THEORETICAL STUDIES ON THE INTERACTIONS OF CYTOSTATIC PYRAZOLE DERIVATIVE WITH DNA BASES

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Introduction

The current anticancer agents have a variety of activity mechanisms. These type of drugs can inhibit cell proliferation, damage DNA of fast proliferating cells, block transcription or translation, as well as inhibit cancer specific enzymes. Their action leads finally to cancer cell apoptosis. Among the anticancer drugs, pyrazole or indazole derivatives like cececoxib, antihypertensive pyrazolones (proxantrone, losoxantrone), and Axitinib have been found to be effective antiangiogenic agents useful in the treatment of breast and prostate cancers, as well as acute leukemia [1,2]. Our results have proved the cytostatic and proapoptotic activity of some condensed pyrazole derivatives [3] tested against the HT29 human cancer cells. We suggested that the mechanism of cytostatic activity of these compounds could be related to their ability to adhere to DNA. It is also possible that they can interfere with the cellular Mg2+ ions that, in turn, participate in many biochemical processes like proliferation, angiogenesis, and apoptosis [4].

Goals and objectives

In a continuation of our attempts to clarify the mechanism of the aforementioned condensed pyrazoles, we present studies concerning interactions of one of these derivatives, namely 3-(3-dimethyl-1H-pyrazol-1-yl)-1H-indazole (25 given in Scheme 1), with some nucleobases and a DNA fragment applying DFT and Molecular Mechanics (MM) calculations.

Discussion

Our recent results have shown that condensed derivatives of pyrazole promote apoptosis of human cancer cells H19, HCT116, K562 (Fig. 1) [3,5]. These compounds migrate into the cancer cell and further intercalate, and damage DNA. As metal ions, including magnesium, can participate in cancerogenesis, the interactions of pyrazole derivative 25 (Scheme 1) with Mg2+ ions were investigated on experimental (NMR) and theoretical levels [6]. Based on the analysis of changes in chemical shifts and matrix operations we have identified the sites susceptible to interactions with magnesium ions. The study revealed significant influence of the water solvation sphere on these interactions. Considering the above findings, we use in the present studies a similar solvation sphere model, i.e. a box with water molecules. To determine which of the structural elements of compound 1 are able to interact with the cell structures, we calculated an analysis of molecular electrostatic potential (MEP) [7]. We observed that the thiol group could be an acceptor of hydrogen bond. Moreover, the indazole NH group could act as a strong hydrogen bond donor. The remaining indazole hydrogen atom can form two hydrogen contacts and their role in the stabilization of the azole 1-nucleoside adduct is poorly important. The above hypothesis was examined more closely by a theoretical simulation of the interactions indazole ring-nucleosides.

The individual compound 25-nucleoside moieties were optimized with the DFT-B3LYP/6-31G(d,p)/PCM method and additionally for solvent box by an explicit model (MM) calculations. We observed that guanine and pyrazole derivative 25 were linked through two strong hydrogen bonds NH-N (Fig. 4). The bond energy equalled -11.4 kcal/mol considering the BSSE error. The system stability as a box with 1049 water molecules (box diameter: 31.7 Å) was confirmed using MM. The theoretical analysis of the interactions between compound 25 and adenosine was carried out using three different models. The analysis showed the presence of NH-N hydrogen bonding between the indazole moiety and the base, as well as CH bond between the benzene ring of indazole and adenosine and NH-O bonds involving the group and adenosine. The calculated energies were -15.7 (Fig. 6), -6.2, and -5.2 kcal/mol, respectively. The MM modeling revealed that in two of the three models the indazole and base rings were nearly coplanar. The box size and water content for the individual models were: a) 33.8 Å, 2281 water molecules; b) 40.0 Å, 2109 water molecules, and c) 31.2 Å, 1009 water molecules. Changes in the dihedral angle between the NH indazole and CH adenosine planes resulted only in small alterations of the N-H distance. The smallest length of this bond was due to the close proximity of the thiol residue and adenosine and was not a feature of the lowest energy conformer. The DFT optimization of the adenosine indazole derivative 25 and cytosine (Fig. 6) showed the presence of two strong hydrogen bonds NH-O=C; their calculated energy was -14.8 kcal/mol, i.e. only about 1 kcal/mol less than for the similar adduct with adenosine. The indazole and cytosine rings were not coplanar due to the close proximity of two sp2-hybridized nitrogen atoms with charges of -0.258 and -0.643 eV that caused mutual repelling. The MM revealed that the box size was 38.3 Å and it contained 1851 water molecules. In order to simulate the interactions of azole 25 with thymidine we put forth two models. The interactions scheme observed in the DNA helix was replicated for both models but the thymidine carbonyl groups were selected as sole hydrogen bond acceptors. The indazole and thymine rings were not coplanar due to the difference in energy from the arrangement of desoxyribose and thymine-indazole complex – the distance between pentose and thymine is significantly larger in the first model given in Fig. 7. In the next step we simulated an interaction of azole 25 with uracil, a base typical for RNA (Fig. 8). We found that the total interaction energy (B3LYP) of -13.5 kcal/mol is composed of contributions from three types of bonding: a strong hydrogen bond N-H⋯O, a weaker N-H⋯H contact, and a weak hydrogen bond C⋯N. Finally, the MM calculations using the Amber96 force field (PMF) shows that azole 25 interacts with the G/C+ (GGA) trinucleotides via hydrogen bonding. Due to the specific interactions of azole with adenosine and thymidine moieties, the indazole ring and GATA are not exactly parallel.

References


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