Review Article

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An Overview of the Clinical Significance of Protein Kinase and Various *N*-based Small Molecule Kinase Inhibitors

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The N-containing heterocycles have always inspired medicinal chemists and compelled them to design novel bioactive N-based scaffolds. Recently interest has grown in developing small molecule *N*-based scaffold as kinase inhibitors for the treatment of diverse types of cancer. Protein kinases are a diverse set of enzymes catalyzing epigenetic modifications in human genome and are involved in pathogenesis of various diseases. Interestingly, the protein kinases are the second only well studied and established drug targets, after the G-protein-coupled receptors (GPCR). Its significance could be understood in a manner that a large number of *N*-based scaffolds as kinase inhibitors are currently in the clinical trials phase or in the advanced level of drug development. The current review compiles the clinical significance of kinase enzyme, its catalytic domain and various US FDA approved nitrogen containing kinase inhibitors. Additionally,an additional small compilation of another small *N*-based famous small organophosphorus compound α-Aminophosphonates (the isosteres of naturally occurred α-Amino acids)protein kinase inhibitory activities have also been pointed out owing to their significant therapeutic applications being discovered during last couple of years.

Introduction:

Over the years Kinases have become one of the most hunted therapeutic target for the treatment of plethora of cancer. It has been found out that there are almost 538 types of protein kinases being expressed by human genome.[1-5] The most significant physiological role played by it is catalyzing the transfer of γ-phosphate group of adenosine triphosphate (ATP)to serine, threonine and tyrosine residues of amino acids and also to phosphatidyl inositol kinases and sphingosine kinases. Phosphatases are another group of enzymes which remove phosphate groups from various proteins. Both kinases and phosphatases are involved in epigenetic modifications and any imbalance of them led to the development of cancer.[6] The clinical importance of kinase inhibitors could be understood in the sense that its global market is approximately US$20 billion per annum. As of January 2023, there are 113 kinase inhibitor drugs in clinical practice out of which 82 are US FDA approved, some are heterocyclic small molecules, and some are monoclonal antibodies.[7-9] The kinase has a catalytic property of transferring phosphate group from ATP depicted below. Figure 1 enlists some of the pertinent pathophysiological role of kinase

Structure of Protein Kinases

Various studies have revealed that kinase contains two catalytic domains, one large C-lobe and a smaller N-lobe. X-ray structure study of cyclic AMP-dependent PK was carried out by knighton in 1991

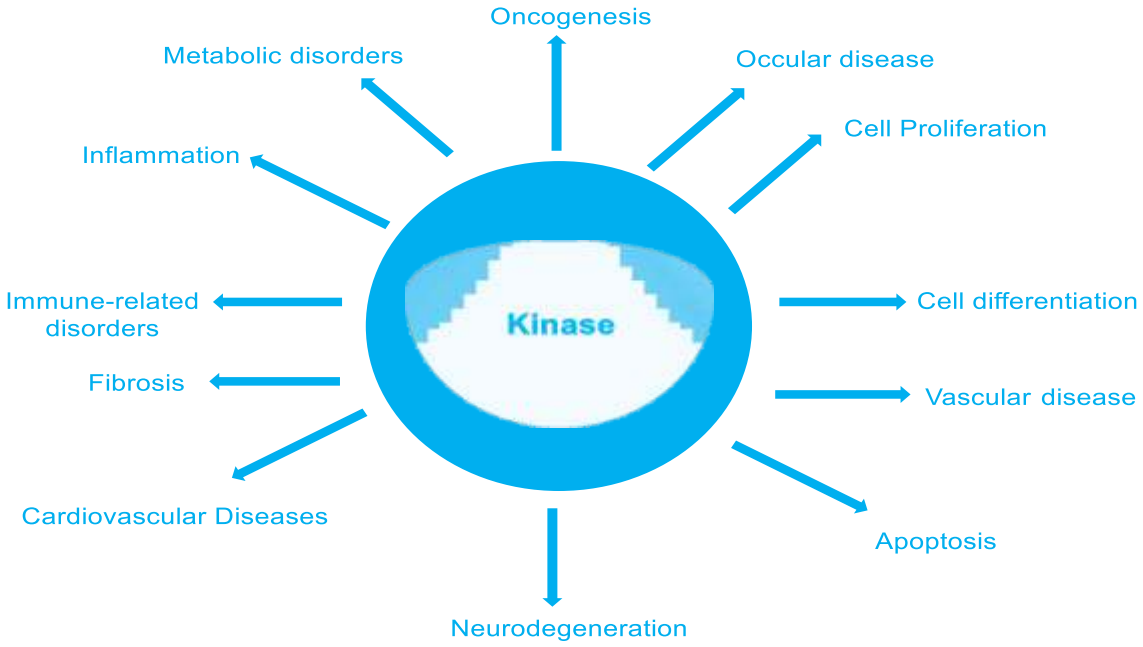


Figure 1: Pathophysiological Role of kinase

and the structure was properly described. It was found that PK structure comprises of a small amino terminal *N*-lobe and a large α-helical carboxy-terminal *C*-lobe. It was also observed that both the terminals are connected via a small hinge region. It has a highly conserved catalytic domain that shares a conserved secondary fold comprising of a twin-lobed catalytic core structure where ATP binds to a deeply seatedcleft between the lobes. The N-lobe was found to be comprised of both β-sheet and α-helix (α*C*-helix), on the other hand the *C*-lobe was found predominantly composed of α-helix. Both the lobes are linked by a hinge region. Kinases contain a highly conserved DFG and APE motif.[10-11] The DFG motif is constituted of amino acids Asp-Phe-Gly present in *N*-lobe. This DFG motif forms part of the ATP binding site and coordinates with the Mg^{2+} ions. The aspartate of the DFG coordinates with the magnesium, the phenylalanine moiety constitutes a hydrophobic region between *N* and *C*-lobe. Figure 2 represents the Crystal Structure of the active EGFR kinase domain in complex with an ATP analogue. An example of the Tyrosine Kinases family (PDB ID: 2GS6).

The active confirmation is known as DFG in and DFG out is the inactive confirmation adopts by kinases. In the active confirmation the DFG-Phe adopts such a topology wherein all the lobes are aligned together and binds with Magnesium efficiently. In case of DFG out confirmation the DFG-Asp changes its topology whereby the DFG-Phe moves out of the DFG-pocket and ATP binding is hampered. DFG-Phe is aligned and packed in the hydrophobic pocket in DFG-in confirmation. Figure 3 depicts the binding pocket of kinase.[12-13] There are mainly six types of kinases inhibitors discovered and explored so far, such as type 1, type II, type III, type IV, type V, type VI and type 11/2. The Type 1 inhibitors bind to the so called "Active Conformation" of the enzyme

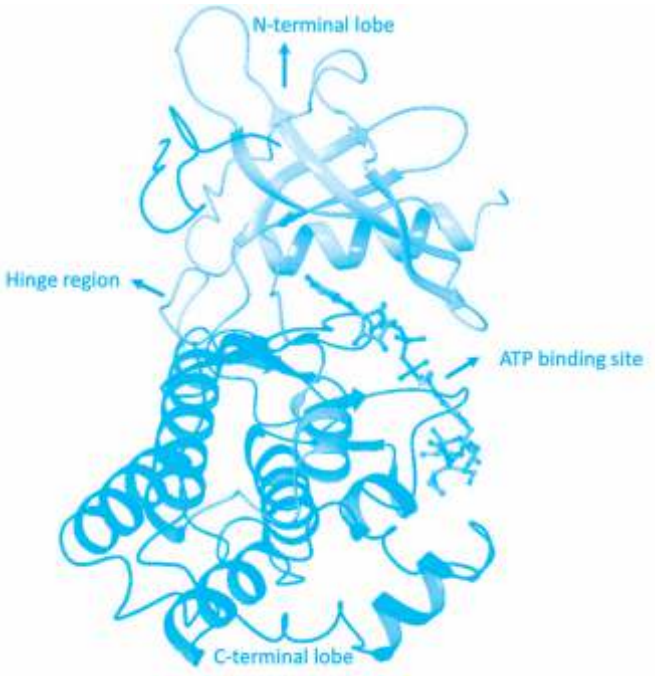


Figure 2. Crystal Structure of the active EGFR kinase domain in complex with an ATP

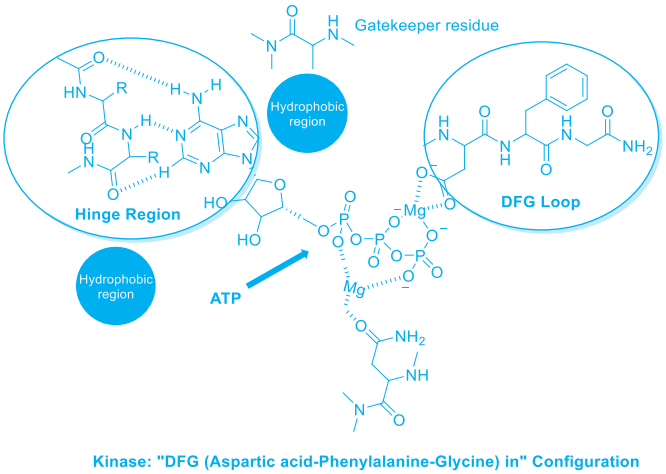


Figure 3: Protein Kinase domains[16]

and are associated with the DFG-in conformation of this loop. Bosutinib, Cabozantinib, Ceritinib and Gefitinib are type I kinase inhibitors. In contrast type II inhibitors bind to the "Inactive Conformation" of the protein, associated with a DFG-out conformation. Imatinib, Sorafenib, and Nilotinib are Type II inhibitors. Type III inhibitors are unique in the sense that they occupy and bind at a site which is next to the ATP-binding pocket. Both type III and type IV inhibitors are allosteric inhibitors. Trametinib are type III inhibitors. Type IV inhibitors do not engage ATP binding site. There are drugs which are under clinical trial as Type IV inhibitors.

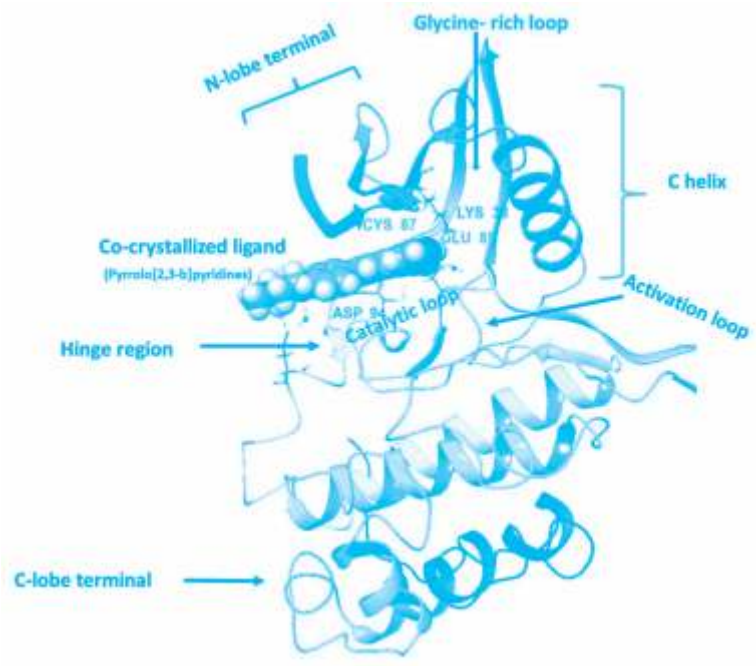


Figure 4.The co-crystal structure of Checkpoint Kinase Chk1, an example of Serine/Threonine Kinases with a pyrrolo-pyridine inhibitor as co-crystallised ligands (PDB ID: 1ZYS)2GS6

Type V inhibitors are considered as bivalent inhibitors as they bind at two different region of protein kinase. Afatinib and Ibrutinib are Type V inhibitors. Type 1, 11/2 and II inhibitors exhibit hydrogen bonding with the hinge region connecting the *N*- and *C*-lobe. These inhibitors occupy the adenine region of the binding pocket. Type VI wages covalent bonding with the kinases enzyme domain.[14-15] Protein kinase containing different catalytic domains exhibits high degree of specificity and are highly conserved.[16]

Figure 4 depicts co-crystal structure of Checkpoint Kinase Chk1, an example of Serine/Threonine Kinases with a pyrrolo-pyridine inhibitor as co-crystallised ligands (PDB ID: 1ZYS)2GS6. Chk1 has a C-lobe terminal, N-lobe terminal, a hinge region, and a glycine rich loop. The activation loop where the co-crystalized ligand resides. Asp94, LYS38, CYS87 and GLU81 amino acids were found to be involved in binding interactions.

Small molecule based Kinase inhibitors

Imatinib was the first kinase inhibitor to get FDA approval in 2001. It is regarded often as 'magic bullet'. In the year 1998, the very first clinical trial of imatinib started and later was approved by FDA in 2001 for Chronic Myelogenous Leukemia (CML). Imatinib is also effective against tumors related with the PDGFR and c-KIT. Figure 5 illustrates the 2D and 3D co-crystallised structure of chicken C-Src kinase domain in complex with imatinib, an anticancer agent.The illustration highlights that the activation loop of the Src domain is distorted from residue number 408-420. This further extends to the phosphate-binding P-loop, thus leaving the solvent side chain of phenylalanine exposed. The critical feature of this imatinib-bound conformation is that it possesses a peculiar, conserved Asp-Phe-Gly motif (DFG motif), which is found to be located at the *N*-terminal activation loop. The fundamental interactions include - interaction between the Phe 405 with the aromatic pyrimidine ring of the imatinib, and Met341 is involved in hydrophobic interaction with the -*N* of the pyridine ring. Thr338, which possesses -OH group, participates in the hydrogen bonding with the bridging NH. While Asp404 stabilizes the imatinib in the active site via the H-bonding of the carbonyl oxygen group.

Imatinib was found to inhibit a deregulated fusion protein known as Abelson (ABL) tyrosine kinase, expressed as BCR-ABL (Figure 6).

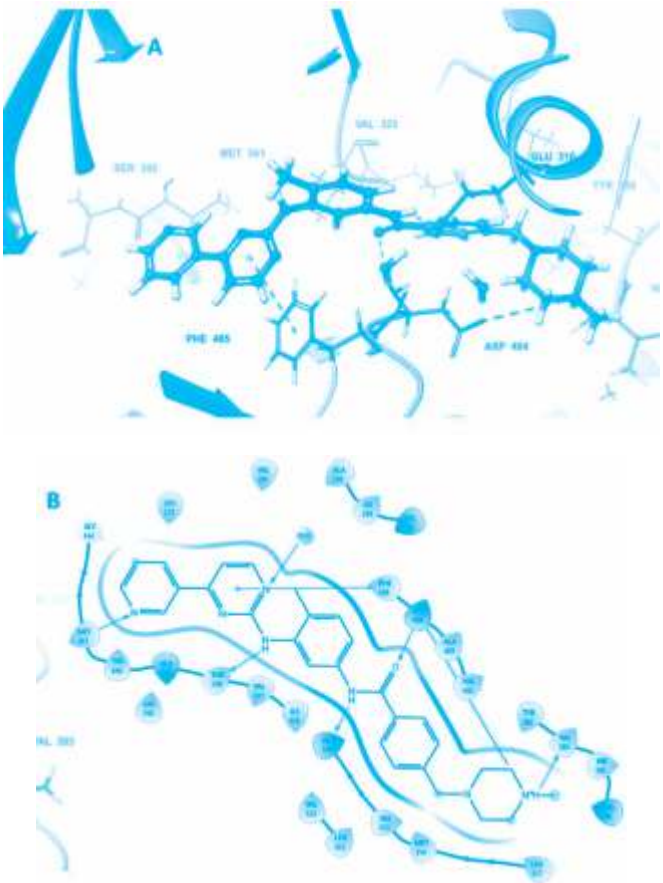


Figure 5. Illustration portraying A. 3D and B. 2D co-crystallised structure of chicken *c*-Src kinase domain in complex with imatinib, an anticancer agent.

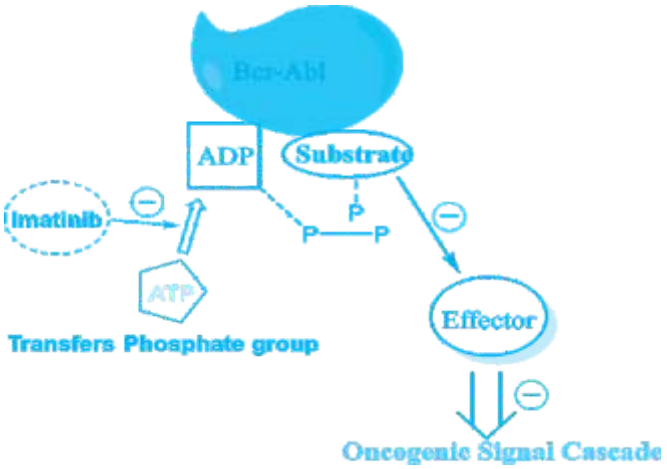


Figure 6: Interruption of BCR-Abl pathway by Gleevec (Imatinib)

Recently, a kinase inhibitor Pirtobrutinib, is approved recently for Mantle Cell Lymphoma (MCL). It was approved on January 27, 2023, by USFDA to treat autoimmune and inflammatory diseases, particularly for the for relapsed or refractory mantle cell lymphoma (MCL). The drug is known to inhibit the Bruton's tyrosine kinase (BTK), a key kinase involved in the activation of B-cells that plays a vital role in mediating immune response and inflammation. The

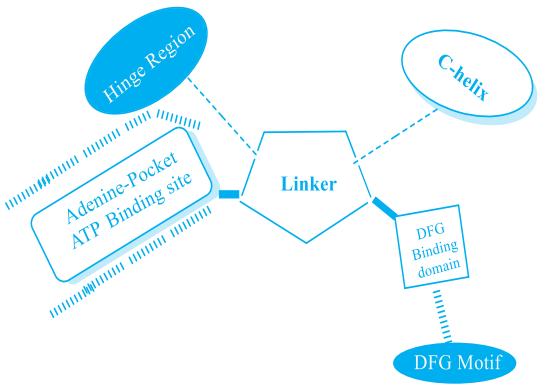


Figure 7: Binding Regions of Kinase inhibitors

current recommended dose of pirtobrutinib is 200 mg orally once daily.

Table 1 comprises of various US FDA approved nitrogen containing kinase inhibitors approved since 2003,their target enzymes and clinical indications.[17] By looking into their chemical scaffolds and individual Q-SAR studies there exists a pattern amongst them which could be understood by figure 2. The major binding sites could be traced as catalytic triad of DFG motif, hinge region and C-helix.[18]

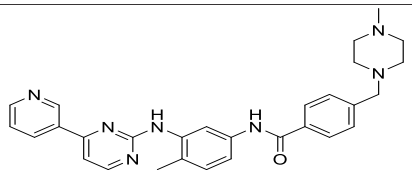
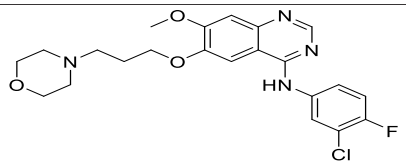
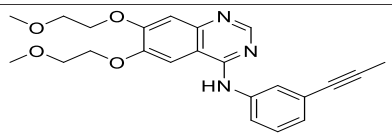
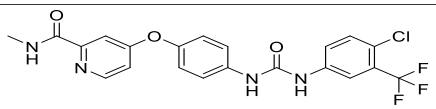
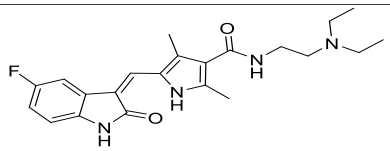
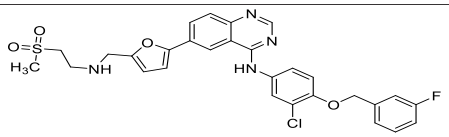
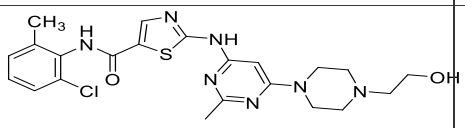
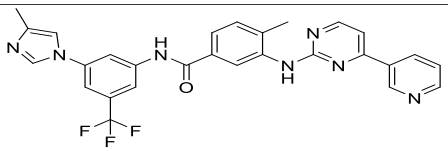
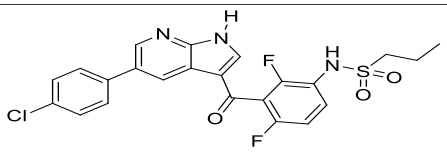
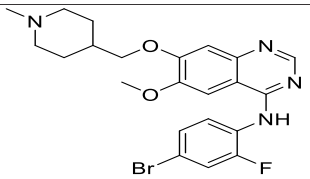
Binding Specificity of imatinib

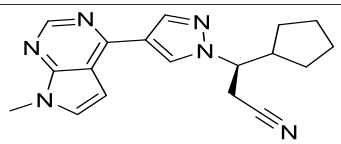
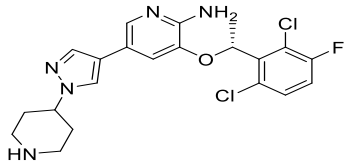
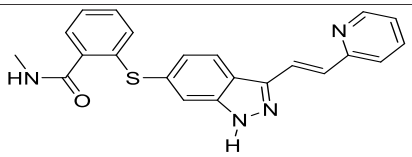
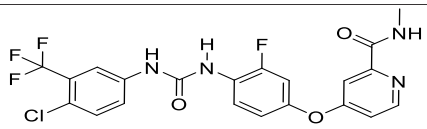
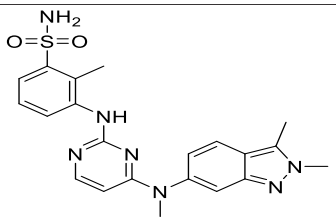
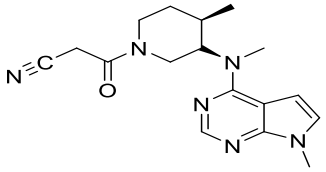
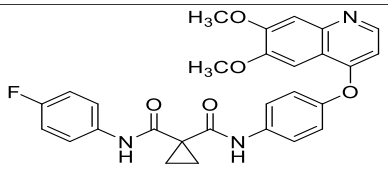
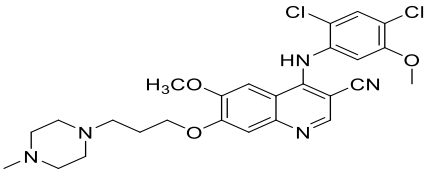
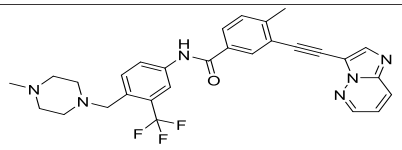
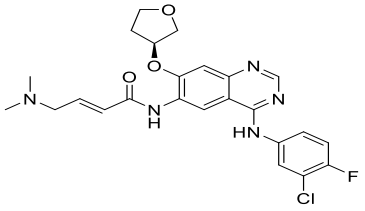
Binding interactions of imatinib was properly studied by various research groups revealing the various interactions pertaining to enzymatic cavity. Lin and coworker have studied the computational analysis of the binding specificity of the gleevec (imatinib). They performed free energy perturbation molecular dynamics (FEP/MD) simulations study to deduce the binding affinity of Gleevec to various kinases such as Abl, c-Kit, Lck, and c-Src. In their study they found the occurrence of various binding interactions in the kinase domain such as Van der Waals dispersive interaction, hydrogen bonding and electrostatic attraction and repulsive interactions. It was found that gleevecengages the kinase activation loop in perfect manner.[23] Pan and co-workers have developed some novel Bcr-Abl inhibitors which further establishes the specific binding of gleevec at the kinase domain. It was further revealed that there are three sub regions where the gleevec exhibits binding in the kinase domain.These three regions are the linker region, which is surrounded by DFG motif and gatekeeper residue, the adenine pocket which is occupied by ATP and two hydrophobic domains.[24] Figure 8 represents some important binding sites of gleevec.

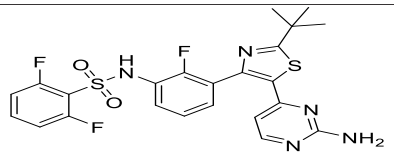
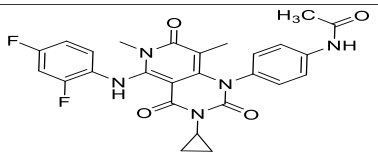
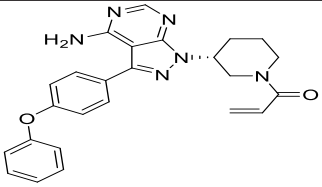
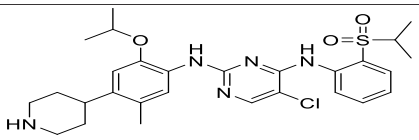
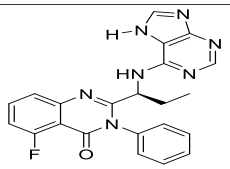
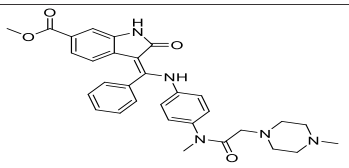
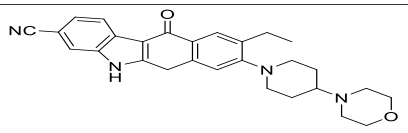
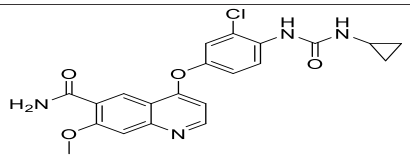
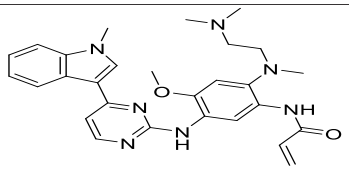
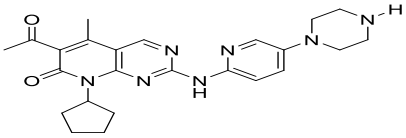
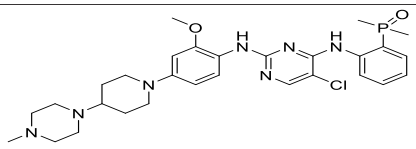
α-Aminophosphonate/phosphinate based protein kinase inhibitors

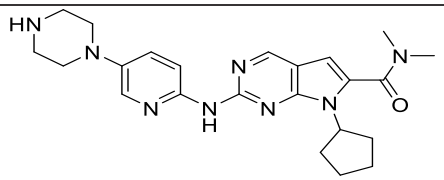
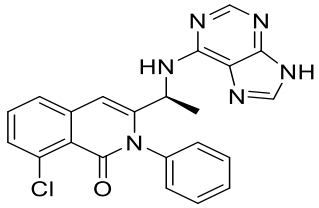
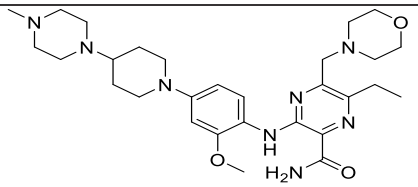
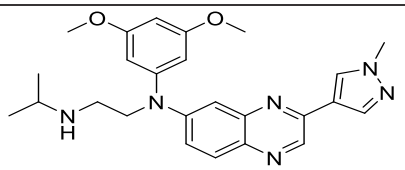
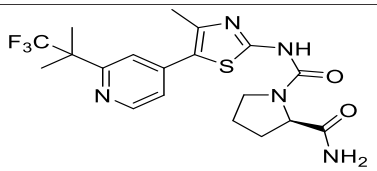
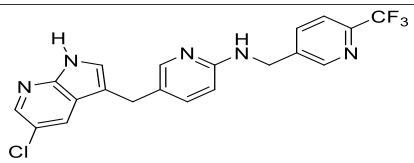
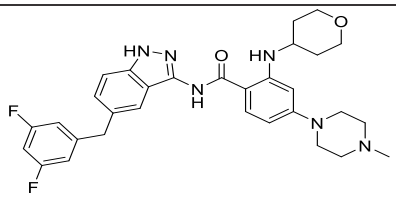
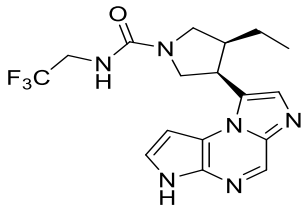
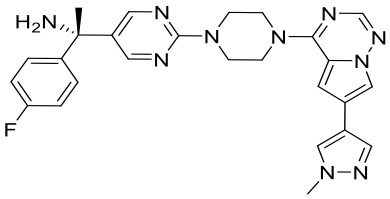
α-aminophosphonates (an organophosphorus isostere of α-Amino acids) have received significant attention

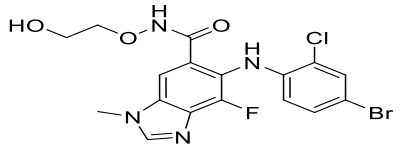
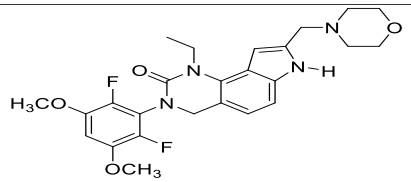
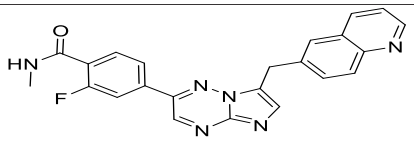
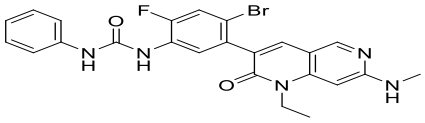
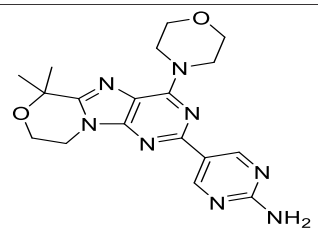
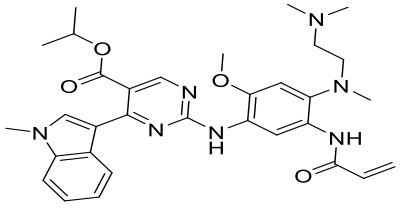
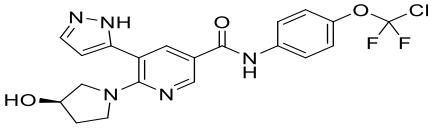
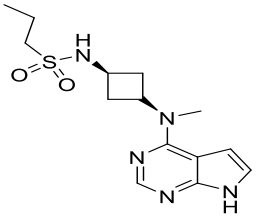
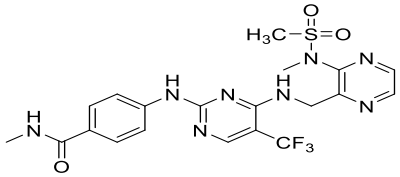
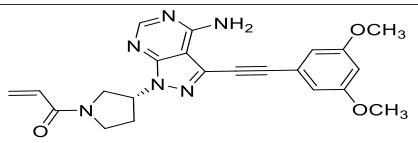
Table 1. Some breakthrough USFDA approved *N*-containing Kinase inhibitors[19-22]

S. No.	Name of Drug	Chemical Structure	Target	Clinical Indication	Year of US FDA approval
1	Imatinib		Bcr-Abl, c-KIT,PDGFR	Chronic Myelogenous Leukemia	2003
2	Gafitinib		EGFR	Non-small Cell Lung Cancer	2003
3	Erlotinib		EGFR	Non-small Cell Lung Cancer (NSCLC) and Pancreatic cancer	2004
4	Sorafenib		VEGFR2	Renal cancer and HCC	2005
5	Sunitinib		VEGFR, PDGFR	Renal Cancer	2006
6	Lapatinib		EGFR	Breast Cancer	2007
7	Dasatinib		ABL, PDGFR	CML	2007
8	Nilotinib		ABL, PDGFR	CML	2009
9	Vemurafenib		BRAF	Malignant Melanoma	2011
10	Vandetanib		VEGFR, EGFR	Thyroid Cancer	2011

11	Ruxolitinib		JAK2	Myelofibrosis	2011
12	Crizotinib		ALK, MET	NSCLC with Anaplastic Lymphoma Kinase (ALK) translocations	2011
13	Axitinib		VEGFR, PDGFR	Renal Cell Carcinoma	2012
14	Regorafenib		VEGFR2	CRC& GIST	2012
15	Pazopanib		VEGFR2, PDGFR and c-KIT	Renal Cell Carcinoma	2012
16	Tofacitinib		JAK3	Rheumatoid Arthritis	2012
17	Cabozantinib		VEGFR2, PDGFR	Medullary Thyroid Cancer	2012
18	Bosutinib		ABL	CML Resistant as well as CML Sensitive therapy	2012
19	Ponatinib		ABL	Resistant CML	2012
20	Afatinib		EGFR	NSCLC	2013

21	Dabrafenib		BRAF	m-Melanoma	2013
22	Trametinib		MEK	m-Melanoma	2013
23	Ibrutinib		BTK	Mantle Cell Lymphoma	2013
24	Ceritinib		ALK	NSCLC	2014
25	Idelalisib		PI3K δ	Chronic Lymphocytic Leukemia	2014
26	Nintedanib		VEGFR and PDGFR	Idiopathic Pulmonary Fibrosis	2014
27	Alectinib		ALK	NSCLC with ALK translocations	2014
28	Lenvatinib		VEGFRs	Thyroid Cancer (DTC)	2015
29	Osimertinib		EGFR	NSCLC	2015
30	Palbociclib		CDK4/6	Advanced Breast Cancer	2015
31	Brigatinib		EGFR	ALK-rearranged metastatic NSCLC	2017

32	Ribociclib		CDK4/6	Advanced (metastatic) Breast Cancer	2017
33	Duvelisib		PI3K δ/ γ	CLL	2018
34	Gilteritinib		FLT3, RTKs	Acute Myeloid Leukemia	2018
35	Erdafitinib		FGFRs	Advanced Metastatic Urothelial Carcinoma	2019
36	Alpelisib		PI3Kα	Breast Cancer	2019
37	Pexidartinib		CSF1R and c-KIT	Tenosynovial Giant Cell tumour	2019
38	Entrectinib		NTRK1/2/3	NSCLC	2019
39	Upadacitinib		JAK1	Rheumatoid Arthritis	2019
40	Avapritinib		Mutants KIT PDGFR	GIST	2020

41	Selumetinib		MEK1/2	Neurofibromatosis	2020
42	Pemigatinib		FGFR	Cholangiocarci-noma	2020
43	CapmatinibTabrecta		MET	NSCLC	2020
44	Ripretinib		KIT	Advanced GIST	2020
45	Paxalisib		PI3K/mTOR	Malignant Glioblastoma	2020
46	Mobocertinib		EGFR	NSCLC	2021
47	Asciminib		Bcr-ABL	CML	2021
48	Abrocitinib		JAK1	Atopic Dermatitis	2022
49	Defactinib		PTK2	Solid tumours	2022
50	Futibatinib		FGFR2	Cholangiocarci n-oma	2022

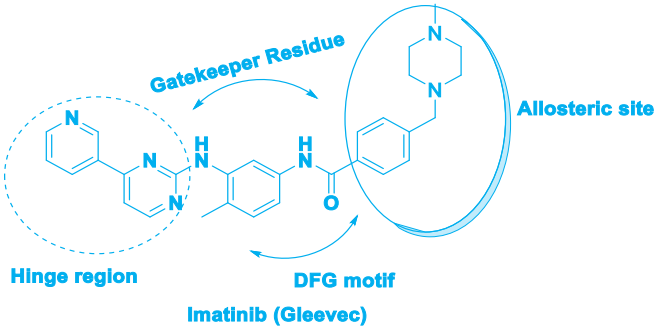


Figure 8: Binding sites of imatinib

in recent times among chemist and biologist owing to their broad range of biological activities[25-33] including significant reports of potent inhibitory activity against human tumors.[34-47] So appreciating these large number of anti-tumor activities reports we have also compiled a small collection of these class of organophosphorus containing molecules specifically reported as protein kinase inhibitors.[48]

Very recently Tiwari, S. V. *et al* reported[49] few novel pyridine-pyrimidine hybrid α-aminophosphonate as potential aurora kinase inhibitors, during explorations in bioactivity by using in vitro aurora kinase inhibitory activity and molecular docking studies. The results showed that these compoundsmentioned below at various IC_{50} concentrations demonstrated distinctive morphological changes such as cell detachment, cell wall deformation, cell shrinkage and reduced number of viable cells in cancer cell lines.

The structure-activity relationship (SAR) revealed that the above structures (a and b) shown in (Figure 9.) are the most promising compounds against selected cancer cell lines(A549, Hep-G2, HeLa, MCF-7 and HL-60).The normal cell line selected was the human normal hepatocyte cell line LO2. The VX-680, an aurora kinase inhibitor, was used as a standard drug for the in vitro anticancer evaluation. Compound (a) was found to be a potent aurora kinase inhibitor with an IC_{50} value of 42 nM and 22 nM against Aurora kinase A and Aurora kinase B, respectively.

The dimethyl ((4-nitrophenyl) (phenylamino)-methyl) phosphonate has shown the most selective inhibitor of cyclin dependent kinase 2 as it shows the lowest

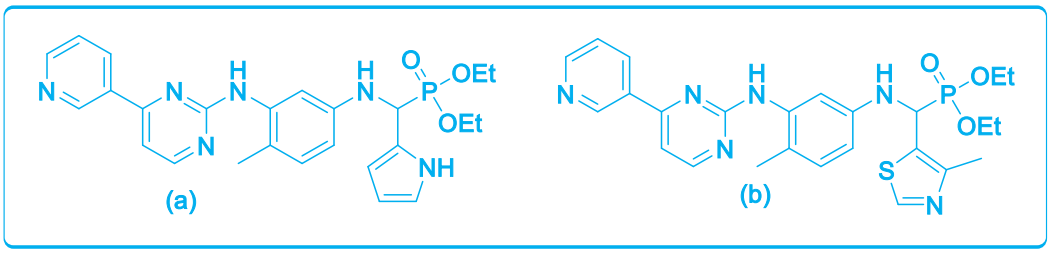


Fig.9: Pyridine-pyrimidine hybrid ?-aminophosphonate as potential aurora kinase inhibitors

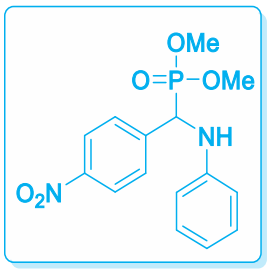


Fig.10.: Cyclin-Dependent Kinase 2 inhibitor aminophosphonate

docked energy in computer modeling and docking simulation of ligand bond complexes study (Autodock software version 1.5.6).[50] This research group have also emphasized the inhibitory phosphorylation sites has a stable number of inter molecular hydrogen bonds, which demonstrates that it has a greater affinity for CDK2 than others phsphonate analogs that act as catalytic site and can be effective to inhibition enzyme. (Figure 10.)

The anticancer activity of a series of novel α-aminophosphonate coupled with indole-2,3-dione moieties, namely thediethyl (substituted phenyl/ heteroaryl)(2-(2-oxoindolin-3ylidene)hydrazinyl)-methylphosphonate derivatives were evaluated in-vitro against six human cancer cell lines (MCF-7, IMR-32, SK-MEL-2, MG-63, HT-29 and Hep-G2) by using the SRB assay method and Adriamycin was used as positive control. All of them were found to be selective towards cancer cells since they did not exhibit cytotoxicity on normal tissuecells even at GI50> 250 μM. Evaluation of these synthesized amino phosphonate derivatives to know the binding interactions,it was observed that the methyl phosphonate derivatives have dual inhibition potential, inhibiting human tyrosine kinase (TRKS) and microtubules both.[51] (Fig 11.)

Various novel α-aminophosphonates were designed with imatinib intermideates[52] have showed better anticancer activity when compared with standard drugs Doxorubicin and Imatinib using MTT assay method. (Figure 12.)

The docking study suggests that the designed compounds occupy the ATP binding site of BCR-ABL tyrosine kinase (Glu286, Met318, Ile360, Ala380, Asp381), with good inhibitory constant (Ki) and with good free binding energy of -9.61 kcal/mole to -7.52kcal/mole. Few of above compounds

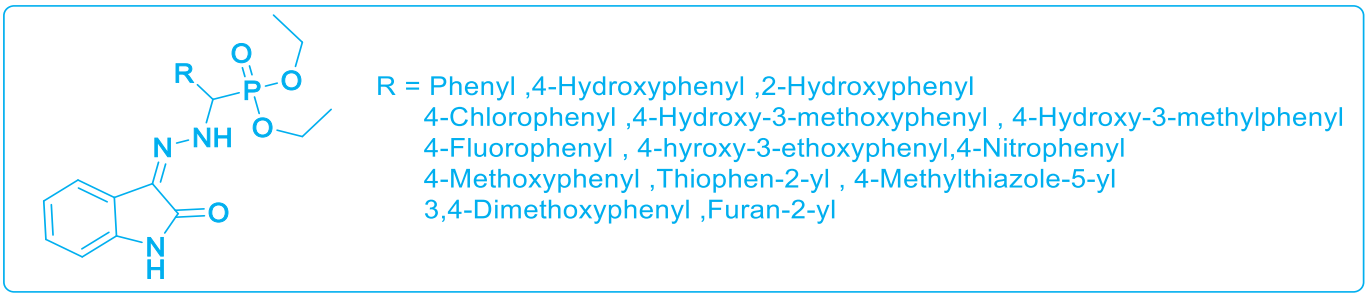


Fig 11: 2-Oxoindolin Phosphonates as human tyrosine kinase (TRKS) inhibitors

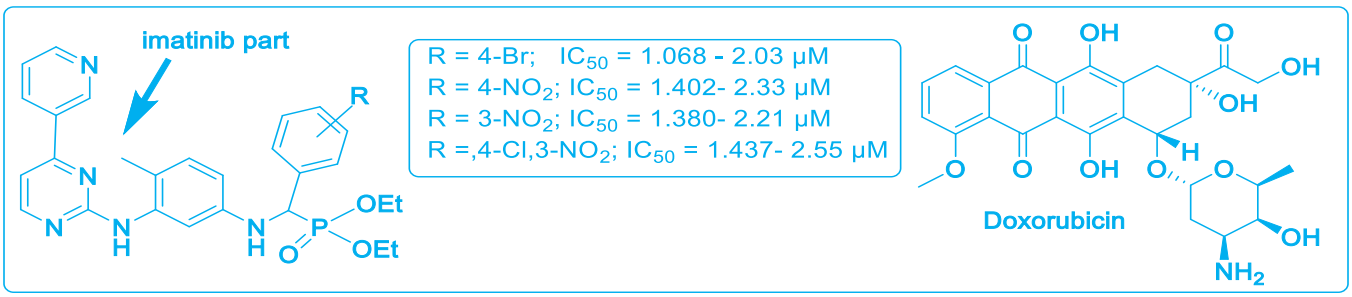


Fig. 12: α-aminophosphonatederivatives of Imatinib with improved cytotoxicity

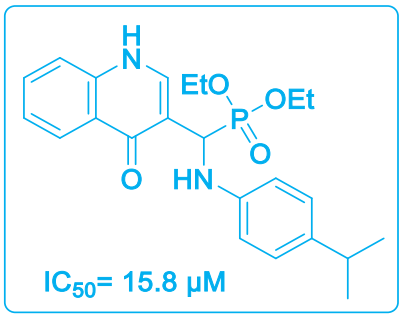


Fig.13: Chromene derivative of α-aminophosphonates

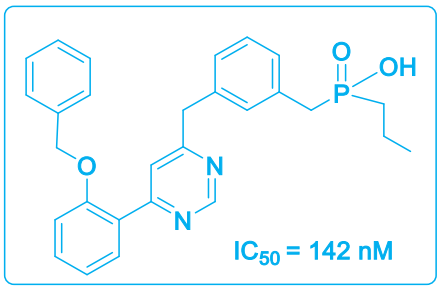


Fig. 14: Phosphinic acid CDK9/CycT1 inhibitors

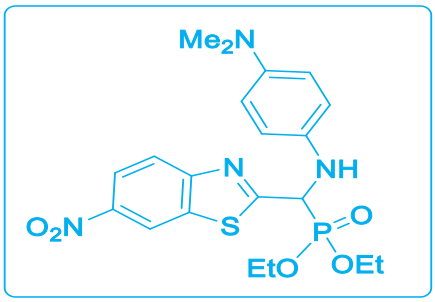


Fig. 15: α-Aminophosphonate containing thiazole as cyclin-dependent kinase 2 inhibitors

have established additional hydrogen bonding apart from Asp381 as in the case of imatinib itself may be the reason behind the improved potency in comparisonwith the standard drug Doxorubicin.

A series of novel chromene/aza-chromone fused α-aminophosphonate derivatives[53] were evaluated for their *c*-Src kinase inhibitory activity in comparison with Staurosporine and PP2 as positive controls. The best result was observed in (Figure 13.)

Docking and molecular dynamic results reveal phosphorylated Src tyrosine kinase protein are more effective results than unphosphorylated tyrosine Src kinase protein. Additionally, observation indicates that Leu273, Gly274 and Val281 from Glycine rich and P-loop region; Lys393 from activation loop and Ala293 from β3 of the *N*-terminal lobe could be considered as potential binding sites for *c*-Src kinase proteins.

Ne`meth, G. *et.al.* prepared[54] various analogs of phosphinates, phosphonates, and phosphonamides which are considered as bioisosteres of sulfonamide-based CDK9 inhibitors. The novel and selective phosphorus containing CDK9/CycT1 inhibitors phosphinic acid shown in (Figure 14.) was proved to be highly specific to CDK9/CycT1 a highly specific, ATP-competitive with antiviral activity which is observed slightly lower than the best CDK9 inhibitors in the literature. This suggests that this compound has the potential to control HIV-1 replication *in vivo* while having a lower risk of inhibiting other kinases and consequently causing undesired toxicity.

A series of 2-aminobenzothiazole combined α-aminophosphonates using sulfonic acid functionalized ionic liquid as recyclable catalyst were synthesized

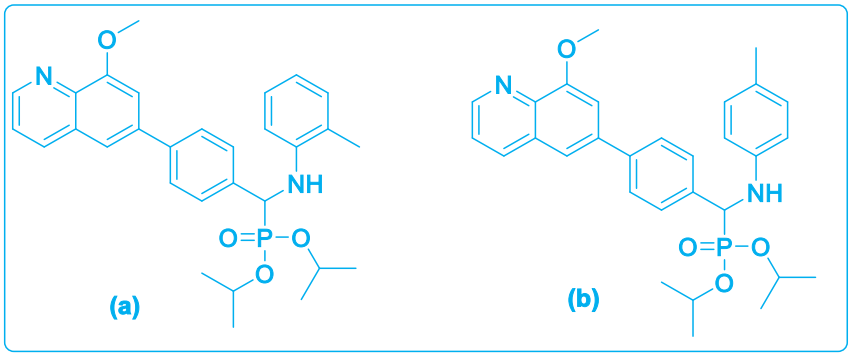


Fig. 16: Quinoline containing α-aminophosphonate moiety and methyl substituted aniline group

and their cyclin-dependent kinase-2 inhibitory activities together with the SAR studies were evaluated.[55] (Figure 15.)

The docking studies suggest the nitro group at 6th carbon position in benzothiazole skeleton and dimethyl amino group at 4-position in amine skeleton of the α-aminophosphonate has higher number of intermolecular hydrogen bonds, which indicates that it has higher affinity for CDK2 than others.

X.-F. Zhu *et al* published their research findings that α-aminophosphonate derivatives containing a quinoline moiety exhibited moderate to high antitumor activities against the tested cancer cell lines (Eca109 and Huh7 cells)by MTT assay and some demonstrated more potent inhibitory activities compared with the reference drug Sunitinib (Figure 16.) a well known potent multi targeted tyrosine kinase inhibitor with antitumor and antiangiogenic activity.[56]

The above phosphonate derivatives (a) and (b) containing methyl substituted aniline group were found to be more active than Sunitinib (IC_{50}= 16.54 - 5.27) against both of two cancer cell lines, with IC_{50} in the range of 2.26 mmol/L - 7.46mmol/L.

A series of structurally diversified N-substituted α-aminobisphosphonic acids (Bisphosphonates derv.) were screened for inhibitory activity against PPK1 and PPK2 enzymes[57] (Figure 17.). Polyphosphate kinases (PPK) are the major enzymes involved in the metabolism of inorganic polyphosphate (polyP), a polymer linked through high-energy phosphoanhydride bonds and abundantly present in cells. The importance of PPKs for virulence of numerous bacterial pathogens, such as mycobacterium tuberculosis, or pseudomonas aeruginosa, as well as the proven higher antibiotic susceptibility of PPK1 mutants of pathogens make these enzymes valuable molecular targets for antimicrobial chemotherapies. Additionally, Bisphosphonates are structural analogs of pyrophosphate, constitute a class of compounds with very high potential for the construction of effective inhibitors of enzymes operating on oligo- and polyphosphates.Burda-Grabowska *et. al.* reported that all of them decreased the activity of

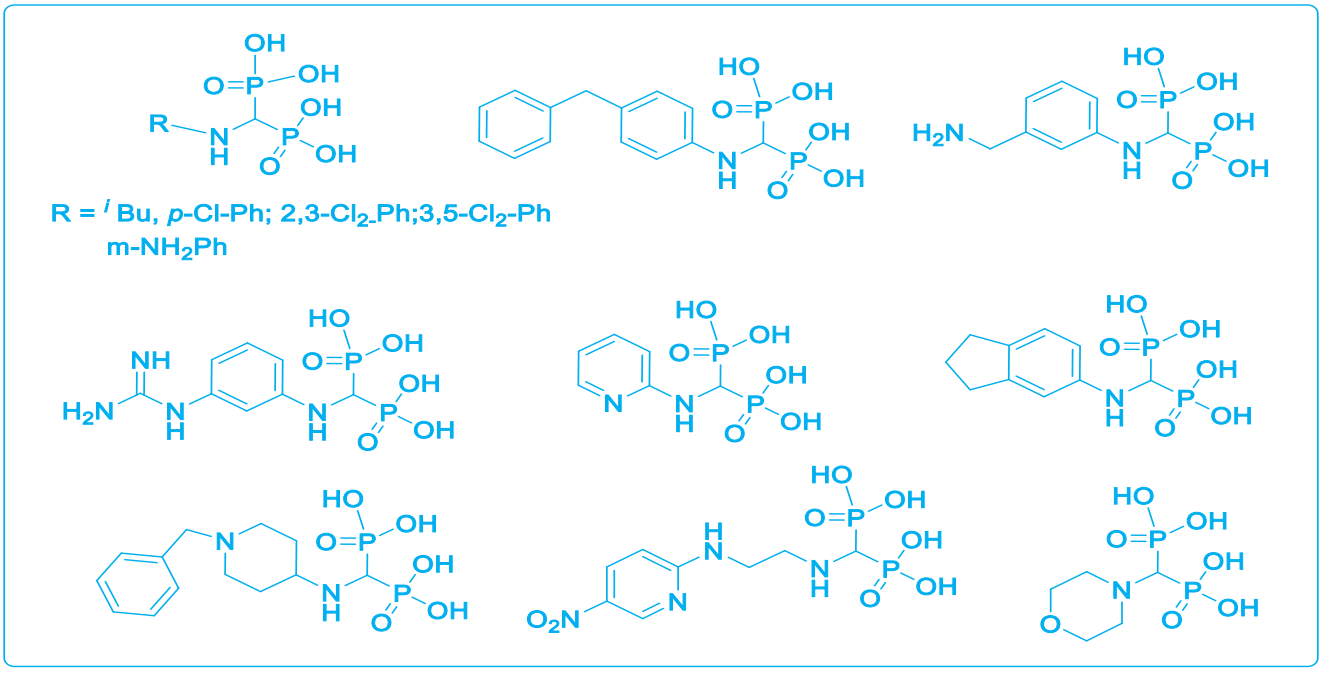


Fig 17: α-Aminobisphosphonic acids derivative as inhibitors of PPK2

PPK2, whereas only a few of them affected PPK1.

CONCLUSION

Due to the growing menace of cancer, it is highly desirable to delve into the molecular mechanism of cancer so as to design and develop molecules that could help fight this deadly disease. Targeting Protein kinases has shown a lot of promise in tackling this dreadful disease. It is pertinent that with progressive enrichment of medicinal chemist's toolbox by various experimental in-silico techniques a paradigm shift is bound to happen.Various research studies have established that number of isoforms of kinases are involved in the pathophysiology and epigenetic changes associated with cancer or other diseases. Therefore, it is need of the hour to come up with some of the potent kinase inhibitors by devising newer pharmacophores to manipulate the DFG motif present in the kinase cavity site and to either lock them in one of the 'in' or 'out' configurations.

Abbreviations:

PK- Protein Kinase; Bcr-Abl: Breakpoint Cluster Region-Abelson Proto-Oncogene; c-KIT: Receptor tyrosine Kinase;GIST: Gastrointestinal Stromal Tumors; PDGFR: Platelet Derived Growth Factor Receptor; EGFR: Endothelium Growth Factor Receptor; VEGFR: Vascular Endothelium Growth Factor Receptor; HCC: Hepatocellular Carcinoma; NSCLC: Non-small Cell Lung Cancer; CML: Chronic MyelogenousLeukemia; CRC: Colorectal Cancer; JAK3: Janus Kinase 3; BTK: Bruton's Tyrosine Kinase; ALK: Anaplastic Lymphoma Kinase; Lck:lymphocyte-specific protein tyrosine kinase; c-Src: Proto-oncogene tyrosine-protein kinase; PI3K: phosphoinositide 3-kinase; CDK: cyclin-dependent kinase; FLT3: fms-like tyrosine kinase 3; RTK: Receptor Tyrosine Kinase; FGFR: Fibroblast Growth Factor Receptor; CSF1R: Colony-Stimulating Factor-1 Receptor; NTRK: Neurotrophic tyrosine receptor kinase; MEK:Mitogen-activated extracellular signal-regulated kinase; mTOR: Mechanistic target of rapamycin; PTK: Papillary thyroid cancer; GI50: 50 % growth inhibition.

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