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Investigation of degradation products of secondary metabolites of Bupropion molecule by DFT methods

S. Kurumoglu*, Y. Y. Gurkan

Tekirdag Namık Kemal University, Department of Chemistry, Tekirdag, Turkey

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Every substance (food, drug, etc.) taken into the body is excreted from the body by enzymatic mechanisms and given to the natural environment it pollutes the nature. Data from the Ministry of Health show that the amount of antidepressant use has increased by about 70 percent in the 11 years until 2020. According to the latest health statistics of the Ministry for 2020, while 29 antidepressant drugs per 1000 people per day were registered in 2009, this rate increased to 49 in 2020. In addition to its use as an antidepressant, Bupropion is also used in the treatment of smoking cessation, methamphetamine and cocaine addiction, behavioral addictions such as pathological gambling, and attention deficit hyperactivity disorder.

Our aim is to optimize with DFT method the 3 secondary metabolites of Bupropion, which are formed because of enzymatic reactions after the drug is taken into the body. It is to theoretically explain the degradation pathways the secondary metabolites given to the natural environment with urine may be exposed to.

Keywords: Gaussian 09, DFT, Antidepressant, Bupropion.

INTRODUCTION

When the annual statistics of antidepressant use in Turkey by the World Health Organization are examined, a linear increase is observed [1]. Every product (food, beverage, drug, etc.) taken into the body undergoes biotransformation as a result of enzymatic reactions, turns into metabolites and is excreted from the body [2].

Due to the increasing environmental pollution and climate crisis in the world, the substances released out of the body must be planned and implemented in a way that will not harm the environment [3]. Qualitative and quantitative analyses should be made whether the drugs used are mixed with soil and water resources. It is important that the analysis results are within tolerance limits that will not adversely affect human health, and if it is above the tolerance limits, drugs should be removed from water and soil resources [4].

Behaviors of drugs in nature are: degradation by soil microorganisms, chemical degradation (e. g. hydrolysis), adsorption and binding by organic and mineral soil, uptake by plant roots, evaporation, diluting effects of water flow processes [5].

Bupropion belongs to the chemical class of aminoketones and it is also known with the generic name of amfebutamone hydrochloride. It is a second-generation antidepressant approved in US and in some European countries, but its exact mechanism of action is not completely clear. With respect to the first generation antidepressants which different sites in the brain, second-generation drugs act at specific neurotransmitter receptor sites. In particular, Bupropion hydrochloride seems to act as a dopamine norepinephrine reuptake inhibitor and it is used also in smoking cessation and for treatment of seasonal affective disorders [6]. Bupropion is approved for use in major depression and seasonal affective disorder and has demonstrated comparable efficacy to other antidepressants in clinical trials. Bupropion is also useful in augmenting a partial response to selective serotonin reuptake inhibitor antidepressants, although Bupropion should not be combined with monoamine oxidase inhibitors [7].

S. Sevvanthi has analyzed the Bupropion molecule reactivity with various DFT methods such as local reactivity descriptors, Molecular electrostatic potential (MEP), Frontier Molecular orbitals (FMOs), Natural bond orbitals (NBO), etc. [8].

The stability in water of Bupropion was determined and the pH-degradation profile was obtained. The effects of hydrogen ion, solvent and hydroxide ion concentration were discussed with particular emphasis on the kinetics of degradation of Bupropion. Kinetics and degradation of Bupropion were determined by both HPLC-UV and LC-MS analysis utilizing high pH chromatographic methods. Degradation of Bupropion in aqueous solutions follows first-order reaction kinetics [9].

Although it is unlikely that any metabolite isomer is chiefly responsible for the stimulus actions of

* To whom all correspondence should be sent:
E-mail: skurumoglu@nku.edu.tr

Bupropion, some probably play a role in the complex actions of this agent [10].

The aim of this study is to computationally examine the degradation reactions of secondary metabolites of the drug molecule Bupropion to remove it from water sources and convert it into harmless molecules.

METHODOLOGY

Degradation reactions of molecules to be investigated will be examined by molecular modeling methods and theoretical approaches will be proposed for reaction pathways. For this purpose, possible reactions were calculated using Gaussian 09 package program. DFT method was used in the theoretical study. Quantum chemical methods are particularly significant in the study of electrochemistry and provide researchers with a relatively quick way of studying the structure and behavior of corrosion inhibitors [11].

In this study, possible reaction pathways of secondary metabolites of the Bupropion molecule were examined. For this purpose, the geometry of the molecules of secondary metabolites of Bupropion was optimized and the most appropriate quantum mechanical method was determined. Possible products were theoretically predicted and calculable examinations were carried out.

Calculations of the most durable conformers of secondary metabolites of the Bupropion molecule were carried out using DFT/B3LYP/6-31G(d) methods. All molecular orbital calculations were used in Gauss view5 molecular representation program and Gaussian 09W program [12].

The energy of the fragmentation reactions of all organic compounds in aqueous environment is affected by the water molecules. In addition, geometric stretching in the solution is induced by H_2O. However, the results obtained in many studies are that the geometry changes of the soluble substance for both open- and closed-shell structures have a trivial effect. Therefore, in order to explain the solvent effect of H_2O on Bupropion molecule +·OH reaction energy in this study; DFT/B3LYP/6-31G(d) method calculations were made and the COSMO (conductor-like screening solvation model) solvation model applied to the Gaussian package program was used [13].

RESULTS AND DISCUSSION

Fig. 1 shows the optimized geometric molecular structure of Bupropion in the drug molecule. Electronegative atoms attached to molecules O, N, Cl are shown in color. The bond lengths, bond angles and Mulliken loads of the molecules in Table 1 give preliminary information about the fragmentation sites of molecules.

In Table 1 presenting the Mulliken loads of the molecules, the atoms with the highest electronegativity C_1, O_{13}, N_{20}, C_{23} are written in bold.

Electrochemical calculations in gaseous and aqueous phase were performed for each molecule. The ΔE energy, ΔH enthalpy and ΔG Gibbs free energy values given in Tables 1, 4, 5, 7, 8, 10, 11 are given separately for each molecule. When the Gibbs free energy values of ΔG were examined, it was seen that the ΔG value of each fragmentation was negative. Thus, we list the drug molecules from the most stable to the most unstable.

The optimized geometric molecular structure of Bupropion is given in Figure 1.

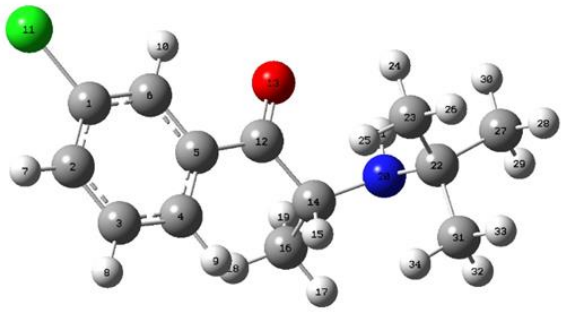


Figure 1. Optimized geometric structure of Bupropion with DFT method (grey: C; white: H; blue: N; red: O; green: Cl).

The ΔE energy, ΔH enthalpy, ΔG Gibbs free energy values and Mulliken loads of the Bupropion molecule are given in Table 1. When the Mulliken loads of the Bupropion molecule (Table 1) are analyzed, the electronegative atoms are C_1, O_{13}, N_{20}, C_{23}. As it can be seen in Figure 1, O_{13} of this atom forms a double bond with C_{12} atom. Since these bonds are stable, the bonds are not expected to break. C_1, N_{20}, C_{23} atoms are other electronegative atoms.

Bupropion's most durable geometric structure was optimized with DFT/B3LYP/6-31G(d) methods. As a result of DFT calculations, Bupropion 's total energy in the gaseous phase is -687692 kcal/mol, enthalpy -687691 kcal/mol, Gibbs free energy -687731 kcal/mol. The values of the total energy in the aqueous phase, enthalpy and Gibbs free energy are -687695.66 kcal/mol, -687695.06 kcal/mol, and -687734 kcal/mol, respectively. Optimized Bupropion 's geometric structure is shown in Figure 1 and geometric parameters; bond lengths, bond angles and Mulliken loads are shown in Table 2.

Table 1. Energy values of Bupropion in gaseous and aqueous phases, and their Mulliken loads in gaseous phase.

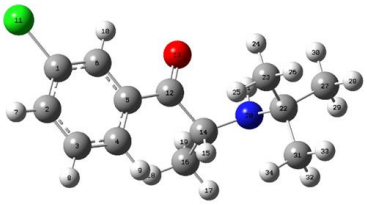
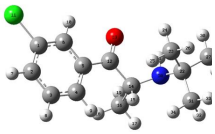
Bupropion ($C_{13}H_{18}O_1N_1Cl_1$)	Gaseous phase (kcal × mol^{-1})	Aqueous phase (kcal × mol^{-1})	Mulliken loads
	ΔE= -687692 ΔH= -687691 ΔG= -687731	-687695.66 -687695.06 -687734	**C_1 -0.249281** C_2 0.087099 C_3 0.009009 C_4 0.024974 C_5 0.041585 C_6 0.101939 Cl_{11} 0.078084 C_{12} 0.305184 **O_{13} -0.437718** C_{14} 0.071671 $C1_6$ 0.056567 **N_{20} -0.259149** C_{22} 0.157157 **C_{23} -0.004864** C_{27} 0.006372 C_{31} 0.011372

Table 2. Bond lengths and bond angles of atoms of Bupropion molecule.

Bupropion ($C_{13}H_{18}O_1N_1Cl_1$)	Bond length	(Å)	Bond length	(Å)	Bond angle	(°)
	$C_1 – Cl_{11}$	1.83	$C_{16} – C_{14}$	1.55	$C_5 – C_1 – Cl_{11}$	119.15
	$C_2 – H_7$	1.08	$N_{20} – C_{14}$	1.46	$C_{14} – C_{12} – O_{13}$	119.03
	$C_3 – H_8$	1.08	$C_{22} – N_{20}$	1.49	$C_{16} – C_{14} – C_{12}$	108.46
	$C_4 – H_9$	1.08	$C_{23} – C_{22}$	1.55	$C_{16} – C_{14} – N_{20}$	109.70
	$C_5 – C_{12}$	1.49	$C_{27} – H_{29}$	1.09	$H_{21} – N_{20} – C_{14}$	109.92
	$C_6 – H_{10}$	1.83	$C_{31} – C_{22}$	1.54	$C_{14} – N_{20} – C_{22}$	120.12
	$C_{12} – O_{13}$	1.25			$C_{31} – C_{23} – C_{22}$	34.87
	$C_{14} – C_{12}$	1.54			$C_{22} – C_{27} – H_{29}$	110.16

Bond lengths of C_5–C_{12}, N_{20}–C_{14} and C_{22}–N_{20} in Table 2 are 1.49 Å; 1.46 Å and 1.55 Å, respectively, and the bond angle of C_{14}–N_{20}–C_{22} is 120.12^0, while the bond angle of C_5–C_1–Cl_{11} is the second widest bond angle with 119.15^0. Based on this information, it is expected that the methyl groups of O_{13}, N_{20}, Cl_{11} atoms will break. So, it is understood that this is the first stage of degradation mechanism and O_{13} is the most electronegative atom. Looking at the area surrounded by this atom, in Table 2, C_6–H_{10} has a bond length of 1.83 Å, although the O_{13} atom is the most electronegative atom. Since there are bonds longer than this bond length, it is predicted that if there is a bond break here, it will happen after the other bonds. Even the fact that C_{14}–N_{20}–C_{22} and C_5–C_1–Cl_{11} in Table 2 have the widest bond angles with 120.12^0 and 119.15^0 respectively, this will not change the situation. Degradation pathway and optimized structure of secondary metabolites of Bupropion and the numbering system are shown in Figures 1, 2.

Secondary metabolites (M: Bupropion, M.2.1: 4’-OH-Bupropion, M.2.2: treo-4’-OH-Bupropion, M.2.3: eritro-4’-OH-Bupropion) of the Bupropion geometric structure and geometric parameters are shown in Tables 3, 4, 6, 7, 9, 10. Possible degradation pathways of the secondery metabolites were identified as breaking of N-C, C-O, Cl-C and aromatic ring bonds. The reaction sites were determined according to the Mulliken loads, bond lengths and bond angles distribution in the molecule. According to the values in the Mulliken loads, the nucleophilic site of the molecule is N_{20}. The hydroxyl radical, which is a very active species, has a strong electrophilic character. Therefore, it is willing to attack the molecule and form reaction intermediates. Degradation pathway and optimized structure of secondary metabolites of Bupropion are given in Figure 2.

Bond lengths, bond angles and Mulliken loads of atoms of M.2.1 molecule are given in Table 3.

The ΔE energy, ΔH enthalpy, and ΔG Gibbs free energy values of M.2.1 molecule are given in Table 4.

Degradation pathway of M.2.1 molecule and optimized structure of metabolites of M.2.1 are given in Figure 3.

The energy values in gaseous and aqueous phase of degradation fragments of M.2.1 molecule at ground state are given in Table 5.

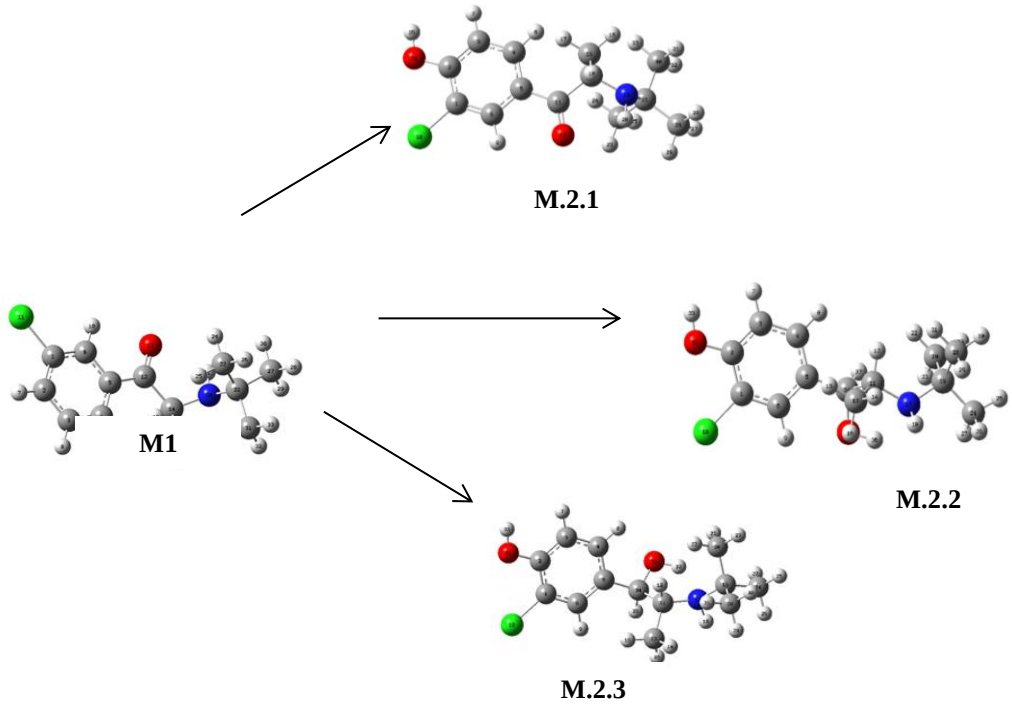
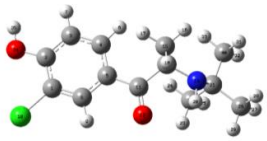


Fig. 2. Degradation pathway and optimized structure of secondary metabolites of Bupropion and the numbering system (grey: carbon; red: oxygen; blue: nitrogen; white: hydrogen; green: chlorine), (M: Bupropion, M.2.1: 4'-OH-Bupropion, M.2.2: treo-4'-OH- Bupropion, M.2.3: eritro-4'-OH- Bupropion)

Table 3. Bond lengths, bond angles and mulliken loads of atoms of M.2.1 molecule.

M.2.1



Bond angle	(°)	Bond length	(Å)			Mulliken loads	
$Cl_{10}– C_1 – C_2$	119.21	$Cl_{10} – C_1$	1.81	C_3	**-0.009240**	C_{15}	0.026049
$C_5- C_{11} - O_{12}$	32.71	$C_{11} - O_{12}$	1.25	C_4	**-0.003966**	N_{19}	**-0.224433**
$C_{13}- N_{19} - C_{21}$	120.02	$N_{19} - C_{21}$	1.49	C_5	0.057623	C_{21}	0.098541
$H_{35}- O_{34} - C_2$	112.13	$O_{34} -C_2$	1.38	C_6	0.075028	C_{22}	0.039640
				Cl_{10}	0.157489	C_{26}	0.011356
				C_{11}	0.334010	C_{30}	**-0.006674**
				O_{12}	**-0.405728**	O_{34}	-0.222987
				C_{13}	0.061775		

Table 4. Energy values in gaseous and aqueous phase of M.2.1 molecule at ground state.

	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.1	Gas	-734869.66	-734869.07	-734910.16
	Cosmo	-734877.14	-734876.54	-734917.65

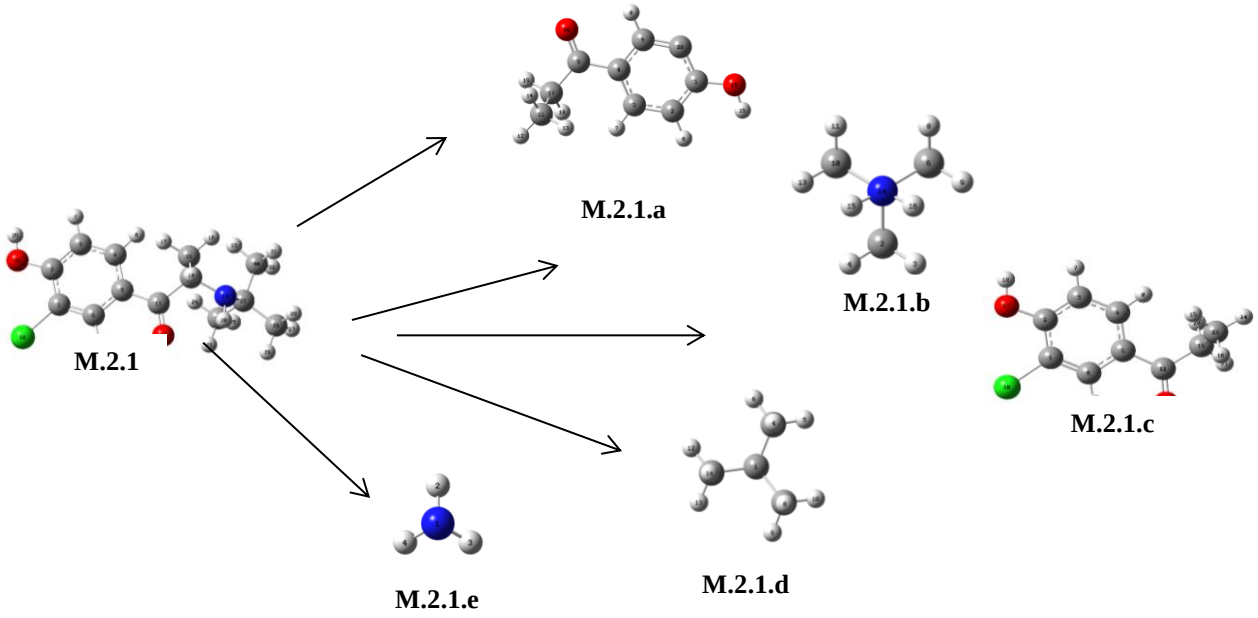


Fig. 3. Degradation pathway and optimized structures of M.2.1 metabolites and the numbering system (grey: carbon; red: oxygen; blue: nitrogen; white: hydrogen; green: chlorine).

Table 5. Energy values in gaseous and aqueous phase of degradation fragments of M.2.1 molecule at ground state.

Fragments	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.1.a	Gas	-60158542	-601584.83	-601616.49
M.2.1.a	*Cosmo*	*-601594.92*	*-601594.32*	*-601626.04*
M.2.1.b	Gas	-134030.38	-134029.79	-134052.88
M.2.1.b	*Cosmo*	*-134033.33*	*-134032.74*	*-134055.77*
M.2.1.c	Gas	-312768.98	-312768.39	-312798.40
M.2.1.c	*Cosmo*	*-312777.40*	*-312776.81*	*-312806.84*
M.2.1.d	Gas	-99347.68	-99347.08	-99368.58
M.2.1.d	*Cosmo*	*-99348.05*	*-99347.46*	*-99368.96*
M.2.1.e	Gas	-35460.88	-35460.29	-35474.00
M.2.1.e	*Cosmo*	*-35464.74*	*-35464.15*	*-35477.85*

Bond lengths, bond angles and Mulliken loads of atoms of M.2.2 molecule are given in Table 6.

The ΔE energy, ΔH enthalpy, ΔG Gibbs free energy values of M.2.2 molecule are given in Table 7.

The energy values in gaseous and aqueous phase of degradation fragments of M.2.2 molecule at ground state are given in Table 8.

Bond lengths, bond angles and Mulliken loads of atoms of M.2.3 molecule are given in Table 9.

The ΔE energy, ΔH enthalpy, ΔG Gibbs free energy values of M.2.3 molecule are given in Table 10.

The energy values in gaseous and aqueous phase of degradation fragments of M.2.3 molecule at ground state are given in Table 11.

Degradation pathway of M.2.3 molecule and optimized structure of metabolites of M.2.3 are given in Figure 5.

Table 6. Bond lengths, bond angles and Mulliken loads of atoms of M.2.2 molecule.

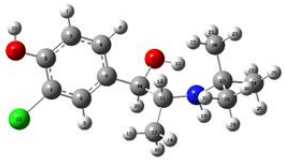
M.2.2							
							
Bond angle	(º)	Bond length	(Å)	Mulliken loads			
Cl_{10} - C_1 – $6C_6$	119.31	Cl_{10} - C $_1$	1.82	C_5	0.030374	C_{24}	-0.000371
C_{11}- N_{17} - H_{18}	111.65	N_{17} - H $_{18}$	1.02	C_6	0.159715	C_{28}	-0.006498
O_{32} - C_2 – C_3	123.05	O_{32} - C $_2$	1.38	Cl_{10}	0.140668	O_{32}	-0.236589
H_{37}- C_{34} - O_{36}	103.31	C_{34} - O_{36}	1.44	C_{11}	0.140356	C_{34}	0.157115
				C_{13}	-0.000515		
				N_{17}	-0.274760		
				C_{19}	0.092619		
				C_{20}	0.058911		

Table 7. Energy values in gaseous and aqueous phase of M.2.2 molecule at ground state.

	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.2	Gas	-735609.60	-735609.01	-735650.43
	Cosmo	-735620.28	-735619.69	-735661.26

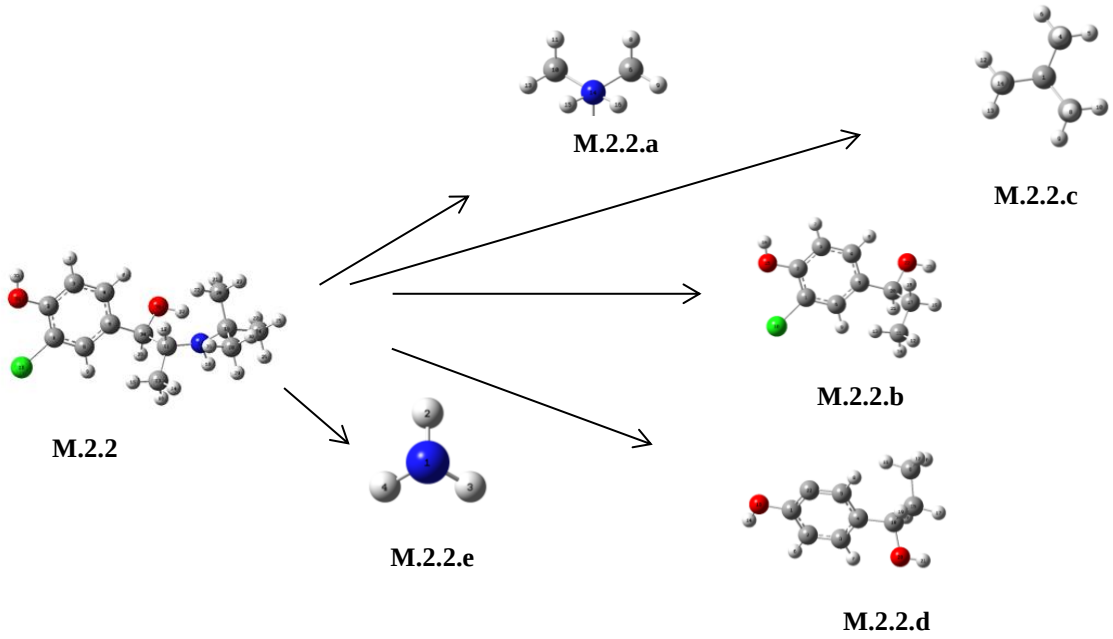


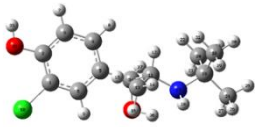
Fig. 4. Degradation pathway and optimized structures of M.2.2 metabolites and the numbering system (grey: carbon; red: oxygen; blue: nitrogen; white: hydrogen; green:chlorine).

Table 8. The energy values at gaseous and aqueous phase of degradation fragments of M.2.2 molecule at ground state.

Fragments	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.2.a	Gas	-602321.20	-602320.60	-602353.09
M.2.2.a	*Cosmo*	*-602330.69*	*-602330.10*	*-602362.60*
M.2.2.b	Gas	-134030.38	-134029.79	-134052.88
M.2.2.b	*Cosmo*	*-134033.33*	*-134032.74*	*-134055.77*
M.2.2.c	Gas	-313503.78	-313503.18	-313533.90
M.2.2.c	*Cosmo*	*-313512.32*	*-313511.72*	*-313542.62*
M.2.2.d	Gas	-99347.68	-99347.08	-99368.58
M.2.2.d	*Cosmo*	*-99348.05*	*-99347.46*	*-99368.96*
M.2.2.e	Gas	-35460.88	-35460.29	-35474.00
M.2.2.e	*Cosmo*	*-35464.74*	*-35464.15*	*-35477.85*

Table 9. Bond lengths, bond angles and Mulliken loads of atoms of M.2.3 molecule.

M.2.3



Bond angle	(°)	Bond length	(Å)	Mulliken loads			
Cl_{10} - C_1-C_6	119.31	Cl_{10} - C_1	1.82	C_5	0.141047	C_{24}	0.006455
C_{13}- C_{11} - H_{12}	42.31	$C1_1$ - H_{12}	1.09	C_6	0.013921	C_{28}	-0.002651
H_{15}- C_{13} - H_{16}	107.79	C_{13} - H_{16}	1.09	Cl_{10}	0.143286	O_{32}	-0.234704
C_{19}-N_{17} - C_{11}	121.24	N_{17} - C_{11}	1.49	C_{11}	0.140635	C_{34}	0.131646
O_{32} - $2C_2$ – C_1	118.56	O_{32} - C_2	1.38	C_{13}	0.012155	O_{35}	-0.215447
C_{34} - O_{35} -H_{36}	104.07	C_{34} - O_{35}	1.45	N_{17}	-0.242171		
				C_{19}	0.102713		
				C_{20}	0.022138		

Table 10. Energy values in gaseous and aqueous phase of M.2.3 molecule at ground state.

	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.3	Gas	-735608.40	-735607.81	-735649.12
	Cosmo	-735607.81	-735618.20	-735659.40

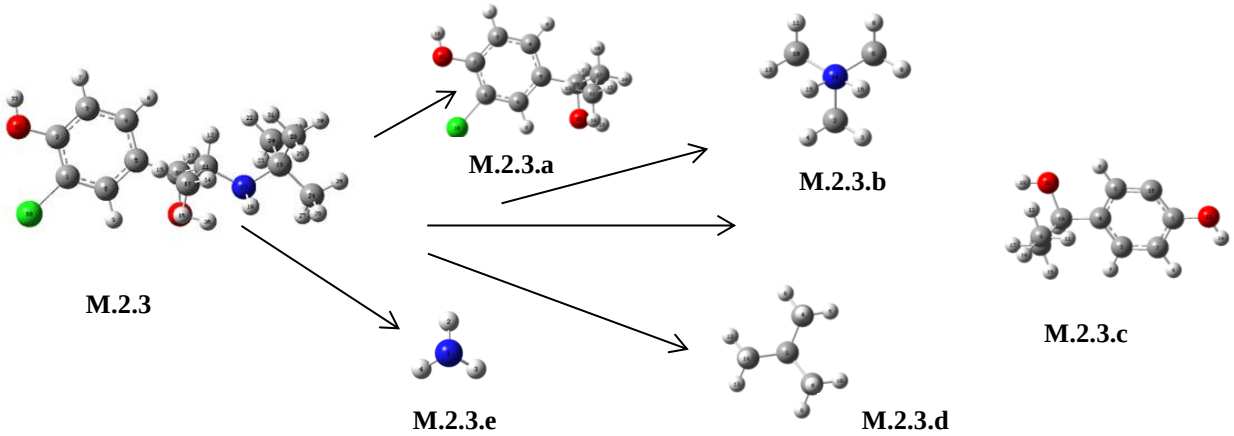


Fig. 5. Degradation pathway and optimized structures of M.2.3 metabolites and the numbering system (grey: carbon; red: oxygen; blue: nitrogen; white: hydrogen; green: chlorine).

Table 11. Energy values in gaseous and aqueous phase of degradation fragments of M.2.3 molecule at ground state.

Fragments	Phase	ΔE Energy (kcal/mol)	ΔH Enthalpy (kcal/mol)	ΔG Gibbs Free Energy (kcal/mol)
M.2.3.a	Gas	-602321.15	-602320.56	-602353.10
M.2.3.a	*Cosmo*	-602330.71	-602330.11	-602362.69
M.2.3.b	Gas	-134030.38	-134029.79	-134052.88
M.2.3.b	*Cosmo*	-134033.33	-134032.74	-134055.77
M.2.3.c	Gas	-313503.86	-313503.27	-313534.11
M.2.3.c	*Cosmo*	-313512.23	-313511.64	-313542.41
M.2.3.d	Gas	-99347.68	-99347.08	-99368.58
M.2.3.d	*Cosmo*	-99348.05	-99347.46	-99368.96
M.2.3.e	Gas	-35460.88	-35460.29	-35474.00
M.2.3.a	*Cosmo*	-35464.74	-35464.15	-35477.85

The ΔE energy, ΔH enthalpy and ΔG Gibbs free energy values in Tables 1, 4, 5, 7, 8, 10, 11 are given separately for each molecule. Looking at the data in Tables 1, 4, 5, 7, 8, 10, 11, the fragment 4 (F4) of Bupropion has the lowest energy, in other words, it has the most stable structure. This fragment is formed by bond breaking from the ring to which the electronegative O atom is attached.

In this study, possible reaction paths in the reaction between secondary metabolites of Bupropion and OH radical were determined. The degradation reaction requires energy. OH radicals are used to degrade drug substances in water. As seen in the fragments obtained, secondary metabolites of Bupropion were reduced to total 15 fragments and became harmless to the environment. Our aim was to break down the drugs that are mixed with water down to the smallest harmless substances and remove their toxic effect from water. As can be seen from the results, this fragmentation took place theoretically.

For the fragments in Tables 4, 5, 7, 8, 10, 11 the energy values in the gaseous and aqueous phase were examined. The lowest energy level, in other words, the degradation path starting from the most stable fragment for secondary metabolites of Bupropion in Figure 2, was determined both in the light of the above mentioned predictions, and by the analysis of the energy values of each fragment in Tables 1, 4, 5, 7, 8, 10, 11.

CONCLUSIONS

In this study, the possible reaction paths between secondary metabolites of the drug Bupropion molecule and OH radicals were determined. For this purpose, geometry optimization of the molecules was made, then the most appropriate quantum mechanical method was determined and the possible products were theoretically predicted.

The fragmentation reaction requires energy. OH radicals are used to degrade drug molecules. Our goal was to break down drug molecules molecules down to the smallest harmless substances. As can be seen from the results, this fragmentation took place theoretically. These results will guide experimental studies and determine the fragmentation mechanism.

The geometrical parameters of bond length, bond angle, Mulliken loads, ΔE energy, ΔH enthalpy, ΔG Gibbs free energy were calculated using DFT analysis with Gaussian 09.

In these days the use of antidepressants has increased considerably, our aim is to determine the metabolites of the Bupropion drug molecule that may occur in wastewater. The aim of this theoretical study is to refine the wastewater matrix and guide experimental studies by determining the fragmentation mechanism.

After the Bupropion drug molecule is taken into the body, it is converted by enzymes into 3 main primary metabolites. However, studies have shown that only 24% of them are in this form in the urine. As a result of the studies, the presence of 3 secondary metabolites excreted in the urine was determined.

In this study, possible degradation pathways of 3 secondary metabolites given to the wastewater matrix with urine were predicted by molecular modeling. It is estimated that the treatment of these degradation products, which are likely to be found in wastewater, will affect the characterization of wastewater, which is a living matrix.

Optimized physicochemical parameters of each secondary metabolite using the DFT/B3LYP/6-31G(d) method: bond lengths, bond angles, Mulliken charges and ΔE energy, ΔH enthalpy, ΔG Gibbs free energy values were calculated. Based on these properties, it has been estimated by computational methods that the OH radical formed in wastewater has reduced to 5 molecules each secondary metabolite as a result of its effects on

secondary metabolites. The physicochemical properties of the 15 new fragments obtained: ΔE energy, ΔH enthalpy, ΔG Gibbs free energy values were calculated.

It is thought that these theoretical calculations made in this period when the importance of environmental pollution has much more increased can be of a quality that can give priority to the treatment of wastewater.

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