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Computational studies on the anastrozole and letrozole, effective chemotherapy drugs against breast cancer

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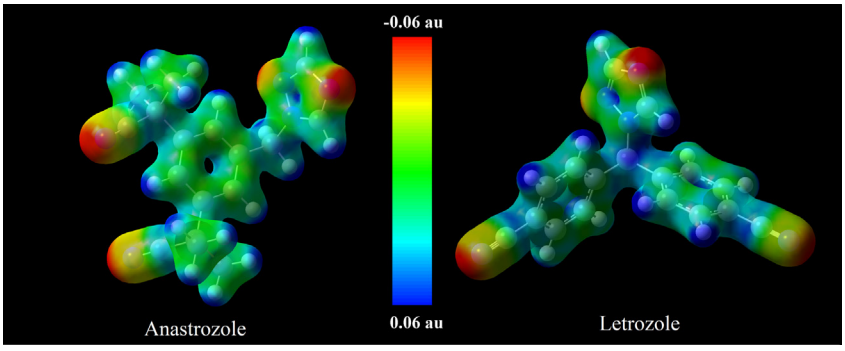
HIGHLIGHTS

- Geometric optimization and vibrational investigation.
- Calculations of chemical shift of the title compounds using DFT method.
- Natural bond orbital analysis of the title compounds.
- Determination of global and local reactivity parameters of the title compounds.

GRAPHICAL ABSTRACT



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ABSTRACT

In this paper, computational studies were carried out on anastrozole and letrozole, chemotherapy drugs used against breast cancer. Optimization and frequency calculations were performed at B3LYP/6–31G (d) basis set and vibrational frequencies were assignment. Single point calculations were performed at DFT method with a hybrid functional B3LYP/6–311G (d, p) basis set. Theoretical NMR data were obtained at DFT method with a hybrid functional B3LYP/6–311G++ (2d, p) with GIAO (Gauge-Independent Atomic Orbital). IEF-PCM method was used as solvation model. NBO calculations were performed by the same basis set and calculation method with single point calculation. Global and localized reactivity parameters; fukui indices (f) chemical hardness (η), softness (S), chemical potential (μ), electronegativity (χ) and electrophilicity index (ω) were calculated. All computational parameters were compared with the experimental results obtained from the literature.

Introduction

Breast cancer, the most common type of cancer among women is an important part of cancer-related death. It is known that the progression of breast cancer is related to the hormone estrogen. Previous studies showed that the concentration of 17β-estradiol (E2) in breast tumor can be ten-fold higher than those in plasma. Breast cancer cells require estrogen to progress thus, blocking of the estrogen synthesis can prevent to progression of the cancer. Aromatase, in other words cytochrome P450 is an enzyme having a function of estradiol E2 synthesis from cholesterol. Estradiol is the most biologically active estrogen. Thus, inhibition of aromatase can provide treatment of the breast cancer [1,2].

Aromatase inhibitors are classified as steroidal- (type I) and non-steroidal-type (type II). Type II inhibitors have heterocyclic azole moiety binding to the heme–iron in aromatase. Anastrozole and letrozole are important type (II) aromatase inhibitors used in the treatment of breast cancer. These compounds having 1,2,4-triazole moieties coordinate the heme–iron of cytochrome P450. In addition, benzonitrile substituted anastrozole and letrozole mimic the structure of enzyme's natural substrate androstenedione. Anastrozole

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and letrozole are marked trade name with Arimidex and Femara respectively. Its known that letrozole are more effective than anastrozole in binding with active site of aromatase [3–11].

The aim of this study was to examine the relationship between inhibition mechanism of the aromatase enzyme and electronic properties of anastrozole and letrozole. For this purpose, determination of structural parameters, vibrational investigations and NMR studies were done computationally and results were confirmed by comparing with the experimental data obtained from literature [12,13]. Then HOMO and LUMO energies, electrostatic potential map, global and local reactivity parameters were calculated and were studied the effect of these parameters on inhibition mechanism of the aromatase enzyme.

Computational details

The crystal structure of anastrozole was determined previously [14]. All experimental results; FT-IR, NMR data, were obtained at literature [12,13]. The geometric optimization study was performed by using its crystal structure parameters. For geometric optimization of letrozole (II), initial geometry was obtained semi-emprical PM3 method. The geometric optimization of two compounds were performed at DFT (density functional theory) calculations with a hybrid functional B3LYP (Becke's three parameter hybrid functional using the LYP correlation functional) 6–31G (d) [15,16] were performed with the Gaussian 03 W [15]. Vibrational frequencies were calculated at same basis set with optimization and obtained vibrational frequencies scaled by 0.9614 [17]. Absence of imaginary frequency indicated the structures were in global minimum. Vibrational assignments and other computational visualizations were performed by using Gauss-view molecular visualization software [16]. Vibrational assignments were compared with literature [12,13]. Single point energies of the optimized structures were calculated DFT calculations with a hybrid functional B3LYP/6–311G(d,p) basis set. ^{1}H and ^{13}C chemical shift calculations were studied at B3LYP/6311++G (2d, p) basis set with GIAO (Gauge-Independent Atomic Orbital). IEF-PCM method was used as solvation model and chloroform was used as solvent. Computational NMR results were compared with literature [12,13]. NBO calculations were performed by using NBO 3.1 program as implemented in Gaussian 03 W [15].

Results and discussion

Molecular geometry of the compounds

The molecular geometries of the two compounds are in Cs group symmetry. For anastrozole, X-ray structural parameters were used for geometric optimization. Geometrical parameters of the compounds were listed in Table S1. Optimized structures of the compounds were shown in Fig. 1. Letrozole is a compound similar with anastrozole as structural properties, so bond parameters of the letrozole obtained from geometric optimization compared with those of the crystal structure of the anastrozole. As can be seen in Table S1, all geometric parameters agreed with each other.

Assignments of the vibrational modes of the compounds

The theoretical vibrational frequencies of the compounds were calculated using B3LYP methods with 6-31G(d) basis set and were compared with the experimental results in literature [12,13]. The vibration bands assignments have been made using Gauss-View molecular visualization program [16]. The frequency values computed at the calculation level contain known systematic errors. Therefore, we have used the scaling factor value of 0.9614 for B3LYP [17]. Some theoretical and experimental vibrational data are shown in Tables 1 and 2. As can be seen in Figs. 2 and 3, the theoretical vibrational frequencies have good correlation with corresponding experimental results. Correlation between the experimental and vibrational of the anastrozole and letrozole were shown in Fig. 4.

C—H vibrations

The aromatic structures have characteristic C—H stretching vibrations at 3000–3100 cm^{-1} range. Similarly, the vibrational frequencies calculated at the range of 3152–3031 cm^{-1} and 3165–3068 cm^{-1} belongs to anastrozole and letrozole aromatic CH stretching vibrations (υ) respectively [18–20]. Experimental aromatic CH stretching vibrations of anastrozole and letrozole obtained from literature [12,13] were observed at 3120–3050 cm^{-1} and 3101, 2985 cm^{-1} respectively.

Aromatic CH in plane bending vibrations were observed at the range of 1300–1000 and out of plane bending vibrations were observed at the range of 675–1000 cm^{-1}. For anastrozole; C—H in plane bending vibrations were calculated at the range of 1449–1108 cm^{-1} and observed at 1387, 1368, 1272, 1195, 1160, 1151 cm^{-1}. The vibrations calculated between 932–697 cm^{-1} and observed at 896, 893, 875, 790, 763, 713 cm^{-1} were assigned C—H out of plane bending vibrations. All experimental C—H vibrations were good agreement with the theoretical results. For letrozole; aromatic CH in plane bending vibrations calculated at the range 1328–1031 cm^{-1} and observed at 1270, 1200, 1139, 1003 cm^{-1} experimentally. Aromatic CH out of plane bending vibrations were calculated at the range of 947–537 cm^{-1} and observed at 955–555 cm^{-1} experimentally [18,21,22].

CH_3 vibrations

Generally CH stretching vibrations in CH_3 units locate at the lower frequency region than those of aromatic ring and asymmetric stretching vibrations are at higher frequencies than the

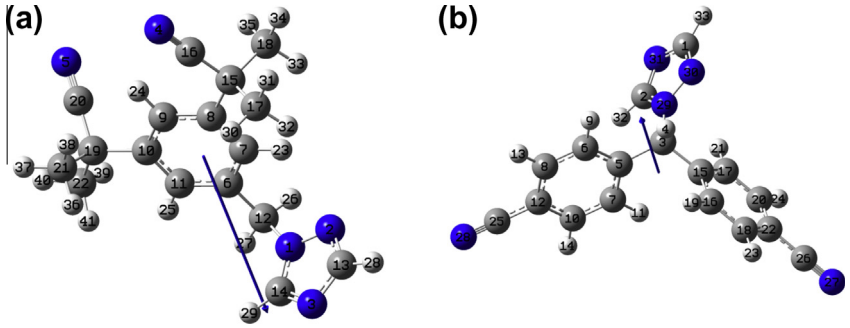

Fig. 1. Optimized geometries of anastrozole and letrozole.