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Density Functional Theory Study of Henry's Law Constant on the Benzimidazole derivatives

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ABSTRACT

*Benzimidazoles are veterinary drugs widely used for prevention and treatment of parasitic infections in agriculture and aquaculture. The benzimidazoles are a large chemical family used as antimicrobial agents against the wide spectrum of microorganisms [1-10]. In this study Henry's law constants at T = 293.2K are calculated for some Benzimidazole and derivatives drugs in water by density functional theory (DFT) methods at B3LYP (6-31+G**) levels of theory using the Poisson-Boltzmann solvation model.*

Keyword: Benzimidazole and derivatives Drug, DFT, Henry law, Free energy.

INTRODUCTION

ΔGsol is a key property to estimate the fate of a chemical once it is released in the environment. From an environmental point of view, an important partition coefficient is the Henry's law constant (K) which can be calculated straightforwardly from the free energies of solvation in water.[11]

$$K(\rho, T) = RT\,\rho \exp\left(\frac{\Delta G\ sol}{RT}\right)$$

Where ρ is the density of the pure solvent, which is equal to that of the solvation in the limit of infinite dilution.

The benzimidazole nucleus, which is a useful structure for further molecular exploration and for the development of new pharmaceutical compounds, has been studied intensively. Some

benzimidazoles have also found applications as pre- or post-harvest fungicides for control of a wide range of fungi affecting field crops, stored fruit and vegetables. Albendazole, fenbendazole and their sulphoxide derivatives are methylcarbamate benzimidazoles with a broad spectrum anthelmintic activity, widely used in human and veterinary medicine [12,13]. They are used against several systemic parasitoses, including nematodoses, hidatidosis, teniasis and others [14,15]. In recent years, benzimidazole derivatives have been attracted particular interest due to their antiviral activity against HCV (Hepatitis C virus) [16,17]. We have selected twelve Benzimidazole derivatives that have important anthelmintic activity.

Computational Method

The geometry of the molecules used here was fully optimized by DFT (B3LYP) calculations with the (6-31+G**) basis set in the Gaussian 03 package. The Gibbs solvation free energies of drugs in water were calculated based on B3LYP method for Benzimidazole derivatives.[18]

Table 1.the solvation Gibbs free energy in water and Henry,s costant based on B3lyp/6-31+G**

compound	ΔGsol(water)/B3lyp	K(ρ,T)/B3lyp
Albendazole	-10.7	8.4590×10^{-6}
Mebendazole	-15.27	3.7768×10^{-9}
fenbendazole	-13.82	4.3662×10^{-8}
Benzimidazole	-10.44	1.3119×10^{-5}
Thiabendazole	-14.61	1.1506×10^{-8}
flubendazole	-16.53	4.5022×10^{-10}
5,6- dimethylbenzimidazole	-9.72	4.4232×10-5
Oxfendazole	-14.5	1.3854×10^{-8}
Oxibendazole	-12.18	6.9558×10^{-7}
compund1	-13.64	5.9162×10^{-8}
compund2	-11.8	1.3210×10^{-6}
compund3	-12.79	2.4840×10^{-7}

Table2. The free energy of cavity formation (kcal/mol) in water for drugs

compound	ΔGcav
Albendazole	34
Mebendazole	35.48
fenbendazole	35.63
Benzimidazole	15.66
Thiabendazole	24.01
flubendazole	37.3
5,6- dimethylbenzimidazole	20.04
Oxfendazole	37.11
Oxibendazole	32.2
compund1	33.87
compund2	36.64
compund3	36.09

RESULTS AND DISCUSSION

The results are presented in Table 1. B3LYP /6-31+G** method estimated more negative solvation free energies. Henry's law constant was calculated from equation (1) by using of free energy solvation. The free energy of cavity formation (kcal/mol) in water for drugs, determined from DFT calculations, are shown in Table 2. Comparison of ΔG_{cav} with surface area shows that the ΔG_{cav} is often high for large-structure drugs and low for small drugs. However, the surface area is calculated in gas phase, but the ΔG_{cav} is calculated in solution. Therefore, the interaction between solute and solvent sometimes results in the lower ΔG_{cav} for small drugs. The calculated values are given in Table 3.

Table 3 . The structure and electronic parameters of drugs fromB3LYP/6-31+G method**

compound	SA
Albendazole	473.878
Mebendazole	437.743
fenbendazole	443.703
Benzimidazole	217.48
Thiabendazole	275.44
flubendazole	458.763
5,6- dimethylbenzimidazole	290.502
Oxfendazole	452.475
Oxibendazole	456.129
compund1	418.099
compund2	444.135
compund3	449.735

CONCLUSION

In this study, we have applied ab initio method for calculation of some properties and the free energy solvation in solvent. The first calculations began with the geometry optimization of drugs by using of DFT methods . Then, solvation free energy of drugs was calculated in the water solvent based on B3LYP estimate with 6-31+G** basis set.

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