In Silico Study, Protein Kinase Inhibition and Molecular Docking Study of Benzimidazole Derivatives

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ABSTRACT: Kinase enzymes play an important role in cellular proliferation, and inhibition of their activity is a major goal of cancer therapy. Protein kinase inhibitors as benzimidazole derivatives can be applied for prevention or treatment of cancers through inhibition of cell proliferation. To evaluate their protein kinase inhibitory effects, as well as the *in silico* study for active benzimidazole derivatives. Benzimidazole derivatives has presented significant therapeutic potential against several disorders and known to have numerous biological activities (such as antibacterial, antiviral and anti-inflammatory). Benzimidazole derivatives have shown significant potential in the reduction of viral load as well as in enhancing immunity. To forecast absorption, distribution, metabolism, excretion and toxicity, simply known as ADMET and the Lipinski rule of five parameters of the examined substances, the admetSAR and Swiss ADME were used. The ADMET predictions revealed that the compounds had good and safe pharmacokinetic features, making them acceptable for further development as therapeutic candidates in clinical trials. This study primarily focused on blocking 2 key targets of kinase proteins (CDK4/CycD1 and Aurora B). 2-Phenylbenzimidazole has shown the greatest inhibitory potential (with a binding energy of −8.2 kcal/mol) against protein kinase inhibitors. This study results would pave the potential lead medication for anticancer therapeutic strategies.

KEYWORDS: Benzimidazole derivatives, *in silico* study, protein kinase and molecular docking

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Introduction

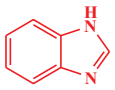
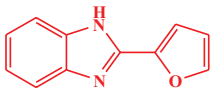
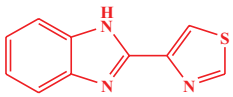
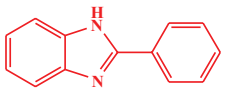
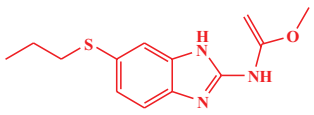
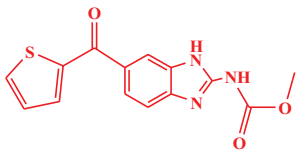
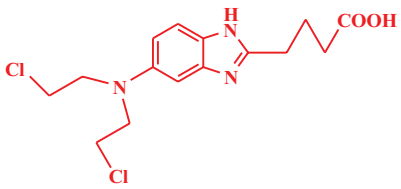
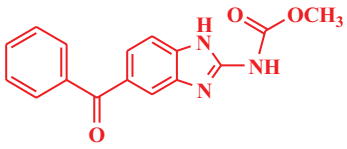
In the search for new anticancer drugs, several promising discoveries have been used for the class of benzimidazole drugs as potent anticancer agents.[1,2] Cancer is one of the leading causes of death worldwide in 2018, and it is estimated that by 2030, cancer mortality rate worldwide will rise up to 12 million annually.[3-7] February 4 was declared as the official world cancer day for creating the awareness of cancer and to encourage its prevention, detection and treatment.[8,9] Rising problem in this area of medicine has initiated intensive research with a goal to discover novel anticancer drugs including benzimidazole derivatives ones.[10-12]

In the phosphorylation processes, protein kinase enzymes play an important role in a specific protein substrate, through transfer of the terminal phosphate moiety of adenosine triphosphate (ATP) molecule. The genome of human body contains approximately 538 different protein kinases; they are classified into 3 different families based on their selectivity for protein substrates. To achieve phosphorylation process, a free hydroxyl moiety is required in the protein substrate, which is freely available in serine, threonine and tyrosine residues.[13-15] Accordingly, serine or threonine residues has a nature that it can identify and attach a phosphate group, on the contrary, tyrosine and histidine-specific protein kinases can phosphorylate a protein at a tyrosine or histidine moieties. Serine/threonine type including Aurora and CDKs kinases contributes in cell division through regulation of the mitotic progression signalling; deregulation of protein kinases is implicated in tumorigenesis.[16,17] Accordingly, one of the major things that is needed to be taken into account of the cancer treatment is depending completely on kinase inhibition. The development and isolation of natural kinase inhibitors has been predicted to be a major object of pharmaceutical growth with more than 135 kinase inhibitors described to be in either phase I or phase II clinical trials, most of these drugs being tested for their potential as anticancer agents.[18]

Benzimidazole bases are one of the most significant types of physiologically active ligands owing to the ease with which they can be synthesized and the high solubility with which they are soluble. They form stable complexes which is very important with numerous transition-metal ions. Because of the –NH groups in their structure, benzimidazole bases containing donor atoms (eg, N, O) plays a crucial part in the transformation mechanism of various processes in biological systems.[19]

Heterocyclic nitrogen-containing ligand has numerous applications based on their structural diversity and much useful in the pharmaceutical field. Benzimidazole containing compounds are a class of compounds that often exhibit anti-inflammatory, antifungal, antibacterial, antioxidant and antitumor activity. A variety of different transition-metal complex

Table 1. List of selected benzimidazole derivatives for docking analysis.

S. NO	COMPOUNDS	PUBCHEM CID	STRUCTURE	REFERENCE
1.	1H-benzimidazole	5798		24
2.	Fuberidazole	19756		25
3.	Thiabendazole	5430		26
4.	2-Phenylbenzimidazole	12855		27
5.	Albendazole	2082		28
6.	Nocodazole	4122		29
7.	N-desmethyl-bendamustine	24882536		30
8.	Mebendazole	4030		28

with benzimidazole ligands have been reported in medicinal applications as reported by various researchers.[20,21]

Benzimidazole derivatives are considered one of the best known anticancer drugs owing to their high potential role as radical scavengers, strong antioxidants, chemopreventive and chemotherapeutic drugs in various types of tumour.

Materials and Methods

Ligand preparation

This study has incorporated benzimidazole derivatives compounds which have been proven for their significant antiviral potential (Table 1). Their 3-dimensional (3D) structure was downloaded from PubChem database and used for assessing their inhibitory potential against protein kinase inhibitors[22,23] and standard drug abiraterone acetate (Figure 1B).

Protein preparation

The crystallographic structures of CDK4/CycD1 and Aurora B (Figure 1) were obtained from Protein Data Bank (PDB ID: 2W96 with resolution 2.3 Å and 4C2V with resolution 1.49 Å, respectively). Structures of selected targets were downloaded from RCSB database (www.rcsb.org).[31] Subsequently, structure of targets was optimized with BIOVIA Discovery studio and finalized for docking studies using AutoDock Tool.

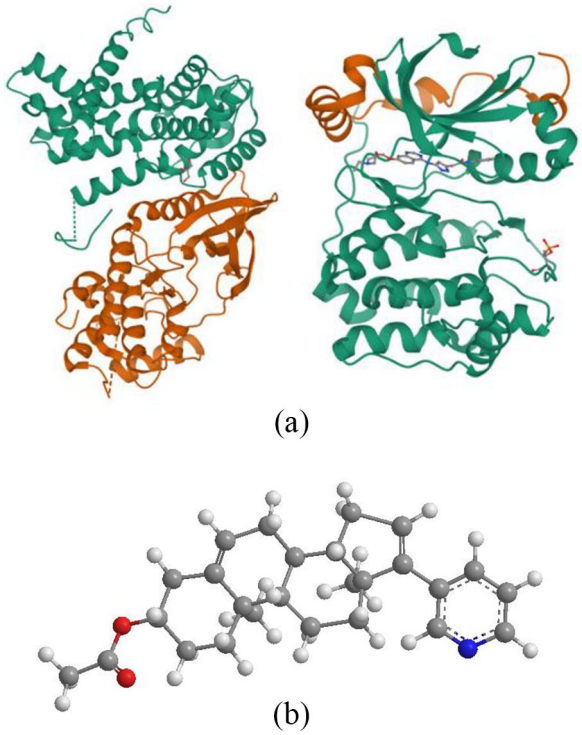


Figure 1. (A) 3D structure of protein. (B) Standard drug (abiraterone acetate).

Drug-likeliness filters

We have selected 4 specific filters including Lipinski (Pfizer) Filter, Ghose Filter, Veber Filter, Egan (Pharmacia) Filter and Muegge (Bayer) Filter for the elucidation of drug-likeliness criteria of benzimidazole derivatives (http://www.swissadme.ch/).[32]

ADMET properties

admetSAR was used to investigate the benzimidazole derivatives physicochemical and ADMET characteristics (http://lmmd.ecust.edu.cn/admetsar1). In this study, several factors were such as Ames test, human intestinal absorption, blood-brain barrier and Caco-2 cell permeability.[33]

Docking (manual docking) analysis using AutoDock Vina software

Benzimidazole derivatives are having specific inhibitory potential, and these potential targets were evaluated by calculating binding energy obtained from AutoDock Vina as described.[34] Further ligand binding interaction was also identified using BIOVIA Discovery studio Tool and AutoDock Vina tool in the target protein. AutoDock Vina software was utilized in all the docking experiments, with the optimized model as the docking target. Potential antiviral drugs were shown by the effective relationship between molecules and receptor targets. Grid box (126 Å × 26 Å × 126 Å) centred at (152.179, 167.664, 166.985) Å.

Docking analysis using online server (PatchDock)

To further validate manual docking analysis, we have used an online server that can be freely accessed (http://bioinfo3d.cs.tau.ac.il/PatchDock/). PatchDock server is based on several algorithms such as geometry-based docking. Benzimidazole derivatives were docked with all different targets selected in this study.[34]

Results and Discussion

Drug-likeliness criteria for benzimidazole derivatives

An additional pharmacokinetic analysis was performed on a total of 8 substances. Tables 2 and 3 show the Lipinski Ro5 criteria for 1H-benzimidazole, fuberidazole, thiabendazole, 2-phenylbenzimidazole, albendazole, nocodazole, N-desmethyl-bendamustine, and mebendazole. Benzimidazole was showing excellent activity and determined to be in

Table 2. Analysis of the Lipinski Ro5 of the benzimidazole derivatives.

S. NO.	COMPOUND	MOLECULAR WEIGHT (≤500 G/MOL)	HYDROGEN BOND ACCEPTORS (≤10)	HYDROGEN BOND DONORS (≤5)	TOPOLOGICAL POLAR SURFACE AREA (≤140 Å)	ROTATABLE BONDS (<10)	LOG P (≤5)
1.	1H-benzimidazole	118.05	2	1	28.68	0	1.319
2.	Fuberidazole	184.06	3	1	41.82	1	2.58
3.	Thiabendazole	201.04	3	1	41.57	1	2.26
4.	2-Phenylbenzimidazole	194.08	2	1	28.68	1	3.339
5.	Albendazole	263.11	4	1	50.27	5	3.543
6.	Nocodazole	301.05	6	2	87.31	4	2.496
7.	N-Desmethyl-bendamustine	343.09	5	2	69.22	9	2.448
8.	Mebendazole	295.1	6	2	87.31	4	2.612

Table 3. Screening of benzimidazole derivatives using several drug-likeliness filters.

COMPOUND	CANONICAL SMILE	LIPINSKI FILTER	GHOSE FILTER	VEBER FILTER	EGAN FILTER	MUEGGE FILTER	BIO AVAILABILITY SCORE
1.	C12=CC=CC=C1NC=N2	Yes	No (n=3)	Yes	Yes	No (n=1)	0.55
2.	C12=CC=CC=C1NC(C3=CC=CO3)=N2	Yes	Yes	Yes	Yes	No (n=1)	0.55
3.	C12=CC=CC=C1NC(C3=CSC=N3)=N2	Yes	Yes	Yes	Yes	Yes	0.55
4.	C12=CC=CC=C1NC(C3=CC=CC=C3)=N2	Yes	Yes	Yes	Yes	No (n=1)	0.55
5.	CCCSC1=CC=C(N=C(NC(OC)=C)N2) C2=C1	Yes	Yes	Yes	Yes	Yes	0.55
6.	O=C(C3=CC=CS3) C1=CC=C(N=C(NC(OC)=O)N2)C2=C1	Yes	Yes	Yes	Yes	Yes	0.55
7.	ClCCN(CCCl) C1=CC=C2C(N=C(CCCC(O)=O)N2)=C1	Yes	Yes	Yes	Yes	Yes	0.55
8.	O=C(C3=CC=CC=C3) C1=CC=C2C(N=C(NC(OC)=O)N2)=C1	Yes	Yes	Yes	Yes	Yes	0.55

violation of 5 of the 6 criteria, indicating that the medicine would pave new strategy improvement in terms of drug delivery systems.

The drug-likeliness criteria of benzimidazole derivatives were assessed using 5 different filters (Lipinski, Ghose, Veber, Muegge and Egan). Apigenin has complied with all drug-likeliness criteria (Table 4). 1H-benzimidazole, on the contrary, has 3 violations and fuberidazole; 2-phenylbenzimidazole has 1 violation out of the 8 compounds (Table 4).

ADMET prediction

Table 4 shows the ADMET profiles of benzimidazole derivatives bioactive chemicals. Due to their strong binding affinity with the target proteins, the putative immunomodulatory chemicals in benzimidazole derivatives were anticipated to have excellent in vitro activity. In vivo and in clinical settings, the binding free energy value, when paired with the ADMET profile, might to useful in predicting the safety and effectiveness of benzimidazole derivatives bioactive compounds.

All 7 compounds had a high rate of intestinal absorption in humans, indicating that they are highly absorbed and may be ingested. The medications distribution was described using the permeability of the blood-brain barrier and their subcellular localization. The high permeability property of the ligands enables it to permeate and spread throughout the brain owing to the blood-brain barriers. The ability of the compounds to spread and permeate at the subcellular level was predicted by their subcellular location. Because none of the substances were CYP2D6 substrates, they were poorly metabolized in the body. On the other side, the human metabolism has the ability to vary a drug's efficacy in the body. The toxicity parameters are hepatotoxicity and acute oral toxicity. Acute oral toxicity is a proxy for the maximal dosage of the researched substances that the body can tolerate, whereas hepatotoxicity is a proxy for organ toxicity.

Analysis of the inhibitory potential of benzimidazole derivatives with standard drug abiraterone acetate

Cancer is a severe threat (to health and wealth) over the world; there is no effective treatment has yet been discovered. Benzimidazole compounds are used in the treatment of a wide range of ailments, such as with cancer, neurological disorders, gastrointestinal issues, and other inflammatory diseases. As a result, simulation studies have been performed to take advantage of the potential of benzimidazole compounds and in silico methods for obtaining a potent drug molecule that can help not only to prevent the anticancer but also boost the body's immunity. For the identification of therapeutic targets and inhibitors, in silico approaches provide a safe and cost-effective solution.

Aurora B is a chromosomal passenger protein that is associated with the centromeres in the early stages of mitosis, later localizes to the spindle midzone and the midbody of mitosis cells. It plays a role in chromosome condensation and cytokinesis. The docked compounds 1 and 7, which had the most active inhibitory impact on the chosen kinase with both Aurora B and CDK4/CycD1, were promising and genuine prospective binding mechanisms, similar to the co-crystalline ligands. Our findings indicated that among the benzimidazole compounds tested, 2-phenylbenzimidazole showed the highest binding efficacy against protein kinase targets (Table 5 and Figures 2 to 9). The phenyl form of benzimidazole is represented by ligand (2-phenylbenzimidazole and mebendazole). It has a high binding affinity (−8.2 kcal/mol), and it bind to 2W96 and 4C2V via the free phenyl, as shown in Figures 2 and 3. In phenyl ring

Table 4. Selected pharmacokinetic parameters after ADMET prediction.

MODE	1H-BENZIMIDAZOLE	FUBERIDAZOLE	THIABENDAZOLE	2-PHENYLBENZIMIDAZOLE	ALBENDAZOLE	NOCODAZOLE	N-DESMETHYL-BENDAMUSTINE	MEBENDAZOLE
Human intestinal absorption	0.009	0.006	0.005	0.004	0.848	0.131	0.006	0.01
Caco-2 permeability	−4.276	−4.692	−4.854	−4.71	−4.762	−4.415	−5.497	−4.531
Blood-brain barrier penetration	0.864	0.882	0.617	0.868	0.776	0.256	0.058	0.916
Plasma protein binding	65.74%	95.75%	91.98%	97.53%	58.20%	88.90%	97.96%	90.46%
Volume distribution	1.488	1.767	0.619	1.08	1.393	0.607	0.301	0.603
CYP1A2 inhibitor	0.983	0.99	0.998	0.997	0.984	0.977	0.327	0.97
CYP1A2 substrate	0.413	0.773	0.935	0.603	0.949	0.978	0.918	0.971
CYP2C19 inhibitor	0.532	0.857	0.454	0.885	0.296	0.689	0.146	0.619
CYP2C19 substrate	0.399	0.069	0.101	0.065	0.578	0.055	0.059	0.054
CYP2C9 inhibitor	0.061	0.13	0.159	0.486	0.095	0.642	0.129	0.754
CYP2C9 substrate	0.841	0.343	0.673	0.357	0.317	0.042	0.375	0.037
CYP2D6 inhibitor	0.684	0.395	0.752	0.266	0.632	0.395	0.218	0.37
CYP2D6 substrate	0.202	0.246	0.194	0.167	0.785	0.014	0.198	0.009
CYP3A4 inhibitor	0.267	0.196	0.136	0.092	0.294	0.67	0.055	0.491
CYP3A4 substrate	0.266	0.246	0.339	0.249	0.51	0.838	0.146	0.824
Clearance	11.63	6.968	6.809	6.113	6.182	2.743	3.218	3.016
Human hepatotoxicity	0.249	0.355	0.813	0.316	0.787	0.995	0.974	0.993
Drug-induced liver Injury	0.723	0.596	0.953	0.641	0.963	0.979	0.947	0.981
AMES toxicity	0.224	0.233	0.434	0.821	0.249	0.982	0.591	0.967

Table 5. List of compounds with binding interaction parameter, ie, binding energy with the PDB: 2W96 and 4C2V of Protein Kinase Inhibition (AutoDock Vina).

S. NO.	COMPOUND	BINDING ENERGY (KCAL/MOL)	
		2W96 (KCAL/MOL)	4C2V (KCAL/MOL)
1.	1H-benzimidazole	–5.2	–5.7
2.	Fuberidazole	–6.8	–7.3
3.	Thiabendazole	–6.4	–7.0
4.	2-Phenylbenzimidazole	–7.2	–8.2
5.	Albendazole	–7.0	–6.9
6.	Nocodazole	–7.5	–8.1
7.	N-Desmethyl-bendamustine	–6.7	–7.5
8.	Mebendazole	–8.2	–7.7
9.	Abiraterone acetate (standard drug)	–8.4	–10.9

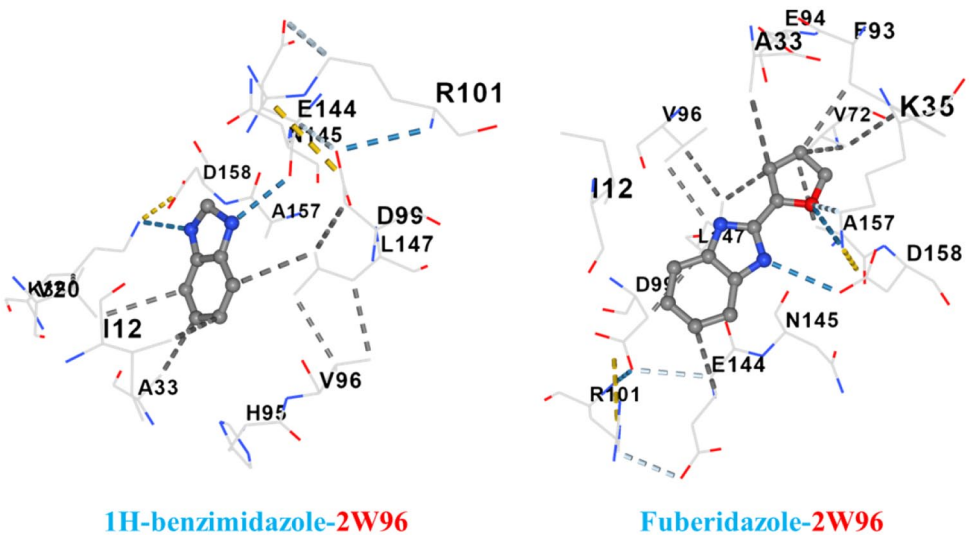


Figure 2. Docking analysis of 1H-benzimidazole and fuberidazole with (2W96) targets of protein kinase inhibition.

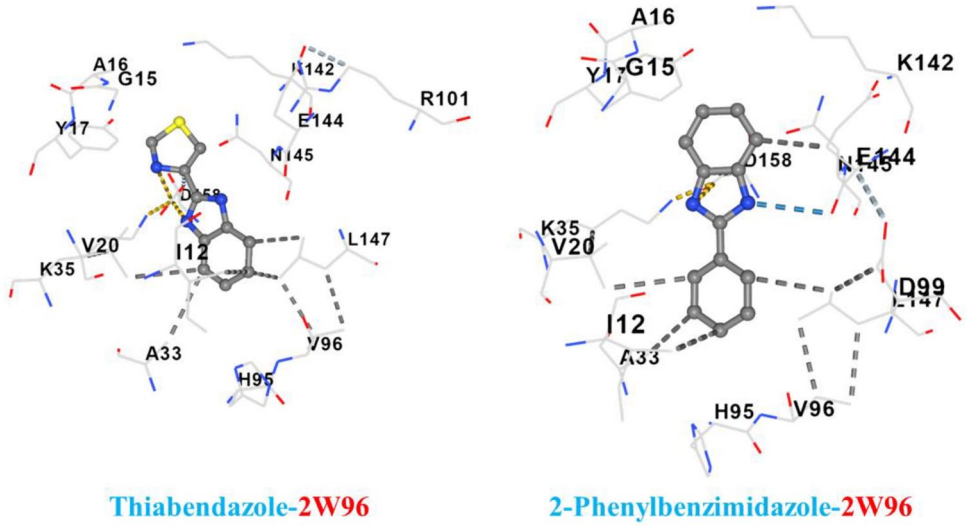


Figure 3. Docking analysis of thiabendazole and 2-phenylbenzimidazole with (2W96) targets of protein kinase inhibition.

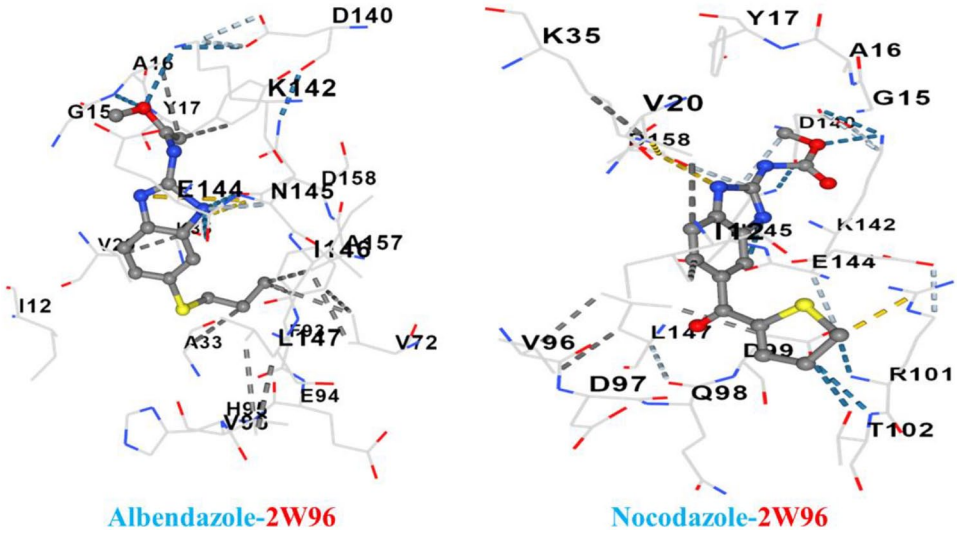


Figure 4. Docking analysis of albendazole and nocodazole with (2W96) targets of protein kinase inhibition.

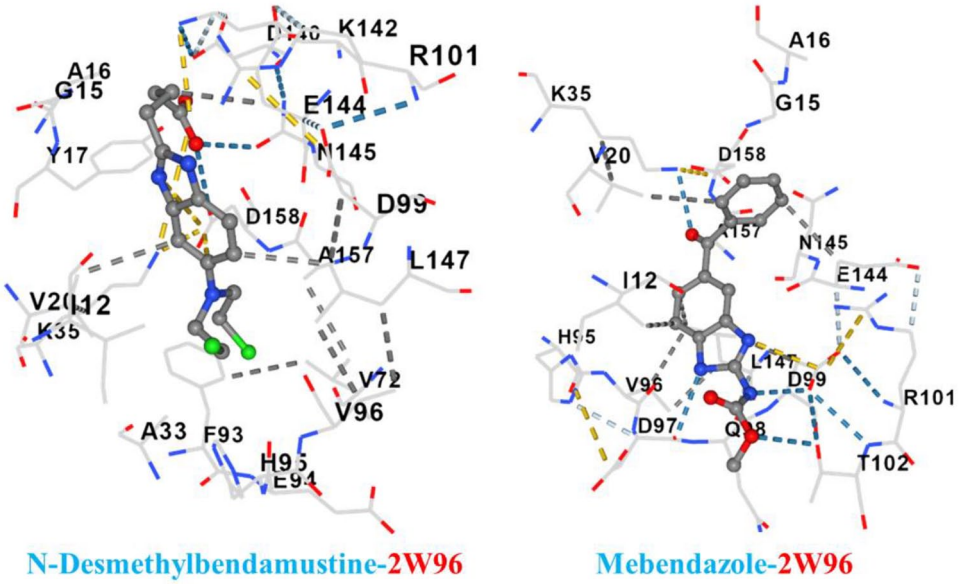


Figure 5. Docking analysis of N-desmethyl-bendamustine and mebendazole with (2W96) targets of protein kinase inhibition.

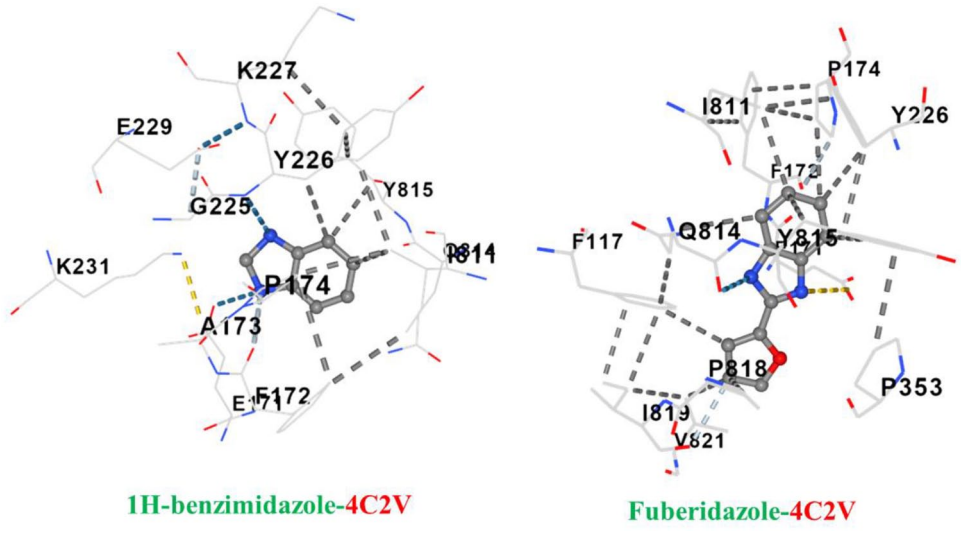


Figure 6. Docking analysis of 1H-benzimidazole and fuberidazole with (4C2V) targets of protein kinase inhibition.

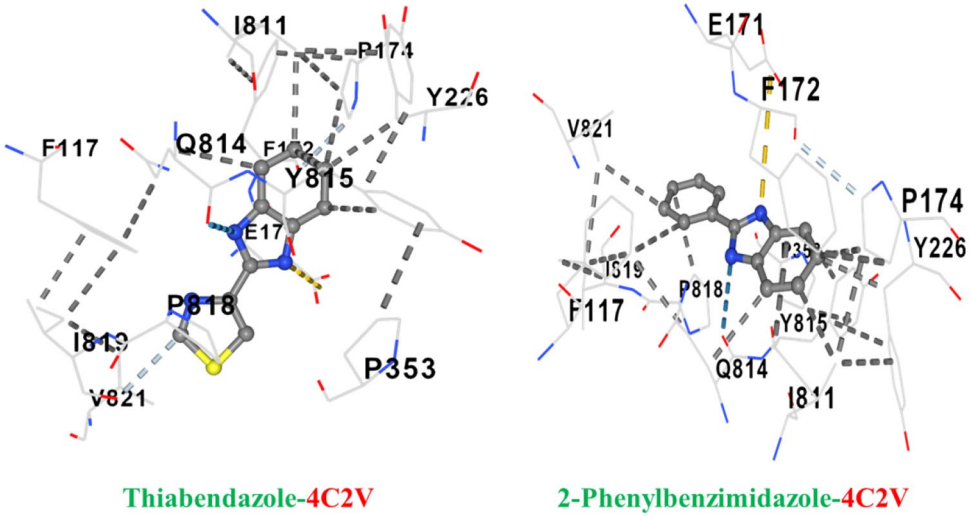


Figure 7. Docking analysis of thiabendazole and 2-phenylbenzimidazole with (4C2V) targets of protein kinase inhibition.

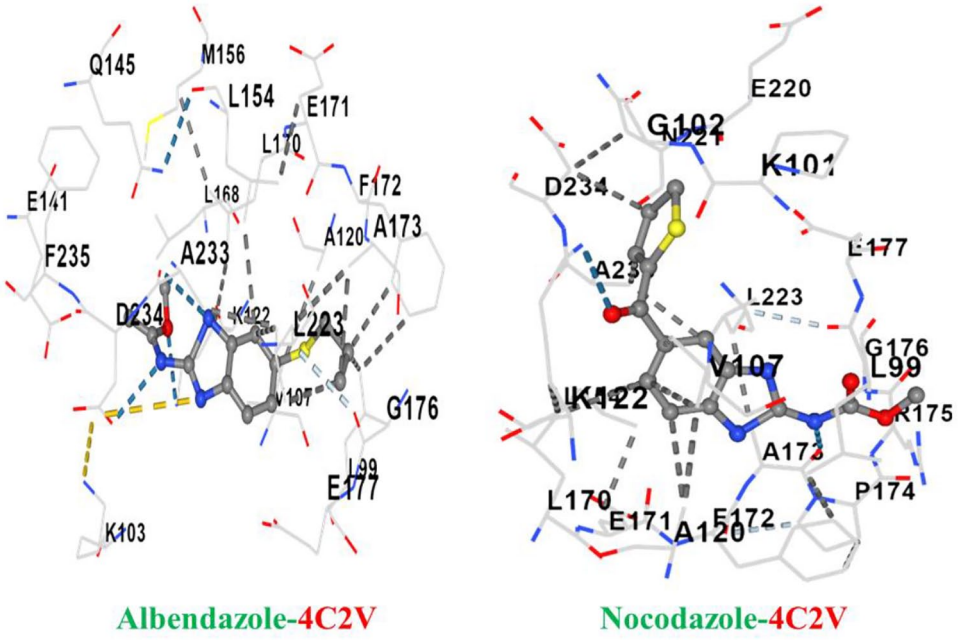


Figure 8. Docking analysis of albendazole and nocodazole with (4C2V) targets of protein kinase inhibition.

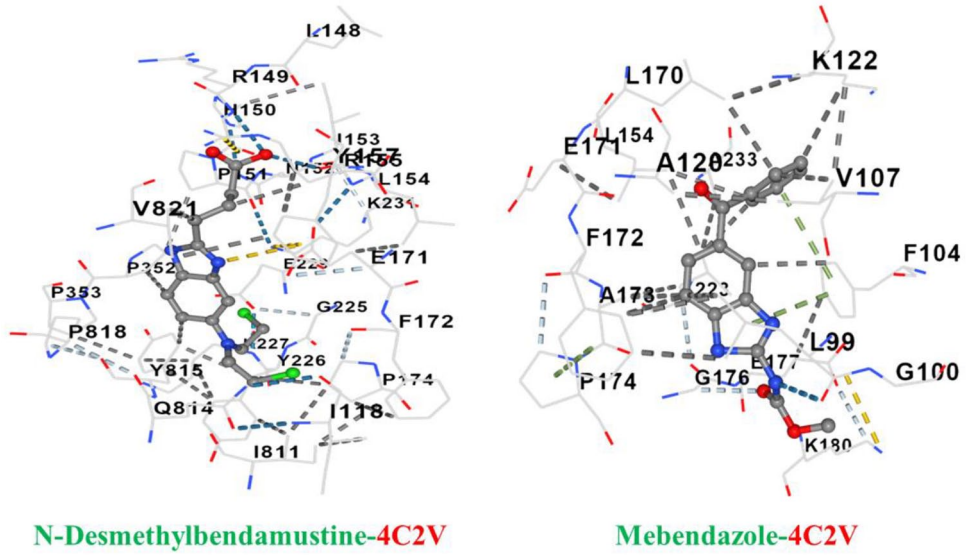


Figure 9. Docking analysis of N-desmethyl-bendamustine and mebendazole with (4C2V) targets of protein kinase inhibition.

Table 6. Binding interaction of different benzimidazole derivatives with the active site of kinase protein (PDB: 2W96) (AutoDock Vina) and (PDB: 4C2V) (AutoDock Vina)..

S. NO.	COMPOUND	ACTIVE SITE 2W96
1.	1H-benzimidazole	Chain A: ILE12 VAL20 ALA33 LYS35 HIS95 VAL96 ASP99 ARG101 GLU144 ASN145 LEU147 ALA157 ASP158
2.	Fuberidazole	Chain A: ILE12 ALA33 LYS35 VAL72 PHE93 GLU94 VAL96 ASP99 ARG101 GLU144 ASN145 LEU147 ALA157 ASP158
3.	Thiabendazole	Chain A: ILE12 GLY15 ALA16 TYR17 VAL20 ALA33 LYS35 HIS95 VAL96 ARG101 LYS142 GLU144 ASN145 LEU147 ASP158
4.	2-Phenylbenzimidazole	Chain A: ILE12 GLY15 ALA16 TYR17 VAL20 ALA33 LYS35 HIS95 VAL96 ASP99 LYS142 GLU144 ASN145 LEU147 ASP158
5.	Albendazole	Chain A: ILE12 GLY15 ALA16 TYR17 VAL20 ALA33 LYS35 VAL72 PHE93 GLU94 HIS95 VAL96 ASP140 LYS142 GLU144 ASN145 ILE146 LEU147 ALA157 ASP158
6.	Nocodazole	Chain A: ILE12 GLY15 ALA16 TYR17 VAL20 LYS35 VAL96 ASP97 GLN98 ASP99 ARG101 THR102 ASP140 LYS142 GLU144 ASN145 LEU147 ASP158
7.	N-Desmethyl-bendamustine	Chain A: ILE12 GLY15 ALA16 TYR17 VAL20 ALA33 LYS35 VAL72 PHE93 GLU94 HIS95 VAL96 ASP99 ARG101 ASP140 LYS142 GLU144 ASN145 LEU147 ALA157 ASP158
8.	Mebendazole	Chain A: ILE12 GLY15 ALA16 VAL20 LYS35 HIS95 VAL96 ASP97 GLN98 ASP99 ARG101 THR102 GLU144 ASN145 LEU147 ALA157 ASP158
S. NO	COMPOUND	ACTIVE SITE 4C2V
1.	1H-benzimidazole	Chain A: GLU171 PHE172 ALA173 PRO174 GLY225 TYR226 LYS227 GLU229 LYS231 Chain D: ILE811 GLN814 TYR815
2.	Fuberidazole	Chain A: PHE117 GLU171 PHE172 PRO174 TYR226 PRO353 Chain D: ILE811 GLN814 TYR815 PRO818 ILE819 VAL821
3.	Thiabendazole	Chain A: PHE117 GLU171 PHE172 PRO174 TYR226 PRO353 Chain D: ILE811 GLN814 TYR815 PRO818 ILE819 VAL821
4.	2-Phenylbenzimidazole	Chain A: PHE117 GLU171 PHE172 PRO174 TYR226 PRO353 Chain D: ILE811 GLN814 TYR815 PRO818 ILE819 VAL821
5.	Albendazole	Chain A: LEU99 LYS103 VAL107 ALA120 LYS122 GLU141 GLN145 LEU154 MET156 LEU168 LEU170 GLU171 PHE172 ALA173 GLY176 GLU177 LEU223 ALA233 ASP234 PHE235
6.	Nocodazole	Chain A: LEU99 LYS101 GLY102 VAL107 ALA120 LYS122 LEU154 LEU170 GLU171 PHE172 ALA173 PRO174 ARG175 GLY176 GLU177 GLU220 ASN221 LEU223 ALA233 ASP234
7.	N-Desmethyl-bendamustine	Chain B: ILE118 LEU148 ARG149 HIS150 PRO151 ASN152 ILE153 LEU154 ARG155 TYR157 GLU171 PHE172 PRO174 GLY225 TYR226 LYS227 GLU229 LYS231 PRO352 PRO353 Chain C: ILE811 GLN814 TYR815 PRO818 VAL821
8.	Mebendazole	Chain A: LEU99 GLY100 LYS101 VAL107 ALA120 LYS122 GLU141 GLN145 LEU154 MET156 LEU168 LEU170 GLU171 PHE172 ALA173 GLY176 GLU177 LEU223 ALA233 ASP234 PHE235

feud compounds, 2 distinct sites of protein kinase interaction have the greatest binding affinity.

Evaluation of docking result by patch docking

PatchDock has been used to accomplish docking interpretation to confirm the AutoDock docking outcomes. Table 6 Binding interaction of different benzimidazole derivatives with the active site of kinase protein. Whereas Table 7 shows the validation of online docking ligand and targets in protein kinase inhibition.

The superior efficacy of fuberidazole over the other 8 benzimidazole compounds was validated by the PatchDock. Fuberidazole showed that significant ligand-receptor interaction with the greatest possible atomic constant energy (ACE) value and patch dock score in correlation to other benzimidazole compounds and selected drug (abiraterone acetate).

Conclusions

In a summary, all simulation studies on both proteins lead to the conclusion that benzimidazole derivatives have the unique potential to inhibit the kinase proteins due to their high

Table 7. Validation of manual docking results using online docking software PatchDock.

S. NO.	COMPOUND	TARGETS IN PROTEIN KINASE INHIBITION			
		2W96		4C2V	
		SCORE	ACE VALUE	SCORE	ACE VALUE
1.	1H-benzimidazole	2558	−92.63	2592	−103.78
2.	Fuberidazole	3442	−47.50	3202	−143.25
3.	Thiabendazole	3232	−139.09	3328	−189.63
4.	2-Phenylbenzimidazole	3770	−85.19	3450	−167.67
5.	Albendazole	4396	−116.83	3950	−202.58
6.	Nocodazole	4450	−150.64	4372	−256.03
7.	N-Desmethyl-bendamustine	4898	−95.27	4710	−148.08
8.	Mebendazole	4626	−99.3	4416	−190.48

affinity with all the targeted proteins. When compared with previous studies, this study discovered that the benzimidazole derivatives compounds have a significantly higher binding free energy to all of the targeted proteins. The Lipinski Ro5 analysis demonstrates that majority of the compounds comply with the criteria and are predicted to be active when administered orally as drugs. The ADMET prediction of the compounds indicates that the ligands have favourable pharmacokinetic properties, implying that they have the potential to be developed as drugs. Hence, benzimidazole derivatives compounds have the potential to treat protein kinase inhibition because of having immunomodulatory effects and suppressing the cytokine storm, and they have the potential to be developed as drugs because of their good and safe ADMET profile. Prevalence of cancer has been raised to an alarming state, and CDKs have been studied extensively as a target for antitumor and anticancer therapy due to their significant roles in cell-cycle. Abnormal expression of CDKs may cause inappropriate regulation of cell cycle, which may provoke the cellular hyperproliferation in lung carcinoma, melanoma, osteosarcoma, ovarian carcinoma, pancreatic carcinoma, and carcinoma.

Author Contributions

K.A. and E.A.J. did the experimental part and designed the work and the Corresponding author, K.K. who is the research team supervisor compiled and corrected the full length article.

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