor [39].

## 4. Polo like kinase inhibitors

The development of therapy regarding neuro-blastoma is still a crucial challenge, most frequently an extra-cranial solid tumor in children. More common PLK1 among PLK1to5 thoroughly discussed. The molecules show antitumor activity also has good selectivity among PLKs family [40]. The one derivative having poor PK value, especially low oral dose, and furthermore drawback is there major alkene-linked blocker. The improvement in their physicochemical properties changed by a there bio isosteric double bond.The PI3K/Akt bio-signaling involved in the stop the progression of neuro-blastoma in children through epithelial mesenchymal transiton (EMT) [41].

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## 5. Aurora kinase inhibitors

Aurora kinase belongs to the highly dynamic protein family that involves the central position of targeted protein to exchanging their one phosphate group from ATP to serine amino acid. It participates in the major, crucial signalling pathways in the human body, such as proliferation, differentiation, and cellular migration. Aurora kinase is a member of the serine/threonine family that plays a key role in mitosis.

The Aurora kinase A and B both contribute the chromosomal maturation and chromosomal segregation and cytokinesis [42].

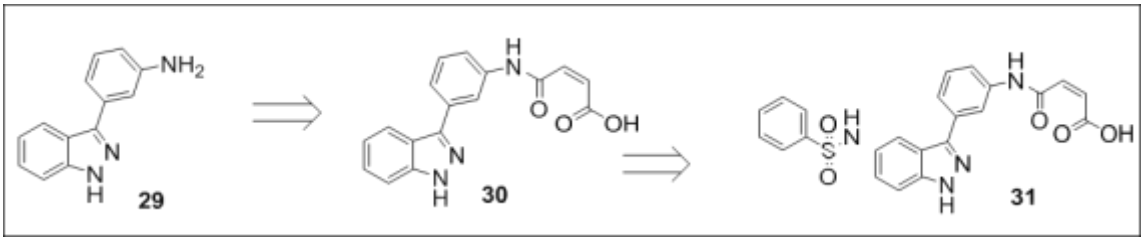


Figure 10: Aurora kinase blockers.

## 6. CDK Inhibitor

The cyclin-dependent kinase (CDK) family involved in controlling the cell cycle(CDK1, CDK4, CDK5) or transcription (CDK7, CDK8, CDK9, CDK19), however, the CDK8 is oncogene promoter in colorectal cancer cells and melanoma cells [43]. The CDK19 most found analogue of CDK8 shown specifically overexpress in the progression of prostate cancer [44].

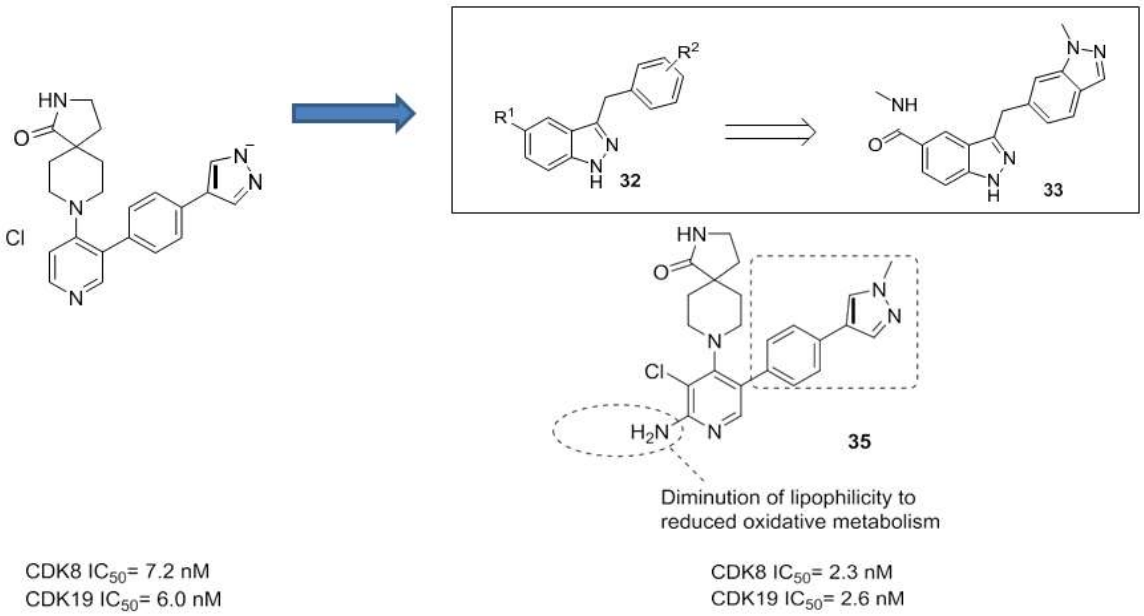


Figure: 11 Indazole as the CDKs inhibitor.

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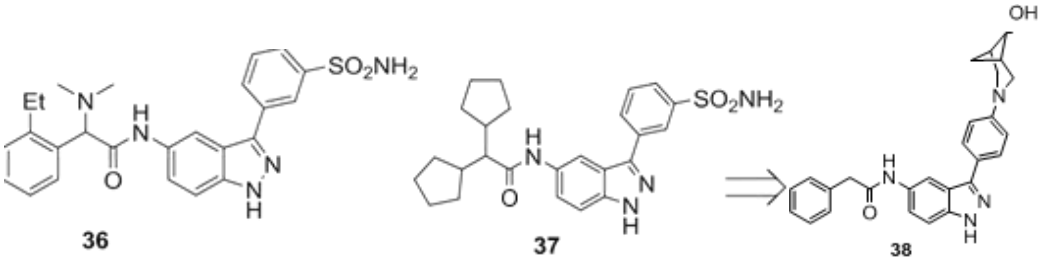
## 7. Blockade of TTKs

Tyrosine threonine kinase well known as a monopolar spindle (Mps1), its critical spindle checkpoint whose point preserves the genomic reliability, this is because of the cancer cells are totally based on spindle assembly checkpoint [45]. These kinases overexpress in many malignancies such as breast cancer due to the Mps1 gene. Remarkably, the reduction in Mps1 gene expression leads to a higher breast cancer survival rate [46].

Novel anthrapyrazolone as preliminary material explores the novel indazole structure- based design therapeutics. Anthrapyrazolone having good inhibitory activity against Mps1 (IC50 = 98 nM), it shows poor restriction on further development. The modification of the phenyl ring of the indazole nucleus at 5 or 6 positions.




The two nitrogen containing indazole moiety generates two hydrogen bonding with hings carbonyl and NH of glycine 605, Asp606. The amino acid residues Lys529, Gln541 and cys604 these residue forms four hydrogen bonds furthermore. Another methreported based on the indazole nucleus that is benzene sulphonamides as potent TTK inhibitors [67].

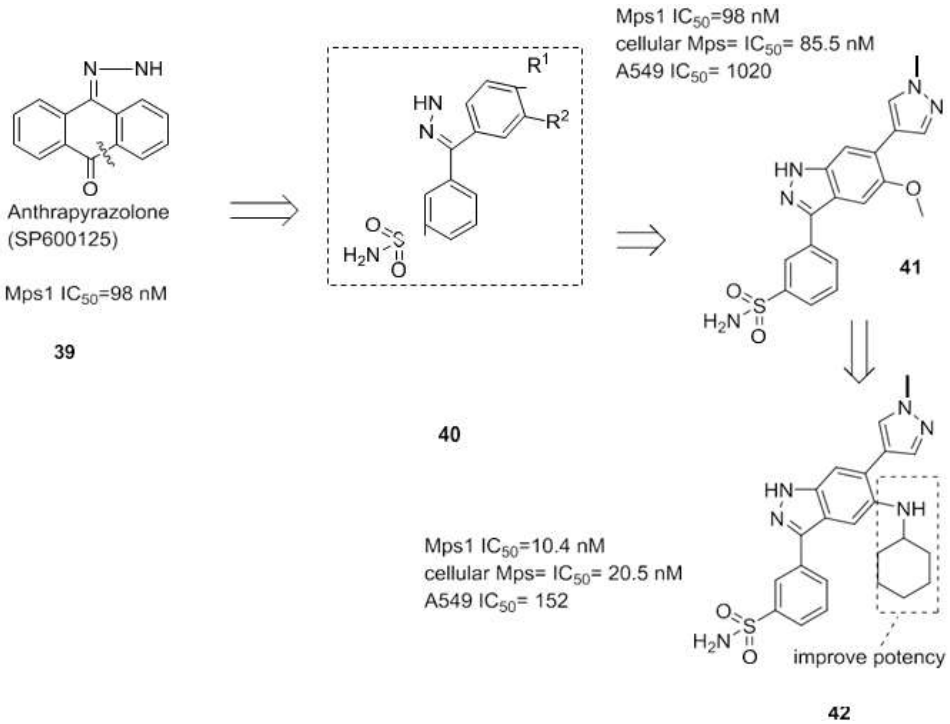



Figure: 12 TTK inhibitors.

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## 8. Inhibition of the Ras/MAPK pathway

The strategy of targeting cancer now changes we can target several hallmarks in a single cancer type. In corresponding to bio-signaling inhibitor another compound was built by the researcher, the nitrogen- containing indazole that interacts with the hydrogen bonding with amino acid residue, especially Asp104 and Met106 in the hinge domain of ERK1/2. This inhibitor shows greater potency, but its poor pharmacokinetics profile precludes them from vivo studies [48].

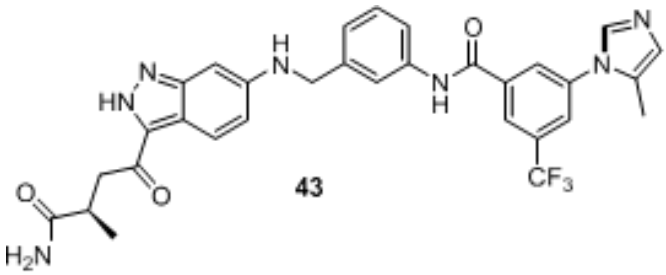


Figure: 13 CRAF inhibitor.

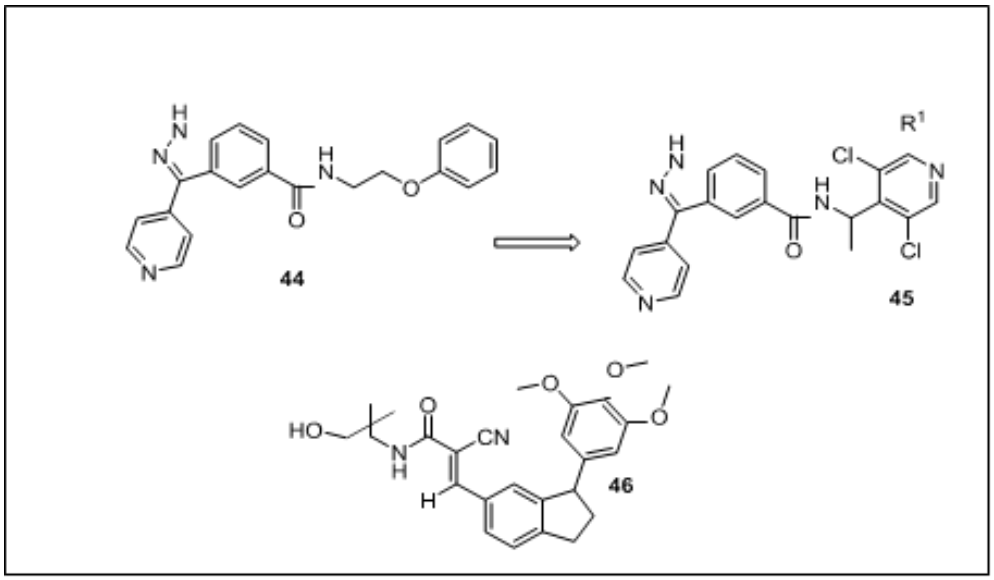


Figure: 14 Selective RSK2 inhibitors.

## 9. Blockade of other kinase (PI3KA and PDK1)

Phosphotidyl inositol-3-phasphate controls the cellular signling that responsible for the cellular life, death, growth and metabolism cellular proliferation specialized differentiation. It is lipid kinase responsible for the phosphorylation on D3 position of their inositol scaffold [49]. The PI3K family segregates into fifteen different types and the divided into four categories as Class I, II, III are lipid kinase and IV is protein kinase [50]. The drug development focused on the targeted decline in the PI3K/m-TOR/ Akt signaling pathways has been inflamed by changing their signaling [51].

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Various chemotherapeutic agent developed and evaluated in clinical studies, GDC-0941(pictililesib) one of them that containing indazole core contain recognized as the powerful selective orally bioactive drugs that inhibit the type 1 PI3Ks, this drug also occupied the boost the efficacy of the antineoplastic drug Axitinib against c-myc amplified medulloblastoma and this manipulate to residential to PI3K inhibitors [52].

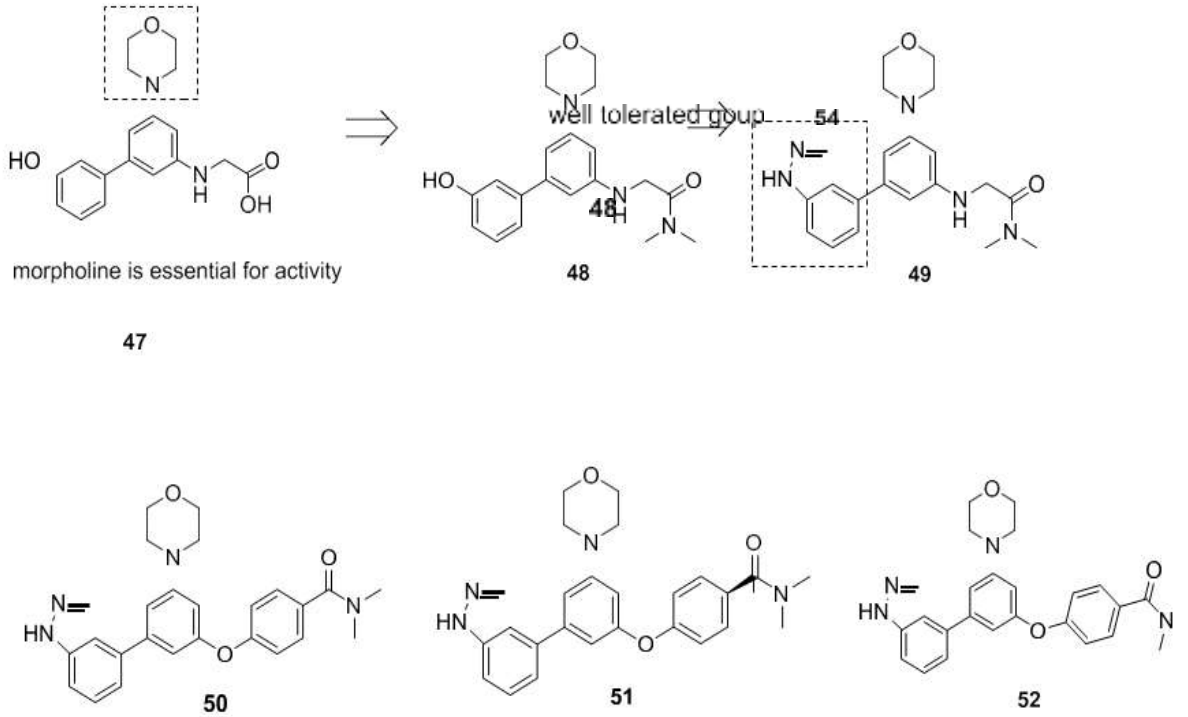


Figure 15: PI3K inhibitors.

## 10. Control of HIF1/ER1 a transcription factors

The biological cell overexpress high level of transcription factor such as HIF1(Hypoxia induce factor) that cause angiogenesis a type of cancer, these (HIF) signaling response like, cell proliferation, angiogenesis, glycolysis, and tumor invasion by binding the hypoxic response element of targeted gene, that is Glucose transporter (GLUT1), carbohydrate ix(CAix), VEGF, and erythropoietin[53]. HIF connected with destructive oncogene growth, therapeutic resistance, and less efficient prediction. Therefore its providing better striking target hypoxia. YC-1, its indazole containing HIF inhibitors both in vitro as well as in vivo, it acts as lead molecules. Amendment in hydroxyethyl molecules of 1, 2, 4-

Oxadiazole signifying for the aryl substitution on that position it is established by the SAR study. One of another better target is estrogen receptor α, it has synchronized by the transcript regulated alpha(ER-α). These ligand-dependent physiologies such as upholding of bone compactness and reproduction [54].

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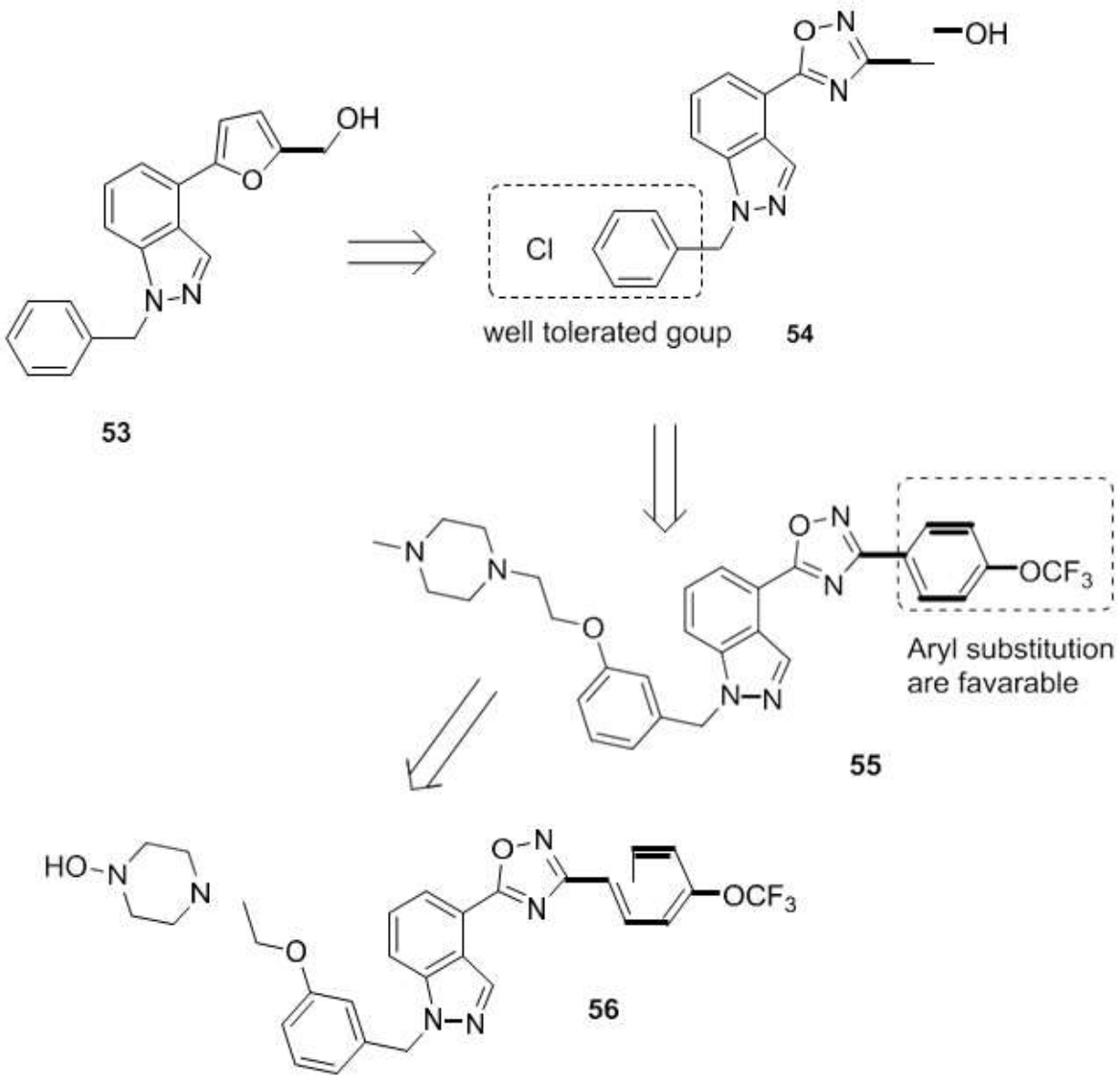


Figure 16: HIF1 inhibitor, Indaole derivatives.

## CONCLUSION:

The new pyrazole-Benz imidazole hybrid molecules have undergone stepwise synthesis and all possible characterization. Firstly we synthesize the different alkyl chain derivatives aldehyde. The reaction of different substituted aldehyde that gives good yield and it get purified by column chromatography. The solvent used in purification of the alkyl substituted aldehydes were ethyl acetate and hexane which is first steps. In the second step we synthesis the chaconne, synthesis of these molecules condense with acetophenone in presence of ethanol and potassium hydroxide as base. Some of the corn is not having good yields. It took more time to complete the reaction—approximately twelve hours. The nitrogen-containing benzimidazole that further liked or fused to form hybrids of pyrazole and benzimidazole, in

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correspondence with making the final compound, was not synthesized; it will further carry out and synthesize the new molecules.

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