Journal of Computational Science & Engineering 29 (2017) 825-827

Available at http://www.asocse.org ISSN 1710-4068

The research progress of Phosphatidylinositol 3-kinase (PI3K) inhibitors

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Abstract: **Phosphatidylinositol 3-kinases (PI3Ks), a family of serine/threonine lipid kinases, are a key signaling component of the PI3K/AKT signal transduction pathway that plays a important role in regulating cell growth, proliferation, motility, and survival. Since the dysregulation of this pathway has been frequently found in human cancers, in particular brain, breast, colon, NSCLC and gastric. Many PI3K inhibitors have been developed as preclinical and clinical drugs in globally pharmaceutical industry. This review contains the research progress of PI3K inhibitors in recent years.**

Keywords: PI3K; cancer; inhibitor; biological activity

Received 2 May 2017, Revised 23 May 2017, Accepted 25 May 2017

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1. Thermal performance of steel and concrete

Cancer is a major public health problem worldwide and is one of the leading cause of death. In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States [1]. In 2015, 429,200 new cancer cases and 281.400 cancer deaths are projected to occur in China[2]. Despite advances in research and development, discovery of novel, safe, and efficacious drugs as therapeutic agents remains a major challenge in the pharmaceutical industry. There are many targeted drugs come into the market with the development of biology information technology, meanwhile, many targeted drugs is still under development, this paper is about the research progress of PI3K inhibitor in recent years.

The phosphatidylinositol 3-kinase (PI3K) signaling pathway plays crucial roles in cell growth, proliferation and survival, and is a frequently dysregulated pathway in human cancers [3]. PI3K are subdivided into three distinct classes depending on sequence, homology and substrate preferences. The class I PI3Ks, comprising four isoforms of PI3Kα, β, γ, and δ, generate phosphatidylinositol 3,4,5-triphosphate (PIP3) to initiate a signal transduction cascade leading to activation of the serine–threonine kinase AKT that in turn promotes the downstream signaling events including mTOR activation[4]. Inhibitors of key kinases in the pathway PI3K/AKT/mTOR, have been extensively pursued in oncology in recent years.

2. The structure and biological activity of PI3K inhibitors

LY294002 and Wortmannin are two classical PI3K inhibitors with a good antitumor activity in vitro and vivo, both of them were failure to enter clinical studies because of the side-effects of skin and liver[5]. Idelalisib(CAL-101) is the first drug approved for use against PI3Kδ inhibitor with the IC50 0.5 um, which used as chronic lymphocytic leukemia, follicular B cell non hodgkin lymphoma and small lymphocytic lymphoma inhibitor[6].

NVP-BEZ235 was a PI3K/mTOR double inhibitor developed by Novartis, the IC50 values of against PI3Kα, β, γ, and δ are 4, 76, 5 and 7nm. It was in the phase Ⅱ of clinical study against bladder cancer and pancreatic cancer; meanwhile, other clinical trials about this drug are being carried out simultaneously [7]. BKM-120 is also developed by Novartis, which is a pan PI3K inhibitor against cancer of the breast in the phase Ⅲ of clinical study [8]. Other PI3K inhibitor BYL-719 was also developed by Novartis which is a selective PI3Ka inhibitor and in the phase Ⅲ of clinical study with good anti-cancer activities [9]. PI3K inhibitors is not only used as anti-cancer drugs but also can be used as immunodeficiency drugs, such as Leniolisib is a PI3Kδ inhibitor used as immunodeficiency inhibitor developed by Novartis, the phase Ⅲ of clinical study is in progress[10].

Copanlisib is a PI3Kα and PI3Kδ inhibitor which was developed by Bayer used as treating non-hodgkin's lymphoma, it was in the phase Ⅲ of clinical study [11]. Taselisib was researched by Genentech and Chugai used treating estrogen receptor positive breast cancer and nonsmall-cell lung cancer, which was in the phase Ⅲ of clinical study.

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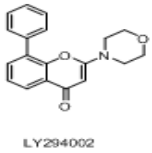
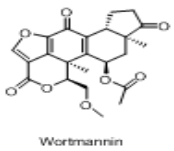

LY294002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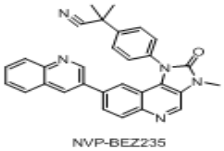
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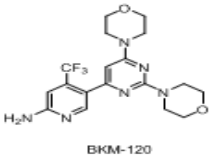
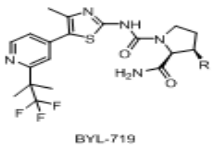

BKM-120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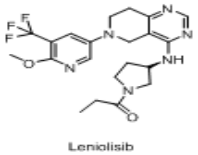
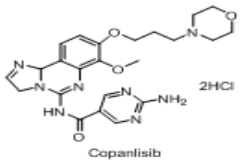
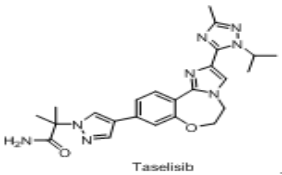
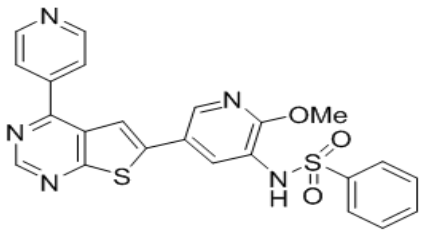

Leniolisib

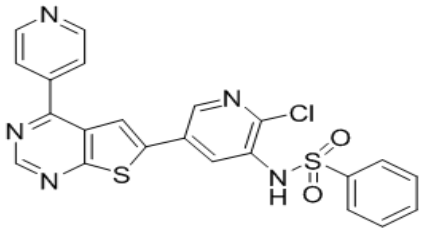

Copanlisib


Taselisib

Although there have been many PI3K inhibitors are in clinical study, the search for new PI3K inhibitor will always remain as an important and challenging task for medicinal chemists with the aim to find a high efficiency and low toxicity PI3K inhibitor.

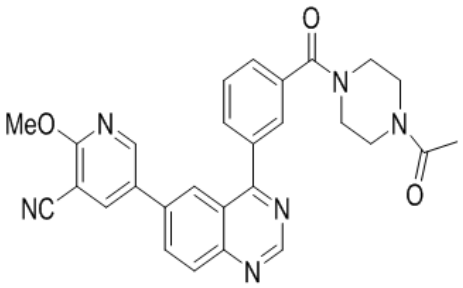
In 2015, Han F. B. et al. prepared a novel series of thienopyrimidine compounds which were demonstrated to bear nanomolar PI3Kα inhibitory potency with over 100-fold selectivity against mTOR kinase. The lead compounds 6g and 6k showed good developability profiles in cell-based proliferation and ADME assays [12].


6g

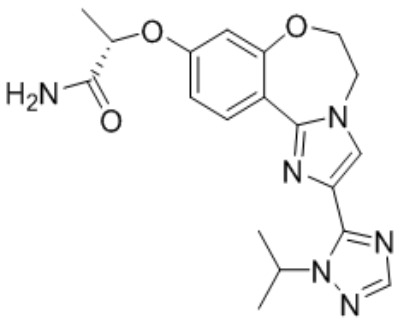

6k

With the advancing in research and development, encoded library technology (ELT) was used as a new hit identification platform. Yang H. F. et al. report a discovery of a novel and potent class of inhibitors of the p110α catalytic subunit of PI3Kα using ELT as the lead identification technology [13].

In 2016, Hoegenauer K., et al. have identified novel quinazoline based PI3Kδ selective inhibitors can be optimized into cellularly potent derivatives. Compound 11 is the candidate with good basic pharmacokinetic properties. Compound 11 demonstrated that the PI3Kδ-dependent inhibition of B cell activation observed in vitro and in rodent PK/PD studies translates into the full inhibition of B cell function, namely, the T-dependent specific antibody response in vivo [14].



In recent studies of Heffron T. P. et al, researched anticancer activity of (S)-2-((2-(1-Isopropyl-1H-1,2,4-triazol-5-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)oxy)propanamide (GDC-0326) and it's PK properties, this series compounds were designed based on target crystal structure of PI3Kα, the overall profile of GDC-0326 led to its selection as a clinical development candidate and allows for further study of a highly optimized specific inhibitor of the PI3Kα isoform [15].


GDC-0326

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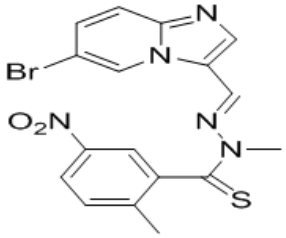
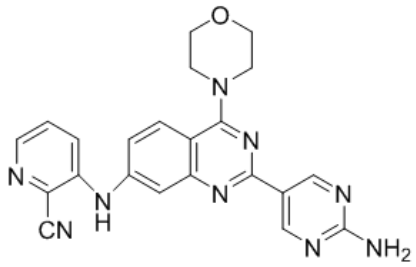
In 2015, some acylhydrazone derivatives were synthesized and evaluated for their anti p110α enzymatic assays. This study was indicated this acylhydrazone derivatives were identified as potential PI3K inhibitors with no apparent inhibition on a panel of other kinases, could be served as lead compound for development of selective anticancer inhibitors[16].



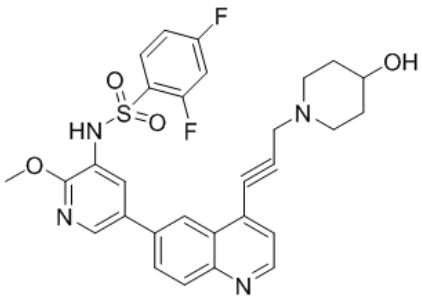
Compound 7

A series of novel 7-or 8-substituted 4-morpholinequinazoline derivatives was designed and synthesized. Their PI3Ka inhibitory activities, anti-proliferative activities against various cancer cell lines were evaluated in vitro. Compound 17f proved to be potential drug candidate with high PI3Ka inhibitory activity and good anti-proliferative activity [17].



17F

A novel series of 4-alkynyl-quinoline derivatives was evaluated as PI3K/mTOR dual inhibitors with potent enzymatic and cellular activities, and 15d was identified as a potentially interesting lead molecule. Most of derivatives exhibited stronger PI3Ka inhibitory activities than that of BEZ235 [18].



15d

3. Conclusion

There are some PI3K inhibitors were reported recently, and this may give an outlook on the latest research developments on PI3K inhibitors, from the report and clinical data, we found that PI3K is a potential therapeutic target, the PI3K inhibitor expected to into drug market to benefiting mankind.

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