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A Concise Review on Cyclin Dependent Kinase 5 (CDK5) Inhibitors

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ABSTRACT

Cyclin dependent kinases 5 (CDK5) carry out many critical roles in the process of cell cycling and play an important role in many physiological functions, including development of central nervous system and their inhibitors have been extensively researched as therapeutic agents in the diagnosis of cancer. CDK5 belongs to Serine/Threonine Cyclin-dependent kinase (cdk) family. CDK5/ p25 complex has emerged as one of the potent principle therapeutic target for various diseases like acute and chronic neurodegenerative disease, including Alzheimer's disease. Excessive upregulation of CDK5 leads to several types of neurodegenerative disorders like Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Niemann pick type C disease and Ischemia. To inhibit the excessive activity of cdk5, several cdk5 inhibitors have been synthesized and discovered naturally by various research groups globally here in this review we are accounting some of them together to show their efficacy.

Keywords: Cyclin dependent kinase, Cdk, Serine, Threonine, Alzheimer's disease. ALS, Ischemia,

INTRODUCTION

Alzheimer's disease (AD) is one of the most prevailing neurodegenerative disease.[1] Alzheimer's disease (AD) is characterized by loss of memory, reasoning, language, abstraction and emotional control and ultimately loss of cognitive behaviour.[2] More than 30 million people are affected worldwide from AD and also number of people affected with this kind of ailment are expected to increase with aging human population which is a result of age demographics.[3-6] Discovery of cyclin dependent kinase 5 was made in early 1990s and since then major progress has been made in order to identification of its function.[7]

Cyclin-dependent kinase 5 (CDK5) also known as neuronal cdc2-like kinase (NCLK), is a bonafide member of the serine/threonine cyclin-dependent kinase (cdk) family.[8] Initially CDK5 was identified by means of biochemical purification from the bovine brain.[9-10] CDK5 plays a crucial role in the development of adult neurons and regulates a number of neurological processes. CDK5 plays a central role in the process of neuronal migration during the development of central nervous system (CNS).[11] CDK5 expresses its predominant activity in postmitotic neurons due to restricted distribution of its activator protein p35. CDK5 helps in the regulation of actin and microtubules skeleton and modulates a variety of process like cell adhesion, neurite outgrowth and cell mobility.[7] Mice lacking CDK5 or double deficient for its two brain activator p35 and p39 express severe defects in the process of layering of cerebral cortex.[12-14] p25 and p29 are the equivalent protein segment produced by proteolytic procession of the C-terminal portion of p35 and p39 protein respectively. p25 can be produced from membrane bound protein p35 by proteolytic action of cysteine protease such as calpains that similarly activates CDK5 by repositioning the activation loop.[15]

Excessive upregulation of CDK5 by curtailed activators leads to several neurodegeneration by altering the phosphorylation state of cytosolic and cytoskeleton protein, and increased CDK5 activity has been revealed in numerous neurodegenerative disorder like Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Niemann-pick type C disease and Ischemia.[16-20]

Development of CDK5 inhibitors have been a validated target in the therapeutics of several neurodegenerative diseases in which the activity of these protein is deregulated.

2. NATURAL ANALOGUES

A number of natural analogues have been accessed with regard to their effects on the activities of cyclin dependent

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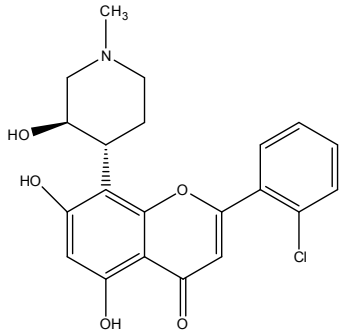
kinases. Flavonoids are a class of natural analogues, generally prominent plant secondary metabolites consumed by human being as dietary supplements in amount 0.1 g/day suggesting their ingestion may play a significant role in health and disease.[21-22] Flavonols are another class of natural analogue which are distinct from Flavanol and present in wide variety of fruit and vegetables.

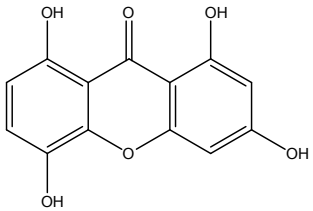
2.1 FLAVOPIRIDOL

A synthetic flavone derivative flavopiridol, **1** is one of the examples satisfying the fact that dietary or other natural flavonoids are known as protein kinase inhibitors. Testing of inhibitory activity of natural flavonoids against cdk5 found that they are potent cdk5 inhibitor ranging their inhibitory activity for many enzymes although they are better known as antioxidants.



1

Compound **2,** a natural product Bellidin that showed promising inhibition of CDK5 at the IC_{50} value of 0.2 µM and to some extent inhibit the excessive upregulation of CDK5/p25 complex.



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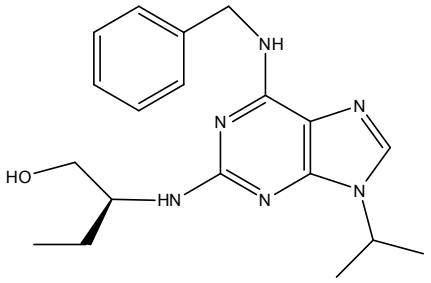
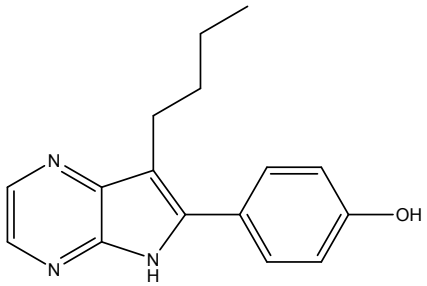
3. SYNTHETIC ANALOGUES

Molecule **3** is purine derivative (2-(1-ethyl-2-hydroxy-ethylamino)-6-benzylamino-9-isopropylpurine and better known as R- Roscovitine contain an asymmetric carbon. Molecule **3** is well known moderate inhibitor of CDK5/p25 that shows it's inhibition at the IC_{50} value of 160 Nm and displays preferential inhibition of CDK5/p25 over other CDKs.[23-24] R isomer display higher CDK1 inhibitory activity than S isomer.[25]



3

Compound **4** is (6-phenyl[5H]pyrrolo-[2,3-b]pyrazines) based scaffold well known as Aloisine A. Compound **4** is selective inhibitor for CDK1/2/5 and GSK3-α/β but most active against CDK5/p25 and shows it's inhibition at IC_{50} value of 0.16-0.20µM.[26-27]



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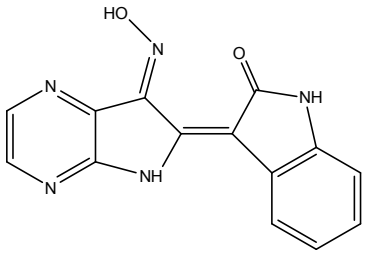
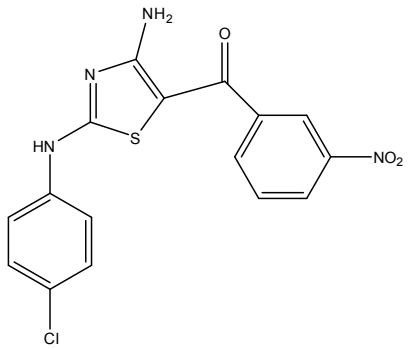
Compound **5** is better known as Indirubin-3'-oxime and is the key constituent of the traditional Chinese leukemia treatment Danggui Longhui Wan.[28] Compound **5** also shows great potency of inhibition against CDK5/p25 at IC_{50} value of 0.10 µM and against GSK3-β at IC_{50} value of 0.022 µM.



5

Compound **6** is an analogue of 2,4 diaminothiazole and inhibit the CDK5/p25 activity at the IC_{50} value of 2.0 µM. Several other derivatives have been synthesizes by G.D Cuny group by keeping 2,4 diaminothiazole ring as pharmacophore and varying different –different substituent and some of them showed very promising inhibition activities against CDK5/p25.[29]



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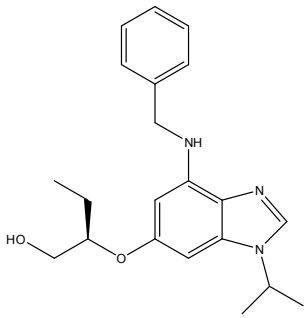
Compound **7** belongs to a series of 6-O-linked benzimidazole, in which pyrimidine ring of R- Roscovitine is replaced by benzene ring because pyrimidine ring was not showing any kind of interaction with surrounding as revealed by SAR studies. Compound 7 showed very promising inhibitory activity against CDK5/p25 complex**.**



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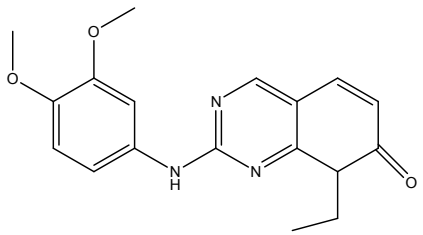
Compound 8 counts to one of the most potent inhibitor of CDK5/p25 complex and showed it's inhibition at the IC_{50} value of 30 nM. Compound 8 also showed its inhibitory property against CDK2 at the IC_{50} value of 540 nM.[30]



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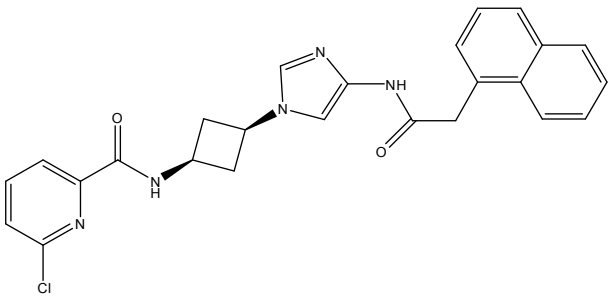
Compound **9** also showed selectivity for CDK5 over CDK2 by expressing its robust inhibition against CDK5/p25 complex at the IC_{50} value of 6 nM while showed inhibition of CDK2 activity at IC_{50} value of 204 nM and accounts to one of the most potent inhibitor of CDK5.[30]



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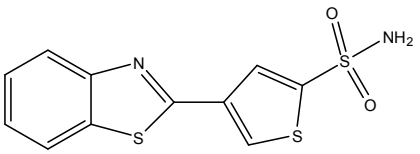
Compound **10** is 4-(1,3-benzothiazol-2-yl)-thiophene-2-sulfonamide based inhibitor of CDK5 showed inhibition at the IC_{50} value of 551 nM suggesting that this molecule is moderate inhibitor of CDK5.[30]



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CONCLUSION

Worldwide number of patients suffering from neurological disorder are increasing enormously and losing their normal life span due to non-availability of targeted treatment. CDK5 inhibitors have emerged as one of the crucial target for the treatment of neurological disorders. A number of small molecules have been examined for their potency against neurological ailments especially for Alzheimer's disease (AD),[31,32] however, more sincere efforts need to be explored with other synthetic molecules[33] and other therapies such as anti-sense therapy[34] in order to acquire the success.

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