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A Review on Synthesis and In-Silico Studies of Pyrazoline-Containing Derivatives as Anti-Cancer Agents

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Abigel Gurung*[1], Preyankul Paliya[2], Gautam Rai[3], Manisha Subba[4]

[1,3,4]Research Scholar, Department Of Pharmaceutical Chemistry, Abhilashi University, Chailchowk, Mandi (H,P) India.

[2]Department Of Pharmaceutical Chemistry, Abhilashi University Chailchowk, Mandi (H.P) India.

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ABSTRACT

The title of the current research is "Synthesis and in-silico studies of pyrazoline-containing derivatives as anti-cancer agents." and relates to the creation and assessment of pyrazoline derivatives for desired delivery to the diseased target.

Two nitrogen atoms are arranged in a five-member ring structure to form the heterocycle pyrazoline. Pyrazolines, also referred to as dihydropyrazolines, are organic compounds with five members that have one double bond next to one nitrogen atom. The current study's objective is to investigate the use of in-silico methods in the creation of pyrazoline analogs that may target a range of receptors, such as the protein kinase inhibitor (PI3K), Akt (FOXO, BAX), and Mtor, which is crucial for the treatment of cancer.

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1 . INTRODUCTION

Malignancy and cancer are both related words and are characterized by the abnormal/ uncontrolled growth of cells. Cancer starts from a cell and spread around various surrounding tissues by splitting, causing closely related diseases. Skin cancer, colon cancer, lung cancer etc. are the types of cancer among more than 100 types of cancer. Each and every cancer have different symptoms (1). Radiation, chemotherapy, surgery including different types of other treatments are being used to treat cancer(2).

These types of masses are developed by many types of cancers. In some types, like blood cancer, leukemia does not form tumors; these formed tumors have the ability to develop and their cells can spread to the other parts of the body through the lymph or blood circulation system, then these cells form new tumors on the other tumor site. Tumors can develop their own veins to survive through metastasis (3).

Tumors are of two types of malignant tumors and benign tumors. Classification is done based on their extension and their invasiveness. Benign tumors are different as they do not extend or invade to the surrounding tissues and if they are removed then they do not grow again. Unlike almost all benign tumors elsewhere in the body, benign brain tumors can be more life threatening (3). Tumors that have the ability to extend or invade the surrounding tissues are termed as malignant tumors.

2 . PI3K

Cell growth and cell death is controlled by many body functions and many pathways which are controlled by various receptors and enzymes like kinase receptors, estrogen receptors etc. PI3K is a kinase receptor that was found in many types of cancer. Phosphatidylinositol 3-kinases (PI3Ks) belongs to the family of enzymes that are associated with various cellular functions such as cell growth, proliferation, differentiation *etc.* overexpression or any changes in these functions may result in various abnormalities which in turn cause cancer. Aberrantly activated PI3K pathway promotes carcinogenesis and tumor angiogenesis (4).

There are three major targets that can be targeted in order to inhibit PI3K:

a. PI3K (by inhibiting phosphorylation)

b. Akt (FOXO, BAX)

c. Mtor Staging explains the seriousness of a person's cancer depending on the size and extent to whichthe primary tumor has reached the other remaining body part(5).

3. STATUS

The projected cancer burden in India for 2021 was 26.7 million DALYsAMI and expected to increase to 29.8 million in 2025. The highest burden was in the north (2408 DALYsAMI per 100,000) and northeastern (2177 DALYsAMI per 100,000) regions of the country and higher among males. More than 40% of the total cancer burden was contributed by the seven leading cancer sites — lung (10.6%), breast (10.5%), esophagus (5.8%), mouth (5.7%), stomach (5.2%), liver (4.6%), and cervix uteri (4.3%)(23).

4. HALLMARK OF CANCER

The hallmarks ("traits ") highlights are (1) Cancer cells fire up their own growth (Self-reliance in growth signals); (2) They counterattack inhibitory signals that might else stop their growth (made it insensitive to anti-growth signals); (3) It resist their programmed cell death (it evades the process of apoptosis); (4) It can multiply for an indefinite period (unlimited replication potential) (5) They stimulate the development of blood vessels to provide nutrients to the tumors (constant angiogenesis); (6) They attack to the local tissues and spread to different sites (Tissue invasion and metastasis). Weinberg and Hanahan reported two new hallmarks: (1) abnormal metabolic pathways; and (2) evading the immune system (3). The summary of cancer hallmarks is shown in Figure 1.

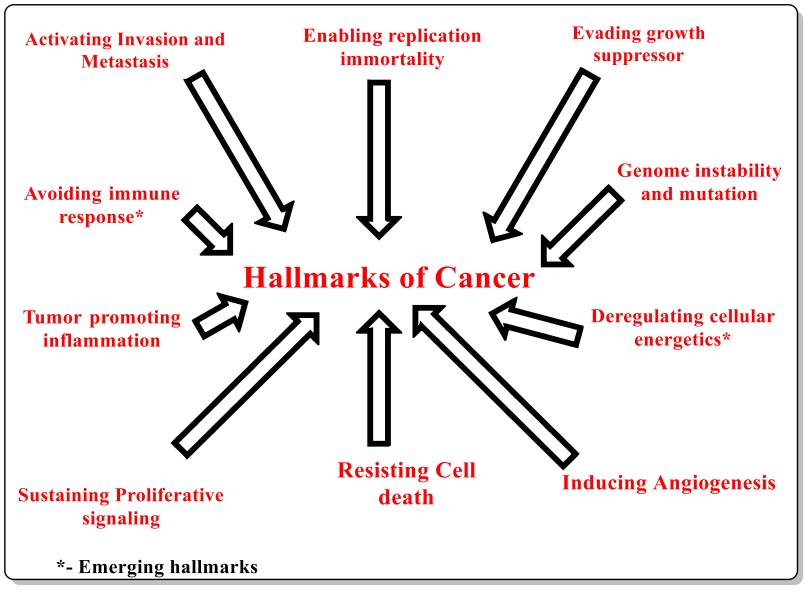


Figure 1: hallmark of cancer

5. PROBLEM STATEMENT AND GAP ANALYSIS

The most of anticancer drugs have very less specificity, and effectiveness and have more side effects (6).

The major problem is the treatment of different types of cancer for which huge efforts employed to implement novel chemotherapeutic agents(7).The current chemotherapeutic agents have restrictive usage for the management of human cancers due to numerous side effect, adverse effect, toxicity and multi-drug resistance (8). Multidrug resistanceis the principal mechanism through which many cancers develop resistance to chemotherapy drugs, it is a major reason for the failure of many forms of chemotherapy. So, there is a requirement for some new anticancer agents having better selectivity, more efficiency, and safety (9).

6. IMPORTANT SIDE EFFECT ASSOCIATE WITH ANTICANCER

The primary obstacles to the clinical efficacy of chemotherapy have been the toxicity to the normal tissues of the body. Rapidly proliferating tissues such as bone marrow, gastrointestinal tract, hair follicle etc. are the major sites of acute toxicities.

In addition, chronic and cumulative toxicities may also occur. It includes hazards during handling of cytotoxic drugs and its interaction with other drugs. There are measures and agents which can ameliorate the toxicities of anticancer drugs. The systemic toxicities of anticancer drugs, common antineoplastic agents causing these toxicities and measures adopted for its management. Some of the most commonly arising problems.

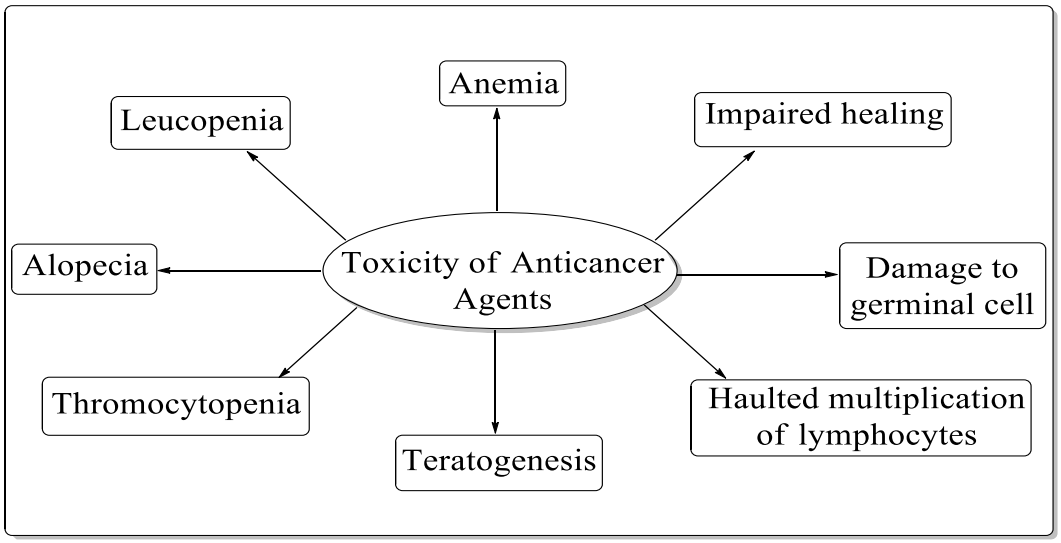


Figure 2: side effect associate with anticancer

7. NEPTHALENE

Naphthalene moiety is an important scaffold in the field of drug discovery and drug development. Apart from its own medicinal applications, Naphthalene derivatives such as quinine, quinidine, saquinavir, ciprofloxacin, Clioquinol, Camptothecin, Irinotecan, topotecanare available in the market as antimalarial, antiarrhythmic, antiviral, antifungal/antiprotozoal, anticancer drugs respectively.

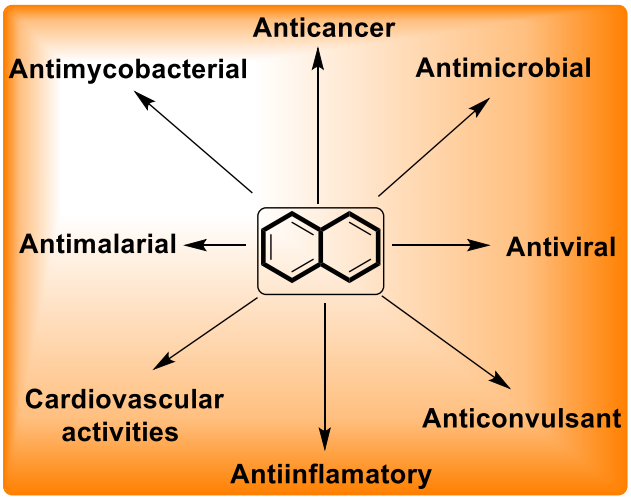


Figure 3: medical application of nepthalene

8. NEPTHALENE AS ANTICANCER DERIVATIVES

Camptothecin, a naturally occurring alkaloid which was found to have anticancer activity. Hence its analogs like topotecan, Irinotecan and exatecan were prepared for increasing its anticancer activity. As they all contain Naphthalene moiety in their structure, these discoveries added a new dimension in the discovery of naphthalene containing anticancer agents. Recent developments of naphthalene analogues has resulted in the discovery of three kinase inhibitors i.e. bosutinib, lenvatinib and cabozantinib and one farnesyl transferase inhibitor (tipifarnib) which have shown good potential against cancer and are being tested under phase of clinical trial. naphthalene derivatives have shown excellent results in the development of anticancer agents as they act as growth inhibitors, apoptosis inducers, angiogenesis inhibitors, cell migration disrupters, and modulation of nuclear receptor responsiveness. The anticancer potential of several of these derivatives have been demonstrated on various cancer cell lines.

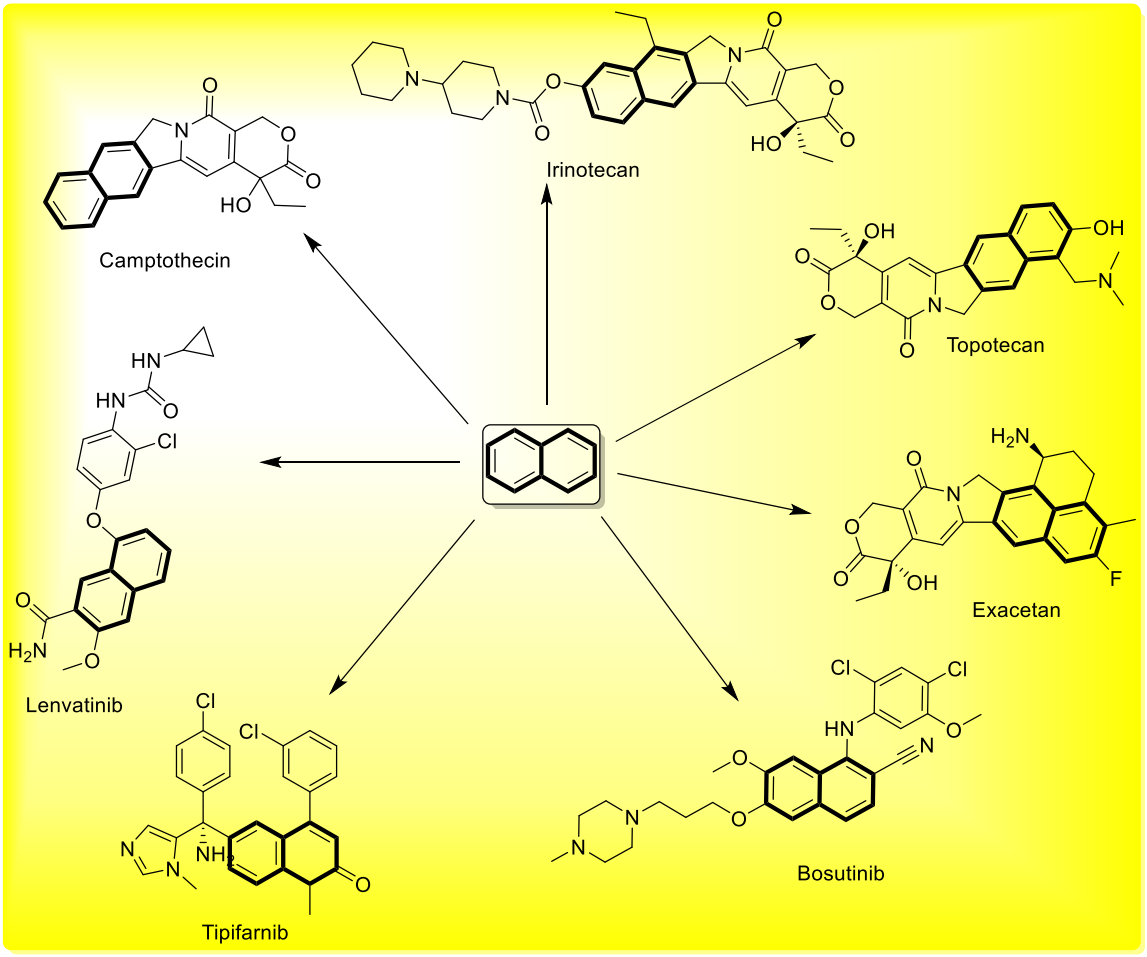


Figure 4: Nepthalene containing anticancer drug

9. PYRAZOLINE

Pyrazoline is a heterocycle which consists of two nitrogen atoms in 5-member ring system. This 5-membered ring contains one double bond adjacent to one nitrogen atom of the ring, pyrazolines are generally known as dihydro pyrazolines(10).

Pyrazoline containing molecules or substituted pyrazolines derivatives embedded with various functional groups have shown diverse biological activities such as antitumor, antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents. These diverse biological activities have attracted the researchers and now a significant amount of research is being carried on this class of compounds. The compounds containing pyrazoline moiety also shows various other activities such as potent selective activities as CB1 receptor antagonists and Nitric Oxide Synthase (NOS) inhibitors.(11).

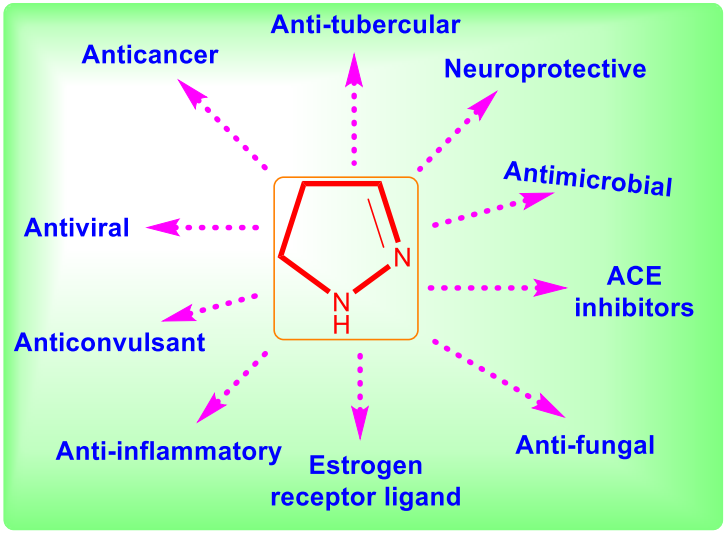


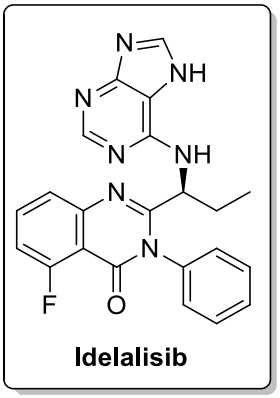
Figure 5: various activity of pyrazoline derivatives

10. SYNTHESIS

Some of the PI3K inhibitors are described below:

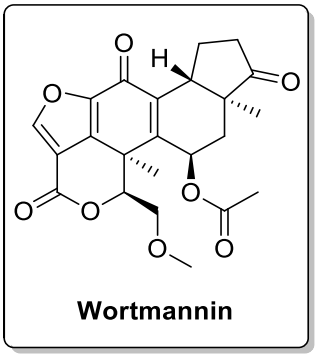
10.1. IDELALISIB

Idelalisib (GS-1101 or CAL-101) is a phosphoinositide 3-kinase inhibitor indicated in the treatment of chronic lymphocytic leukemia and belongs to 6-alkylaminopurines class *i.e.* the compounds containing an alkylamine group attached at the 6-position of a purine. Idelalisib is a specific inhibitor which specifically inhibits the delta isoform of the enzyme PI3K (P110δ).Inhibition this enzyme by idelalisib inhibits several cell signaling pathways and induces apoptosis of malignant cells.(12).



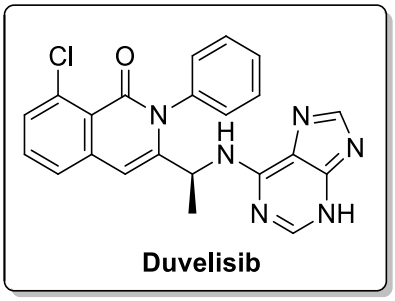
10.2. WORTMANNIN

It is a steroid metabolite of the fungi *Penicilliumfuniculosum* and is a non-specific, covalent inhibitor of PI3K. It has IC_{50} of around 5 nM, making it a more potent inhibitor than LY294002, another commonly used PI3K inhibitor(13).



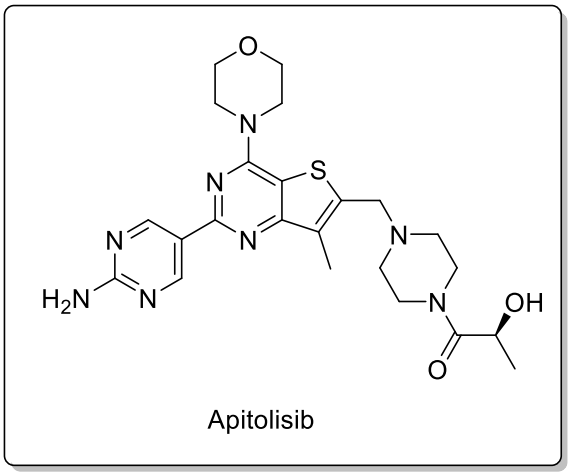
10.3. DUVELISIB

Duvelisib (IPI-145) is a novel targeted oral PI3K-δ,γ inhibitor used for the treatment of hematologic malignancies. It is a PI3K inhibitor which acts by inhibiting the PI3k/AKT/mTOR pathway cancer cell growth/proliferation.(14).



10.4. APITOLISIB

Apitolisib (GDC-0980)is also an orally available agent which is used as dual PI3K/mTOR inhibitor, targeting mammalian target of rapamycin (mTOR) kinase and phosphatidylinositol 3 kinase (PI3K) in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. Apitolisib inhibits both PI3K kinase and mTOR kinase, which may result in tumor cell apoptosis and inhibition of cancer cells growth(15).

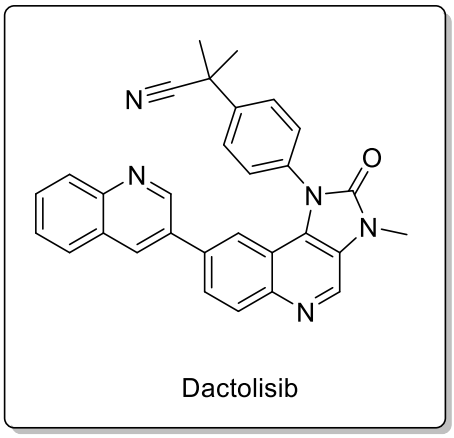


Apitolisib

11. ANTICANCER INHIBITOR IN CLINICAL TRIAL

11.1. DACTOLISIB

Dactolisib, also known as BEZ235, is an orally bioavailable phosphatidylinositol 3-kinase (PI3K) inhibitor with potential anticancer activity. In PI3K/AKT kinase signaling pathway, dactolisib specifically inhibits PI3K.Dactolisib causes apoptosis of cancer cells as it inhibits PI3K which triggers the cytosolic Bax translocation to the outer membrane of mitochondria resulting in increased permeability of mitochondrial membrane due to which apoptotic cell death may occur (16).



Dactolisib

11.2. OMIPALISIB

Omipalisib, also known as GSK2126458, is a small-molecule pyridylsulfonamide inhibitor of phosphatidylinositol 3-kinase (PI3K) with potential anticancer activity. Omipalisib binds to PI3K in the PI3K/mTOR signaling pathway and inhibits this pathway.(17).

11.3. COPANLISIB

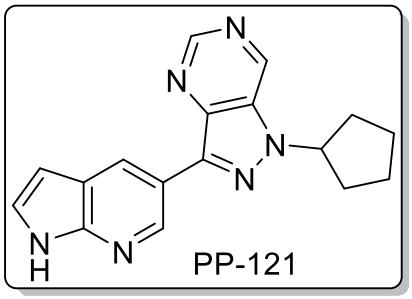
Copanlisib (BKM120) is a novel pan-Class I phosphatidylinositol-3-kinase (PI3K) inhibitor with potent preclinical inhibitory activity against both PI3K-δ and PI3K-α isoforms.(18). It shows high *in vitro* and *in vivo* potency against multiple myeloma and various tumor cell lines.(19).

11.4. PP-121

PP-121 is a Dual PI3K-Akt inhibitor which acts by interaction with hydrophobic pocket present in PI3K. PP-121 inhibits role of PI3K by substituting the role of catalytic lysine which further results in ordering of helix C by which a stable active conformation of PI3K is formed. This whole process occurs when PP-121 forms a H- bond to Glu-310.

PP-121 also blocks action of Akt by blocking the phosphorylation of Akt.

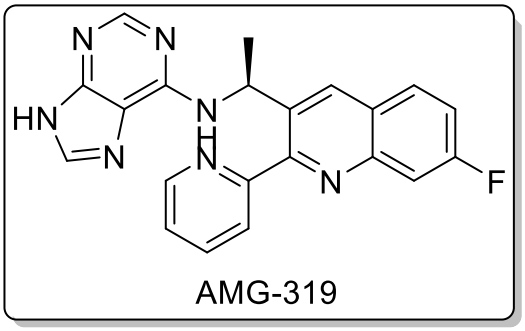
IC_{50} value of PP-121 is 52 nM(20).



11.5. AMG-319

AMG-319 inhibits the function of PI3K protein by inhibiting the activation of PI3K signaling pathway by the inhibition of production of PIP3 (Phosphatidyl- 3,4,5- trisphosphate). PIP3 acts as a second messenger in PI3K signaling cascade. Inhibition of production of PIP3 results in decreased proliferation and it induces cell death because the PI3K pathway does not gets activated.

IC_{50} value of AMG-319 is 18 nM (21).



AMG-319

12. Design of proposed molecule

PP-121 and AMG-319 are the clinical trial candidates as PI3K inhibitors. PP121 is effective at suppressing cell viability, inducing cell apoptosis, and inhibiting cell migration and invasion. The potential anticancer mechanism for PP121 is inhibitory effects on phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathways (Che, Guo, Si, You, & Lou, 2014).

PI3K-delta inhibitor AMG 319 prevents the activation of the PI3K signaling pathway through inhibition of the production of the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3), thus decreasing proliferation and inducing cell death(Herko, Mavis, Czuczman, & Hernandez, 2012).

The design of our compounds was done by taking PP-121 and AMG-319 as reference.

1. PP-121 contains 7- azaindole moiety and AMG-319 contains 9-H purine moiety which was replaced by Naphthalene moiety.

2. 5 membered cyclo-pentane ring of PP-121 and phenyl ring of AMG-319 was replaced by substituted 6 membered aromatic ring.

3. Flexibility of the compound was increased by removing pyrimidine ring attached to pyrazoline moiety and replacing it by substituted 6 membered aromatic ring, it is done by extension of aromatic ring with one single bond.

5. With reference of AMG-319 Naphthalene moiety is introduced in our compound and chlorine is used in case of fluorine.

Figure 3.1 shows the design of proposed molecule

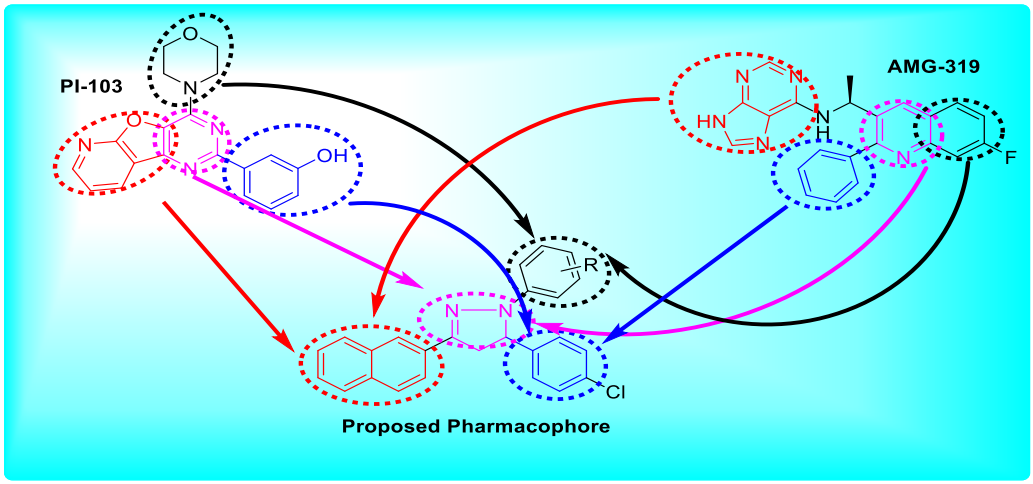


Figure 6: Design

13. CONCLUSION

In summary, this review paper offers an overview of PI3K inhibitors' use in the management of cancer, highlighting their potential as therapeutic agents. The necessity of comprehending the PI3K pathway and its deregulation in cancer formation is emphasized in the paper. The review talks about different PI3K inhibitors and how they work to block the PI3K pathway, including GDC-0941, BYL719, CAL-130, BAY 80-6946, PX-866, SAR245408, GSK2636771, and TG100-115.

The paper emphasizes the importance of clinical trials in evaluating the safety and efficacy of PI3K inhibitors. It provides an overview of the development status of different inhibitors, including those that have received FDA approval for specific cancer types. However, it acknowledges the need for up-to-date information from reliable sources, such as clinical trial registries, to stay abreast of the latest developments in this rapidly evolving field.

In the review article, the potential negative effects of PI3K inhibitors are also covered, including diarrhea, an increased risk of infections, heap toxicity, skin rashes, hyperglycemia, and exhaustion. It focuses on the need of regularly monitoring patients during therapy and managing side effects to guarantee their wellbeing and adherence to the prescribed course of action.

The report also addresses the drawbacks and difficulties of PI3K inhibitors, such as the emergence of drug resistance, attaining enough selectivity, patient stratification, toxicity management, choosing the best combination therapy, and issues with cost and accessibility.

These difficulties highlight the importance of continuing research and suggested directions for the future.

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