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Evaluation of Some Benzimidazole Derivatives as Hepatitis B&C Protease Inhibitors: Computational Study.

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ABSTRACT

Hepatitis is the inflammation of the liver caused by viral infection. It is classified as hepatitis A, B,C,D and E. The symptoms of hepatitis include, fatigue, flu, dark urine, abdominal pain, loss of appetite and most importantly yellow skin and eye. Hepatitis is the major public health problems and the cause of millions of deaths every year all over the world. The potency of some benzimidazole analogs as anti-Hepatitis B and C proteases was investigated. Herein six benzimidazole derivatives were docked with hepatitis B and C proteases with the view to determining the best inhibitor for the disease. The benzimidazole derivatives employed are Albendazole (1), Mebendazole (2), Thiabendazole (3), Flubendazole (4), Fenbendazole (5) and Triclabendazole (6). The computational study was done via density functional theory and molecular docking approaches. The density functional theory (DFT) reactivity descriptors were calculated for the six benzimidazole derivatives at B3LYP/6-311++G(d,p) level of theory so as to analyse the reactivity in vacuum and solvent phase. Proteins responsible for the diseases were downloaded from the protein data bank, cleaned using PyMOL-v1.7.4.4-Win 32 and docked with the ligands with Autodock tool 1.5.6. Flubndazole, Fenbendazole and Triclabendazole are the best inhibitor benzimidazole derivatives for Hepatitis B protease and they have equal potency for curing Hepatitis B, while Flubendazole showed the highest inhibition for Hepatitis C protease.

Keywords: Spartan 14, DFT, Molecular Docking, Binding affinity, Amino-acid residue, Hepatitis B virus (HBV) and Hepatitis C virus (HCV).

Introduction

Hepatitis disease is a viral disease which causes inflammatory of the liver. Apart from the viral infection another cause of hepatitis is as a result of medications, drugs, toxin and alcohol consumption and the disease could also be due to the formation of antibodies against the liver tissue.[1,2] Hepatitis B infection is prevalent in the Western Pacific and African regions of the world with less infections in the Eastern Mediterranean, South East Asia, European and the Americas.[3-6] However, the good news is that hepatitis can be controlled through immunization and life style precautions.[7-9] Prominent among the viral disease are hepatitis A, B, C, D and E. Hepatitis A is most commonly transmitted by consuming food or water contaminated by faeces from an infected person. Hepatitis B and C are disseminated mainly through contact with infectious body fluid. Hepatitis D being a serious liver disease is contracted through direct contact with infected blood while Hepatitis E is a waterborne disease and it is commonly found in areas with poor sanitations. Symptoms of hepatitis includes- fatigue, flu-like symptoms, dark urine, pale stool, abdominal pain, loss of appetite, weight loss, yellow skin and eyes. Hepatitis is diagnosed mainly by liver function test and liver biopsy.
Hepatitis A causes short term illness hence it does not require treatment. However, Hepatitis A vaccines are available for children and adults.

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Hepatitis B is treated with antiviral medications for several months or years.[10-14] Antiviral medications are used for the treatment of acute and chronic form of hepatitis C and the use of antiviral drug therapies as been found to be effective.[15] However, cirrhosis of the liver which is caused by hepatitis C may lead to liver transplant for which there is no vaccination.[16,17] Furthermore, no antiviral medications exist for the treatment of hepatitis D as of today. However, alpha interferon drug can be used to treat hepatitis D with 25-30% effectiveness. Hepatitis D can be prevented by vaccination for hepatitis B simply because infection with hepatitis B is necessary for the growth of hepatitis D. Moreover, presently there are no medical therapies for the treatment of hepatitis E. Hepatitis A and E can be prevented by good hygiene while hepatitis B, C and D can possibly be prevented by avoiding contaminated blood. Moreover, vaccination can prevent the development of hepatitis A and B. However, research is on-going for the discovery of potent vaccines for hepatitis C. Chronic hepatitis B or C can lead to liver cancer called cirrhosis which can lead to liver transplant.[18-20]
Benzimidazole is a heterocyclic bicyclic aromatic organic compound consisting of the fusion of benzene and imidazole aromatic rings. They are among the most utilized ring systems for small molecule drugs. Benzimidazole drugs have a variety of therapeutic properties such as antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine and also found great application in cardiovascular disease, neurology, endocrinology and ophthalmology. It has been used to treat gastrointestinal parasites like roundworms, hookworms and tapeworms. Benzimidazole drugs have been reported to be useful in the treatment of hepatitis disease and the first report of the successful treatment of four patients with hydrated liver cysts was in 1977.[21] Mebendazole was introduced first, but albendazole eventually became the drug of choice owing to its superior absorption in the gastrointestestinal tract and better clinical results.[22]

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This study compares the potency of some benzimidazole derivatives as hepatitis B & C inhibitors by computational method. However, 1 FN-α, lamivudine and adefovir are among the few drugs used for the treatment of Hepatitis B.[23]The researchers herein investigated the potency of some benzimidazole analogs as potential anti-Hepatitis B and C drugs.

Materials and Methods

An lntel core i5 computer system with a random access memory of 8 GB was deployed in this research. Spartan 14 for quantum chemical calculations, Discovery studio 4.1, Autodock tool 1.5.6 and Autodock Vina 1.1.2 for docking and scoring evaluation and Pymol 1.7.4.4 for molecular visualization were utilized.

Protein structure
The protein molecules were downloaded from the protein data bank online and unwanted materials apart from the amino-acid components were removed.

Optimization of ligands
The ligands were optimized using Spartan 14 software. The molecular descriptors for the ligands (Figure 1) were obtained using DFT at B3LYP/6-311++G(d.p) level in vacuum and aqueous phase.

Molecular docking
The optimized ligands were docked into the active sites of the hepatitis protease in their PDBQT format using AutoDock tool with grid box center in the dimensions, X= -22.233, Y= 26.468, Z= 72.634) with box size X= 56, Y= 46, Z= 40 and spacing was maintained at 1.00Å.

Analysis of docked results
The ligand-receptor interaction with the lowest binding affinity was used to select the best docked ligand model. The binding interactions were visualized at the Discovery studio. The bonds exhibited are the conventional hydrogen bond, van der Waals, carbon-hydrogen bond, pi-alkyl, pi-sigma, pi-pi, pi-anion and pi-donor hydrogen bond.

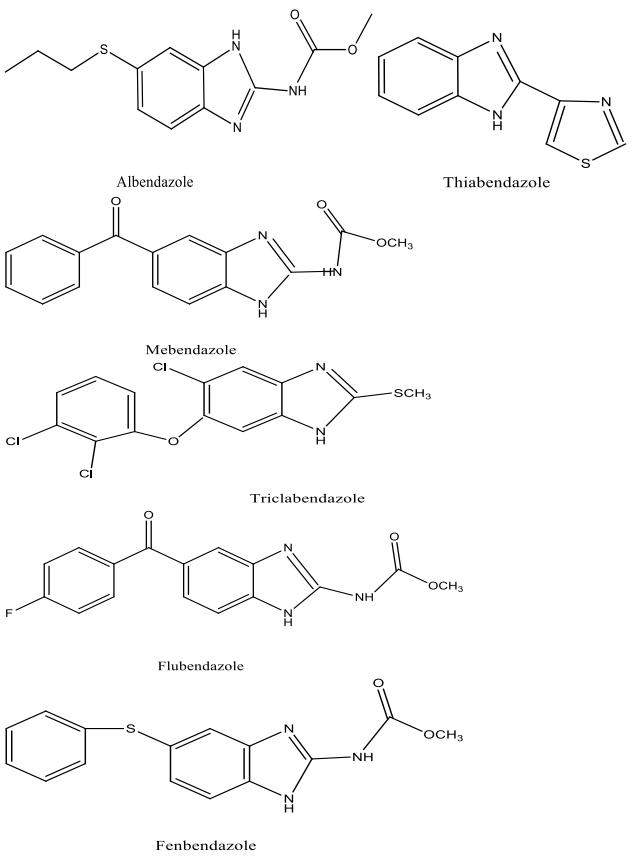

Figure 1: Structures of Ligands

Results and Discussion

Hepatitis B Virus is a spherical shaped 42 nm diameter double-shelled structure composed of a lipid envelope containing HBsAg which engulfs an inner nucleocapsid composed of hepatitis B core antigen (HBcAg) which complexes with virally encoded polymerase and the viral DNA genome (Figure 2).[24] While Hepatitis C Virus is 55 to 65 nm diameter particle composed of a lipid membrane envelope. E1 and E2 viral envelope glycoproteins are enclosed in the lipid envelope. The two viral envelope glycoproteins are used for viral attachment and entry into the cell and enclosed within the envelope is an icosahedral core of 33-40 nm diameter size (Figure 3).[25-27]

The calculated molecular descriptors are shown in Table 1. Band gap which is the difference in the energy of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) is a molecular descriptor which helps to define the stability of a molecule in chemical reactions. The order of stability of the molecules is 6>3>2>4/5>1. Lipophilicity (Log p) is a measure of the distribution of a compound between non-aqueous and aqueous phases of solvents; it is a veritable molecular descriptor which suggests the biological activity of a molecule. The log p values for all the molecules investigated are less than 5, the accepted standard value being less than or equal to 5. Higher values of log p (>5) indicates that the molecule may not have good oral absorption properties.[28] However, the general low values Log p for all the molecules is an indication that they would be effective in terms of lipophilicity and that they are good central nervous system drugs which are ideal for oral and intestinal absorption. Dipole moment is a measure of the polarity of a chemical bond within a molecule and helps to determine the extent of interactions of a molecule in solvents.[29] The values of the dipole moments for all the molecules suggests reasonable polarity. The polarity is in the order; 2>4>5>1>3>6.Moreover, polarizability of a molecule shows the tendency of distortion of electron cloud from the normal shape of a molecule. The higher the polarizability, the higher the tendency to bind to other substances because of the great distortion in the electron cloud of the molecule. Polarizability of the molecules is in the order: 4/6>2>5>1>3. This shows that molecules 4 and 6 with the highest polarizability value would have the greatest binding interaction with the proteins, while molecule 3 would have the least binding interaction. The polar surface area (PSA) otherwise known as Topological Polar Surface Area(TPSA) defines the amount of molecular surface arising from polar atoms, the sum over all polar atoms or molecules(primarily oxygen and nitrogen and including their attached hydrogen atoms). Polar Surface Area is an important molecular descriptor used to predict the absorption of drugs. It is used for the optimization of drug's ability to permeate cells. Molecules with a polar surface area of greater than 140 $Å^2$ tend to be poor at permeating cell membrane, for molecules to penetrate the blood-brain barrier a polar surface area less than 90 $Å^2$ is usually needed.[30,31] The Surface Area (A) of the molecules is in the order: 4>6>5>2>1>3. The volume is in the order: 6>4>2>5>1>3. Moreover, ovality helps determine how spherical a molecule is, that is it is a measure of the degree of deviation from perfect circularity of the cross section of the core.[32] The order of ovality is 5>6/4/1>2>3. Ovality helps indicate how the shape of a molecule approaches a sphere and it is a ratio of volume per area.[33] Furthermore, high affinity binding of ligands to receptors is often without any restriction to the ligand's molecular weight. The molecular weights of the molecules are not expected to be above 500 g/mol. Here in all the molecules under study have molecular weights less than 500 g/mol.

Table 2 shows the amino-acid residues and types of bonds involved in the binding interactions between the molecules with Hepatitis B & C proteases and their binding affinities. The analysis of binding mode of Albendazole(1) with HBV showed that it has interactions via pi-Alkyl bond with PRO H:155, LEU H:114 and VAL H:94, carbon hydrogen bond with LYS H:41, GLY L:44 and GLN H:40 and conventional hydrogen bond with GLN H:40. The analysis of binding mode of Albendazole(1) with HCV showed interactions with residues TRP :A 397 via pi-Alkyl bond and Conventional Hydrogen bond with ARG A:394 and GLU A:398. The binding affinity of Albendazole with HBV was -5.20 kcal/mol and -5.70 kcal/mol for HCV.

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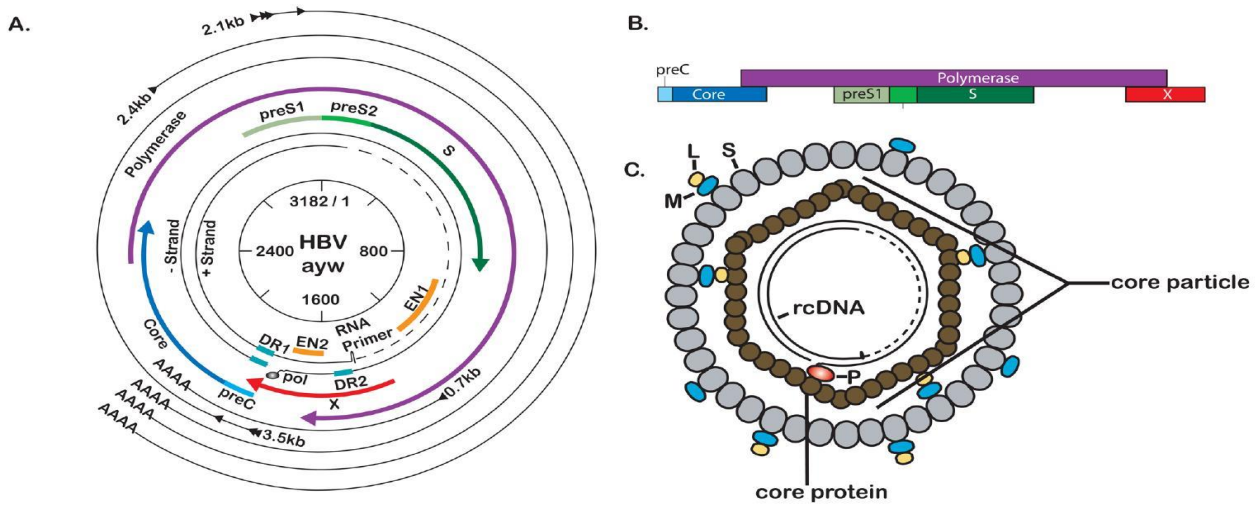

Figure 2: Molecular biology of hepatitis B virus (HBV).
(A) Scaled depiction of the HBV (genotype ayw) genome. Internal circle shows genomic position relative to EcoRI site at position 1. Partially double-stranded genome is shown with attached RNA primer and polymerase protein. Open reading frames (ORFs) are indicated by the thicker, colored lines. The outermost black circles represent the viral transcripts with the shared polyadenylation site;(B) schematic representation of the overlapping nature of the HBV ORFs.

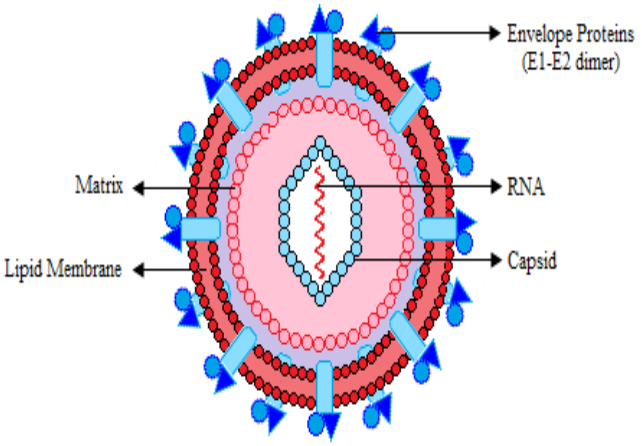

Figure 3: Molecular biology of hepatitis C virus (HCV).

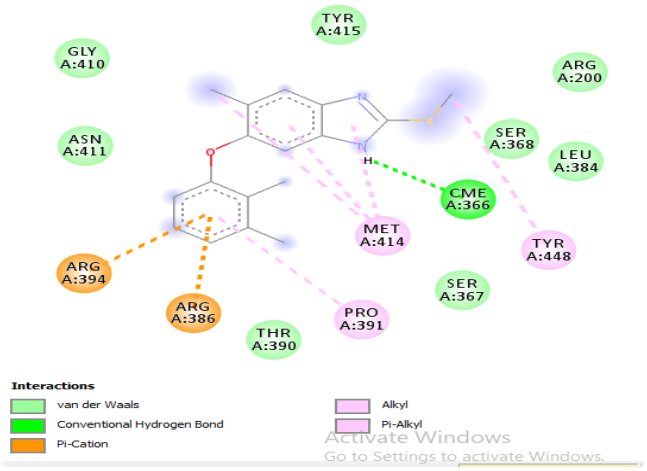

Figure 4: 2D Structure of the docked-ligand complex (Interaction between Hepatitis C and Triclabendazole ligand).

Table 1: The calculated molecular descriptors from the compounds 1-6 for anti –Hepatitis B&C

M	HOMO(eV)	LUMO (eV)	BG	LOG P	DM (Debye)	P	PSA (Å^2)	A (Å^2)	V (Å^3)	OVALITY
1	-5.23	-2.03	3.20	0.23	4.17	61.83	51.90	292.75	261.50	1.48
2	-6.21	-1.73	4.48	0.51	7.98	63.87	66.26	312.07	290.37	1.47
3	-5.97	-1.37	4.60	-0.57	3.67	55.72	27.46	207.80	190.31	1.30
4	-6.11	-1.68	4.43	-0.02	7.34	64.25	65.89	317.67	294.97	1.48
5	-5.76	-0.78	4.43	-0.11	5.12	63.68	52.26	314.48	289.50	1.49
6	-5.88	-0.87	5.01	-0.30	3.36	64.25	26.19	317.59	296.64	1.48

BG- Band gap, DM- Dipole moment, P- Polarizability, , P- Polar surface area A-Area, V- Volume

This suggests that Albendazole is a better inhibitor for HCV than HBV. Moreover, the analysis of binding mode of Mebendazole with HBV showed PRO H:11 and TYP H:96 interactions via conventional hydrogen bond, pi-Alkyl bond with VAL H:94 and pi-sigma bond with VAL H:94. The amino acid residue interaction of HCV with Mebendazole showed pi-cation bond with ASP A:225 and ARG A;158 and pi-alkyl bond with ARG A:158 and carbon hydrogen bond with LEU A:159 and GLY A:317. The binding affinities of Mebendazole interaction with HBV and HCV are -7.30 kcal/mol and -7.50 kcal/mol respectively. This indicates that Mebendazole is a better drug for HCV than HBV. The analysis of binding mode of Thiabendazole(3) with HBV revealed pi-Alkyl interaction with LEU H:34, LEU L:91 and PRO H:105 and pi-pi stacked bond with TYR L;93, pi-Donor hydrogen bond with SER H:100, pi-cation bond with ARG L:98 and conventional hydrogen bond with GLN H:36. Consequently, interactions of Thiabendazole with HCV showed pi-Alkyl bond with MET A:414, LEU A:384, pi-pi T- shaped interaction with TYR A:448 and pi-sulfur bond with CME A:366. The binding

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affinity with HBV was -7.10 Kcal/mol and -6.10 kcal/mol for HCV, suggesting Thiabendazole a better curing drug for HBV than HCV.
Flubendazole (4) binds to HBV only via carbon-hydrogen bond with SER L:205. The analysis of binding mode of Flubendazole with HCV showed interactions via unfavorable Donor-Donor bond with ASP A:291, pi-cation with ASP A:225, ARG A:158 and CSD A:223 and pi-Alkyl bond with ARG A:158 and VAL A:52. The binding affinities of Flubendazole interaction with HBV and HCV are -7.80 kcal/mol and -7.60 kcal/mol respectively, suggesting Flubendazole has greater inhibition for HBV than HCV. Furthermore, the analysis of binding mode of Fenbendazole(5) with HBV showed interaction via pi-Alkyl bond with ALA H:98, PRO H:105 and ARG L:98, pi-cation bond with ARG L:98, pi-sigma bond with LEU L:91 and pi-pi stacked bond with TYR L:93. While the analysis of binding mode of Fenbendazole with HCV showed pi-cation bond with CSD A:283, ARG A:158 and ASP A:225 and carbon- hydrogen bond with SER A:556 and GLY A:317 and pi-Alkyl bond with VAL A:52 and ARG A:158. The binding affinity with HBV was -7.80 kcal/mol and -7.10 kcal/mol,for HCV, showing Fenbendazole to be a better drug for inhibiting HBV than HCV. Moreover, analysis of the binding mode of Triclabendazole(6) with HBV showed an unfavorable Donor-Donor interaction with GLY L:44, conventional hydrogen bond with LYS L:41 and pi-alkyl bond with VAL H:94 and PRO L:42. The analysis of binding mode of Triclabendazole with HCV showed pi-Alkyl bond with MET A:414, PRO A:391, TYR A:448, conventional hydrogen bond with CME A:366 and pi-cation bond with ARG A:394 and ARG A:386. Triclabendazole has greater inhibition for HBV than HCV by virtue of the values of the binding affinities of -7.80 kcal/mol and -6.90 kcal/mol for HBV and HCV respectively.
Pi-cation interaction is a noncovalent molecular interaction between the electron rich π ligand and an adjacent cation and it contributes 2.6 kcal/mol to the binding. Furthermore, pi-alkyl is the interaction of pi-electron cloud over an aromatic group of the ligand and electron group of the alkyl group on the receptor, van der Waals force is weak force of attraction between the ligand and receptor. Consequently, hydrogen bond is the electrostatic force of attraction between a hydrogen atom in the ligand bonded to a more electronegative atom or group in the receptor covalently.
The potency of some oxime derivatives of dehydrocholic acid as anti-Hepatitis B virus was reported,[34] and the bioactivity of N-(4-chlorophenyl)-4-Methoxy-3-(Methylamino) Benzamide as a potential anti-HBV agent was found in the literature.[35] Research has shown that N-(4-chlorophenyl)-4-Methoxy-3-(Methylamino) Benzamide has higher anti-HBV activity than lamivudine drug, and benzamide derivatives have been reported to show great inhibition for Hepatitis B.[36,37] New biaryl amide derivatives and their inhibitory effects against hepatitis C virus have been investigated.[38]A novel fluorinated cytidine analog, NCC(N-cyclopropyl-4′-azido-2′-deoxy-2′-fluoro-β-d-cytidine) have been found to inhibit lamivudine-resistant hepatitis B virus.[39] Literature has shown the efficacy of the combination of lamivudine and adefovir as rescue therapy for hepatitis B.[40-42] However, since the cost of lamivudine and adefovir is beyond the reach of the poor as reported by the investigation made in China,[43]and benzimidazole derivatives has shown good inhibition for Hepatitis B and C.[44-47] Therefore the need to investigate new set of benzimidazole derivatives which has hitherto not been reported. Herein the result showed that Flubedazole, Fenbendazole and Triclabendazole have the same potency to inhibit Hepatitis B followed by Mebendazole then Thiabendazole with Albendazole being the least effective drug for Hepatitis B. Flubendazole is the most effective drug for Hepatitis C, closely followed by Mebendazole, then Febendazole, then Triclabendazole followed by Thiabendazole and the least is Albendazole.

Table 2: Binding Affinity and Interactions of Hepatitis B&C Proteases with Benzimidazole Ligands

Molecule	Hepatitis	Types of Bond Interaction and Residue	Binding Affinity (kcal/mol)
Albendazole (1)	HBV	pi-alkyl: VAL:94 LEU H:114 PRO H:155 carbon hydrogen bond: GLY L:44 LYS H:41 GLN H:40 conventional hydrogen bond: GLN H:40	-5.20
	HCV	pi-alkyl: TRP A:197 conventional hydrogen bond: ARG A:394 GLU A:398	-5.70
Mebendazole (2)	HBV	pi-alkyl: VAL H:94 conventional hydrogen bond: PRO H:111, TYR H:96 pi- sigma: VAL H:94	-7.30
	HCV	pi-alkyl: ARG A:158 carbon hydrogen bond: GLY A:317 LEU A:159 pi-cation: ARG A:158 ASP A:225	-7.50
Thiabendazole (3)	HBV	pi-alkyl: PRO H:105 LEU L:91 LEU H:34 pi-pi stacked: TYR L:93 pi-cation: ARG L:98 conventional hydrogen bond: GLN H:36	-7.10
	HCV	pi-alkyl: LEU A:384 MET A:414 pi-pi T- shaped: TYR A:448 pi-sulfur: CME A:366	-6.10
Flubendazole (4)	HBV	carbon-hydrogen bond: SER L:205	-7.80
	HCV	pi-alkyl:VAL A:52 ARG A:158 pi-cation: ASP A:225 ARG A:158 CSD A:223 unfavorable donor-donor ASR A:291	-7.60
Fenbendazole (5)	HBV	pi-alkyl: ALA H:98 ARG L:98 PRO H: 105 pi-sigma: LEU L:91 pi-pi stacked: TYR L:93 pi-cation: ARG L:98	-7.80
	HCV	pi-alkyl: VAL A:52 ARG A:158 pi-cation CSD A;283 ARG A:158 ASP A:225 carbon-hydrogen bond: SER A:556 GLY A:317	-7.10
Triclabendazole (6)	HBV	pi- alkyl VAL H:94 PRO L:42 conventional hydrogen bond: LYS L:41 unfavorable donor-donor: GLY L:44	-7.80
	HCV	pi-alkyl: PRO A:391 MET A:414 TYR A:448 pi-cation: ARG A:394 ARG A:386 conventional hydrogen bond: CME A:366	-6.90

Conclusion

Albendazole showed least inhibition for both Hepatitis B and C, while Flubendazole is the best drug for Hepatitis C and any of Flubendazole, Febendazole or Triclabendazole can be deployed for attacking Hepatitis B virus. Therefore, Flubendazole, Fenbendazole and Triclabendazole can complement 1 FN-α, lamivudine, adefovir and any other known drug for the treatment of Hepatitis B.

Conflict of Interest

The authors declare no conflict of interest.

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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