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DFT CALCULATIONS OF SOME ANTIMICROBIAL ACTIVE 3,4-DIHYDRO-l,4-BENZOXAZIN-3-ONE DERIVATIVES

BAZI ANTİMİKROBİYAL ETKİLİ 3,4-DİHİDRO-l,4-BENZOKSAZİN-3-ON TÜREVLERİNİN DFT HESAPLAMALARI

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ABSTRACT

In this study, five antimicrobial active ethyl 3,4-dihydro-6-and/or 7-substituted-3-oxo-2H-l,4-benzoxazine-2-acetate derivatives geometrically have been optimized with DFT in Gaussian-98 at the Becke3LYP/6-31G(d,p) level. It was discussed the relationships between structures and their activity.

Key Words: Benzoxazines, DIMBOA, Antimicrobial activity, DFT, Becke3LYP/6-31G(d,p)

ÖZET

Bu çalışmada, beş adet antimikrobiyal etkili etil 3,4-dihidro-6-ve/veya 7-sübstitüe-3-okso-2H-1,4-benzoksazin-2-asetat türevleri DFT ile Becke3LYP/6-31G(d,p) , düzeyinde Gaussian-98 kullanılarak geometrileri optimize edilmiştir. Yapı ve aktivite arasındaki ilişki tartışıldı

Anahtar kelimeler: *Benzoksazinler, DIMBOA, Antimikrobiyal etki, DFT, Becke3LYP/6-31G(d,p)*

INTRODUCTION

Almost all the major classes of antibiotics have encounterde resistance in clinical applications (1-5). The emergence of bacterial resistance to β-lactam antibiotics, macrolides, quinolnes, and vancomycin is becoming a major worldwide health problem (4-8). In particular, antibiotic resistance among Gram-positive bacteria (staphylococci, enterococci, and streptococci) is becoming increasingly serious (9-12). In order to overcome these emerging resistance problems, there is an urgent need to discover novel antibacterial agents in structural classes distinct from existing antibiotics.

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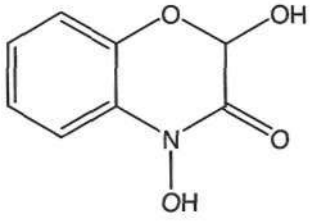
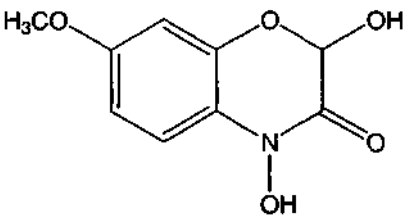
A group of l,4-benzoxazine-3-ones was isolated from Job's tears, rye, wheat, and corn plants (13,14). The 2,4-dihydroxy-l,4-benzoxazin-3-one derivatives such as DIBOA and DIMBOA (Figure I) isolated as glycosides from which the aglycones are rapidly released by enzymatic hydrolysis after physical and biological injury of the plants. They exhibited antibacterial, antifungal, insecticide and mutagenic activities (15).



DIBOA



DIMBOA

Figure I: Derivatives of 2,4-dihydroxy-l,4-benzoxazin-3-one

Only, limited number of compounds containing 1,4-benzoxazine ring system have been studied for their chemotherapeutic activity.

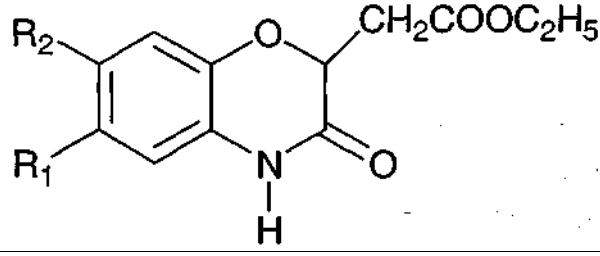
Density Functional Theory (DFT) has used for geometry optimization in theoretical drug design (16). In the last few years, methods based on Denstiy Functional Theory (DFT) have gained steadily in popularity. The best DFT methods achieve significantly greater accuracy than Hartree-Fock theory at only a modest increase in cost. They do so by including some of the effects of electron correlation much less expensively than traditional correlated methods.

DFT methods compute electron correlation via general functionals of the electron density. DFT, functional partition the electronic energy into several components which are computed separately: the kinetic energy, the electron-nuclear interaction, the Coulomb repulsion, and an exchange-correlation term accounting for the remainder of the electron-electron interaction which is itself divided into separate exchange and correlation components in most actual DFT formulations.

In this study, DFT was used as a tool to describe the accurate geometries of 5 ethyl 6-and/or 7-substituted-3-oxo-2[H]-3,4-dihydro-l,4-benzoxazine-2-acetate derivatives and DIMBOA. The structure of the compounds, which previously were synthesized as antimicrobial agents by us, were presented in Table 1 except DIMBOA (17). They showed significant activity against some Gram-

positive and Gram-negative bacteria and a fungus *Candida albicans* between MIC values 12.5-50 u*g/mL* (Table 1). Although our structures were rasemic but we used R isomer of them for theoretic study because of DIMBOA. It was found as R isomer in nature (14,15). The geometry optimization for the investigated molecules were carried out with the GAUSSIAN 98. The calculations were performed within the DFT at Becke3LYP/6-31G(d,p) level single point energy evaluation.

Table 1. Derivatives of previously synthesized ethyl 6-and/or 7-substituted-3-oxo-2[H]-3,4-dihydro-l,4-benzoxazine-2-acetate and their antimicrobial activities as Minimum Inhibitory Concentrations (ug/mL).



			Microorganisms*					
			Gram-positive		Gram-negative			Fungus
Comp.	**R_1**	**R_2**	***Sa***	*Bs*	*Ec*	***Kp***	***Pa***	***Ca***
1	**-CH_3**	**-H**	**50**	**50**	**25**	**25**	25	25
2	**-H**	**-CH_3**	**50**	**50**	**50**	**50**	50	25
3	**-CI**	**-H**	**50**	**50**	**25**	**25**	25	12.5
4	**-H**	**-NO_2**	**25**	**25**	**25**	**25**	50	25
5	**-CI**	**-NO_2**	**50**	**25**	**25**	**25**	50	12.5

5a: *Staphylococcus aureus; Bs: Bacillus subtilis; EcEscherichia coli; Kp:Klebsiella pneumonia; Pa: Pseudomonas auruginosa;* ***Ca:*** *Candida albicans*

COMPUTATIONAL METHODOLOGY

Gas-phase full geometry optimization for the investigated molecules was carried out the GAUSSIAN 98 series of programs (18). The calculations were performed within the DFT (19,20). Becke's nonlocal three-parameter hybrid exchange and correlation functional in conjunction with the Lee-Yang-parr correlation formula (B3LYP) (21,22) was used. The 6-31G(d,p) double-zeta

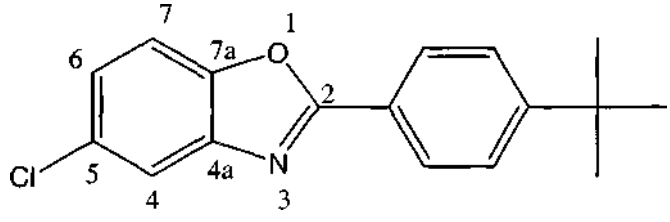
valance basis set with polarization functions on both hydrogen and heavy atoms was employed throughout the study (23). The single point calculations for effect modelling were performed in order to describe environmental influence on the properties of the molecule.

RESULTS AND DISCUSSION

In this study, atomic coordinates of 5-chloro-2-(p-?-butylphenyl)benzoxazole were utilized as a base to construct the molecules for series of benzoxazine derivatives (24). At first, 5-chloro-2-(p-t-butylphenyl)benzoxazole which determined as a X-ray structure has been optimized using Becke3LYP/6-31G(d,p) basis set to provide if this method is reliable for geometry optimization of structures. We compared the crystallographic bond lengths ($d_{x\text{-}ray}$) for 5-chloro-2-(p-t-butylphenyl)benzoxazole with calculated by DFT in Gaussian-98 at the level Becke3LYP/6-31G(d,p) as a single point energy calculation in Table 2. Bold letters were used to distinguish the values closest to crystallographic ones.

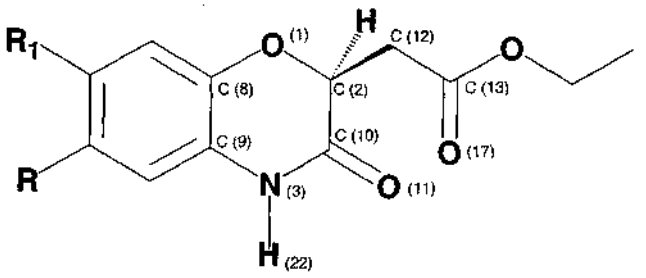
In the present paper, a set of previously synthesized antimicrobial active five ethyl 6-and/or 7-substituted-3-oxo-2[H]-3,4-dihydro-l,4-benzoxazine-2-acetate derivatives and DIMBOA were optimized with DFT in Gaussian-98 at Becke3LYP/6-31G(d,p) level. The results related to bond lenghts and torsion angles of benzoxazine derivatives and DIMBOA were given in Table 3. Besides, 3D visualizations of them from Sybyl 6.6 (25) were shown in Scheme 1.

Table 2. Comparison of selected bond lengths [A] for Becke3LYP/6-31G(d,p)

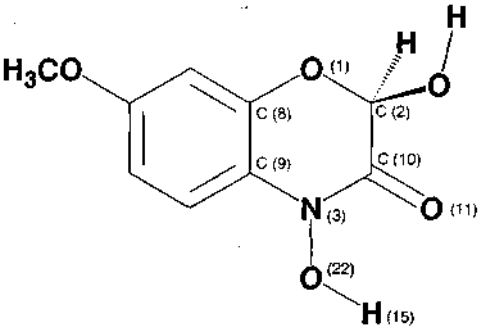


Bond	$d_{x\text{-}ray}$	B3LYP/6-31G(d,p)
C2-N3	1.293	**1.302**
N3-C4a	1.398	**1.390**
C4a-C7a	1.371	1.402
C7a-01	1.382	**1.370**
01-C2	1.387	**1.382**

Table 3. Selected bond lengths [Å] and Torsion angles (°) of benzoxazine derivatives (1-5) and DEMBOA for Becke3LYP/6-31G(d,p)

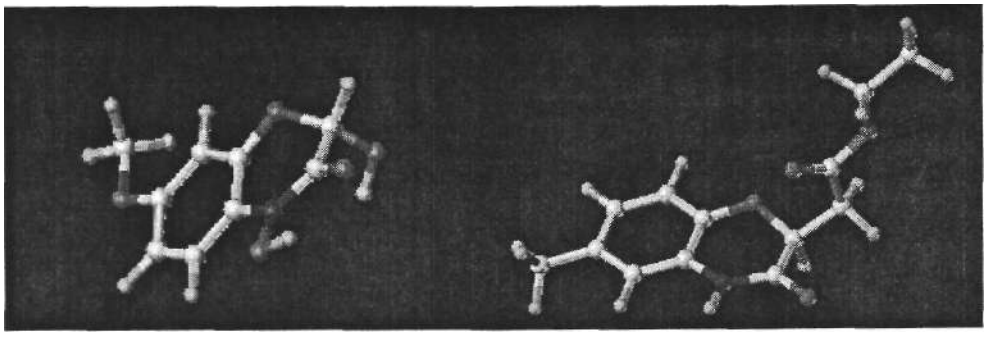


Benzoxazine derivatives (1-5)

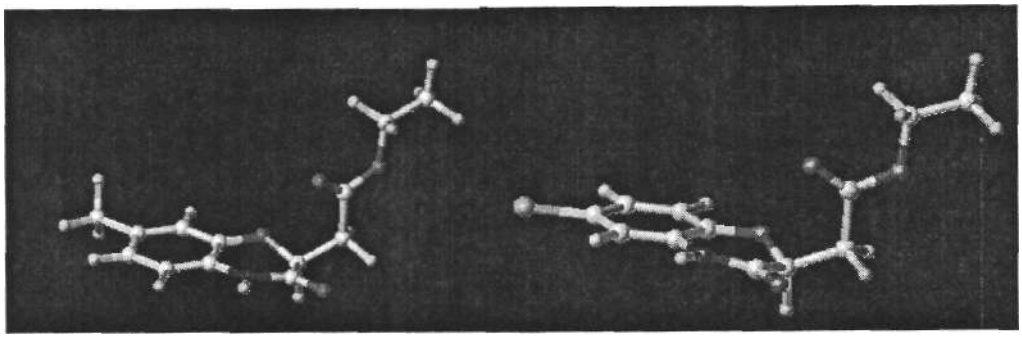


DIMBOA

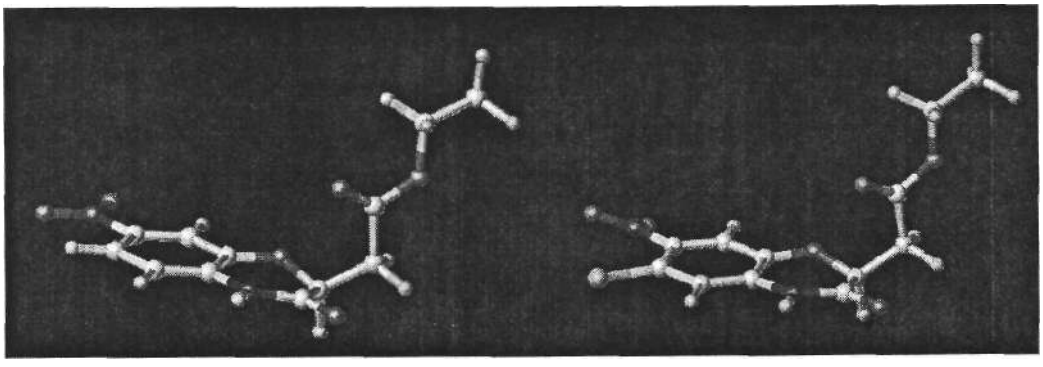
Compounds	Bond lenghts (A)	Torsion angles(°) 6
DIMBOA	0(1)-C(2) = 1.45; C(2)-C(10) = 1.53 C(10)-N(3) = 1.34; N(3)-C(9) = 1.41 C(9)-C(8) = 1.40; C(8)-0(l) = 1.37 O(ll)-H(15) = 2.05	O(l)-C(2)-C(10)-N(3) = 47.42
1	0(1)-C(2) = 1.43; C(2)-C(10) = 1.54 C(10)-N(3) = 1.37; N(3)-C(9) = 1.40 C(9)-C(8) = 1.40; C(8)-0(l) = 1.37 0(11)-H(22) = 2.48	O(l)-C(2)-C(10)-N(3) = 24.14 0(17)-C(13)-C(112)-C(2)= 17.38
2	0(1)-C(2) = 1.43; C(2)-C(10) = 1.54 C(10)-N(3) = 1.36; N(3)-C(9) = 1.40 C(9)-C(8) = 1.40; C(8)-0(l) = 1.37 0(11)-H(22) = 2.48	O(l)-C(2)-C(10)-N(3) = 24.21 0(17)-C(13)-C(112)-C(2) = 15.98
3	0(1)-C(2) = 1.44; C(2)-C(10) = 1.54 C(10)-N(3) = 1.37; N(3)-C(9) = 1.40 C(9)-C(8) = 1.40; C(8)-0(1) = 1.37 0(11)-H(22) = 2.47	O(l)-C(2)-C(10)-N(3) = 23.44 0(17)-C(13)-C(112)-C(2) = 16.95
4	0(1)-C(2) = 1.44; C(2)-C(10) = 1.53 C(10)-N(3) = 1.37; N(3)-C(9) = 1.39 C(9)-C(8) = 1.41; C(8)-0(l) = 1.36 0(11)-H(22) = 2.47	O(l)-C(2)-C(10)-N(3) = 19.98 0(17)-C(13)-C(112)-C(2)= 18.59
5	0(1)-C(2) = 1.44; C(2)-C(10) = 1.53 C(10)-N(3) = 1.37; N(3)-C(9) = 1.39 C(9)-C(8) = 1.41; C(8)-0(l) = 1.36 0(11)-H(22) = 2.47	O(l)-C(2)-C(10)-N(3) = 19.60 0(17)-C(13)-C(112)-C(2)= 16.08



DIMBOA Compound No 1



Compound No 2 Compound No 3



Compound No 4 Compound No **5**

Scheme 1: 3D Structure of Geometry Optimized of DIMBOA and Benzoxazine Derivatives (1-5)

In conclusion, first point here is that Becke3LYP/6-31G(d,p) level give some information for small molecule which is much closed values to X-Ray structure. The geometry results of some of optimized antimicrobial active ethyl 6-and/or 7-substituted-3-oxo-2[H]-3,4-dihydro-l,4-benzoxazine-2-acetate derivatives with DFT in Gaussian-98 at Becke3LYP/6-31G(d,p) level showed that a distinctly planar configuration of the cyclic moieties. However, benzoxazine ring with ethyl ester group at position 2 showed nonplanar configuration each other. They nearly seemed to be as a L shape. There was no more different either microbiological or geometrical values between all compounds (1-5). When we compared the geometries of DDVIBOA and our structures there was significantly differ about torsion angles of θ_1 (O(l)-C(2)-C(10)-N(3)). Consequently, it could be important θ_1 of 3-oxo-2[H]-3,4-dihydro-l,4-benzoxazine derivatives for further studies to get new antimicrobial agents.

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