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Characters of Frontier Orbitals of Antiviral Drugs

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Abstract

Ab initio molecular orbital calculations are performed for model molecules of antiviral drugs. Frontier orbitals (highest occupied molecular orbital and lowest unoccupied molecular orbital) at optimized structure of each molecule are obtained. Similar shapes of frontier orbitals are found for these three molecules. Efficacy for Ebola virus disease is discussed. We suggest Cytosine arabinoside (also known as Ara-C) (Cylocide®) may be promising as a drug against Ebola virus disease.

Keyword: Frontier orbitals, Favipiravir, Lamivudine, Ara-C, Ebola virus disease

1. Introduction

Frontier orbitals play important role in molecular interactions and chemical reactivity[1]. Frontier orbitals are general term both of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Investigation for characters and patterns of frontier orbitals is useful for understanding various properties of molecules. For example, researches on classification of frontier orbital patterns by statistical analysis are developed and applied to toxicities of dioxins[2)-4)] and drug activities[5), 6)]. In this work we investigate frontier orbitals of antiviral drugs. Activity against Ebola virus disease is discussed.

2. Method

Favipiravir (Avigan®) (also known as T-705), Lamivudine and Cytosine arabinoside (Cylocide®) (also known as Ara-C) are calculated as antiviral drugs. Favipiravir (T-705) is an experimental antiviral drug developed by Toyama Chemical of Japan which is active against RNA viruses and effective for influenza viruses, West Nile virus, yellow fever virus, so on. On October 2014, it was reported that a patient with Ebola virus disease recovered after the treatment of Favipiravir[7].

Chemical formula of Favipiravir (T-705) is shown in Figure 1 (a). Furuta *et al.*[8] reported that T-705 can be converted to T-705 ribofuranosyl triphosphate (T-705RTP). They confirmed that T-705RTP is potent inhibitor for influenza viral polymerase. Chemical formula of T-705RTP is shown in Figure 1 (b). We construct a model molecule of T-705RTP, which is used for ab initio calculation. As shown in Figure 1 (c) ribofuranosyl triphosphate of T-705RTP is replaced by methyl group in this model molecule.

Chemical formula of Lamivudine is shown in Figure 2 (a). Lamivudine is a drug for chronic hepatitis B and HIV. On September 2014, a Liberian physician reported 13 patients survived Ebola virus disease out of 15 patients treated with Lamivudine[9].

Chemical formula of Cytosine arabinoside (Ara-C) is shown in Figure 2 (b). Ara-C is a drug for the treatment of cancers of white blood cells. Ara-C also has antiviral activity to be treated for herpes virus infections. Model molecule for Ara-C is shown in Figure 2 (c). In this model molecule five-membered ring of Ara-C is replaced by methyl group.

Ab initio molecular orbital calculations are performed for a model molecule of T-705RTP,

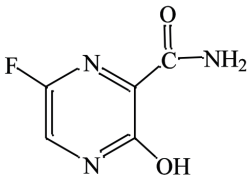
Lamivudine and a model molecule of Ara-C by using Gaussian 09 program systems[10]. Basis set is STO-3G. Optimized structures and frontier orbitals (HOMO and LUMO) are calculated.

3. Results and discussion

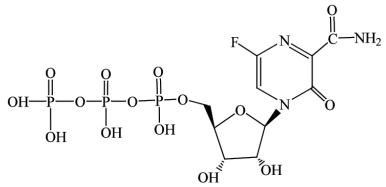
Ebola virus disease (EVD) (also known as Ebola hemorrhagic fever) is a severe and often fatal illness. The Ebola outbreaks occurred more than 20 times since 1976. On March 2014 World Health Organization (WHO) reported the Ebola outbreak in Guinea. Since then EDV spread out mainly in West Africa. WHO announced 10141 people have suffered EDV and 4922 people have passed away up to October 24, 2014. It is urgent task to hunt drugs which are effective for EDV.

Calculated optimized structures and frontier orbitals (HOMO and LUMO) of model molecules of T-705RTP, Lamivudine and model molecule of Ara-C are shown in Figure 3. In this figure, carbon is gray, hydrogen is white, oxygen is red, nitrogen is blue, fluorine is cyan and sulfur is yellow. According to the orbital phase, lobe of molecular orbital is shown green and red in HOMO and LUMO.

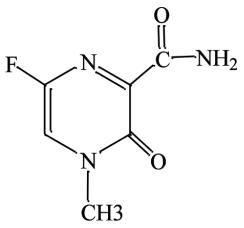
As shown in Figure 3, we can see the simi-



(a) Favipiravir (T-705)

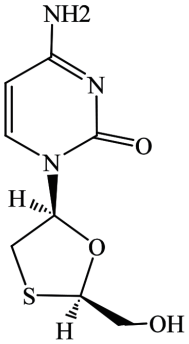


(b) T-705RTP

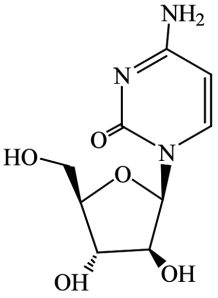


(c) Model molecule for T-705RTP

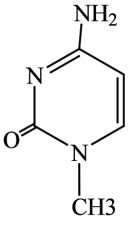
Figure 1 Structural formula of (a) Favipiravir (T-705), (b) T-705RTP and (c) model molecule for T-705RTP.



(a) Lamivudine

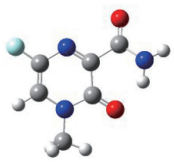


(b) Cytosine arabinoside (Ara-C)

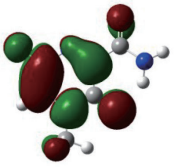


(c) Model molecule for Ara-C

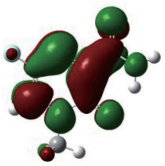
Figure 2 Structural formula of (a) Lamivudine, (b) Cytosine arabinoside (Ara-C) and (c) model molecule for Ara-C.



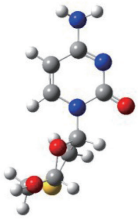
(a) Optimized structure of model molecule for T-705RTP (#1)



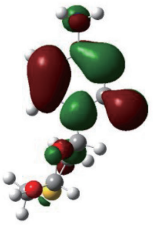
(b) HOMO of #1



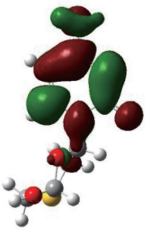
(c) LUMO of #1



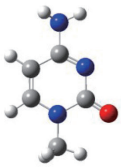
(d) Optimized structure of Lamivudine (#2)



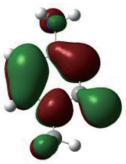
(e) HOMO of #2



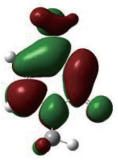
(f) LUMO of #2



(g) Optimized structure of model molecule for Ara-C (#3)



(h) HOMO of #3



(i) LUMO of #3

Figure 3 Optimized structure, HOMO and LUMO of model molecule for T-705RTP ((a), (b), (c)), Lamivudine ((d), (e), (f)) and model molecule for Ara-C ((g), (h), (i)).

lar pattern of HOMO and LUMO for these three molecules. Each molecule has HOMO with three lobes on six-membered ring and one lobe on oxygen and LUMO with four lobes on six-membered ring and one lobe on oxygen. Six-membered ring with a carbonyl group will play important role in molecular recognition with RNA or DNA polymerase. If T-705 is effective for EVD, Lamivudine is also expected to be effective for EVD because of its similar frontier orbital pattern. In addition, it is reasonable to suggest Ara-C also may be effective for EVD due to its shapes of frontier orbitals. Ara-C is a prescription drug (Cylocide®), so it is good idea to try Ara-C for the treatment of EVD. Care is needed for the side effect of Ara-C.

We should point out that Brincidofovir (CMX001) is another candidate drug against EVD. Brincidofovir is an experimental antiviral drug for the treatment of cytomegalovirus, adenovirus and smallpox. Brincidofovir is effective for DNA virus. Though Ebola virus is RNA virus, Brincidofovir is expected to be a drug against EVD.

Considering Brincidofovir, it is not unreasonable to expect Ara-C, which is effective for DNA virus, to be a drug against EVD. Clinical test should be needed as soon as possible.

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