

DRUG DELIVERY: CAPECITABINE

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Abstract – Capecitabine is an anticancer drug which is applied in the treatment of pancreatic, non-small cell lung, ovary, bladder and breast cancers. Its delivery using single walled carbon nanotubes (SWCNTs) is investigated employing quantum mechanical calculations. These calculations show that it is alignment inside SWCNT so that aliphatic tail becomes much closer to the SWCNT's internal surface by departure from six membered (cytosine) ring. The cytosine ring also aligns so that its fluorine becomes up to 3.95 angstrom close to the carbon atoms of nanotube to form anion- π interaction. This sort of interaction also determines alignment of five membered (ribose) ring so that 2'-OH and 3'-OH groups show closest distances of 4.05Å and 4.65Å, respectively.

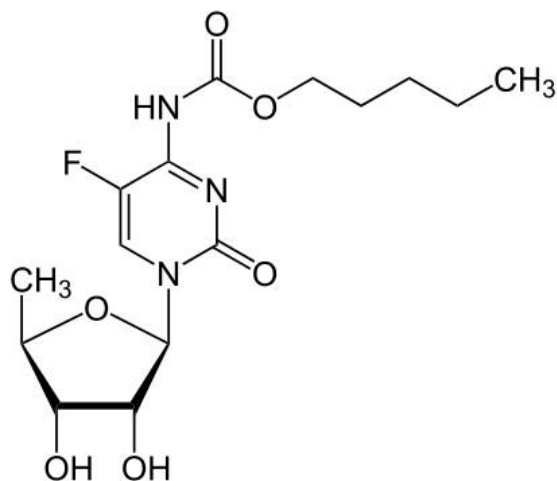


Fig. 1. Capecitabine.

1. Introduction

Capecitabine prodrug (N4-n-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is approved for the use as a second-line therapy of metastatic breast cancer, gastric, colorectal, bladder cancer and other solid malignancies (Fig. 1). Capecitabine is changed to 5-fluorouracil by some enzymes mainly located in liver and tumors. The 5-fluorouracil is commonly applied to the treatment of various types of cancers [1]. Meanwhile its delivery within liver is of great importance. One of the most proposed delivery methods is the use of carbon nanotubes (CNTs). On the other hand computationally optimized geometries provide valuable information for the structural determination of biological compounds in different matrix conditions. Thus, we try to survey its delivery inside (24,0) single walled CNT (SWCNT) by optimizing their geometry.

2. Computational Details

Initial structure for alignment of capecitabine inside SWCNT was obtained from molecular dynamics study of gemcitabine alignment inside (18,0) SWCNT [2]. Due to the existence of an aliphatic tail in capecitabine, the diameter of SWCNT was changed from (18,0) to (24,0). Its initial length is set to 122Å which is reduced during geometry optimization up to 26Å.

At first, the structure of capecitabine inside 122Å SWCNT was optimized at the oniom(HF/STO-3G:UFF) level of theory in which the high level comprises capecitabine and middle 26Å of SWCNT and low level comprises two lateral parts of SWCNT. Then, optimized structure became shorter by truncating the low part and was reoptimized after adding water as solvent at HF/STO-3G level of theory.

Solvent effects in these calculations were taken into account using a conductor-like polarizable continuum model [3].

All calculations were done using Gaussian 09 software [4].

3. Results and Discussion

Optimized alignment of capecitabine inside (24,0) SWCNT is presented in Fig. 2. In this figure, for clarity, carbon atoms of different parts of capecitabine and SWCNT are shown in different colors. Those of drug's tail, cytosine ring, ribose ring, closer part of SWCNT and remaining of SWCNT are shown in orange, black, purple, green and gray, respectively. As it is seen from this figure, the aliphatic tail of drug tends to become much closer to the SWCNT's internal surface by departure from cytosine ring. Slope of this bending which starts from 1'-C of the ribose ring, is %10 that is equivalent to a 6° angle between SWCNT's surface and this backbone. Of course the cytosine ring itself bends so that anion- π interaction

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takes place between its negatively charged fluorine and π electrons of SWCNT (shortest distance between fluorine and carbon atoms of nanotube is 3.95\AA). This bending of cytosine ring causes its oxygen to become more than 5.95\AA far from the carbon atoms of nanotube.

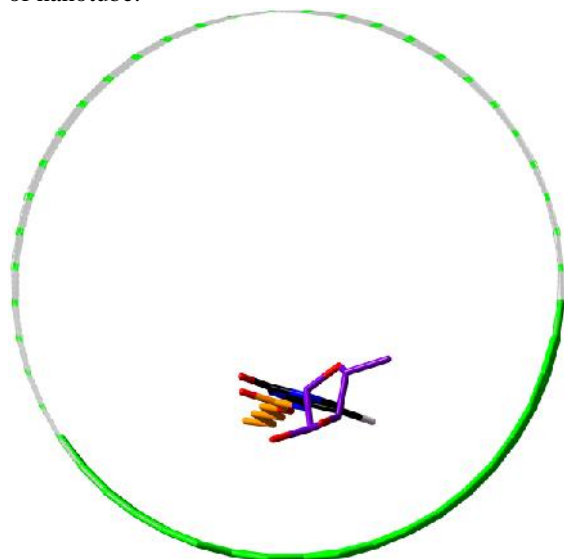


Fig. 2. Alignment of Capecitabine inside (24,0) SWCNT. For clarity, carbon atoms of drug's tail, cytosine ring, ribose ring, closer part of SWCNT and remaining of SWCNT are shown in orange, black, purple, green and gray, respectively.

This is maintained for alignment of oxygen atoms of ribose ring so that 2'-OH and 3'-OH groups become, respectively up to 4.05\AA and 4.65\AA close to the carbon atoms of nanotube to form anion- π interaction. These findings show relatively strong interaction between drug and SWCNT which suggest improved delivery of capecitabine with CNTs compared to bare drug.

4. Conclusion

Improved delivery of capecitabine as an anticancer drug using (24,0) SWCNT was confirmed. In this confirmation, quantum mechanical geometry optimization was applied.

5. References

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