

Theoretical Study of N-Methyl-3-Phenyl-3-(4-(Trifluoromethyl) Phenoxy) Propan as a Drug and Its Five Derivatives

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Abstract

Quantum chemical calculation was correlated with geometrical structure and total energy of fluoxetine and its five derivatives. Theoretical vibrational frequencies and geometric parameters (bond lengths and bond angles) have been calculated using ab initio (HF), density functional theory (B3LYP), semi-empirical (AM1, PM3) methods with different basis sets to design the fluoxetine drugs and its derivatives by a Gaussian 09 W program. Theoretical optimized geometric parameters and vibrational frequencies of fluoxetine 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 results of the four methods were not very clear, but an correlation between the dipole moment (potential character), static distribution (an active site character) and HOMO-LUMO energies (energy for electron transfer) shows that the patent 1.5 was important derivatives as a recommended drug relative to fluoxetine drug.

Keywords

Fluoxetine, AM1, PM3, DFT and HF: Thermodynamic Properties

1. Introduction

Fluoxetine hydrochloride ($C_{17}H_{18}F_3NO$) (**Figure 1**) is the first agent of the class of antidepressants known as selective serotonin-reuptake inhibitors (SSRIs).

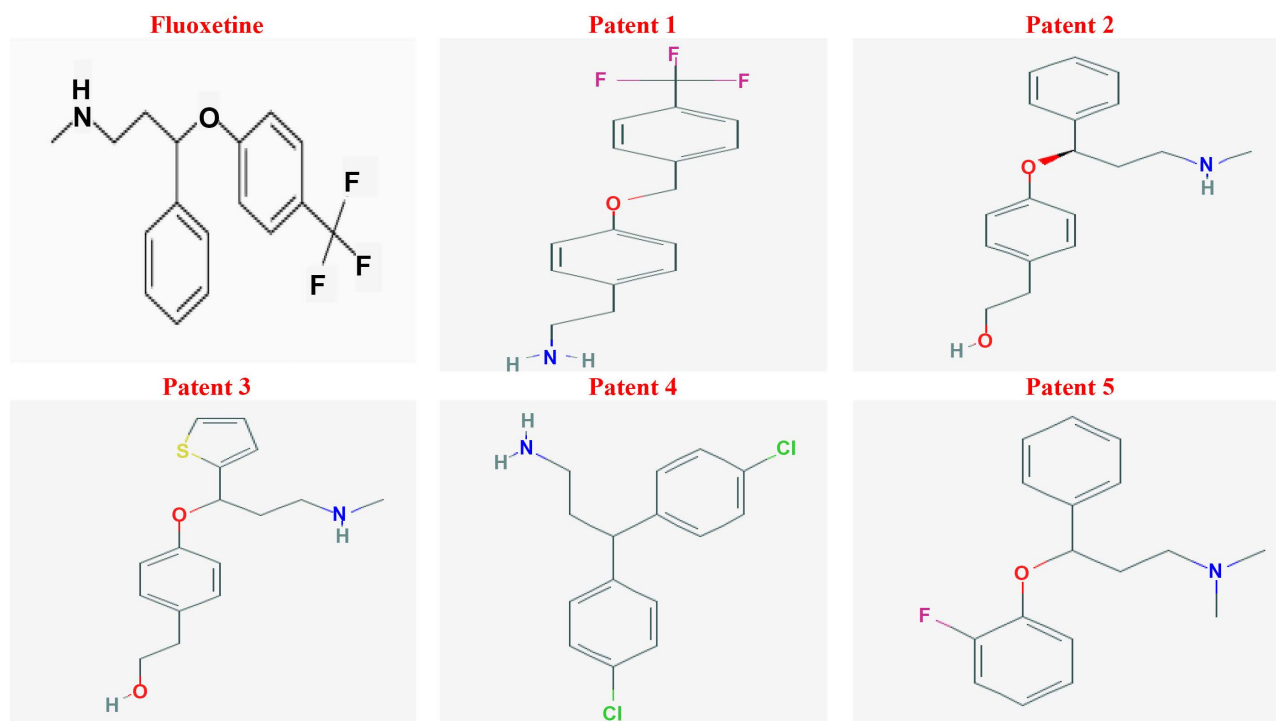


Figure 1. Structure of fluoxetine drugs and its derivatives.

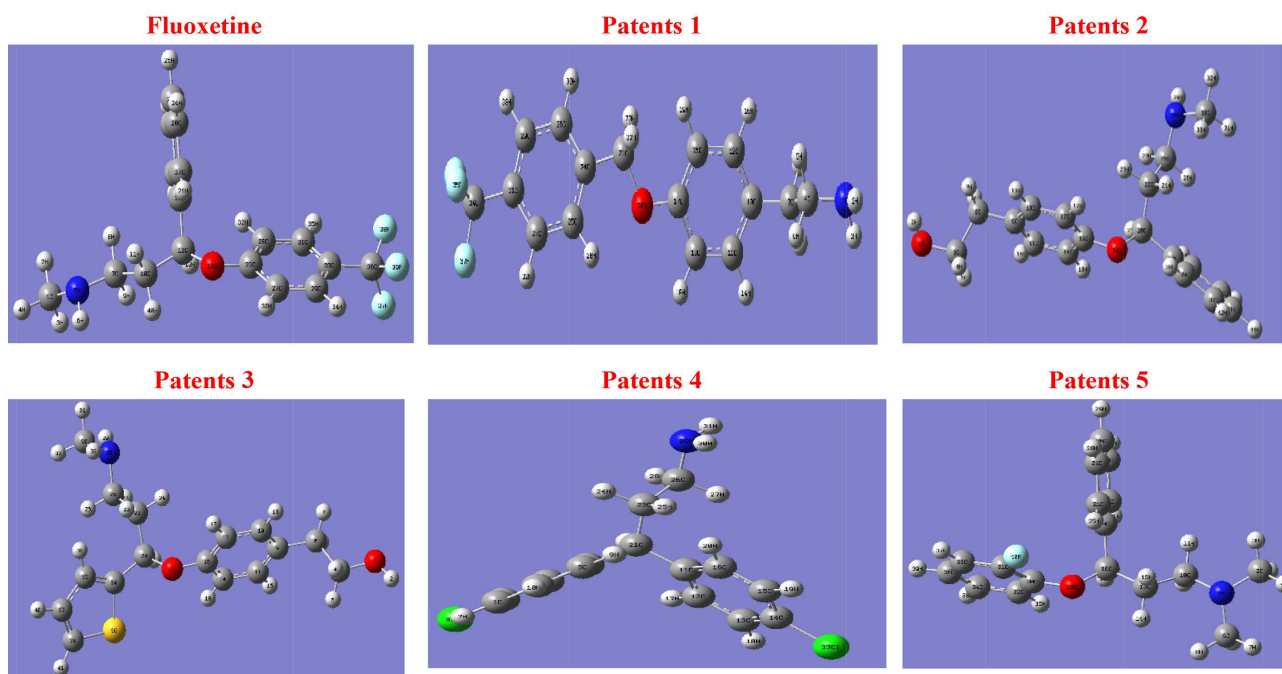
Fluoxetine is a racemic mixture of the R- and S-enantiomers and are of equivalent pharmacologic activity. Despite distinct structural differences between compounds in this class, SSRIs possess similar pharmacological activity, as with other antidepressant agents [1]. The overall clinical effect of increased mood and decreased anxiety is thought to be due to adaptive changes in neuronal function that leads to enhanced serotonergic neurotransmission. Side effects include dry mouth, nausea, dizziness, drowsiness, sexual dysfunction and headache. Side effects generally occur within the first two weeks of therapy and are usually less severe and frequent than those observed with tricyclic antidepressants [1] [2]. 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 [3] [4] [5]. Hence amides and their derivatives have attracted continuing interest over the years. The five fluoxetine derivatives were prepared previously, but its bioactivity has not been characterized yet.

2. Materials and Method

The molecular structures of fluoxetine and its derivatives are presented in **Table 1** and **Figure 2** shows the structural formula, and the atomic position numbers assigned in this work.

Table 1. Fluoxetine data with its derivatives.

Name	Formula	Molecular Weight	IUPAC Name
Fluoxetine	C ₁₇ H ₁₈ F ₃ NO	309.332 g/mol	N-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan
Patent 1	C ₁₆ H ₁₆ F ₃ NO	295.305 g/mol	2-[4-[[4-(trifluoromethyl)phenyl]methoxy]phenyl]ethanamine
Patent 2	C ₁₈ H ₂₃ NO	285.387 g/mol	2-[4-[(1S)-3-(methylamino)-1-phenylpropoxy]phenyl]ethanol
Patent 3	C ₁₆ H ₂₁ NO ₂ S	291.409 g/mol	2-[4-[(1S)-3-(methylamino)-1-thiophen-2-ylpropoxyl]phenyl]ethanol
Patent 4	C ₁₅ H ₁₅ Cl ₂ N	280.192 g/mol	3,3-bis(4-chlorophenyl)propan-1-amine
Patent 5	C ₁₇ H ₂₀ FNO	273.351 g/mol	3-(2-fluorophenoxy)-N,N-dimethyl-3-phenylpropan-1-amine

**Figure 2.** 3D structure of fluoxetine and its derivatives using Gaussian 09 program.

The program that used in the search.

2.1. Gaussian 09

Gaussian 09W (G09) is a computational chemistry program that runs on any modern windows 32 bit PC, or on a 64 bit PC [6]. An electronic structure package capable of predicting many properties of atoms, molecules, reactive system, e.g.:

- Molecular energies;
- Structure;
- Vibrational frequencies;
- Utilizing an initio, density functional theory, semi-empirical.
- * semi-empirical methods (AM₁, PM₃, PM₆, MNDO);
- * ab initio methods (HF, MP₂, CCSD, QCISD);
- * density functional theory (B₃LYP, MO₆, Custom).

2.2. Gauss View 5.08

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

3. 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 and bond angles were 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 219.57 Kcal/mole⁻¹ (AM1), 213.34 Kcal/mole⁻¹ (PM3), 230.67 Kcal/mole⁻¹ (HF), and 216.51 Kcal/mole⁻¹ (DFT) for fluoxetine and compare with the thermal correction energy for five derivatives.

4. Result and Discussion

4.1. Molecular Structure

The schematic depiction of fluoxetine and optimized structure are shown in **Figure 2** and optimized bond lengths, bond angles of fluoxetine molecule which were calculated by using HF, DFT, AM1, PM3 methods with different basis sets are shown in **Tables 2-5** compares the calculated geometric parameters with the five derivatives data. Based on this comparison, the bond length, angles for the derivatives showed good agreement with the drugs. From the theoretical values, we can find that most of the optimized bond lengths and bond angles for drug its slightly alike with the derivatives values, comparing bond angles and length of B3LYP with those of H, DFT and AM1, PM3. In spite of the differences, calculated geometric parameters represent a good approximation and they are the best for calculating other parameters, such as vibrational frequencies and thermodynamic properties.

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 at 310 k. Total energies and dipole

Table 2. Selected bond distances (Å) bond lengths for fluoxetine and its five derivatives.

Bond	Bond Length (G09)											
	Fluoxetine		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
C ₁ -N	1.44	1.47	1.45	1.48	1.44	1.47	1.44	1.47	1.44	1.48	1.45	1.48
N-C ₇	1.45	1.48	1.45	1.48	1.45	1.48	1.46	1.49
C ₁₂ -O ₁₄	1.44	1.44	1.43	1.41	1.44	1.48	1.45	1.44	1.44	1.43
O ₁₄ -C ₂₆	1.37	1.37	1.38	1.38	1.38	1.38	1.39	1.39	1.38	1.37
C ₁₀ -C ₁₂	1.53	1.53	1.53	1.50	1.52	1.52	1.53	1.52	1.53	1.52	1.52	1.52
C ₇ -C ₁₀	1.52	1.52	1.52	1.52	1.53	1.53	1.53	1.54	1.52	1.53	1.53	1.53
C-F	1.37	1.36	1.37	1.35	1.35	1.34
C-S	1.68	1.74
C-Cl	1.70	1.68

Table 3. Selected bond distances (Å) bond lengths for fluoxetine and its five derivatives.

Bond	Bond Length (G09)											
	Fluoxetine		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT
C ₁ -N	1.45	1.47	1.45	1.47	1.45	1.46	1.45	1.47	1.46	1.47	1.46	1.46
N-C ₇	1.45	1.46	1.46	1.47	1.46	1.47	1.46	1.47
C ₁₂ -O ₁₄	1.45	1.48	1.45	1.45	1.48	1.46	1.46	1.50	1.46	1.48
O ₁₄ -C ₂₆	1.36	1.38	1.39	1.39	1.39	1.38	1.39	1.40	1.38	1.38
C ₁₀ -C ₁₂	1.52	1.53	1.50	1.51	1.53	1.53	1.53	1.53	1.53	1.53	1.52	1.53
C ₇ -C ₁₀	1.52	1.53	1.52	1.48	1.53	1.53	1.53	1.53	1.54	1.55	1.53	1.53
C-F	1.35	1.36	1.37	1.41	1.37	1.39
C-S	1.80	1.82
C-Cl	1.82	1.84

Table 4. Selected bond distances (Å) bond lengths for fluoxetine and its five derivatives.

Bond	Bond Angles (°) (G09)											
	Fluoxetine		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
C ₇ -N ₅ -C ₁₀	112.9	110.6	109.4	110.6	113.6	110.7	113.5	110.5	113.4	110.8	113.7	110.6
C ₇ -C ₁₀ -C ₁₂	109.5	110.4	120.4	117.3	109.9	110.7	110.2	111.0	110.2	111.0	1109.5	110.4
C ₁₂ -O ₁₄ -C ₂₆	117.3	117.6	115.6	1.45	113.9	113.5	114.2	114.6	115.5	116.8
C ₃₃ -C ₃₆ -F ₃₇	114.6	114.1	114.8	114.9
C ₂₉ -C ₃₃ -C ₃₁	120.5	120.6	119.5	121.0	120.9	120.2	120.4	120.0

Table 5. Selected bond distances (Å) bond lengths for fluoxetine and its five derivatives.

Bond	Bond Angles (°) (G09)											
	Fluoxetine		Patent 1		Patents 2		Patent 3		Patent 4		Patent 5	
	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT
C ₇ -N ₅ -C ₁₀	110.4	110.4	110.5	110.6	111.6	111.7	111.4	111.5	110.1	110.3	112.1	112.6
C ₇ -C ₁₀ -C ₁₂	113.7	113.3	112.6	112.7	113.4	113.0	113.6	113.6	113.1	113.0	113.0	112.8
C ₁₂ -O ₁₄ -C ₂₆	124.2	121.2	117.6	118.9	120.1	120.8	119.9	117.9	120.7	120.3
C ₃₃ -C ₃₆ -F ₃₇	113.3	113.3	112.9	113.0
C ₂₉ -C ₃₃ -C ₃₁	119.8	119.3	119.7	120.1	120.9	121.0	120.9	120.9

moments have been calculated in solvent media with (AM1, PM3) and (HF, DFT/B3LYP/6-31G) level for fluoxetine drug and its derivatives. **Table 6** and **Table 7** list the calculated values of some thermodynamic parameters (such as zero-point vibrational energy, enthalpy, E_{HOMO} , E_{LUMO} , Gibbs free energy), E_{HOMO} , E_{LUMO} , thermal corrections to (energy, enthalpy, entropy, and Gibbs free energy) fluoxetine and its derivatives. Were obtained using (AM1, PM3) methods, showed that the Patent 3, 4 are more stable than the other patents. The prediction of accurate dipole moments is a very important issue because the magnitude of the dipole moment is strongly related to structure activity of drug. The results obtained using (HF, DFT) method predicts the same evaluation. The value of the dipole moment (D.M) for drugs was also calculated in **Table 6** and **Table 7**. The dipole moment is a measure of the molecular charge distribution. A direction of the (D.M) in a molecule depends on the centers of positive and negative charges. As a result of calculations, the highest dipole moment was observed for a drug in HF/6-31G (6.121) whereas the smallest one was observed for a drug in PM3 (4.029) the value of 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. As **Table 6**, **Table 7** shows that Patent 1, 5 is a D.M have a similar D.M to the drug, relatively has the same activity. These parameters may also play an important role in the biological activity of drugs. The vibration entropy and C_v are found considerably change by changing the methods. The DFT/B3LYP/6-31G result has been given the biggest value for fluoxetine for vibrational entropy (84.47) (Cal/mole-Kelvin) and the biggest vibrational C_v (73.474) (Cal/mole-Kelvin) value whereas the five derivatives have been given the more stability for Patents 3 and 4. Mostly, DFT method is a more professional way to evaluate the methods of characters due to its modern and complex calculations, there its results more reliable than other method. DFT method gives relatively similar results for the energy evaluations but not for the HOMO, LUMO energies and the dipole moment which give relatively different results as **Table 6** and **Table 7** show. Because the study is a correlation study, there the difference in results will not affect the study.

Table 6. Selected thermodynamic parameters for AM1, PM3 of the drug and its derivatives in G09.

Thermodynamic Parameter	Fluoxetine		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)	205.91	199.49	186.97	182.83	240.85	232.46	219.26	211.55	170.11	164.02	214.63	207.43
Thermal Correction to Energy (Kcal.mole ⁻¹)	219.57	213.34	196.49	195.81	254.82	246.67	233.07	225.64	181.26	175.48	227.26	220.37
Thermal Correction to Enthalpy (Kcal.mole ⁻¹)	220.19	213.96	197.11	196.43	255.43	247.28	233.68	226.25	181.88	176.09	227.87	220.99
Thermal Correction to Gibbs Free Energy (Kcal.mole ⁻¹)	170.15	163.32	159.97	146.79	203.89	195.88	182.39	175.03	138.56	132.18	181.05	226.01
C _v (Cal/mole-Kelvin)												
Total	77.14	79.43	62.09	74.45	78.52	82.06	76.38	79.93	63.40	66.06	72.33	75.52
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	71.15	73.474	56.14	68.49	72.55	76.10	70.42	73.96	57.45	60.10	66.37	69.55
S (Entropy) (Cal/mole-Kelvin)												
Total	161.42	163.34	119.79	160.11	166.27	165.79	165.45	165.28	139.72	141.66	151.01	153.48
Translation	43.28	43.27	43.14	43.14	43.04	43.03	43.09	43.09	42.97	42.97	42.91	42.90
Rotational	35.43	35.59	35.06	35.37	35.21	35.18	35.19	35.18	34.75	34.76	34.39	34.51
Vibrational	82.72	84.47	41.59	81.59	88.03	87.58	87.16	87.01	62.005	63.94	73.70	76.06
E _{Homo} (eV)	-9.653	-9.5	-9.635	-9.290	-9.375	-9.495	-9.358	-9.511	-9.584	-9.457	-9.518	-9.380
E _{Lumo} (eV)	-0.329	-0.448	-0.447	-0.645	-0.042	-0.143	-0.265	-0.587	-0.191	-0.261	-0.118	-0.128
E _g = E _{Lumo} - E _{Homo} (eV)	9.323	9.065	9.188	8.644	9.334	9.352	9.093	8.924	9.3926	9.196	9.399	9.252
Ionization Potential (IE = -E _{HOMO})	0.329	0.448	9.635	9.290	9.375	9.495	9.358	9.511	9.584	9.457	9.518	9.380
Electron Affinity (EA = -E _{LUMO})	9.653	9.513	0.447	0.645	0.042	0.143	0.265	0.587	0.192	0.261	0.118	0.128
Dipole Moment (Debye)	4.416	4.029	3.811	2.087	2.655	2.400	2.511	2.019	1.434	1.685	4.287	4.506

4.3. Theoretical Atomic Charge Calculation

Mulliken atomic charge calculation plays an important role in the application of quantum chemical calculation to molecule system [12]. Since the charge distribution on the molecule has an important for the vibration spectra.

Calculated atomic charges are a different matter. Atomic charges can be defined in various ways. Mulliken atomic charges are commonly used in molecular orbital theory and are used in and G09. They have varying values according to the basis set and the method of calculation [13]. **Table 8** and **Table 9** show effective atomic charge calculations which have an important role in the application of quantum chemical calculation to the molecular system the atomic charge levels to the dipole moment, molecular polarization, electronic structure of drug, and the comparison of the different methods to describe the electron distribution of the drugs with its derivatives. Milliken charge distributions were calculated by determining the electron population of each atom as defined by the four

Table 7. Selected thermodynamic parameters for HF, DFT of the drug and its derivatives in G09.

Thermodynamic Parameter	Fluoxetine		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)	217.78	202.77	198.47	184.63	255.59	238.74	232.84	216.89	180.01	167.59	227.68	212.55
Thermal Correction to Energy (Kcal/mole ⁻¹)	230.67	216.51	209.90	197.70	268.83	252.73	245.99	230.83	190.63	178.97	239.61	225.26
Thermal Correction to Enthalpy (Kcal/mole ⁻¹)	231.28	217.12	210.49	198.32	269.44	253.34	246.60	231.45	191.25	179.58	240.22	225.87
Thermal Correction to Gibbs Free Energy (Kcal/mole ⁻¹)	183.28	167.58	165.69	212.17	220.39	203.03	197.53	180.83	149.29	135.76	195.03	179.08
C _v (Cal/mole-Kelvin)												
Total	73.11	79.23	66.66	74.98	74.63	80.67	73.14	79.02	60.54	65.63	68.43	74.20
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	69.14	73.27	60.70	69.03	68.66	74.70	67.17	73.05	54.58	59.67	62.47	68.24
S (Entropy) (Cal/mole-Kelvin)												
Total	154.83	159.79	150.27	157.75	158.20	162.31	158.28	163.30	135.32	141.36	145.76	150.49
Translation	43.28	43.27	42.95	43.14	43.03	43.03	43.09	43.09	42.97	42.97	42.90	42.90
Rotational	35.40	35.44	35.01	35.16	35.29	35.35	35.31	35.34	34.82	34.85	34.37	34.55
Vibrational	76.15	81.07	72.32	79.45	79.87	83.93	79.88	84.34	57.53	63.54	68.49	73.48
E _{HOMO} (eV)	-9.215	-5.754	-8.822	-5.945	-8.716	-5.699	-8.790	-5.723	-9.061	-5.989	-9.176	-5.582
E _{LUMO} (eV)	3.107	-0.777	2.598	-1.024	3.573	-0.295	3.175	-0.859	3.110	-0.643	3.326	-0.402
E _g =E _{LUMO} - E _{HOMO} (eV)	12.321	4.977	11.419	4.920	12.289	5.403	11.965	4.864	12.171	5.3466	12.502	5.1804
Ionization Potential (E = -E _{HOMO})	-3.107	0.777	8.822	5.945	8.716	5.699	8.790	5.723	9.061	5.989	9.176	5.582
Electron Affinity (EA = -E _{LUMO})	9.215	5.754	-2.598	1.024	-3.573	0.295	-3.175	0.859	-3.110	0.643	-3.326	0.402
Dipole Moment (Debye)	6.121	5.869	5.880	6.320	3.394	3.094	3.047	2.983	4.438	4.152	5.445	4.787

methods. The results in the (AM1, PM3, HF, and DFT) were in **Table 8** and **Table 9**. The charge change with the method, basis set presumably occurs due to polarization. In the atomic charge calculation O₁₆, N₅ atoms exhibit a substantial negative charge, which is donor atom. But S and C₈, C₁₁, S₃₅ atoms exhibit a positive charge, which is an acceptor atom (See **Table 8**, **Table 9**).

4.4. 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 [13]. The Eigen values of HOMO (π donor) 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 [13]. The relatively large LUMO-HOMO energy gap of the studied molecule indicates that it can be considered as kinetically stable. In addition, energy

Table 8. Selected atomic charges of drugs and its derivatives in AM1, PM3 in Gaussian G09.

Atoms	Fluoxetine		Patent 1		Patent 2		Patent 3		Patent4		Patent 5	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
1C	-0.132	-0.101	-0.136	-0.116	-0.137	-0.116	-0.129	-0.093
2H	0.083	0.046	0.086	0.053	0.086	0.045	0.087	0.048
3H	0.056	0.032	0.053	0.032	0.052	0.032	0.058	0.035
4H	0.087	0.046	0.083	0.048	0.083	0.053	0.086	0.048
5N	-0.323	-0.087	-0.370	-0.065	-0.323	-0.085	-0.323	-0.084	-0.365	-0.065	-0.278	-0.096
6H	0.162	0.056	0.156	0.037	0.166	0.057	0.167	0.053	0.150	0.037
8H	0.150	0.034	0.157	0.034
8C	-0.081	-0.091	-0.080	-0.101	-0.078	-0.091	-0.076	-0.087	-0.087	-0.065	-0.076	-0.082
9H	0.093	0.060	0.089	0.056	0.065	0.048	0.094	0.062	0.090	0.104	0.095	0.049
10H	0.065	0.048	0.056	0.041	0.092	0.059	0.062	0.045	0.059	0.057	0.068	0.045
11C	-0.165	-0.143	-0.126	-0.055	-0.184	-0.153	-0.180	-0.151	-0.160	-0.116	-0.161	-0.128
12H	0.104	0.076	0.097	0.061	0.098	0.070	0.099	0.077	0.098	0.067	0.103	0.077
13H	0.106	0.077	0.094	0.062	0.099	0.076	0.100	0.073	0.093	0.068	0.102	0.071
14C	0.068	0.106	0.068	0.119	0.102	0.152	-0.035	-0.011	0.070	0.111
15H	0.113	0.085	0.107	0.072	0.109	0.079	0.116	0.084	0.108	0.082
16O	-0.217	-0.193	-0.228	-0.200	-0.244	-0.222	-0.245	-0.220	-0.231	-0.192
17C	0.005	0.083
18H	0.110	0.076
19H	0.107	0.071
20C	-0.134	-0.104
21H	0.087	0.049
22H	0.057	0.036
23H	0.087	0.059
24C	-0.127	-0.117	-0.056	-0.092	-0.095	-0.110	-0.412	-0.306	-0.062	-0.065	-0.122	-0.133
25C	-0.123	-0.085	-0.124	-0.083	-0.126	-0.086	-0.140	-0.093	-0.125	-0.101	-0.116	-0.089
26C	-0.113	-0.092	-0.117	-0.091	-0.115	-0.094	-0.175	-0.125	-0.127	-0.106	-0.124	-0.084
27C	-0.137	-0.111	-0.082	-0.051	-0.139	-0.111	-0.121	-0.108	-0.148	-0.110
28C	-0.139	-0.108	-0.083	-0.044	-0.141	-0.112	-0.129	-0.144	-0.139	-0.111
29C	-0.126	-0.095	-0.171	-0.187	-0.130	-0.100	-0.440	-0.285	-0.085	-0.087	-0.131	-0.098
30H	0.146	0.115	0.161	0.125	0.145	0.116	0.163	0.137	0.151	0.127	0.149	0.116
31H	0.146	0.121	0.159	0.125	0.147	0.117	0.162	0.135	0.155	0.121	0.144	0.117
32H	0.145	0.113	0.160	0.125	0.145	0.113	0.186	0.161	0.152	0.116	0.143	0.114
33H	0.144	0.113	0.160	0.127	0.144	0.113	0.154	0.123	0.144	0.113
34H	0.143	0.112	0.142	0.112	0.143	0.112
35S	0.591	0.280
36C	0.114	0.130	0.066	0.065	0.037	0.045	0.038	0.043	-0.069	-0.078	0.021	0.062
37C	-0.172	-0.158	-0.168	-0.148	-0.160	-0.131	-0.146	-0.121	-0.120	-0.097	-0.148	-0.159
38C	-0.208	-0.195	-0.200	-0.179	-0.146	-0.123	-0.164	-0.131	-0.120	-0.090	0.056	0.006

Continued

39C	-0.042	-0.011	-0.099	-0.070	-0.085	-0.085	-0.089	-0.091	-0.127	-0.104	-0.122	-0.100
40C	-0.051	0.008	-0.101	-0.064	-0.116	-0.091	-0.116	-0.086	-0.127	-0.149	-0.151	-0.114
41C	-0.217	-0.244	-0.111	-0.116	-0.116	-0.085	-0.113	-0.084	-0.088	-0.100	-0.124	-0.078
42H	0.165	0.134	0.153	0.125	0.153	0.123	0.151	0.124	0.152	0.127	0.157	0.134
43H	0.164	0.140	0.152	0.131	0.153	0.123	0.152	0.124	0.153	0.119	0.153	0.116
44H	0.160	0.121	0.145	0.115	0.147	0.117	0.147	0.117	0.156	0.124	0.160	0.119
45H	0.161	0.124	0.146	0.116	0.147	0.117	0.147	0.117	0.156	0.124	0.154	0.128
46C	0.474	0.411	0.469	0.469	-0.164	-0.096	-0.133	-0.076
47F	-0.177	-0.150	-0.174	-0.147
48F	-0.175	-0.141	-0.173	-0.145
49F	-0.175	-0.149	-0.172	-0.142	-0.108	-0.097
50H	0.100	0.066	0.103	0.067
51H	0.103	0.067	0.075	0.066
52H
53C	-0.019	0.071	-0.017	0.076
54H	0.106	0.054	0.075	0.034
55H	0.076	0.037	0.075	0.034
56O	0.385	-0.341	-0.361	-0.344
57H	0.216	0.203	0.219	0.207
58Cl ₂	-0.020	-0.064

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 [13]. LUMO-HOMO gap energy of fluoxetine and its derivatives are calculated by four methods and various levels which are given in **Table 6**, **Table 7** and **Figure 3**. As a result, at the HOMO energies calculated by the (AM1, PM3, HF, DFT) methods by using the Gaussian 09 program by the different basis sets with diffuse function are higher than those of the other basis sets. The HOMO energy value for drug calculated at (AM1, PM3, HF, DFT) (-9.6533, -9.5124, -9.2147, -5.754) eV. The biggest HOMO energy value calculated at DFT/6-31G/B3LYP, whereas the smallest one is calculated at AM1. The biggest LUMO energy value is (3.1066) eV obtained using HF/6031G, band energy gap (E_g) value is (12.3213) eV obtained using HF/6-31G (**Table 6**, **Table 7** and **Figure 3**).

4.5. Ionization Energy

The ionization energy associated with a relationship with a higher energy of occupied orbital as follows [14] [15]. $IE = -E_{HOMO}$ the high value in the energy of ionization mean the high stability of the molecule and on the other hand, the ionization energy means high effectiveness of the molecule. The calculated ionization energy of the drug fluoxetine and its derivatives have studied theoretically by using G09W program according to the methods (AM1, PM3, HF, and DFT)

Table 9. Selected atomic charges of drugs and its derivatives in HF, DFT in Gaussian 09.

Atoms	Fluoxetine		Patent 1		Patent 2		Patent 3		Patent 4		Patent 5	
	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT
1C	-0.240	-0.261	-0.244	-0.267	-0.244	-0.268	0.243	-0.257
2H	0.163	0.148	0.164	0.149	0.169	0.151	0.169	0.147
3H	0.137	0.119	0.137	0.119	0.138	0.128	0.169	0.153
4H	0.163	0.148	0.168	0.151	0.163	0.149	0.135	0.149
5N	-0.787	-0.596	-0.889	-0.733	-0.780	-0.590	-0.781	-0.589	-0.888	-0.736	-0.693	-0.455
6H	0.334	0.291	0.331	0.291	0.339	0.295	0.341	0.290	0.336	0.290
8H	0.339	0.294	0.331	0.294
8C	-0.084	-0.101	-0.079	-0.103	-0.107	-0.123	-0.106	-0.123	-0.094	-0.119	-0.092	-0.104
9H	0.174	0.116	0.147	0.118	0.173	0.121	0.153	0.123	0.169	0.124	0.144	0.148
10H	0.144	0.148	0.170	0.143	0.150	0.144	0.177	0.140	0.152	0.144	0.170	0.114
11C	-0.276	-0.239	-0.315	-0.307	-0.244	-0.220	-0.292	-0.229	-0.275	-0.228	-0.274	-0.234
12H	0.180	0.151	0.173	0.139	0.168	0.148	0.186	0.149	0.165	0.140	0.104	0.148
13H	0.180	0.152	0.177	0.140	0.137	0.146	0.176	0.150	0.179	0.144	0.177	0.155
14C	0.120	0.005	0.100	0.103	0.120	0.130	-0.266	-0.274	0.109	0.099
15H	0.202	0.160	0.194	0.156	0.200	0.161	0.211	0.156	0.199	0.159
16O	-0.830	-0.589	-0.790	-0.598	-0.804	-0.608	-0.795	-0.587	-0.799	-0.588
17C	-0.001	-0.078
18H	0.194	0.182
19H	0.194	0.180
20C	-0.230	-0.257
21H	0.166	0.147
22H	0.168	0.149
23H	0.135	0.116
24C	-0.127	-0.117	0.009	0.059	-0.101	-0.106	-0.552	-0.451	-0.100	-0.103	-0.045	-0.089
25C	-0.123	-0.085	-0.213	-0.136	-0.216	-0.145	-0.139	-0.074	-0.155	-0.122	-0.194	-0.161
26C	-0.214	-0.160	-0.213	-0.152	-0.214	-0.148	-0.107	-0.047	-0.214	-0.106	-0.214	-0.150
27C	-0.215	-0.144	-0.148	-0.123	-0.224	-0.145	-0.210	-0.154	0.219	-0.145
28C	-0.215	-0.143	-0.148	-0.118	-0.218	-0.164	-0.162	-0.146	-0.213	-0.143
29C	-0.214	-0.160	-0.206	-0.017	-0.195	-0.133	-0.391	-0.299	-0.312	-0.240	-0.216	-0.133
30H	0.212	0.147	0.246	0.164	0.229	0.150	0.245	0.192	0.255	0.173	0.235	0.151
31H	0.223	0.147	0.246	0.171	0.218	0.146	0.240	0.165	0.253	0.157	0.228	0.147
32H	0.223	0.148	0.266	0.175	0.219	0.145	0.253	0.169	0.236	0.160	0.221	0.146
33H	0.230	0.153	0.266	0.174	0.220	0.145	0.238	0.173	0.221	0.147
34H	0.233	0.152	0.219	0.145	0.222	0.152
35S	0.453	0.380
36C	0.440	0.311	0.336	0.285	0.353	0.283	0.340	0.266	-0.127	-0.133	0.355	0.279
37C	-0.235	-0.138	-0.205	-0.148	-0.216	-0.152	-0.210	-0.134	-0.155	-0.160	-0.203	-0.133
38C	-0.250	-0.155	-0.206	-0.144	-0.210	-0.141	-0.219	-0.138	-0.151	-0.107	-0.359	-0.149

Continued

39C	-0.130	-0.138	-0.224	-0.190	-0.219	-0.172	-0.041	-0.094	-0.230	-0.174	0.212	0.245
40C	-0.131	0.116	-0.225	-0.174	-0.218	-0.188	-0.218	-0.177	-0.205	-0.104	-0.211	-0.138
41C	-0.029	-0.021	-0.027	0.100	-0.036	-0.094	-0.219	-0.183	-0.317	-0.233	-0.209	-0.157
42H	0.253	0.171	0.225	0.164	0.226	0.145	0.236	0.147	0.255	0.175	0.247	0.150
43H	0.246	0.163	0.225	0.171	0.229	0.143	0.228	0.146	0.255	0.159	0.252	0.152
44H	0.266	0.176	0.231	0.147	0.233	0.143	0.227	0.145	0.238	0.175	0.235	0.153
45H	0.266	0.175	0.231	0.150	0.227	0.157	0.231	0.155	0.238	0.160	0.234	0.165
46C	1.136	0.682	1.136	0.687	-0.351	-0.338	-0.328	-0.318
47F	-0.419	-0.293	-0.406	-0.287
48F	-0.409	-0.293	-0.414	-0.291
49F	-0.415	-0.290	-0.414	-0.291	-0.471	-0.344
50H	0.187	0.141	0.149	0.150
51H	0.182	0.151	0.149	0.150
52H
53C	-0.043	-0.022	-0.047	0.015
54H	0.168	0.141	0.165	0.140
55H	0.183	0.156	0.165	0.140
56O	0.800	-0.649	-0.805	-0.656
57H	0.423	0.378	0.426	0.382
58Cl ₂	0.044	0.020

as in **Table 6** and **Table 7**. The calculated ionization energy for the drug according to DFT and PM3 method was similar to that of Patent 2, 3, on other and was similar to Patent 5 as AM1 and HF indicated.

4.6. Electron Affinity

The energy of electron affinity is given by the equation: $EA = -ELUMO$ [15]. The high value of the energy of electronic affinity means high stability and thus leads to less efficiency of the molecule to link; the low energy electronic affinity means high efficiency and less stability of a molecule. The energy of electronic affinity of the drug fluoxetine and its derivatives studied theoretically by using program G09W. The result of the electron affinity shows that Patent 3 was a comparable value with a drug in methods (HF, DFT) showed relatively similar value for the affinity between the drug and Patent 3, 4.

4.7. 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 10**. In order to facilitate assignment of the observed peaks we have analyzed some vibrational frequencies and compared our calculated results of the fluoxetine with their five derivatives shown in **Table 10** and **Figure 4**. **Figure 5**

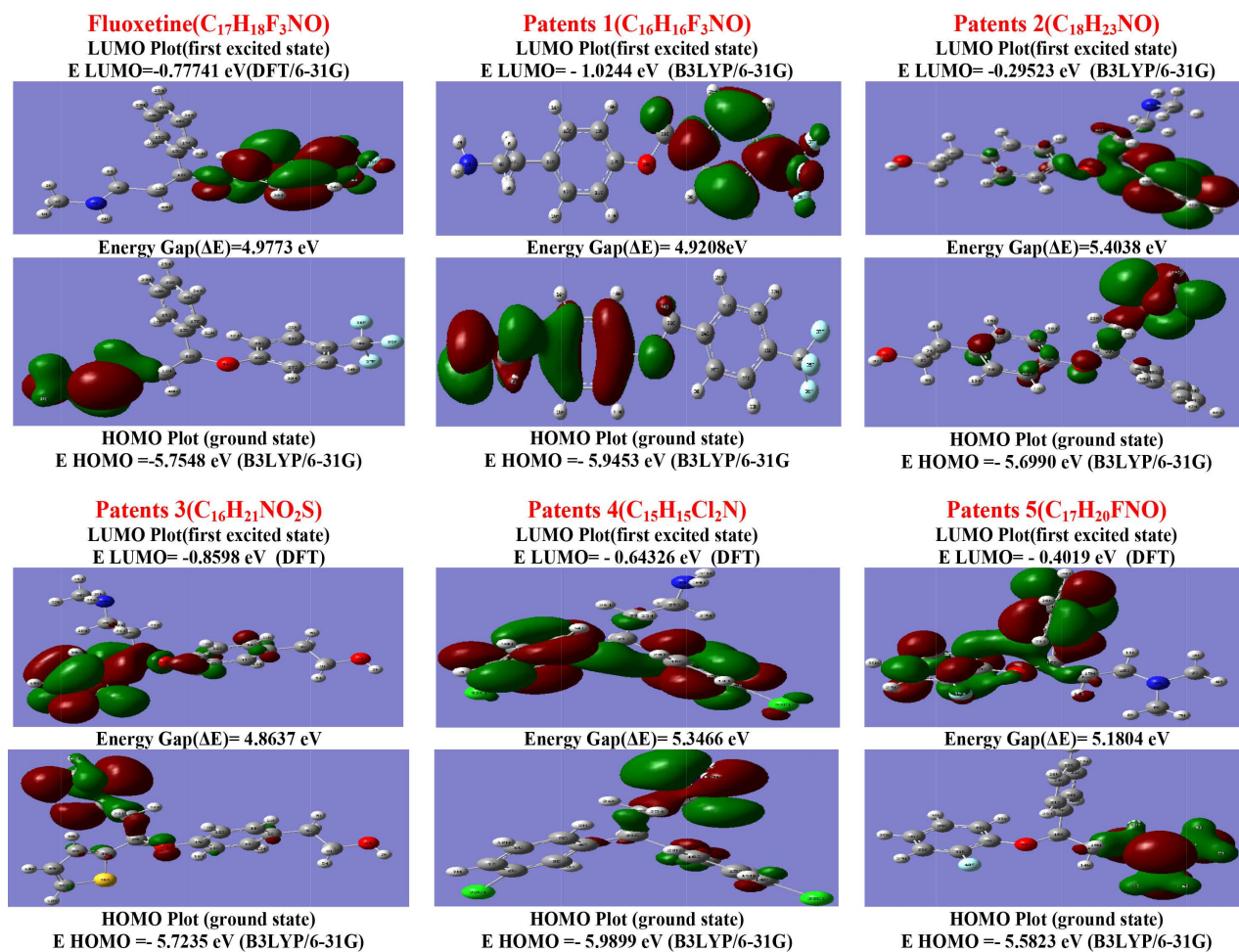


Figure 3. Calculated HOMO-LUMO plots of drug and its derivatives using DFT/B3LYP/6-31G.

shows IR-spectra of the fluoxetine 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.

4.7.1. C-H Vibrations

The assignment of carbon-hydrogen stretching mode is straightforward on the basis set of the scaled four methods predicted frequencies as well known group frequencies. The heteroaromatic structure shows the presence of C-H stretching vibrations in the region 3150 - 3050 cm^{-1} [16] [17].

Which is the characteristic region for ready identification of C-H stretching vibration? In this region, the bands are affected appreciably by the nature of the substituents. In the present theoretical study, there are three C-H stretching vibrations observed in the aromatic ring [16] [17]. The strong and medium bands observed in IR spectrum at (3190, 3070, 3434, and 3263) in four methods for drugs are assigned to C-H stretching vibrations as reported with the derivatives.

Table 10. Comparison between experimental and theoretical values of the patterns of seismic movement frequencies drug fluoxetine and its derivatives when the geometry of the equilibrium on according to method of calculation (AM1, PM3, HF, DFT).

Fluoxetine									
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
N-H	3300 - 3500	3395	23.31	3361	3.84	3772	31.36	3502	31.02
C-H _{aromatic}	3150 - 3050	3190	96.40	3073	62.75	3434	6.83	3263	5.97
C-C	1400 - 1650	1540	405.3	1468	570.3	1401	442.9	1339	447.4
C-N		1358	4.11	1334	11.6	1298	2.77	1268	84.58
C-F	1250	1278	127.7	1208	58.94	1285	181.9	1114	226.2
Patent 1									
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
N-H	3300 - 3500	3472	18.17	3517	7.40	3859	137.5	3609	167.18
C-H _{aromatic}	3150 - 3050	3402	215.8	3065	55.15	3402	43.39	3239	14.15
C-C	1400 - 1650	1321	318.3	1462	86.82	1458	468.1	1336	500.06
C-N	1358 - 1130	1331	3.37	1367	44.98	1350	6.16	1430	23.63
C-F	1250	1321	318.3	1371	168.43	1245	373.06	1117	221.78
Patent 2									
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
N-H	3300 - 3500	3393	29.21	3373	4.32	3795	2.77	3530	0.39
C-H _{aromatic}	3150 - 3050	3181	65.67	3074	34.36	3392	18.73	3218	59.91
C-C	1400 - 1650	1450	61.27	1376	75.20	1331	97.67	1561	212.04
C-N	1358 - 1130	1465	22.42	1416	1.16	1251	21.49	1376	75.20
O-H	3500 - 3450	3478	79.15	3879	15.69	4005	62.59	3633	16.69
Patent 3									
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
N-H	3300 - 3500	3394	28.81	3373	4.36	3798	3.36	3532	0.33
C-H _{aromatic}	3150 - 3050	3242	161.49	3125	116.3	3359	29.38	3195	33.91
C-C	1400 - 1650	1670	177.4	1431	32.96	1691	179.6	1558	152.25
C-N	1358 - 1130	1403	6.91	1415	1.01	1380	8.25	1268	7.17
O-H	3500 - 3450	3482	97.55	3899	23.27	4014	63.29	3648	11.78
Patent 4									
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
N-H	3300 - 3500	3459	16.73	3516	7.52	3798	3.36	3532	0.33
C-H _{aromatic}	3150 - 3050	3187	91.65	3125	116.3	3359	29.38	3195	33.91
C-C	1400 - 1650	1620	69.78	1431	32.96	1691	179.6	1558	152.25
C-N	1358 - 1130	1479	12.62	1415	1.01	1380	8.25	1268	7.17
C-Cl		3482	97.55	3899	23.27	4014	63.29	3648	11.78

Continued

	Patent 5								
	Experimental [13]	AM1		PM3		HF		DFT	
	Freq-cm ⁻¹	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity	Freq-cm ⁻¹	Intensity
C-H _{aromatic}	3150 - 3050	3190	54.16	3072	69.66	3386	44.27	3229	25.11
C-C	1400 - 1650	1691	227.25	1684	191.61	1691	179.6	1549	197.89
C-N	1358 - 1130	1497	25.04	1393	5.78	1429	1.81	1306	6.79

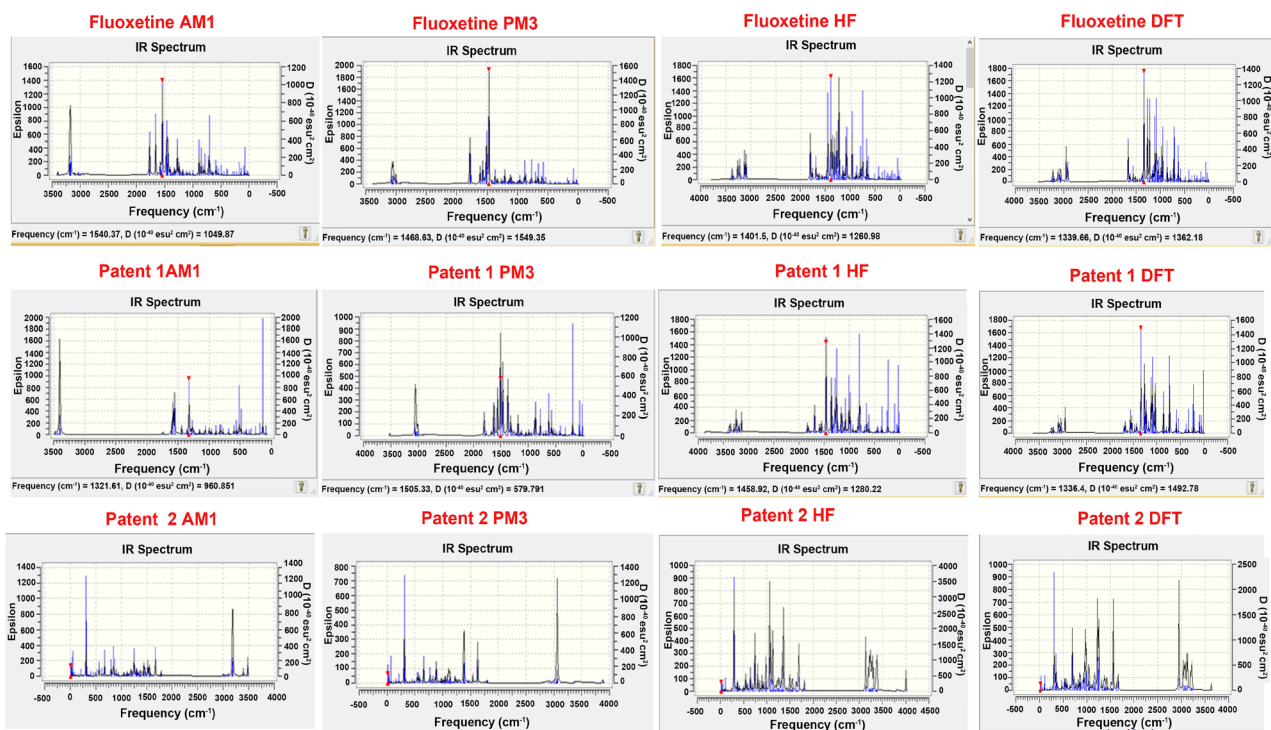


Figure 4. Calculated theoretical IR-spectra of the fluoxetine and its derivatives in four method (AM1, PM3, HF, DFT).

4.7.2. C-C Vibrations

There are six equivalent C-C bonds in benzene and consequently, there will be six C-C stretching vibrations. Due to the high symmetry of benzene, many modes of vibrations are infrared inactive. In general, the bands around 1400 - 1650 cm⁻¹ in drug are assigned to skeletal stretching C-C bands [16] [17]. The bands observed at (1540, 1468, 1401, and 1339) in (AM1, PM3, HF, DFT) assigned to C-C stretching vibrations as reported with the derivatives.

4.7.3. C-F Vibrations

Infrared spectra of a number of tri-fluoro group have been studied, they assigned the frequency 1250 cm⁻¹ to a C-F stretching mode of vibration [18]. The C-F stretching vibration observed at (1278, 1208, 1285, and 1114) in (AM1, PM3, HF, DFT). In the present case, a band assigned to C-F stretching vibration is assigned at 1250 cm⁻¹ according to the reported values [19].

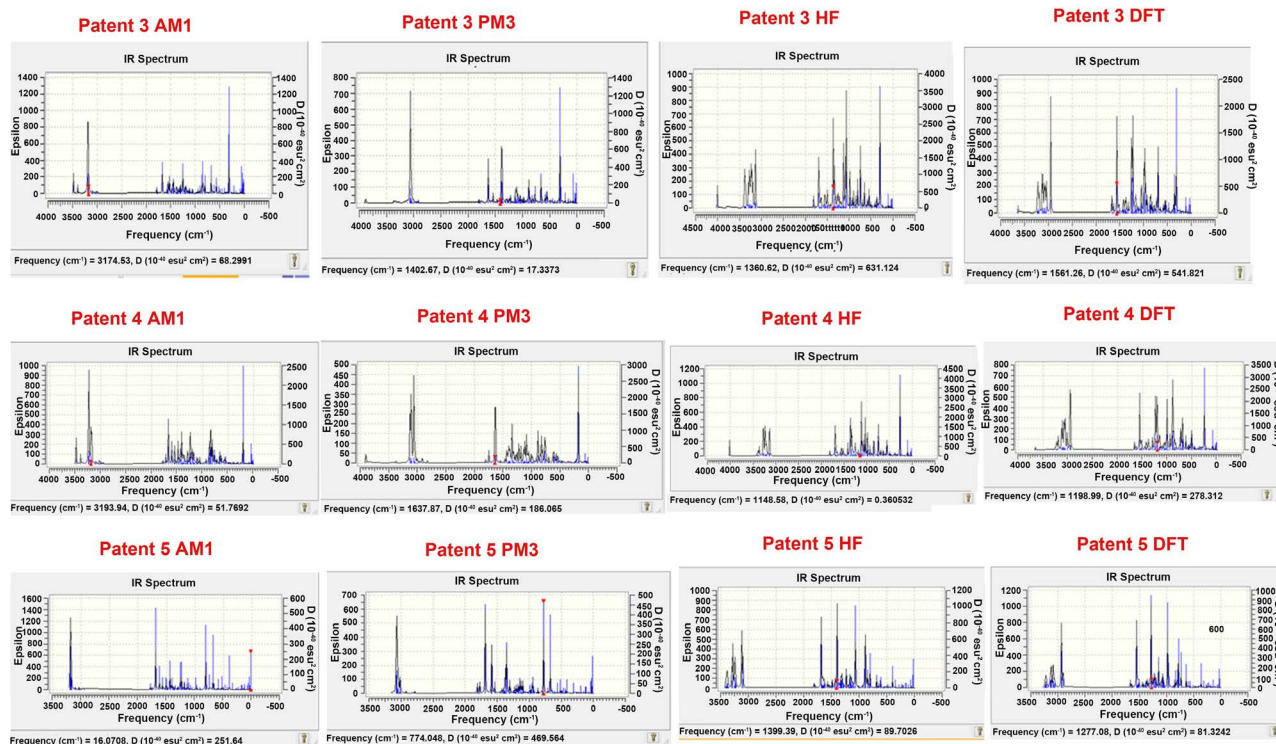


Figure 5. Calculated theoretical IR-spectra of the fluoxetine and its derivatives in four method (AM1, PM3, HF, DFT).

4.7.4. N-H Vibrations

Stretching type vibrations of amine functional group have $3300 - 3500 \text{ cm}^{-1}$ characteristic IR absorption frequencies [13]. N-H stretching modes have been calculated as (3395AM1, 3361PM3, 3772HF 3502DFT) cm^{-1} . Which are assigned the N-H stretching modes to the frequency of drug with the derivatives? The NH-stretching wave number in IR spectrum as weak intensity from the computed wave number indicates the weakening of the N-H bond resulting in proton transfer.

4.8. Molecular Electrostatic Potential

DFT method was applied to predict the molecular electrostatic potential surface of the drug and its derivatives. **Figure 6** shows that the electrostatic potential as a range of color from blue to red relation to the compound activity, blue colour point to lower activity and red O atom to higher activity. Fluoxetine shows a higher stability (blue color) with an active tri-fluo ring group, on other hand Patents 3, 4 is the most similar activity character to the drug which show a stable compound with an active group (yellow color). Patent 3, 4 shows a yellow color in zone of OH and Chloro group respectively. Patent 1, 2, 5 shows a different active group apart from drug.

5. Conclusions

Theoretical studies were conducted using (AM1, PM3, HF, and DFT) methods to calculate the physical and chemical properties of fluoxetine and its five

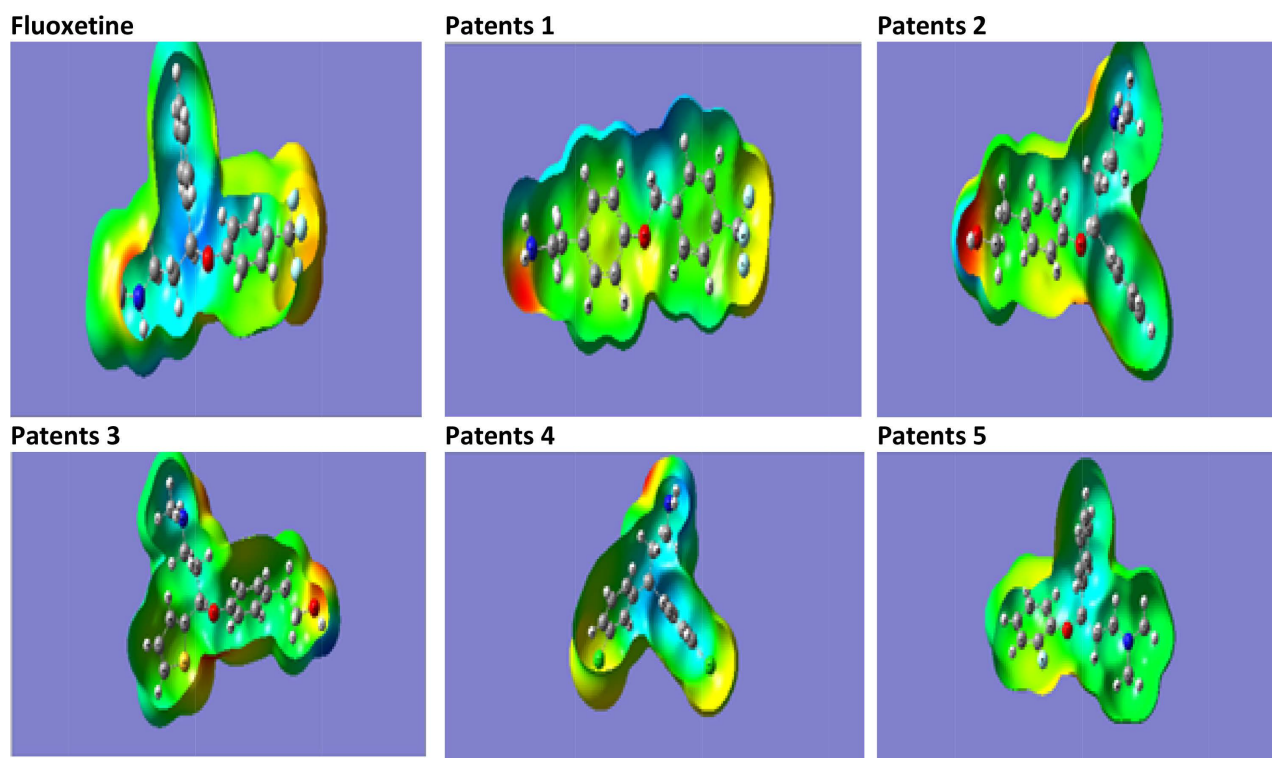


Figure 6. Molecular electrostatic potential surface of drug and its derivatives in DFT method.

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 1, 5 was important derivatives as a recommended drug relative to fluoxetine drug.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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