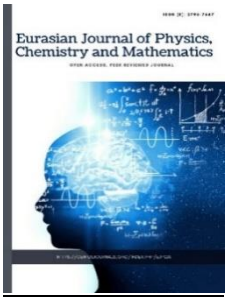


Study on molecular structure for Bupropion and its Derivatives using Quantum Mechanics Methods

Qabas M. AL – Makhzumi* Ministry of Health, Baghdad Health Office, Al-Rusafa Specialized Center of Allergy
*Corresponding Authors: qabas.mh55@yahoo.com

Samar Salah Raheem Ministry of Health, Baghdad Health Office, Al-Rusafa Specialized Center of Allergy

ABSTRACT

Quantum chemical calculation was correlated with geometrical structure and total energy of Bupropion and its five derivatives. Theoretical vibrational frequencies and geometric parameters (bond lengths) have been calculated using ab initio (HF), density functional theory (B3LYP), semi-empirical (AM1, PM3) methods with different basis sets to design the Bupropion drugs and its derivatives by a Gaussian 09 W program with GUI(Graphical User interface) called Gauss View 5.08. Theoretical optimized geometric parameters and vibrational frequencies of Bupropion have been compared with the corresponding five derivatives data. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies have been determined. The theoretical study includes the calculation of the thermodynamic properties of the drugs and its derivatives like zero-point energy, enthalpy, entropy, ionization energy, electron affinity to make a correlation between the gained results. the drug was Bupropion as an antidepressant and drug adduct treatments. The theoretical different methods showed that the derivatives (4) are one of the best addicts which have a drug charactors.

Keywords: Bupropion, AM1, PM3, DFT, and Hartree-Fock: Thermodynamic properties

Introduction

Depression is a common, chronic and potentially debilitating illness that has tempered the human condition since the beginning of recorded history [1]. It is a potentially life- threatening disorder that affects hundreds of millions of people all over the world. It can occur at any age from childhood to late life and is a tremendous cost to society as this disorder causes severe distress and disruption of life and, if left untreated, can be fatal (2). The area of pharmacotherapy of depression started in the 1950s, with landmark publications and discoveries that still govern the manner in which we treat depression. Bupropion is a medication primarily used as an antidepressant and smoking cessation aid. Bupropion is taken in tablet form and is available only by prescription in most countries. Bupropion is one of the most widely prescribed antidepressants, and the available evidence indicates that it is effective in clinical depression[2]. Bupropion has several features that distinguish it from other antidepressants: for instance, unlike the majority of antidepressants, it does not usually cause sexual dysfunction[3] Bupropion treatment also is not associated with the sleepiness or weight gain that may be produced by other antidepressants.[3] Bupropion is helpful for smoking cessation in smokers with no history of depression; thus, the effectiveness of bupropion is not due to its antidepressant effect. The chemical formula is $C_{13}H_{18}ClNO$ and structure as shown in figure 1

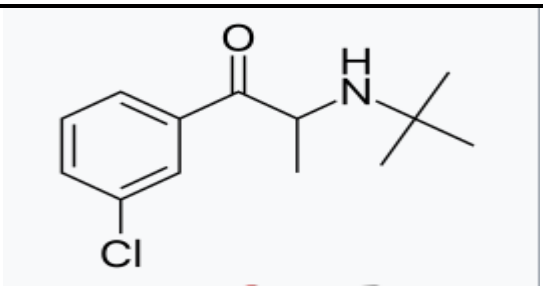
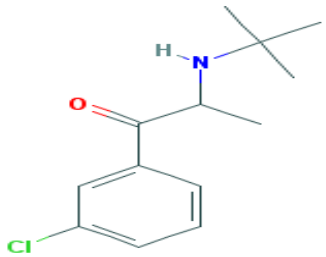
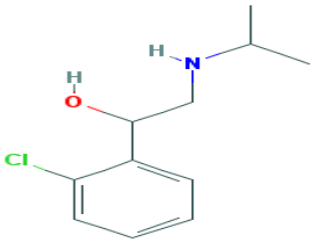
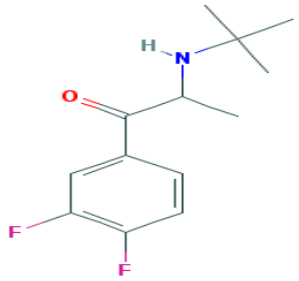
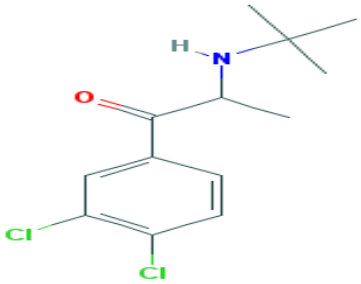
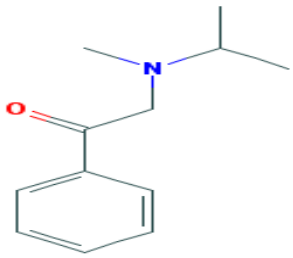
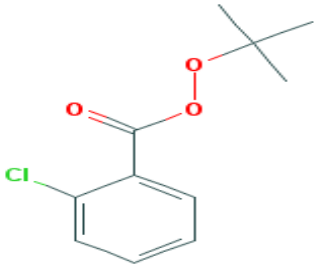


Figure 1:- Structure of Bupropion

Employed in the present work, calculations were used to determine the spectroscopic and electronic characters of the drug and its derivatives which are used to make a correlation in bioactivity future of them. It is important to identify the appropriate structures and the detailed electronic charge distribution; dipole moment, total energy and other properties in fluoxetine and its derivatives. Amide bonds are indeed present in a huge array of molecules, including major marketed drugs [4; 5]. Hence amides and their derivatives have attracted continuing interest over the years. The four Bupropion derivatives were prepared previously, but its bioactivity has not been characterized yet.

Figs (2) - The molecular structure Bupropion drug and its derivatives

Bupropion	Patent 1	Patent 2
		
Patent 3	**Patent 4**	**Patent 5**
		

Materials and Method

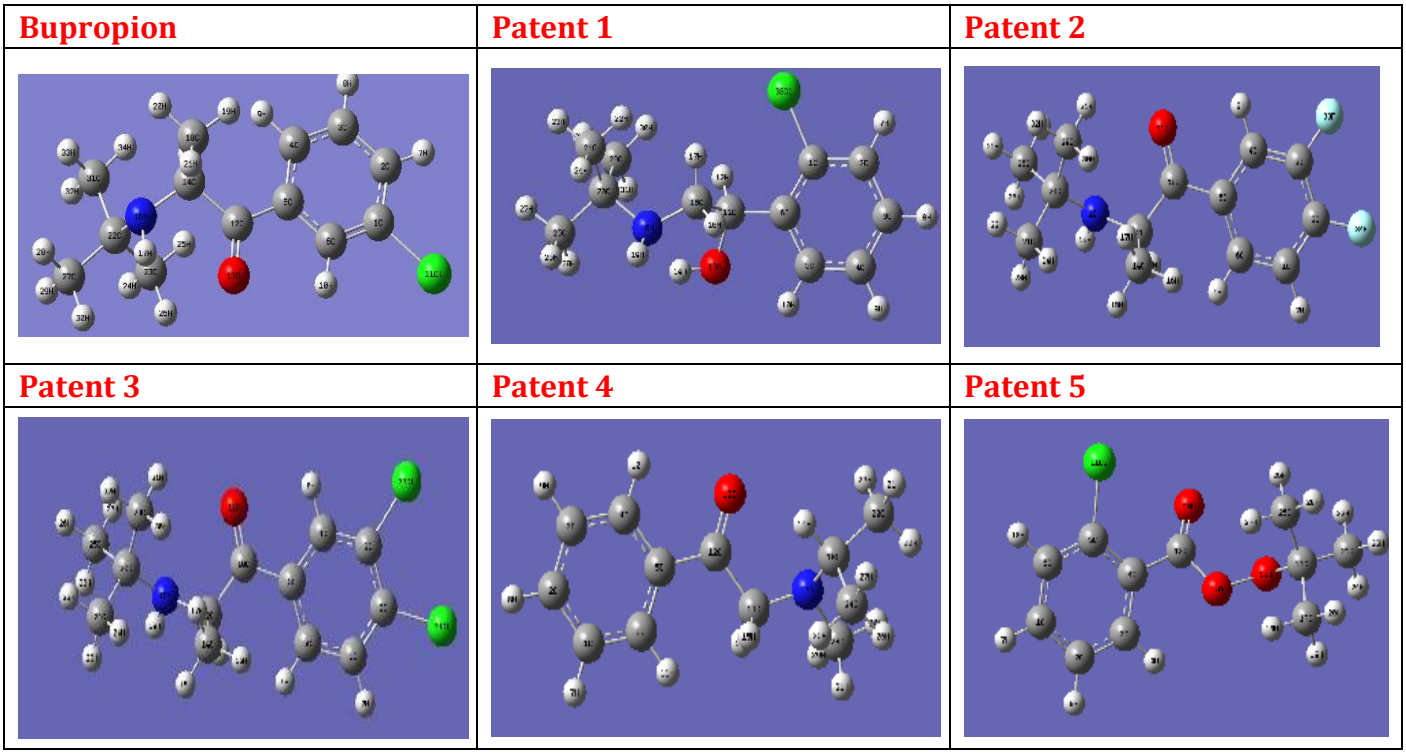
(Fig 3) Show the structural formula and the atomic position numbers in this work, the molecular structures of Bupropion and its derivatives are presented in (fig 3) and Table 1 respectively.

Name	Formula	Molecular Weight	IUPAC Name
Bupropion	$C_{13}H_{18}ClNO$	239.743 g/mol	2-(tert- butylamino)-1-(3-chlorophenyl)propan-1-one
Patent 1	$C_{12}H_{18}ClNO$	227.732 g/mol	2- (tert-butylamino) -1-(2-chlorophenyl)ethanol
Patent 2	$C_{13}H_{17}F_2NO$	241.282 g/mol	2-(tert – butylamino) -1- (3,4-difluorophenyl)propan -1- one

Patent 3	**$C_{13}H_{17}Cl_2NO$**	**274.185 g/mol**	**2-(tert – butylamino) -1- (3,4- dichlorophenyl)propan -1-one**
Patent 4	**$C_{12}H_{17}NO$**	**191.274 g/mol**	**2-[methyl(propan -2-yl)amino]-1-phenylethaneone**
Patent 5	**$C_{11}H_{13}ClO_3$**	**228.672 g/mol**	**Tert – butyl -2 – chlorobenzene carboperoxoate**

Tables (1) - Physical properties for Bupropion drug and its derivatives

Fig. (3) - 3D structure of various of Bupropion drug and its Derivatives in G09



The program that used in the search

Gaussian 09

An electronic structure package capable of predicting many properties of atoms, molecules, reactive system[6], e.g.:

- Molecular energies
- Structures
- Vibrational frequencies
- Electron densities
- Utilizing ab-initio, density functional theory, semi-empirical, e.g.

Gauss View 5.08

- Graphical interface for Gaussian 09[7; 8]
- Sketch molecules
- Setup Gaussian 09
- Graphically examine results.

Molden

- A graphical interface for Gaussian 09 and other program
- Setup Gaussian 09 input files
- Graphically examine results

Computational Details

In the first step of the calculation, geometrical parameters of these structures were further optimized by using density functional theory DFT (B3LYP)/6-31G, HF, AM1, PM3 methods. On the basis of the lowest energy conformer, the bond length was obtained using the four methods. The electronic properties: HOMO-LUMO energies are calculated by four methods, based on the optimized structure for soluble in water solvent [9; 10]. Thermodynamic properties of the title compound at 310 k temperature have been calculated using four methods. Moreover, the dipole moment and Mulliken atomic charge have also been studied using Gaussian 09 W program package. The initial atomic coordinates

for geometry optimization was taken from Gauss View software database [11]. The molecular structure of drug in the ground state (in water) was optimized by HF and DFT/B3LYP with AM1 and PM3 methods for basis set levels. The optimized structure of the molecule was used to calculate the vibrational frequency at four methods. The calculated thermal correction to energy was scaled by 194.22 Kcal/mole^{-1} (AM1), 190.52 Kcal/mole^{-1} (PM3), 204.46 Kcal/mole^{-1} (HF), and 192.52 Kcal/mole^{-1} (DFT) for Bupropion and compare with the thermal correction energy for five derivatives.

Results and Discussion

Molecular Structure

The schematic depiction of the drug with its derivatives by structure optimization are shown in fig.3 and the optimized bond length of Bupropion and its derivatives which were calculated by using four methods with different basis set are shown in Table 2. By compares the calculated geometric parameters for the drug and its derivatives. The relative energies of the molecule have been calculated employing (Semi-empirical, ab initio, and density functional theory). The optimized structural parameters(bond lengths)shows a good relationally agreement for the different methods[12; 13]. The geometry optimization of bond length for the derivatives show a slight difference from the Table 3, drug bond length. Due to fact that the theoretical calculation deals with an isolated molecule in water solvent and 310 K temperature in two programs. The mean values of (C- Cl) , (N- C), (C-O), bond length which calculates by (AM1, PM3) (1.70, 1.45, 1.24), (1.68, 1.49, 1.21)Å .But bond length which calculate by (HF, DFT) in G09 (1.81, 1.83)Å,(1.45,1.46)Å, (1.22,1.23)Å, a bond length which calculate by (AM1, PM3) were longer than that of (HF, DFT) which used force field theory. Its not possible to predict the activity of a compound depending on the bond length character alone, on other hand derivatives (2,4) give the most similarity in bond length with a drug for all methods.

			Bond Length(G 09) Å									
Bond	**Bupropion**		**Patent 1**		**Patent 2**		**Patent 3**		**Patent 4**		**Patent 5**	
	AM1	**PM3**	**AM 1**	**PM3**	**AM 1**	**PM3**	**AM 1**	**PM3**	**AM 1**	**PM3**	**AM 1**	**PM3**
C_{22} – N_{16}	**1.47**	**1.51**	**1.44**	**1.48**	**1.45**	1.50	**1.50**	**1.50**	**1.45**	**1.49**	**.....**	**.....**
N_{16} – C_{24}	**1.45**	**1.49**	**1.47**	**1.51**	**1.47**	1.49	**1.49**	**1.49**	**1.46**	**1.48**	**.....**	**.....**
C_{12} – O_{13}	**1.24**	**1.21**	**1.42**	**1.41**	**1.23**	**1.21**	**1.23**	**1.21**	**1.23**	**1.21**	**1.22**	**1.21**
C_{12}– C_5	**1.47**	**1.52**	**1.50**	**1.54**	**1.52**	**1.49**	**1.48**	**1.47**	**1.48**	**1.49**	**1.47**	**1.49**
C_{14} – C_{18}	**1.53**	**1.52**	**1.54**	**1.53**	**1.48**	**1.53**	**1.52**	**1.53**	**1.51**	**1.51**	**1.52**	**1.53**
C $_{22}$ – C_{23}	**1.52**	**1.53**	**1.53**	**1.51**	**1.54**	**1.52**	**1.52**	**1.53**	**1.52**	**1.53**	**1.53**	**1.53**
C - F	**.....**	**……**	**.....**	**.....**	**1.35**	**1.34**	**....**	**.....**	**....**	**.....**	**...**	**...**
C - Cl	**1.70**	**1.68**	**1.70**	**1.69**	**.....**	**.....**	**1.69**	**1.68**	**.....**	**……**	**1.69**	**1.68**
			Bond Length(G 09) Å									
Bond	**Bupropion**		**Patent 1**		**Patent 2**		**Patent 3**		**Patent 4**		**Patent 5**	
	HF	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**
C_{22} – N_{16}	**1.47**	**1.49**	**1.46**	**1.49**	**1.45**	**1.46**	**1.44**	**1.46**	**1.44**	**1.46**	**……**	**.....**
N_{16} – C_{24}	**1.45**	**1.46**	**1.47**	**1.47**	**1.47**	**1.49**	**1.47**	**1.46**	**1.47**	**1.49**	**.....**	**....**

C_{12} – O_{13}	1.22	1.23	1.43	1.44	1.22	1.24	1.22	1.24	1.22	1.25	1.20	1.22
C_{12}– C_5	1.49	1.49	1.51	1.51	1.50	1.50	1.50	1.50	1.51	1.49	1.48	1.49
C_{14} – C_{18}	1.53	1.55	1.50	1.57	1.52	1.54	1.52	1.52	1.49	1.52	1.53	1.52
C_{22} – C_{23}	1.54	1.55	1.54	1.54	1.53	1.54	1.53	1.51	1.53	1.52	1.52	1.54
C - F	….	……	…..	…..	1.37	1.38	….	…	…..	…	…..	….
C - Cl	1.81	1.83	1.82	1.84	…..	…..	1.80	1.81	…..	……	1.81	1.82

Table 2: Bond length for the drug and its derivatives in water solvent at 310k temperature

4.2. Thermodynamic Parameters and Molecular Properties

To evaluate the energetic behavior of the title compound in water solvent media theoretical calculations were carried out to determine total energies and dipole moments, using (AM1, PM3) in Hyper Chem. and Gaussian 09 by(HF, DFT/6-31G) level for Bupropion drug, Bioactive and its derivatives. Table (3),(4) lists the calculated values of some thermodynamic parameters (such as Zero-point vibrational energy, enthalpy, Gibbs free energy). Patent (4) have the highest energy, which means that both compounds were more stable than the drug, on other hand patents(5) is less stable due to lower energy, the only patent has similar energy is patent (2,3). The result obtained using (HF. DFT) method predicts the same evaluation. The value of the dipole moment(D.M) for a drugs was also calculated in Table(3),(4). The dipole moment is a measure of the molecular charge distribution. Direction of the (D.M) in a molecule depends on the center of positive and negative charges, As a result of calculations, the highest dipole moment was observed for drug in HF/6-31G (5.9814) whereas the smallest one was observed for drug in AM1(3.9092) the value of the dipole moment due to their effect on the charge density of the molecule. The value of the (D.M) for the compounds is a character for the polarity of the compounds mostly, the higher the compound polarity the higher that activity of it. Table(3)(4) shows that patent 4 was the only derivative has a (D.M) similar to that of the drug. Gaussian predicts various important thermodynamic quantities at the specified temperature and pressure, including the thermal energy correction, heat capacity, and entropy. It also gives the zero- point energy (ZPE). Their terms are broken down into their source components in the output: for example data for AM1:

Zero-point correction = 0.291710 (Hartree/Particle)

Thermal correction to Energy = 0.309517 ($E_{therm} = ZPE + E_{trans} + E_{rot} + E_{vib}$)

Thermal correction to Enthalpy = 0.310498 ($E_{therm} = E_{therm} + pV$)

Thermal correction to Gibbs Free Energy = 0.243165 ($G_{therm} = H_{therm} - TS$)

Sum of electronic and zero-point Energies = 0.235472 ($E_0 = E_{elect} + ZPE$)

Sum of electronic and thermal Energies= 0.253278 ($E = E_0 + E_{tran} + E_{rot} + E_{vib} = E_{elect} + E_{therm}$)

Sum of electronic and thermal Enthalpies = 0.254260 ($H = E + Pv = E_{elect} + H_{therm}$)

Sum of electronic and thermal Free Energies = 0.186927 ($G = H - TS = E_{elect} + G_{therm}$)

The entropy is also given in the output, along with the heat capacity (C_V) and broken down to individual contributions. The Entropy S can be used to calculate the Gibbs free energy from enthalpy. Note though that these are in different units than the quantities above:

	E (Thermal)	CV	S
	kcal/mol	cal/mol-Kelvin	cal/mol- Kelvin
Total	194.225	63.701	136.298
Electronic	0.000	0.000	0.000
Translational	0.924	2.981	42.510

Rotational 0.924 2.981 33.381

To calculate total energies, enthalpies and Gibbs free energies, you need to add the electronic energy to the thermal corrections. The electronic energy is in the log file from the original job:

SCF Done: E(RAM1) = -0.562384092353 A.U. after 16 cycles

To see that it works, let us add the thermal corrections from the freq. output to the electronic energy E and compare to the summed energies:

Sum of electronic and Zero- point Energies= -0.562384092353 + 0.291710 = 0.235472A.U.

As you can see the energy (under sum of electroinc and ZPE) is 0.122869 A.U, which is

0.235472× 627.5 Kcal.mol^{-1}= 147.75868 kcal.mol^{-1}

Table (3) - Selected thermodynamic parameters for AM1,PM3 of the drug and its Derivatives in G09

Thermodynamic Parameter	Bupropion		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
Zero-Point Vibrational energy (Kcal.mole^{-1})	183.04	179.32	179.77	175.32	179.55	176.08	177.28	173.21	170.56	165.92	140.87	136.88
Thermal Correction to energy (Kcal.mole^{-1})	194.22	190.52	190.25	186.04	190.82	187.35	189.04	185.08	180.13	175.49	151.23	147.72
Thermal Correction to enthalpy (Kcal .mole^{-1})	194.83	191.14	190.86	186.65	191.44	187.97	189.65	185.69	180.74	176.11	151.84	148.33
Thermal Correction to Gibbs Free Energy (Kcal .mole^{-1})	152.58	149.36	150.58	146.13	148.94	146.60	145.83	142.54	142.17	132.0	110.80	105.37
C_V (Cal/mole-Kelvin)												
Total	63.70	65.42	60.61	62.90	65.12	66.83	67.00	69.17	54.29	56.20	56.74	59.47
Translation	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981
Rotational	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981
Vibrational	57.73	59.46	54.65	56.94	59.16	60.87	61.04	63.20	48.33	50.23	50.78	53.51
S (Entropy) (Cal/mole-Kelvin)												
Total	136.29	134.76	129.93	130.74	137.11	133.44	141.36	139.19	124.40	148.95	132.40	138.58
Translation	42.51	42.51	42.35	42.35	42.53	42.45	42.90	42.40	41.84	41.84	42.36	42.36
Rotational	33.38	33.41	32.77	32.93	33.26	33.26	34.02	33.95	32.10	32.14	32.62	32.84
Vibrational	60.40	58.84	54.79	55.45	61.31	75.64	64.43	62.33	50.45	48.95	57.41	63.37

E_{Homo}(eV)	-9.7347	-9.6261	-9.6065	-9.5287	-9.8931	-9.6843	-9.7295	-9.5526	-9.4158	-9.3869	-10.002	-9.736
E_{Lumo} (eV)	-0.7001	-0.6478	-0.0731	-0.1330	-0.5823	-0.7303	-0.6440	-0.0164	-0.4410	-0.4108	-0.5624	-0.688
$E_g = E_{Lumo} - E_{Homo}$(eV)	9.0345	8.9782	9.5333	9.3956	9.3107	8.9539	9.0854	9.5361	8.9747	8.9760	9.4397	9.047
Ionization Potential (IE = - E_{HOMO})	9.7347	9.6261	9.6065	9.5287	9.8931	9.6843	9.7295	9.5526	9.4158	9.3869	10.0022	9.736
Electron affinity (EA = - E_{LUMO})	0.7001	0.6478	0.0731	0.1330	0.5823	0.7303	0.6440	0.0164	0.4410	0.4108	0.5624	0.688
Dipole moment (Debye)	3.9092	4.9586	2.2928	3.3023	4.7209	5.2617	4.6402	4.6925	4.5203	4.6557	3.9588	4.188

Table (4) - Selected thermodynamic parameters for HF,DFT of the drug and its Derivatives in G09

Thermodynamic Parameter	Bupropion		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT
Zero-Point Vibrational energy (Kcal $mole^{-1}$)	193.82	181.18	190.95	178.37	188.90	176.51	187.17	174.82	182.73	169.69	149.18	138.89
Thermal Correction to energy ($Kcal.mole^{-1}$)	204.46	192.52	200.85	188.85	199.96	188.28	198.70	187.06	189.12	179.25	158.81	149.26
Thermal Correction to enthalpy ($Kcal.mole^{-1}$)	205.08	193.14	201.47	189.46	200.57	188.90	199.32	187.68	189.73	179.86	159.43	149.87
Thermal Correction to Gibbs Free Energy ($Kcal.mole^{-1}$)	164.36	151.09	162.73	149.39	159.55	146.58	156.76	143.73	159.27	142.10	120.68	109.42
Cv (Cal/mole-Kelvin)												
Total	61.44	65.49	58.08	61.89	64.28	68.82	65.85	64.44	41.34	55.51	54.31	58.73
Translation	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981
Rotational	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981	2.981

Vibrational	**55.48**	**59.98**	**52.12**	**55.93**	**58.32**	**62.85**	**59.89**	**64.44**	**35.38**	**49..01**	**48.35**	**52.77**
S (Entropy) (Cal/mole-Kelvin)												
Total	**131.34**	**135.61**	**124.94**	**129.28**	**132.31**	**136.50**	**137.32**	**141.79**	**98.25**	**121.80**	**125.01**	**130.50**
Translation	**42.51**	**42.51**	**42.357**	**42.35**	**42.53**	**42.53**	**42.90**	**42.90**	**41.84**	**41.84**	**42.36**	**42.36**
Rotational	**33.45**	**33.49**	**32.93**	**32.95**	**33.40**	**33.44**	**34.19**	**34.23**	**32.01**	**32.17**	**32.88**	**32.93**
Vibrational	**55.38**	**59.60**	**49.66**	**53.95**	**56.37**	**60.53**	**60.23**	**64.64**	**24.40**	**47.78**	**49.35**	**55.20**
E_{Homo}(eV)	**-9.6365**	**-5.7831**	**-9.2615**	**-6.2666**	**-9.4022**	**-5.5666**	**-9.4057**	**-5.5891**	**-9.1584**	**-5.4509**	**-9.7731**	**-7.2808**
E_{Lumo} (eV)	**1.7714**	**-2.1151**	**3.4479**	**-0.3763**	**1.9396**	**-1.9730**	**1.7839**	**-2.1088**	**2.1578**	**-1.7768**	**-0.1480**	**-1.9148**
$Eg = E_{Lumo} - E_{Homo}$(eV)	**11.4079**	**3.6679**	**12.7089**	**5.8902**	**11.341**	**5.5666**	**11.1896**	**3.4803**	**11.3162**	**3.6735**	**9.9211**	**5.3659**
Ionization Potential (IE = - E_{HOMO})	**9.6365**	**5.7831**	**9.2615**	**6.2666**	**9.4022**	**3.07251**	**9.4057**	**5.5891**	**9.1584**	**5.4509**	**9.7731**	**7.2808**
Electron affinity (EA = - E_{LUMO})	**-1.7714**	**2.1151**	**-3.8136**	**0.3763**	**-1.9396**	**1.9730**	**1.7839**	**2.1088**	**-2.1578**	**1.7768**	**-0.1480**	**1.9148**
Dipole moment (Debye)	**5.9814**	**5.2444**	**3.5711**	**4.0352**	**7.4164**	**6.3861**	**7.3668**	**6.6943**	**5.4806**	**4.9310**	**6.5988**	**5.6407**

Theoretical Atomic Charge Calculation

Table (5),(6) shows effective atomic charge calculated which has an important role in the application of quantum chemical calculation for the molecular system atomic charge levels, and the comparison of the different method to describe the electron distribution of the drugs with its derivatives. The result of (AM1, PM3, HF, DFT) methods illustrated in Table (5), (6) the charge change with the method, basis set presumably occurs due to polarization. The atomic charge calculation for O_{15}, N_{20}, atoms exhibits a substantial negative charge, which is a donor atom. Cl_{12} and C_{13} atoms exhibit a positive charge or negative charge because has depended on the group sub situation. The vibration entropy and CV are found considerably change by changing the methods. The DFT/ B3LYP/6-31G result have been shown given the biggest value for Bupropion for vibrational entropy (59.98) (Cal/mole- Kelvin) and biggest vibration CV value whereas the five derivatives have been showed a more stability for patents 3 and 4. Mostly, DFT methods give a relatively similar result for the energy evaluations but not for the HOMO. LUMO energies and the dipole moment which give relativity different results as Table (3), (4) shows. Because the study is a correlation study, the difference in result will not affect the study.

Table (5) - Selected atomic charges of Bupropion and its derivatives in AM1, PM3 in Gaussian

Atoms	Bupropion		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
G09	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
1C	-0.096	-0.151	-0.070	-0.122	-0.138	-0.102	-0.118	-0.091	-0.092	-0.113	-0.090	-0.061
2C	-0.094	-0.074	-0.133	0.113	0.064	0.048	-0.060	-0.135	-0.171	-0.078	-0.131	-0.103
3C	-0.131	-0.093	-0.119	-0.085	0.049	0.026	-0.080	-0.154	-0.087	-0.117	-0.075	-0.046
4C	-0.082	-0.064	-0.133	-0.103	-0.113	0.028	-0.083	-0.058	-0.146	-0.055	-0.122	-0.144
5C	-0.152	-0.162	-0.105	-0.087	-0.134	-0.072	-0.139	-0.146	-0.105	-0.183	-0.038	-0.105
6C	-0.080	-0.056	-0.083	-0.102	-0.087	-0.142	-0.086	-0.057	-0.145	-0.078	-0.129	-0.107
7H	0.161	0.125	0.154	0.124	0.170	0.134	0.164	0.132	0.148	0.116	0.165	0.129
8H	0.159	0.121	0.151	0.116	0.172	0.138	0.169	0.131	0.149	0.113	0.160	0.119
9H	0.157	0.124	0.150	0.116	0.166	0.140	0.167	0.134	0.148	0.116	0.161	0.122
10H	0.162	0.129	0.155	0.123	……	…..	…..	…..	0.150	0.117	0.162	0.124
11H	……	….	…..	…..	……	…..	…..	…..	0.148	0.120	…..	…..

12Cl	-0.010	0.074	-0.018	0.068	….	…..	0.013	0.102	….	……	0.005	0.090
13C	0.256	0.350	0.065	0.112	0.293	0.357	0.291	0.358	0.287	0.359	0.345	0.445
14H	……	……	0.097	0.072	……	…..	…..	…..	…..	….	….	…..
15O	-0.338	-0.350	-0.349	-0.336	-0.309	-0.347	-0.311	-0.351	-0.337	-0.364	-0.334	-0.398
16H	…..	…..	0.226	0.212	…..	……	…..	….	….	….	…..	…..
17C	-0.062	-0.134	-0.099	-0.148	-0.054	-0.092	-0.061	-0.092	-0.120	-0.154	….	…..
18H	0.125	0.099	0.077	0.072	0.130	0.090	0.127	0.089	0.124	0.091	….	……
19H	……	…..	0.100	0.074	……	…..	……	….	0.104	0.096	……	…..
20N	-0.299	-0.118	-0.322	-0.079	-0.303	-0.078	-0.304	-0.079	-0.268	-0.078	…..	……
21H	0.170	0.069	0.173	0.054	0.173	0.086	0.137	0.067	….	….	…..	…..
22C	….	….	….	….	….	….	….	….	-0.128	-0.106	…..	…….
23H	….	….	….	….	….	….	….	….	0.086	0.050	….	…….
24H	….	….	….	….	….	….	….	….	0.093	0.052	…..	….
25H	….	….	….	….	….	….	….	….	0.059	0.053	…..	……
26C	-0.211	-0.118	……	…..	-0.244	-0.163	-0.243	-0.163	……	….	…..	…….
27H	0.088	0.051	……	….	0.092	0.065	0.091	0.069	…..	….	…….	……
28H	0.095	0.052	……	….	0.094	0.059	0.094	0.066	….	….	….	…….
29H	0.089	0.062	…..	….	0.088	0.066	0.089	0.065	…..	….	……	…….
30C	0.021	-0.031	0.021	-0.034	0.024	-0.025	0.026	0.025	-0.028	-0.060	0.054	0.084
31C	-0.246	-0.148	-0.221	-0.149	-0.214	-0.157	-0.246	-0.157	…..	….	-0.231	-0.140

32H	0.090	0.051	0.079	0.054	0.071	0.055	0.080	0.054	……	….	0.088	0.056
33H	0.076	0.050	0.082	0.049	0.089	0.052	0.079	0.051	….	….	0.097	0.054
34H	0.081	0.057	0.086	0.055	0.086	0.058	0.084	0.058	….	….	0.068	0.059
35C	-0.213	-0.121	-0.208	-0.119	-0.245	-0.119	-0.211	-0.119	-0.242	-0.147	-0.235	-0.125
36H	0.083	0.046	0.073	0.048	0.081	0.045	0.073	0.047	0.077	0.053	0.100	0.051
37H	0.086	0.048	0.079	0.046	0.080	0.049	0.089	0.049	0.080	0.050	0.093	0.065
38H	0.079	0.051	0.082	0.049	0.085	0.047	0.083	0.045	0.085	0.050	0.068	0.057
39C	-0.267	-0.127	-0.238	-0.126	-0.205	-0.135	-0.207	-0.136	-0.210	-0.123	-0.214	-0.140
40H	0.084	0.056	0.086	0.052	0.080	0.055	0.079	0.051	0.077	0.050	0.088	0.055
41H	0.082	0.050	0.079	0.050	0.082	0.049	0.082	0.055	0.082	0.050	0.090	0.055
42H	0.077	0.046	0.081	0.048	0.076	0.051	0.076	0.050	0.079	0.050	0.102	0.055
43C	…..	…..	….	…..	….	……	….	…..	….	….	…..	…..
44H	…..	……	…..	….	…	…..	….	…..	….	….	…….	……
45H	…..	…..	…..	….	…..	……	….	….	….	….	…..	….
46F	….	….	….	….	-0.099	-0.085	……	…..	……	……	…….	…..
47F	…	….	…..	……	-0.099	-0.085	……	…	……	…..	…..	…..
48Cl	…….	…..	….	….	…..	……	0.009	0.100	……	……	…..	…..
49H	….	….	….	….	….	….	….	….	0.103	0.096	…..	……
50O	…	…	…	…	…	…	…	…	…	…	-0.134	-0.102
51O	….	…	…	…	…	…	…	…	…	…	-0.151	-0.158

Table (6) - Selected atomic charges of Bupropion and its derivatives in HF, DFT in Gaussian

Atoms	Bupropion		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
G09	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT

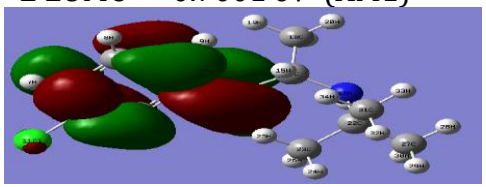
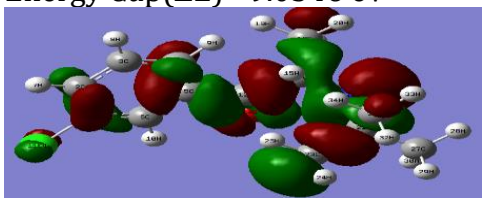
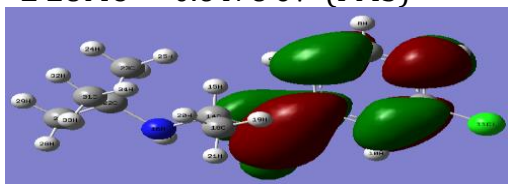
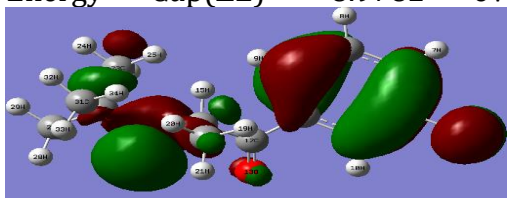
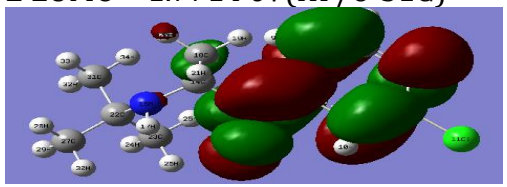
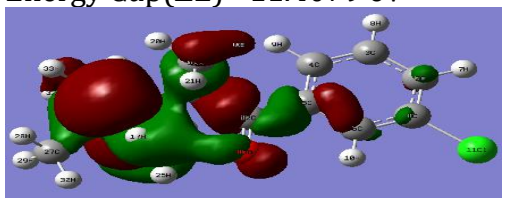
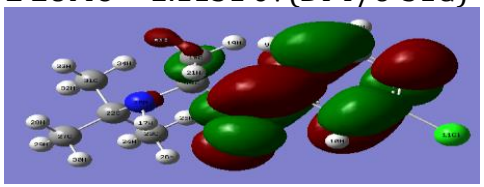
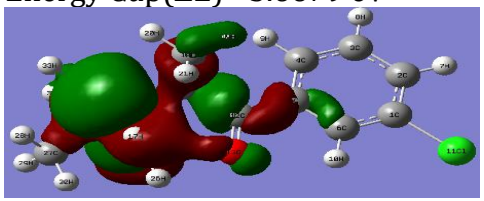
1C	-0.335	-0.247	-0.335	-0.275	-0.224	-0.154	-0.163	-0.107	-0.231	-0.143	-0.173	-0.134
2C	-0.126	-0.081	-0.157	-0.114	0.392	0.287	-0.272	-0.217	-0.186	0.035	-0.215	-0.108
3C	-0.228	-0.145	-0.209	-0.131	0.357	0.266	-0.299	-0.232	-0.227	-0.143	-0.143	0.061
4C	-0.153	-0.122	-0.201	-0.133	-0.165	-0.147	-0.103	-0.096	-0.171	-0.144	-0.290	-0.249
5C	-0.145	0.048	-0.193	-0.146	-0.150	0.033	-0.142	-0.037	-0.160	-0.119	-0.173	-0.114
6C	-0.100	-0.096	0.013	0.122	-0.157	-0.129	-0.154	-0.120	-0.177	-0.148	-0.088	-0.107
7H	0.266	0.186	0.252	0.171	0.274	0.191	0.273	0.195	0.229	0.160	0.252	0.186
8H	0.248	0.173	0.235	0.157	0.267	0.182	0.269	0.186	0.231	0.159	0.248	0.175
9H	0.259	0.176	0.231	0.153	0.289	0.192	0.288	0.197	0.228	0.153	0.272	0.171
10H	0.284	0.190	0.250	0.160	……	…..	….	….	0.249	0.155	0.263	0.185
11H	……	….	…..	…..	……	…..	…..	…..	0.242	0.154	….	……
12Cl	0.065	0.041	0.059	0.033	……	……	0.134	0.103	…..	….	0.129	0.092
13C	-0.531	0.317	0.168	0.049	0.556	0.347	0.558	0.351	0.543	0.326	0.831	0.490
14H	….	….	0.199	0.150	……	……	….	…..	….	…..	…..	……
15O	-0.630	-0.478	-0.810	-0.670	-0.598	-0.456	-0.595	-0.452	-0.623	-0.475	-0.565	-0.422
16H	…	….	0.443	0.385	…..	……	…..	….	……	….	……	……
17C	-0.068	-0.074	-0.109	-0.138	-0.026	-0.053	-0.028	-0.054	-0.169	-0.193	…..	……
18H	0.207	0.168	0.183	0.161	0.214	0.171	0.215	0.171	0.196	0.186	…..	……
19H	…..	….	0.190	0.159	…..	…..	……	…..	0.221	0.161	…..	……

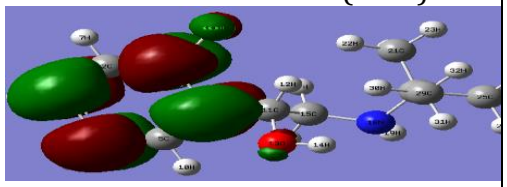
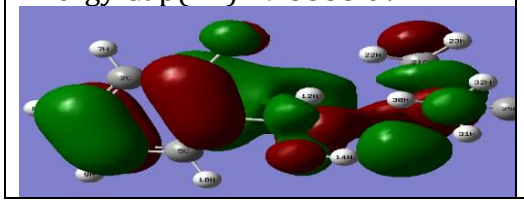
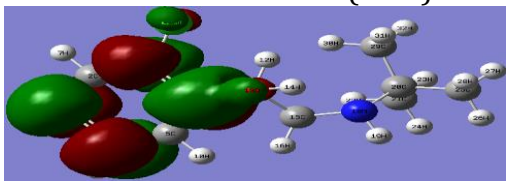
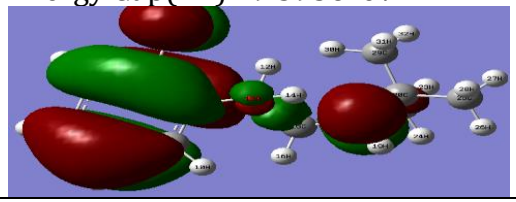
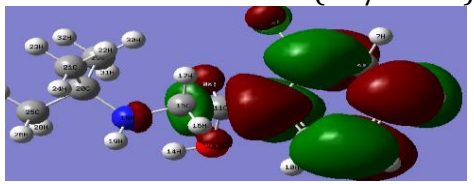
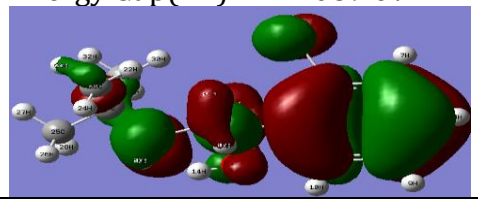
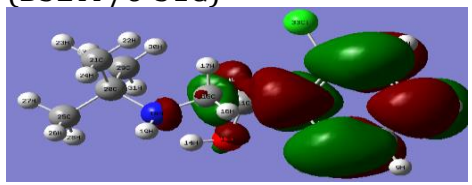
20N	-0.763	-0.569	-0.813	-0.624	-0.815	-0.601	-0.815	-0.600	-0.597	-0.461	…..	……
21H	0.347	0.287	0.349	0.312	0.350	0.295	0.351	0.296	…….	….	……..	……
22C	….	….	….	….	….	….	….	….	-0.239	-0.264	……	……
23H	….	….	….	….	….	….	….	….	0.157	0.152	……	……
24H	….	….	….	….	….	….	….	….	0.143	0.149	…..	……
25H	….	….	….	….	….	….	….	….	0.147	0.124	…..	……
26C	-0.438	-0.365	-0.437	….	-0.465	-0.417	-0.466	-0.418	…….	……	….	……
27H	0.156	0.148	0.161	……	0.174	0.146	0.174	0.146	……	……	……	……
28H	0.163	0.157	0.162	……	0.187	0.160	0.179	0.162	…..	……	….	……
29H	0.161	0.142	0.160	…..	0.176	0.171	0.187	0.161	……	….	……	……
30C	0.135	0.157	0.127	0.156	0.159	0.177	0.160	0.176	0.038	0.032	0.210	0.205
31C	-0.443	-0.403	-0.430	-0.397	-0.425	-0.400	-0.425	-0.395	…..	……	-0.456	-0.397
32H	0.149	0.135	0.156	0.141	0.177	0.129	0.155	0.151	…..	…..	0.180	0.199
33H	0.161	0.136	0.156	0.136	0.147	0.153	0.147	0.128	……	…..	0.182	0.152
34H	0.157	0.130	0.156	0.141	0.145	0.135	0.148	0.125	……	…..	0.181	0.149
35C	-0.419	-0.404	-0.426	-0.397	-0.430	-0.393	-0.426	-0.395	-0.459	-0.418	-0.444	-0.407
36H	0.153	0.135	0.159	0.140	0.156	0.126	0.177	0.128	0.155	0.137	0.183	0.166
37H	0.159	0.138	0.162	0.135	0.151	0.132	0.147	0.133	0.152	0.138	0.185	0.159
38H	0.155	0.134	0.154	0.139	0.154	0.128	0.145	0.135	0.158	0.138	0.185	0.159
39C	-0.425	-0.386	-0.437	-0.401	-0.426	-0.394	-0.430	-0.394	-0.437	-0.401	-0.434	-0.405
40H	0.155	0.134	0.162	0.142	0.155	0.134	0.161	0.134	0.153	0.135	0.175	0.154

41H	**0.183**	**0.135**	**0.161**	**0.142**	**0.148**	**0.125**	**0.156**	**0.125**	**0.151**	**0.134**	**0.183**	**0.154**
42H	**0.178**	**0.134**	**0.160**	**0.142**	**0.147**	**0.127**	**0.151**	**0.127**	**0.162**	**0.135**	**0.185**	**0.155**
43C	**…..**	**…..**	**…..**	**…..**	**….**	**…**	**…..**	**….**	**…..**	**……**	**….**	**….**
44H	**……**	**…..**	**….**	**….**	**….**	**….**	**…..**	**….**	**…..**	**……**	**…**	**….**
45H	**…..**	**……**	**…..**	**….**	**….**	**……**	**…..**	**….**	**…..**	**…..**	**….**	**…..**
46F	**….**	**….**	**….**	**…..**	**-0.452**	**-0.327**	**…..**	**…..**	**….**	**…..**	**….**	**….**
47F	**….**	**…..**	**…..**	**….**	**-0.448**	**-0.321**	**……**	**….**	**….**	**……**	**….**	**…**
48Cl	**…..**	**…..**	**….**	**……**	**……**	**……**	**0.135**	**0.113**	**…..**	**…..**	**….**	**….**
49H	**…..**	**….**	**….**	**….**	**….**	**….**	**….**	**….**	**0.179**	**0.145**	**…….**	**….**
50O	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**-0.565**	**-0.290**
51O	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**……**	**-0.491**	**-0.338**

HOMO and LUMO Molecular Orbital

In principle, there are several ways to calculate the excitation energies. The simplest one involves the difference between the highest occupied molecular orbital (HOMO) of a neutral system, which is a key parameter in determining molecular properties[25]. The eigenvalues of HOMO (πdonor) and LUMO (π acceptor) and their energy gap between HOMO and LUMO characterizes the molecular chemical stability. The energy gap reflects the chemical activity of the molecules [26, 27]. The relatively large LUMO-HOMO energy gap of the studied molecule indicates that it can be considered as kinetically stable. In addition, the energy of the HOMO is directly related to the ionization potential, while the energy of the LUMO is directly related to the electron affinity. The energy gaps are largely responsible for the chemical and spectroscopic properties of the molecules[26]. LUMO-HOMO gap energy of Bupropion and its derivatives are calculated by four methods and various levels in Gaussian09 programs which are given in Tables (7), (8), and Figs. (4), (5), (6). As a result, at the biggest HOMO energy value for Bupropion is (-5.7831eV) calculated at DFT/B3LYP/6-31G whereas the smallest one is (-9.7347eV) calculated at AM1. The biggest LUMO energy value is (1.7714eV) obtained using HF; band energy gap (E*g*) value is (11.4079eV) obtained using B3LYP/6-31G. LUMO is an electron acceptor represents the ability to accept an electron; HOMO represents the ability to donate an electron. The LUMO-HOMO energy gap of drugs shows that the energy gap reflects the chemical reactivity of the molecule. That is the smaller value of E*g*, the easer electron transfers from HOMO orbital to LUMO orbital. According to the results obtained by methods (AM1, PM3, HF, DFT) of E HOMO, E LUMO, and Eg for the drug and its derivatives , it was found that patent 2,3,4 in a good an agreement with drug characters.

Bupropion (AM1)	Bupropion (PM3)	Bupropion (HF)	Bupropion (DFT)
LUMO Plot(first excited state) E LUMO= - 0.7001 eV (AM1)  Energy Gap(ΔE)= 9.0346 eV  HOMO Plot (ground state) E HOMO = -9.73473 eV (AM1)	LUMO Plot(first excited state) E LUMO= - 0.6478 eV (PM3)  Energy Gap(ΔE)= 8.9782 eV  HOMO Plot (ground state) E HOMO =-9.6261 eV (PM3)	LUMO Plot(first excited state) E LUMO= 1.7714 eV(HF/6-31G)  Energy Gap(ΔE)= 11.4079 eV  HOMO Plot (ground state) E HOMO =-9.6365 eV (HF/6-31G)	LUMO Plot(first excited state) E LUMO=- 2.1151 eV(DFT/6-31G)  Energy Gap(ΔE)= 3.6679 eV  HOMO Plot (ground state) E HOMO =-5 .7831 eV (B3LYP/6-31G)

Patent 1 (AM1)Hyper chem.	Patent 1(PM3)	Patent 1 (HF)	Patent 1 (DFT)
LUMO Plot(first excited state) E LUMO= - 0.07319 eV (AM1)  Energy Gap(ΔE)= 9.5333 eV 	LUMO Plot(first excited state) E LUMO= - 0.13306 eV (PM3)  Energy Gap(ΔE)= 9.3956 eV 	LUMO Plot(first excited state) E LUMO= 3.4479 eV (HF/6-31G)  Energy Gap(ΔE)= 12.7089 eV 	LUMO Plot(first excited state) E LUMO= - 0.37632 eV (B3LYP/6-31G)  Energy Gap(ΔE)= 5.89027 eV

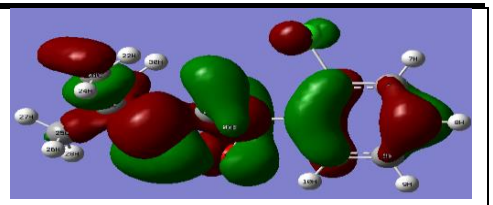
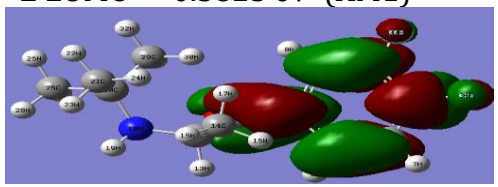
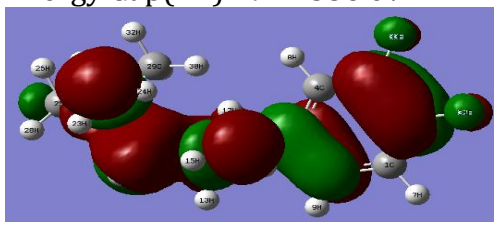
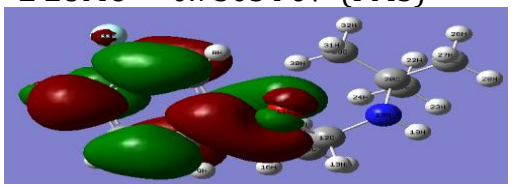
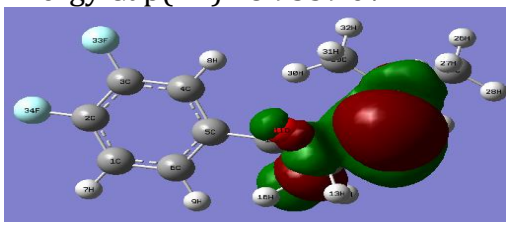
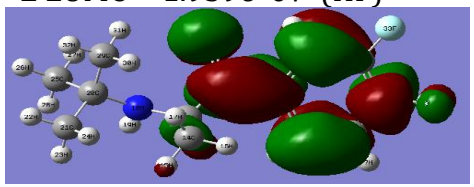
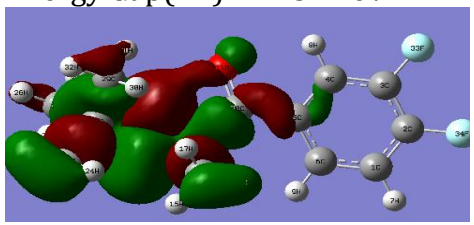
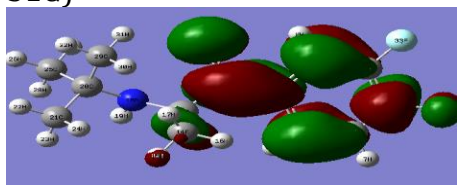
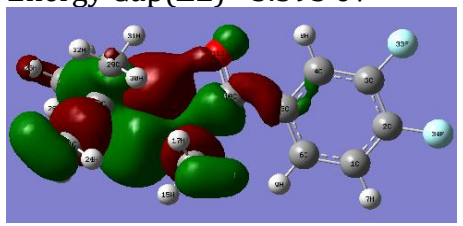
HOMO Plot (ground state) E HOMO =- 9.6065 eV (AM1)	HOMO Plot (ground state) E HOMO =- 9.5287 eV (PM3)	HOMO Plot (ground state) E HOMO =- 9.26153 eV (HF/631G)	 HOMO Plot (ground state) E HOMO =- 6.2666 eV (B3LYP/6-31G)

Fig.(4)- HOMO- LUMO plot and energy orbital and its energy using (AM1, PM3, HF, DFT) methods ,red values represent negative Bupropion and Patent 1 in G09

Patent 2 (AM1)	**Patent 2 (PM3)**	**Patent 2 (HF)**	**Patent 2 (DFT)**
LUMO Plot(first excited state) E LUMO= - 0.5823 eV (AM1)  Energy Gap(ΔE)= 9.17336 eV  HOMO Plot (ground state) E HOMO =- 9.75568 eV (AM1)	LUMO Plot(first excited state) E LUMO= - 0.73034 eV (PM3)  Energy Gap(ΔE)= 8.9539 eV  HOMO Plot (ground state) E HOMO =- 9.6843 eV (PM3)	LUMO Plot(first excited state) E LUMO= 1.9396 eV (HF)  Energy Gap(ΔE)= 11.341 eV  HOMO Plot (ground state) E HOMO =- 9.4022 eV (HF/631G)	LUMO Plot(first excited state) E LUMO= -1.9730 eV (B3LYP/6-31G)  Energy Gap(ΔE)= 3.593 eV  HOMO Plot (ground state) E HOMO =- 5.5665 eV (B3LYP/6-31G)

Patent 3(AM1)	**Patent 3(pm3)**	**Patent 3 (HF)**	**Patent 3(DFT)**
LUMO Plot(first excited state)	LUMO Plot(first excited state)	LUMO Plot(first excited state)	LUMO Plot(first excited state)

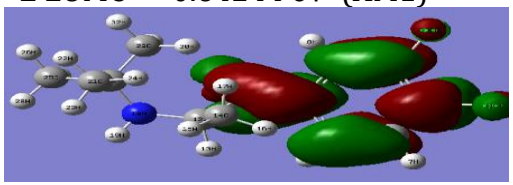
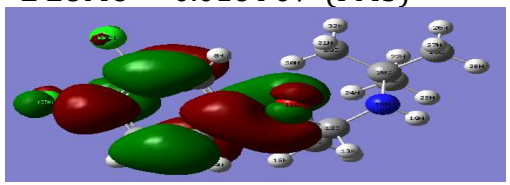
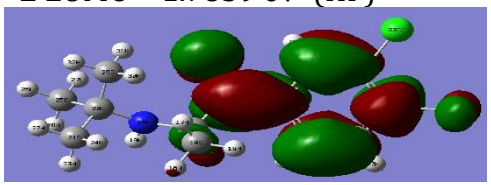
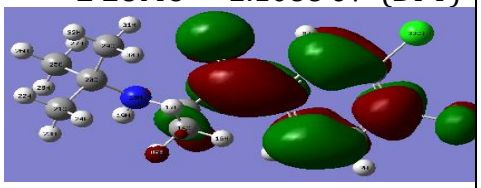
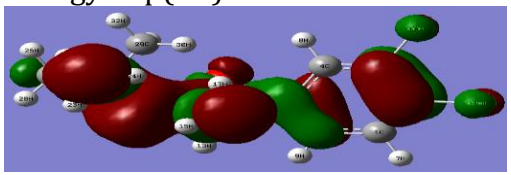
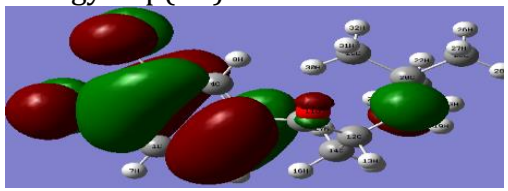
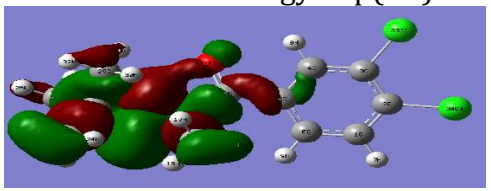
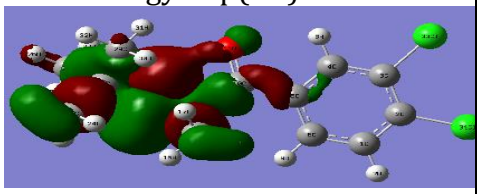
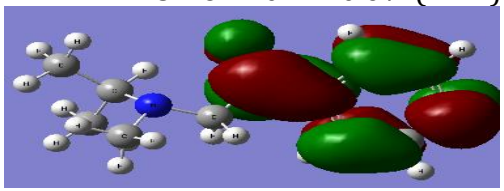
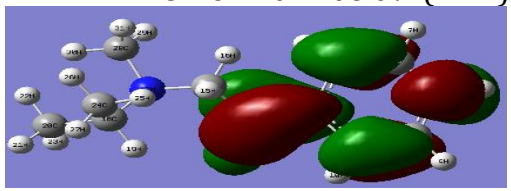
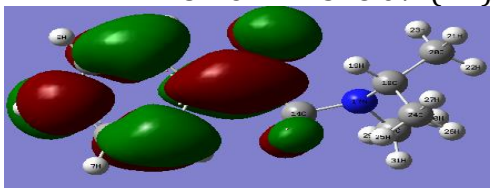
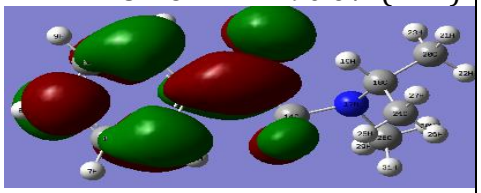
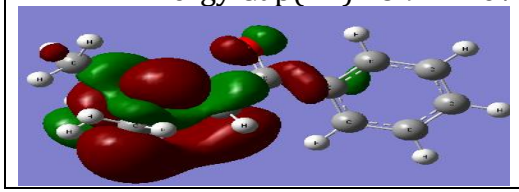
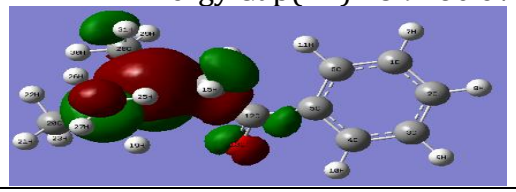
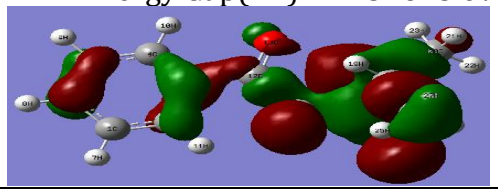
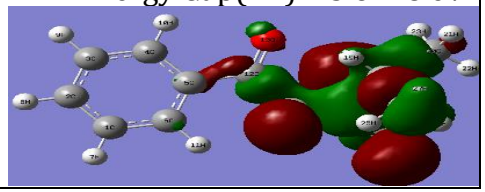
E LUMO= - 0.64244 eV (AM1)	E LUMO= - 0.0164 eV (PM3)	E LUMO= 1.7839 eV (HF)	E LUMO= - 2.1088 eV (DFT)
			
Energy Gap(ΔE)= 9.08701 eV	Energy Gap(ΔE)= 9.5361 eV	Energy Gap(ΔE)= eV	Energy Gap(ΔE)= 3.4802 eV
			
HOMO Plot (ground state) E HOMO =- 9.7295 eV (AM1)	HOMO Plot (ground state) E HOMO =- 9.5526 eV (PM3)	HOMO Plot (ground state) E HOMO =- 9.40575 eV (HF/6-31G)	HOMO Plot (ground state) E HOMO =- 5.5891 eV (B3LYP/6-31G)

Fig.(5)- HOMO- LUMO plot and energy orbital and its energy using (AM1, PM3, HF, DFT) methods ,red values represent negative Patent2 and Patent 3 in G09

Patent 4(AM1)	**Patent 4(PM3)**	**Patent 4(HF)**	**Patent 4(DFT)**
LUMO Plot(first excited state) E LUMO= - 0.4410 eV (AM1)	LUMO Plot(first excited state) E LUMO= - 0.4108 eV (AM1)	LUMO Plot(first excited state) E LUMO= 2.1578 eV (HF)	LUMO Plot(first excited state) E LUMO= - 1.7790 eV (DFT)
			
Energy Gap(ΔE)= 8.9747 eV	Energy Gap(ΔE)= 8.9760 eV	Energy Gap(ΔE)= 11.31623 eV	Energy Gap(ΔE)= 3.6718 eV
			

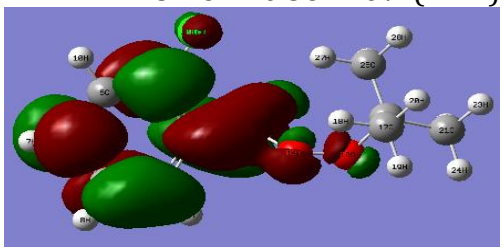
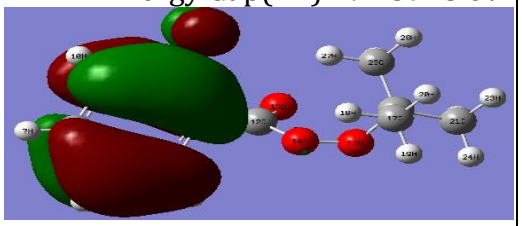
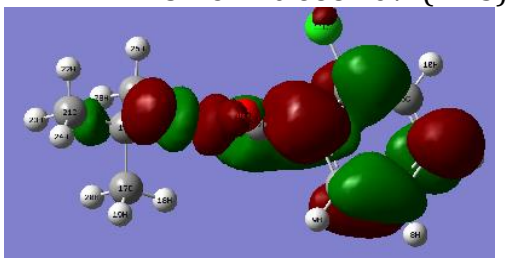
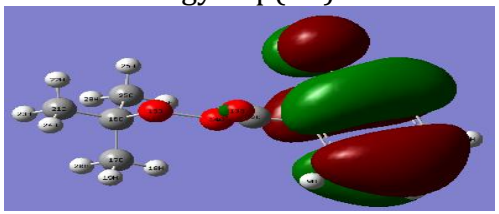
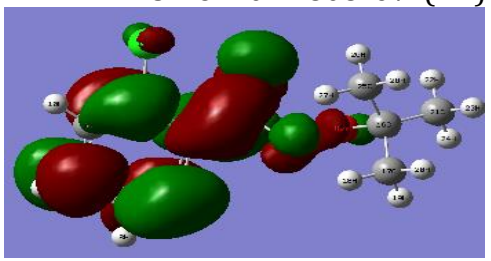
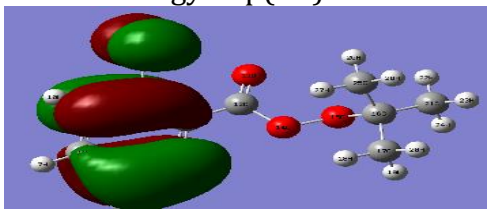
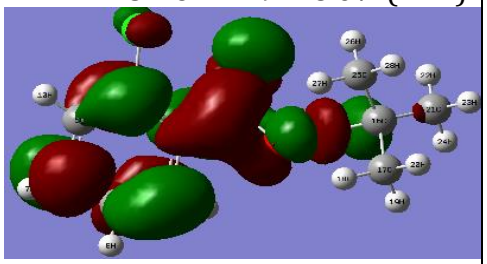
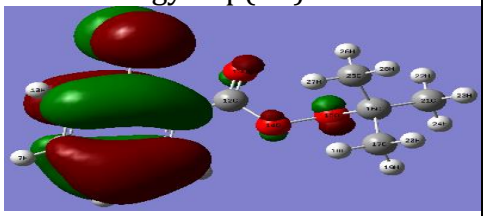
HOMO Plot (ground state) E HOMO =- 9.41582 eV (AM1)	HOMO Plot (ground state) E HOMO =- 9.3869 eV (PM3)	HOMO Plot (ground state) E HOMO =- 9.1584 eV (HF/6-31G)	HOMO Plot (ground state) E HOMO =- 5.4509 eV (B3LYP/6-31G)
Patent 5(AM1)	**Patent 5(PM3)**	**Patent 5 (HF)**	**Patent 5 (DFT)**
LUMO Plot(first excited state) E LUMO= - 0.5624 eV (AM1)  Energy Gap(ΔE)= 9.43975 eV 	LUMO Plot(first excited state) E LUMO= - 0.6887 eV (PM3)  Energy Gap(ΔE)=9.04838 eV 	LUMO Plot(first excited state) E LUMO= 0.14808 eV (HF)  Energy Gap(ΔE)= 9.9211 eV 	LUMO Plot(first excited state) E LUMO= - 1.9148 eV (DFT)  Energy Gap(ΔE)= 5.3659 eV 
HOMO Plot (ground state) E HOMO =- 10.0022 eV (AM1)	HOMO Plot (ground state) E HOMO =- 9.7371 eV (PM3)	HOMO Plot (ground state) E HOMO =- 9.7731 eV (HF/6-31G)	HOMO Plot (ground state) E HOMO =- 7.2808 eV (B3LYP/6-31G)

Fig.(6)- HOMO- LUMO plot and energy orbital and its energy using (AM1, PM3, HF, DFT) methods ,red values represent negative Patent 4 and Patent 5 in G09

Ionization Energy

The ionization energy associated with a relationship with a higher energy of occupied orbital as follows[14; 15]. IE= - EHOMO the high value in the energy of ionization mean high stability of the molecule and on the other hand, the ionization energy means the high effectiveness of the molecule. Ionization energy can be calculated using equation.

IE(ionization) = - E_{HOMO}

At biggest (IE) means high stability for molecular, but the smallest of (IE) give the high activity for molecular and increased the activity for a drug. As a result, IE value for a drug (Bupropion is (9.7347, 9.6261, 9.6365, 5.7831), (AM1, PM3, HF, DFT) in G09 programs. According to the result obtained by methods(AM1, PM3, HF, DFT) for a drug and derivatives, it was found that patent 3 in a good an agreement with drug characters Table (3),(4).

Electron affinity

Electron affinity related to E_{LUMO} equation[16; 17]. EA = - E_{LUMO}. The high value of electron affinity means less stability and then give high efficiency for inhibition. The low value of electron affinity means high stability and then gives low efficiency for inhibition.

_A high (EA) offer less for molecular, subsequently formation of high capacity for molecular of the results calculated in G09 and Hyper Chem.8.0.8 by difference methods, that smallest EA value for drug Bupropion is (0.7001, 0.6478, -1.7714, 2.1151) in Gaussian 09. Accordingly to the result obtained by methods (AM1, PM3, HF, and DFT) for drug and its derivatives, it was found that patent-3 in a good agreement with drug characters Table (3),(4)

Vibration Analysis

The observed and calculated frequencies using four methods (AM1, PM3, HF/6-31G, DFT/B3LYP/6-31G) with their absolute intensities were shown in Table (7),(8). In order to facilitate assignment of the observed peaks we have analyzed some vibrational frequencies and compared our calculated results of the Bupropion with their five derivatives shown in Table (7),(8) and figure (7),(8).

Shows IR-spectra of the Bupropion and its derivatives in four method (AM1,PM3,HF,DFT). The present study, theoretical calculations of vibrational spectra using different methods and different basis sets were compared drugs with the derivatives to obtain the best expectation. The best frequencies calculated by DFT which was in a good agreement with drug frequencies results.

C=C Vibrations

The ring carbon - carbon stretching vibration occurs in the region 1625–1430cm^{-1} and is usually stronger. This occurs as two or three bands in the region due to skeletal vibration. In this case of substituted benzenes with groups, the vibrations produce the band at 1625-1590 cm-1. In the present compound aspirin, a very strong band at 1629 cm^{-1} is due to C=C stretching vibration. A fairly weak band is observed in the region due to 1420–1400 cm^{-1} for substituted benzene due to C=C stretching vibration. In Bupropion, these vibrations occur at 1454 cm^{-1} and 1412 cm^{-1} . Both the peaks are of medium intensity

O–H Vibrations

As a result of the presence of hydrogen bonding, carboxylic acid in the liquid and solid phase exhibit a broad band at around 3300-3500 cm^{-1} . Due to the O-H stretching vibration, carboxylic acids will observe vibrations in the region 2700-2500 cm^{-1} . The vibration 3467 cm^{-1} is very strong in intensity and it assigned to O-H stretching. Also weak vibration at 2810-2600 cm^{-1} belongs to O-H stretching vibration .

C–N Vibrations

In our present work, theoretical high values in IR spectrum have been assigned to C– N stretching vibrations of Bupropion (1564.07, 1518.54, 1354.67 , 1340.44)cm^{-1} in (AM1, PM3, HF, DFT), because the amide group with the main contributions coming from deformational in –plan C…N…H and stretching C– N vibration [18].

After compared the drugs in theoretical with experimental results, the assignment of the vibrational bands was made on the basis of the theoretical calculations for drugs and a comparison of the drugs measured vibrational spectra of the five derivatives and shown to be the derivatives 4 similarities with the Bupropion.

C– Cl Vibrations

The vibrations belonging to C– X(X= F, Cl, Br) bonds which are formed between the ring and the halogen atoms are worth to discuss here, since mixing of vibrations are possible due to the lowering of molecular symmetry and the presences of heavy atoms. The C– Cl absorption is observed in the broad region between 850 and 550 cm^{-1}.(19) When Cl atoms are attached to one carbon atom, the band is usually more intense and at high- frequency end of the assigned limits. In view of this, in FTIR is assigned to C– Cl stretching vibration. The theoretical wave number of C– Cl (486, 416,436,447) for patent 4 in G09 but in Hyper chem. (424, 420).(20)

Others Vibrations

The theoretical vibrational frequencies for the molecule Bupropion drug calculated by semi–empirical (AM1 and PM3), (HF and DFT) methods are presented in Tables (7, and 8) In the molecule Buproion, C – F, N–H,O_2 stretching frequency assigned with its derivatives

G09	Drugs				Patents 1				Patents 2			
	AM1		PM3		AM1		PM3		AM1		PM3	
	Freq.Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq.Cm^{1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol
N– H	3385.40	38.4528	3359.30	5.9025	3385.60	38.7441	3369.82	4.1934	3380.31	41.3671	3346.59	40.5545
C– N	1564.07	25.1686	1518.54	21.0568	1588.58	2.5633	1404.89	1.5366	1336.42	3.6756	13321.61	1.6544
C = O	2018.46	401.2701	1946.35	434.4810	……	……	……	……	1980.33	432.7590	1994.24	310.7502
O– H	…..	…..	……	….	3458.04	126.6700	3876.99	38.2159	….	….	…..	…..
C= C	1766.35	34.4229	1789.11	19.7636	1770.06	14.1414	1791.22	9.6584	……	……	,……	……
O–O	…..	……	….	…..	……	……	……	….	…..	…..	…..	……
C– Cl	486.05	1.4218	416.26	4.3703	423.79	4.3881	410.79	4.1361	……	……	……	……
C– F	……	……	……	……	……	……	……	……	521.31	233.9864	491.42	148.6819
	Patents 3				Patents 4				Patents 5			
	AM1		PM3		AM1		PM3		AM1		PM3	
	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}.	Intensity Km/mol	Cm^{-1} Freq.	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol
N– H	3376.08	41.0064	3356.51	5.0898	…….	……	…..	…..	…..	…..	….	…..

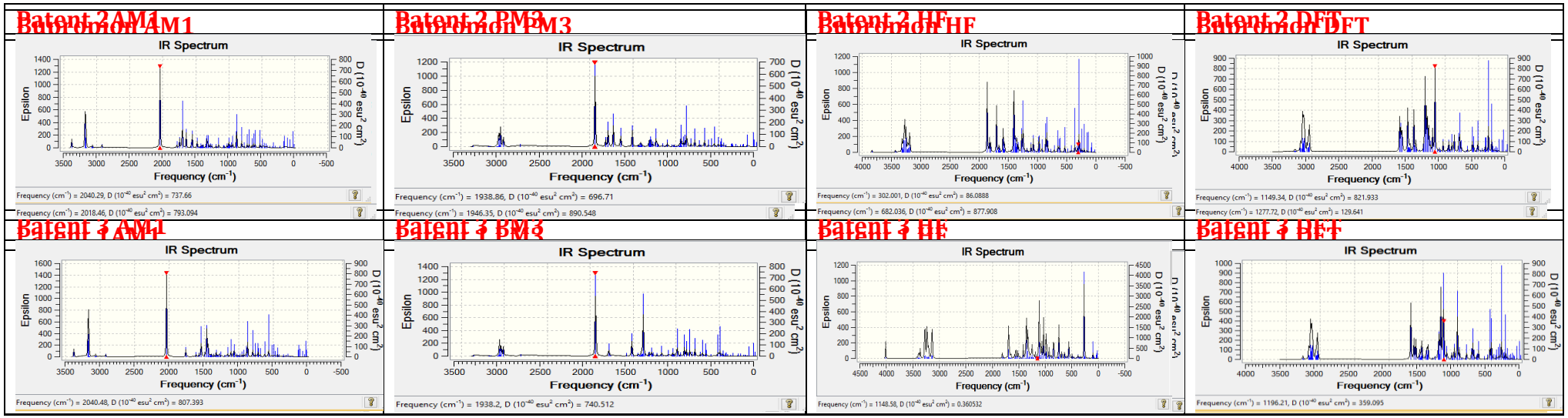
C– N	1484.86	16.3993	1383.11	20.7689	1475.21	48.6459	1359.36	79.4946	.....	....	...	.....
C = O	2040.48	412.6916	1938.20	359.7689	2027.29	465.1610	1943.09	473.3088	1942.84	429.2322	1937.69	494.0399
O– H	……..	……	……	……	……	……	……..	……	……	……	……	…….
C= C	1762.12	39.9239	1784.49	48.7755	1772.64	48.7538	1793.53	36.1794	1751.71	22.2528	1731.17	35.2838
O– O	……	....	……	.....	....	....	.....	....	862.30	11.8311	811.63	22.2826
C– Cl	474.44	6.5450	460.25	5.5309	……	.....	…….	……..	462.90	8.8444	466.62	2.1941
C– F	……..	……..	……..	……..	…….....	…….....	…….....	…….....	.....	....	.....	.....

Table (7) - Theoretically calculated spectra of Bupropion and its derivatives inG09.

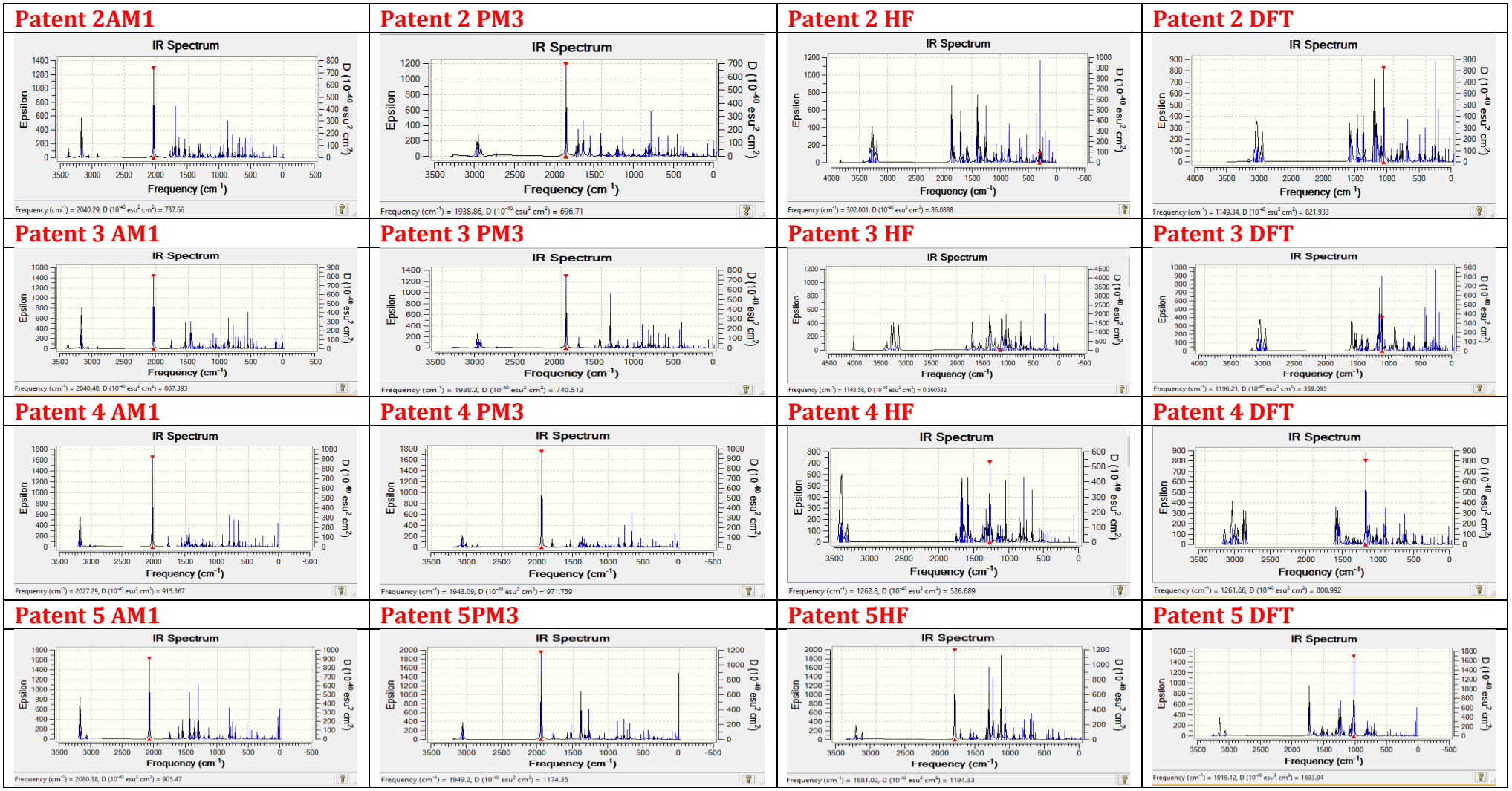
Table (8) - Theoretically calculated spectra of Bupropion and its derivatives inG09.

G09	Drugs				Patents 1				Patents 2			
	HF		DFT		HF		DFT		HF		DFT	
	Freq.Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq.Cm^{1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol
N– H	3789.48	12.2386	3494.28	2.8979	3789.97	6.7605	3246.92	12.8358	3422.31	16.4691	3346.22	12.7654
C– N	1354.67	30.4156	1340.44	34.7916	1344.79	11.3894	1320.40	10.5256	1420.99	36.6588	1414.08	11.6077
C = O	1657.99	14.8982	1660.07	129.2109	……	……	…….	……	1880.30	322.7590	1804.24	310.7302
O– H	…..	….	…..	……	3927.84	173.3204	3534.80	1.9884	…..	…	….	….
C= C	1765.16	84.7005	1660.07	52.6321	1794.36	12.5492	1799.87	16.4194	……..	……..	,…….	……..
O–O	……	…….	…..	……	…..	……	….	….	….	…	….	……
C– Cl	436.31	23.8096	447.04	25.9248	432.67	24.7098	415.89	15.8287	……..	……..	……..	……..
C– F	……..	……..	……..	……..	…….	…….	…….	…….	421.31	3.9864	491.42	4.6819
	Patents 3				Patents 4				Patents 5			
	HF		DFT		HF		DFT		HF		DFT	
	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}.	Intensity Km/mol	Cm^{-1} Freq.	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol	Freq. Cm^{-1}	Intensity Km/mol
N– H	3406.08	6.0213	3565.79	1.1594	…..	…	….	….	…..	……	……	…
C– N	1431.81	39.3212	1424.72	48.6969	1375.21	73.6459	1359.36	79.4946	……	…..	….	….

C = O	1987.37	144.9715	1679.50	183.7226	1674.30	112.5657	1668.62	137.9493	1742.84	329.2322	1723.88	380.1368
O– H	….	….	….	….	…..	…	….	……	…….	……	…..	……
C= C	1650.92	65.2005	1633.80	77.2866	1744.66	15.7538	1704.64	21.1794	1655.54	67.9511	1648.12	74.9863
O– O	……	…	…	….	……	….	…..	……	862.30	3.8311	860.86	0.7745
C– Cl	445.87	9.9348	424.25	9.5309	……	…..	…….	……..	441.55	20.5456	437.64	16.0266
C– F	……..	……..	……..	……..	…….	…….	…….	…….	….	…	…	….



Figures (7) – Calculated theoretical IR – Spectra of the Bupropion and its derivatives in four methods (AM1, PM3, HF ,DFT) in G09



Figures (8) – Calculated theoretical IR – Spectra of the Bupropion and its derivatives in four methods (AM1, PM3, HF, DFT) in G09

Molecular Electrostatic Potential Surface

AM1, PM3, HF and DFT method was applied to predict the molecular electrostatic potential surface of the drug and its derivatives. An important feature of the electrostatic potential is that it is a real physical property that can be determined theoretically by different methods, as well as computationally[21; 22]. In Figures (9), (10), the different values of the electrostatic potential at the surface are represented by different colures. Electrostatic potential increases in the order red< orange< yellow< green< blue. Colures code of the maps is in the range between (-6.618) a.u. (deepest red) and (6.618) a.u. (deepest blue) in title molecule, where blue colures indicate the strongest attractions and red indicates the strongest repulsion. Figure (9, 10) shows the electrostatic potential of the different compounds, that method (AM1, PM3) gives mostly a yellow colure (Low potential) for all species. These results have not resembled. In other hand methods (HF, DFT) results range from low (yellow) to high potential (blue). Both methods showed that patent (4) is the most compound which has a similar molecule due to a static potential of the Bupropion. This indicates that patent 4has an intermolecular chemical similar to that of Bupropion. The electron charge density obtained in both methods allowed as finding out different molecular properties such us the electrostatic potential and the dipole moment, which were finally subject to a comparison leading to a good match obtained between both methods. The intermolecular charge transfer has also been confirmed by a HOMO-LUMO analysis[23; 24]in figure (11),(12).

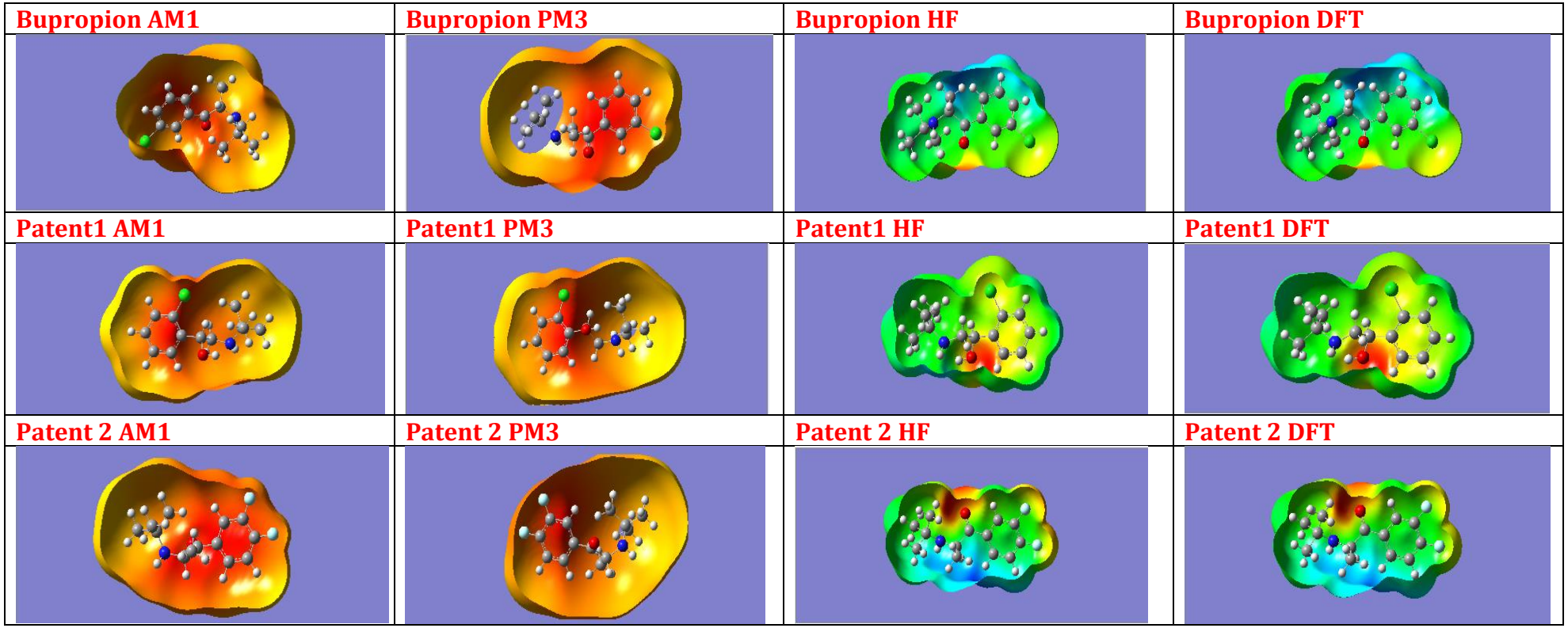


Fig.(9)- The Molecular Electrostatic Potential Surface of the Bupropion with bioactive and its derivatives in G09

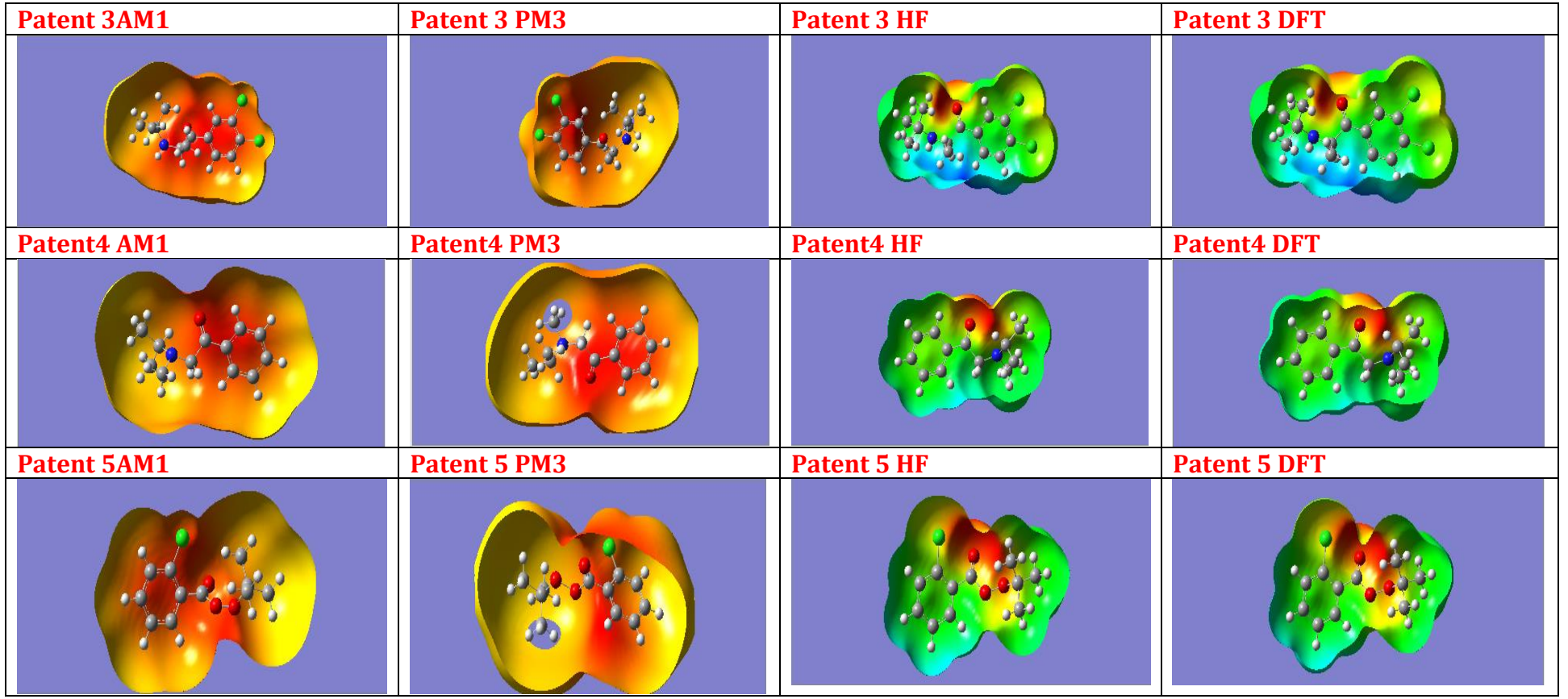


Fig.(10)- The Molecular Electrostatic Potential Surface of the Bupropion with bioactive and its derivatives in G09

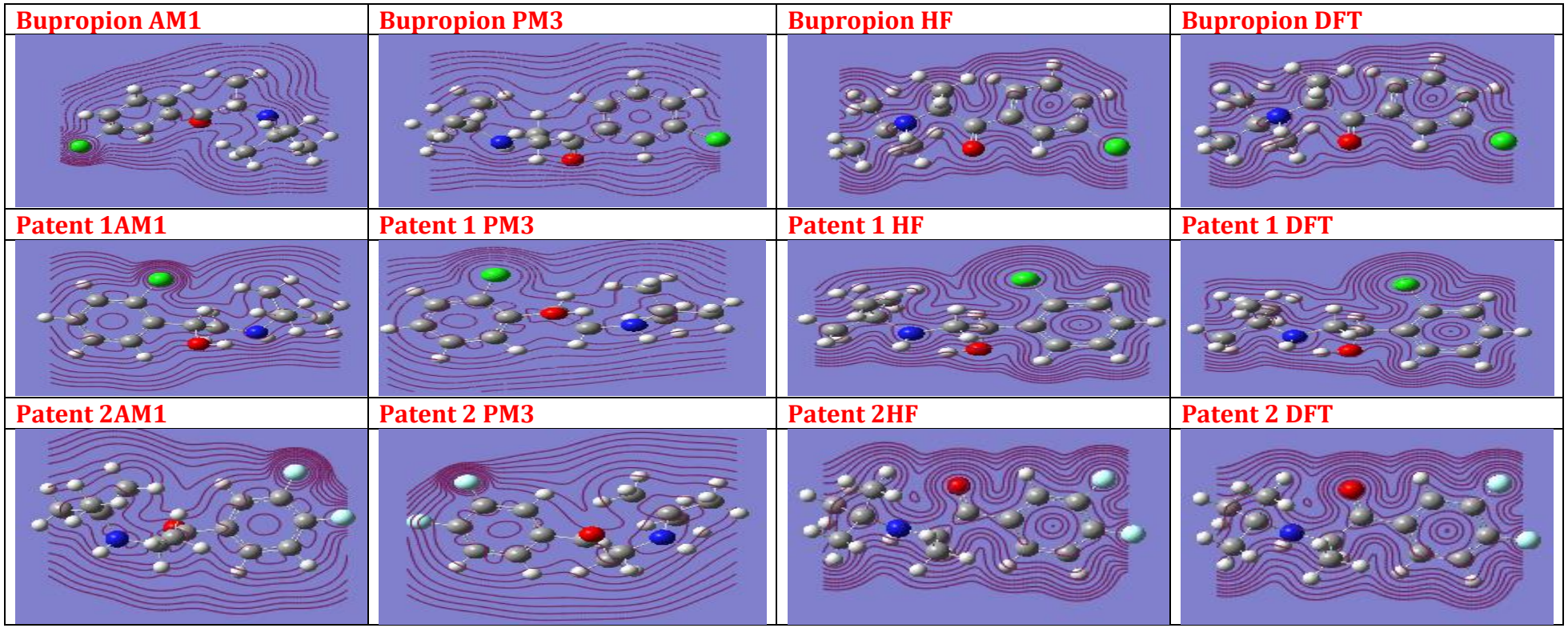
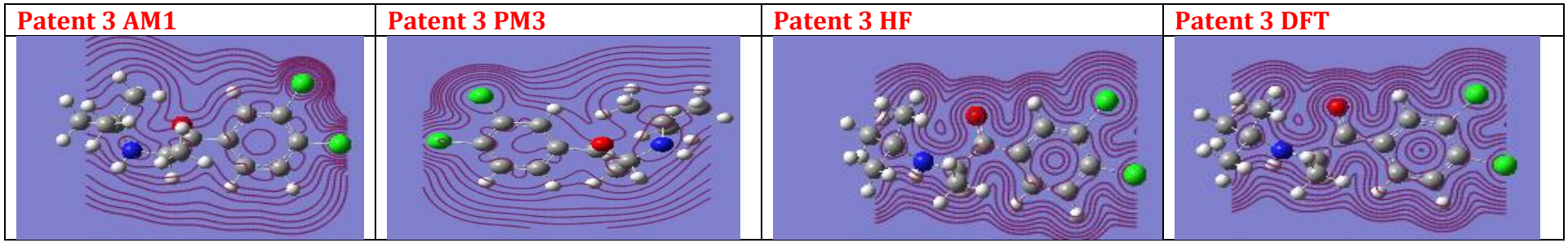


Fig. (11) Electronic Density of Bupropion and its derivatives using (AM1, PM3, HF, DFT) in G09



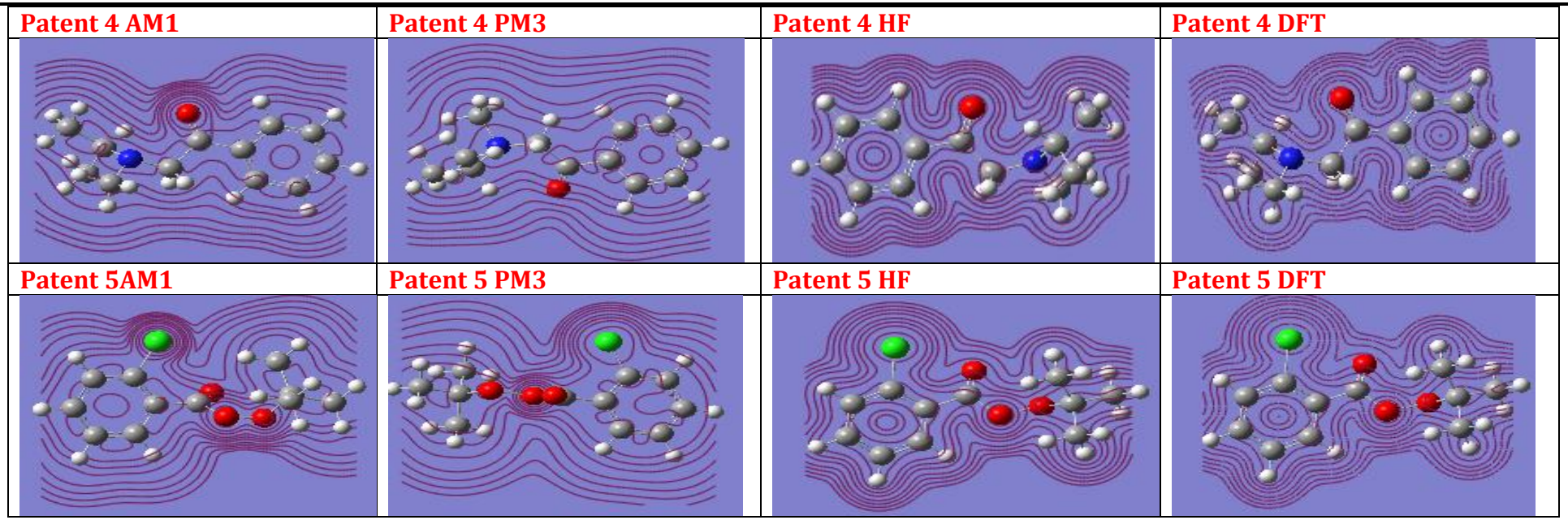


Fig. (12) Electronic Density of Bupropion and its derivatives using (AM1, PM3, HF, DFT) in G09

Conclusions

Theoretical studies were conducted using (AM1, PM3, HF, and DFT) methods to calculate the physical and chemical properties of Bupropion and its five derivatives as a patent, but its biological activity has not been studied. To make an evaluation for derivatives as a drug, the energies, dipole moment, static charge, bond length, HOMO-LUMO energies and a spectrum was calculated for the optimum structure. The results of the four methods were not very clear, but a correlation between the dipole moment (potential character), static distribution (an active site character) and HOMO-LUMO energies (energy for electron transfer) show that the Patent 4 was important derivatives as a recommended drug relative to Bupropion drug.

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