International Journal of Multidisciplinary Research Education Analysis and Development – IJMREAD

Peer-Reviewed : Open Access Journal

Role of Cyclin Dependent Kinase Inhibitors as Anticancer Drug in Present Medicinal System

Deepanshu Sharma*[a] &Dr Pramod Kumar*[b]

a- Asst. Prof.-Pharmaceutical Chemistry, Sanskar College of Pharm. and Research, NH-24, Ahead Masuri Canal, Opp. Jindal Nagar Ghaziabad

b- HOD-Chemistry,Govt. DegreeCollege Manikpur

Email id-deepanshusharma87@hotmail.com

Abstract

A group of disease which includes uncontrolled cell division is known as cancer. It has the capacity to spread from one part to the another part of body. So the uncontrolled cell division is the major cause of cancer. Normally the cell cycle division is regulated by Cyclin Dependent Kinases. Cyclin Dependent Kinases belong to the kinases family, which mainly regulate the cell cycle by the transfer of phosphate groups.

Keywords: CDK, Cancer, Enzyme etc.

1. Introduction-

Computational drug design is a technique in which molecular interaction and drug activity are considered by visualization technique, geometric consideration and detailed energy calculat ion. By this process, data are filtered out from huge database. The main advantage of computational drug design is that it is cost effective and less time consuming for development of a novel drug. QSAR (Quantitative Structure Activity Relationship) summarize a supposed relationship between chemical structure and biological activity in a data set of compounds and by this, predict the activity of new compound [6].

Cancer-

Cancer is a mortal disease for our body. Inaccurate regulation of the control mechanism in the cell cycle leads to an excessive cell proliferation and is the cause of cancer. Changing in the genes that are responsible for division is the main reason of cancer. Genetic changes that cause cancer are often inherited from the oldsters. In a person's life span, cancer can also arise by some errors during

cell cycle like damage of DNA due to certain environmental exposure. Environmental exposure which causes cancer, include some substances like chemicals in tobacco smoke and radiation such as ultravi olet rays from the sun. The genetic changes, which are mainly responsible for cancer, tend to affect mainly three types of genes.

- **Proto-oncogenes-** Proto-oncogenes helps in regulation of growth and maintenance of healthy organs as it exhilarate cell division and regulate apoptosis. Oncogens that interfere with cell regulation are made by changing in proto-oncogenes (DNA sequence changing), this result in unregulated cell division and by this a normal cell converts into a cancerous cell.

- **Tumor Suppressor Genes-** Tumour suppressor genes are often defined as genes which encode proteins that normally inhibit the formation of tumours. A tumour suppressor directs the assembly of a protein that's a part of the system that regulates cellular division. The tumour suppressor protein plays a task keep cellular division in restraint. The first insight into the activity of tumour suppressor genes came from cell hybridization experiments, initiated by Henry Harris and his colleagues in 1969. The fusion of normal cells with tumour cells yielded hybrid cells containing chromosomes from both parent. In most cases, such hybrid cells weren't capable of forming tumours in animals. Therefore, it appeared that genes derived from the traditional cell parent acted to inhibit (or suppress) tumour development.

- **DNA Repair Genes**- DNA repair genes are involved in fixing damaged DNA. Mutation in these cells starts mutation in other genes and by these mutations other normal cells convert in to cancerous cell[7].

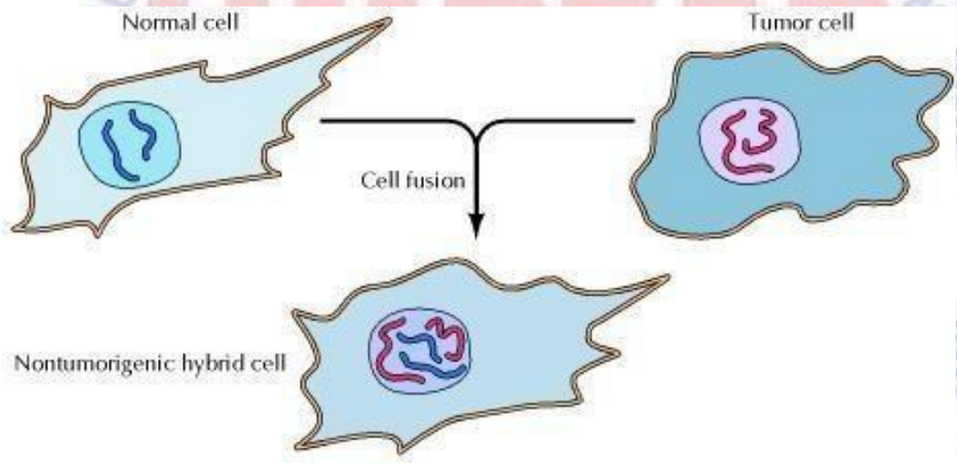

Figure 1. The fusion of Normal Cell with Tumor Cell (Henry Harris Experiment)

Epidemiology

According to World Health Organisation 8.2 million people die each year from cancer, an estimated 13% of all deaths worldwide. There are several causes of cancer deaths that are-

- Low fruit and vegetable intake
- Lack of physical activity
- Tobacco use
- Alcohol use.

The reason of 20% of cancer deaths is only using Tobacco. Africa, Asia and Central and South America are the countries, which have more than 60% world's total new cases. Hepatitis B (HBV), hepatitis C virus (HCV) and a few sorts of Human Papilloma Virus (HPV) increase the danger for liver and cervical cancer respectively. Infection with HIV substantially increases the risk of cancer such as cervical cancer[16].

Current Anti-Cancer Drug therapyAnti-cancer Drug Therapy[19]

Alkylating agents-	Mechlorethamine, Cyclophosphamide,Ifosfamide, Chlorambucil, Melphalan Thio-TEPA, Busulfan, Carmustine (BCNU),Lomustine (CCNU), Dacarbazine (OTIC)
Antimetabolites	
Folate antagonist	Methotrexate (Mtx)
Pyrimidine Antagonist	5-Fluorouracil (5-FU), Cytarabine
Vinca alkaloids	Vincristine (Oncovin), Vinblastine
Taxanes	Paclitaxel, Docetaxel
Epipodophyllotoxin	Etoposide
Camptothecin Analogues	Topotecan, Irinotecan

Current Challenges of Cancer Therapy

Chemotherapy **is** now the main strategy for the treatment of cancer but development of resistance of drugs in cancer is limiting the success of chemotherapy. Resistance of many drugs develop via many various mechanisms, such as

- Decrease in uptake of the agents
- Over expression of energy-dependent efflux proteins
- Increase or alteration in drug targets
- Modification of cell cycle checkpoints
- Inactivation of the agents
- Compartmentalization of the agents
- Inhibition of apoptosis and aberrant bioactive sphingolipid metabolism[8]

Cyclin-Dependent Kinase (CDK)

CDK is the subgroup of serine/threonine kinase family which itself does not show any activity until it combines with its corresponding cyclins. Kinase is a type of enzyme which catalyses some bioreactions which include the transfer of phosphate groups from high energy compounds to particular substrates and after phosphorylation converting them in to serine, threonine, tyrosine, or histidine residues. Cyclins are the active proteins which combine with kinase and control the cell cycle. CDK(s) mainly regulate cell cycle, apoptosis and transcription process. 7 CDK(s) (CDK 1, CDK 2, CDK 3, CDK 4, CDK 6, CDK 10, CDK 11) are directly involved in cell cycle progression. Other CDKs are involved in other function. CDK 3 mainly involves in activation of other CDK(s), CDK 5 in neuronal function, CDK 7-9 in regulation of transcription[13].

CDK	Main activators	Cell. functions	Main cell. phosphorylation goals
CDK 1	B-type cyclins	Cell cycle (G2/M)	Cytoskeleton proteins involved in mitosis, histones
CDK 2	A- and E-type cyclins	Cell cycle (G1/S)	Pocket proteins, DNA replication proteins, E2F, histones
CDK 3	C- and E-type cyclins	Cell cycle	Unknown
CDK 4	D-type cyclins	Cell cycle (G1)	Priming phosphorylation of pocket proteins
CDK 5	p35 (p25) and p39 (p29)	Cell cycle	Neuroskeletal proteins
CDK 6	D-type cyclins	Cell cycle (G1)	Priming phosphorylation of pocket proteins
CDK 7	Cyclin H, MAT1, TFIIE	Cell cycle and transcription	CAK; CTD of promoter-bound RNAP-II
CDK 8	Cyclin C	Transcription	CTD of free RNAP-II
CDK 9	K- and T-type cyclins	Transcription	CTD of stalled RNAP-II
CDK 10	Unknown	Cell cycle	Unknown
CDK 11	Cyclin L	Cell cycle and transcription	RNAP-II

Table 1. Different CDKs

Role of CDK in Cell Cycle

Cell cycle is a multiple step process in which one cell divides and forms new cells. It contains four functional phases: S phase where DNA replicates, M phase (mitosis) where cellular components divide and form two daughter cells, G1 phase between mitosis and S phase where cell replicates and prepares for DNA replication, G2 phase between S and M phase where cell prepares for mitosis[13]. CDK plays an important role in the regulation of cell cycle by transferring the cell from one phase to another phase. G1 phase is regulated by at least three CDK(s) – CDK4, CDK6, CDK2. Cyclin D1/CDK4, 6 complex is essential for crossing the restriction and pushing cells in to replication. CDK 4, 6 are involved in the starting of G1 phase. From G1 to S phase transfer is regulated by Cyclin E/CDK2. In breast cancer Cyclin E is over expressed where it may increase the proliferative capacity of tumour cell. Another kinase CDK3 might also be participative in inactivation of pRb (member of retinoblastoma protein family) CDK3 makes complex with cyclin A and cyclin E. Recently, it has shown that CDK3 interacts with cyclin C at last of G_0 during G_0-G1 transition. CDK 2 plays an important role in S phase. CDK2/cyclin E complex is IJMREAD :

essential for initiatin g DNA replication. CDK2/cyclin A complex is essential for proper completion and exitfrom S phase. During G2 type-A of cylin degrades and type-B of

cyclins are actively synthesized and bind with CDK1 and it is essential for triggering mitosis. CDK1 and cyclin B complex also regulate G2-M phase transition. CDK1 cyclin B complex also active during prophase where they phosphorylate centrosome associated motor protein Eg5, which is essential for promoting centrosome separation. Finally, CDK 1 cyclin B inactivation is necessary for completion of mitosis and it is completed by degradation of cyclin B[12].

CDK Inhibitor

Many heteroaromatic compounds, including flavonoid, indenopyrazole, oxindole, thiazole, purine, pyrimidine and arylcarbazole derivatives, have been identified as CDK inhibitor, which show ATP competitive CDK inhibitory activity[13]. There are some strategies developed which is responsible for CDK inhibition. Firstly synthesis of peptidomimetics. This strategy activity of CDK mainly depend upon the association of Kinase with their corresponding cyclins. So the first target to achieve the CDK inhibitory activity is blocking this recruitment. But this association is so much tight that no small molecule has the ability to disturb this association till now. But an indirect approach is also possible. This indirect approach is based on the development of some synthetic CDK inhibitors that are functionally equivalent to endogenous CDK inhibitor like p16, p21, p27 which are responsible for some conformational changes necessary for activation of cyclin and CDK complex. Second scheam is mainly based on Replacement with Partial Ligand Alternatives through Computational Enrichment(REPLACE) strategy. This strategy is based on the repetitive conversion of peptidic blocker of Cyclin and CDK interaction in to therapeutic active compound, which develop a new lead compound for Non-ATP competitive CDK inhibitor. Third strategy is covalent inhibition of amino acids which is responsible for CDK. In 2014, a group of scientist of Harvard Medical School, Boston, Massachusetts, USA, used this approach and developed a THZ1, a CDK 7 inhibitor. THZ1 covalently bind the cysteine residue and shown irreversible CDK inhibitor activity. Fourth strategy is ATP- competitive inhibitor. Many scientists show huge interest in this strategy. ATP binding site is an active site which is found as a cleft between a small amino terminal lobe and a large carboxy terminal lobe and in CDK it is regulated by cyclin binding[13]. The list of CDK inhibitors is given below[13]:

Compound	CDK	Clinical Phase
MM-D37K	CDK4/D1	Phase I
PTD4-D1	CDK4/D1	Preclinical
PTD4-D3	CDK4/D1	Preclinical
PTD4-K4	CDK4/D1	Preclinical
Abemaciclib= LY2835219	CDK4/6	Phase III
Ribociclib = LEE-011	CDK4/6	Phase III
TG-02 = SB-1317 = EX45	CDK1/2/3/5/7/9	Phase I
AT-7519	CDK2/5/9	Phase II
Dinaciclib = SCH-727965 = MK-7965	CDK1/2/5/9	Phase II
AG-024322	CDK1/2/4	Discontinued
P1446A-05	CDK4	Discontinued
Riviciclib = P276-00	CDK1/4/9	Discontinued
BMS-387032 = SNS-032	CDK2/7/9	Discontinued

Conclusion-

Based on promising result of CDK inhibitors, it can be said that CDK could be a great target for the treatment of cancer. It can be give better result if the more precise methods are used during design and synthesis of CDK inhibitors. It can be also said that the CDK could be give promising more accurate result in the treatment of cancer like dangerous disease.

References-

1. Ali, I., Wani, W.A. and Saleem, K. (2011) 'Cancer scenario in India with future perspectives", *Cancer Therapy*, 8, pp. 56-70.
2. Brazidec, J.Y.L., Pasis, A., Tam, B., Boykin, C., Black, C., Wang, D., Claassen, G., Chong, C.H., Chao, J., Fan, J., Nguyen, K., Silvian, L., Ling, L., Zhang, L., Choi, M., Teng, M., Pathan, N., Zhao, S., Li, T. and Taveras, A. (2012) 'Synthesis, SAR and biological evaluation of 1,6-disubstituted-1H-pyrazolo[3,4-d] pyrimidines as dual inhibitors of Aurora kinases and CDK1', *Bioorganic & Medicinal Chemistry Letters* ,22, pp. 2070–2074.
3. *Cancer* (2015) Available at: http://www.who.int/mediacentre/factsheets/fs297 / en/ (Accessed: 19-05-2015).
4. *Cancer* (2015) Available at: https://en.wikipedia.org/wiki/Cancer (Accessed: 15-05-2015).
5. Chorawala, M.R., Oza, P.M. and Shah, G.B. (2012) 'Mechanisms of anticancer drug resistance', *International Journal of Pharmaceutical Sciences and Drug Research*, 4(1), pp. 1-9,
6. Finn, P.W. and Kavraki, L.E. (1999) 'Computational approaches to drug design', *Algorithmica*, 25 (2), pp. 347-371.
7. "Genes and Cancer", American Cancer Society, pp. 1-10, 2014.
8. Gottesman, M.M. (2002) 'Mechanism of anticancer drug resistance', *Annual Review of Medicine*, 53, pp. 615-627
9. Horiuchi, T., Nagata, M., Kitagawa, M., Akahane, K., and Uoto, K. (2009) 'Discovery of novel thieno[2,3-d]pyrimidin-4-yl hydrazone-based inhibitors of Cyclin D1-CDK4: Synthesis, biological evaluation and structure–activity relationships. Part 2', *Bioorganic & Medicinal Chemistry*, 17, pp.7850–7860.
10. Ibrahim, D.A., and Ismail, N.S.M. (2011) 'Design, synthesis and biological study of novel pyrido[2,3-d]pyrimidine as anti-proliferative CDK2 inhibitors', *European Journal of Medicinal Chemistry*, 46, pp. 5825e5832.
11. Jaramillo, C., Diego, E.D., Hamdouchi, C., Collins, E., Keyser, H., Sa´nchez-Martinez, C., Prado, M.D., Norman, B., Brooks, H.B., Watkins, S.A., Spencer, C.D., Dempsey, J.A., Anderson, B.D., Anderson, R.M., Leggett, T., Patel, B., Schultz, R.M., Espinosa, J., Vieth, M., Zhang, F., and Timm, D.E. (2004) 'Aminoimidazo[1,2 a] pyridines as a new structural class ofcyclin-dependent kinase inhibitors. Part 1: Design, synthesis and biological evaluation' *Bioorganic & Medicinal Chemistry Letters* ,14, pp., 6095–6099.
12. Malumbres, M. and Barbacid, M. (2005) 'Mammalian cyclin-dependent kinases', *Trends in Biochemical Sciences*, 30(11), pp. 630-641.
13. Martínez, C.S., Gelbert, L.M., Lallena, M.J. and Dios, A.D. 2015 'Cyclin dependent kinase (CDK) inhibitors as anticancer drugs', *Bioorganic &Medicinal Chemistry Letters*, 25, pp. 3420–3435.

14. Massuard, M.C.V., Baltus, C.B., Jorda, R., Marot, C., Berka, K., Bazgier, V., Krystof, V. and Pri_e, G. (2016) 'Synthesis, biological evaluation and molecular modeling of a novel series of 7-azaindole based tri-heterocyclic compounds as potent CDK2/ Cyclin E inhibitors', *European Journal of Medicinal Chemistry*, 108, pp. 701-719.
15. Murthy, N.S., Chaudhary, K. and Rath G.K. (2008) 'Burden of cancerand projections for 2016, Indian scenario: Gaps in the availability of radiotherapy treatment facilities', *Asian Pacific Journal of Cancer Prevention*, 9, pp. 671-677.
16. Panno, J. (2005) *Cancer: The role of genes , lifestyle & environment.* [Online]. Available at: http://ebookdb.info/download/0816049505/ Cancer%3A+The+ Role+of +Genes%2C+ Lifestyle%2C+and+Environment +%28New +Biology % 29/ (Accessed: 15 May 2016).
17. Pevarello, P., Fancelli, D., Vulpetti, A., Amici, R., Villa, M., Pittala, V., Vianello, P., Cameron, A., Ciomei, M., Mercurio, C., Mercurio, J.R., Roletto, F., Varasi, M., and Brasca, M.G. (2006) '3-Amino-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazoles: A new class of CDK2 inhibitors', *Bioorganic & Medicinal Chemistry Letters*, 16, pp. 1084–1090.
18. Singh, S.K., Tripathi, S.K., Dessalew, N. and Singh, P. (2012) 'Cyclin Dependent Kinase as significant target of cancer treatment', *Current Cancer Therapy Reviews*, 8, pp. 225-235.
19. Tripathi, K.D. *Essentials of Medical Pharmacology*. 6th edn. New Delhi Jaypee Brothers Medical Publishers (P) LTD.
20. Wang, S., Shao, H., Shi, S., Foley, D.W., Lam, F., Abbas, A.Y., Liu, X., Huang, S., Jiang, X., Baharin, N. & Fischer, P.M. (2013) 'Synthesis, structureeactivity relationship and biological evaluation of 2,4,5-trisubstituted pyrimidine CDK inhibitors as potential anti-tumour agents', *European Journal of Medicinal Chemistry*, 70, pp. 447-455.
21. Wang, S., Shao, H., Shi, S., Huang, S., Hole, A.S., Abbas, A.Y., Baumli, S., Liu, X., Lam, F., Foley, D.W., Fischer, P.M., Noble, M., Endicott, J.A. and Pepper, C. (2013) 'Substituted 4-(Thiazol-5-yl)-2-(phenylamino)pyrimidines Are Highly Active CDK9 Inhibitors: Synthesis, X-ray Crystal Structures, Structure−Activity Relationship, and Anticancer Activities', *Journal of Medicinal Chemistry*, 56, pp. 640-659.
22. Zhu, H.L., Sun, J., Lv, X.H., Qiu, H.Y., Wang, Y.T., Du, Q.R., Li, D.D. and Yang, Y.H. (2013) 'Synthesis, biological evaluation and molecular docking studies of pyrazole derivatives coupling with a thiourea moiety as novel CDKs inhibitors', *European Journal of Medicinal Chemistry*, 68, pp. 1-9.

****