Research Article

Theoretical Study of Chlorpropamide Drug and its Derivatives by using Quantum Mechanics Method

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Received: 05-04-2018; **Revised:** 26-04-2018; **Accepted:** 08-05-2018.

ABSTRACT

Accurate quantum chemical computational calculation is a valuable tool estimating the (geometry, total energy, Dipole moment, charge distribution) on a series of Chlorpropamide derivatives. Thermodynamics properties like entropy, heat capacity, Zero point energy have been calculated for the molecule. The calculated HOMO and LUMO energies showed that charge transfer occurs in Chlorpropamide molecule and it derivatives which have been systematically studied using (HF,DFT/B3LYP) at the level of 6-31G and Semi empirical (AM1,PM3) methods, the method calculations has been performed using Gaussian 09 program with GUI(Graphical User Interface) called Gauss View 5.08. On the basis of vibrational analysis. The activity characters of the drug and its derivatives can be predicted through calculated HOMO – LUMO, energy gap and the dipole moments. The correlation between the drug characters and its derivatives can predict an expectation for the best drug derivatives.

Keywords: Chlorpropamide; AM1, PM3, DFT and HF: Thermodynamic properties.

INTRODUCTION

Chlorpropamide $C_{10}H_{13}ClN_2O_3S$ (fig 1) is an antidabetic drug, Chlorpropamide is an oral hypoglycemic drug belonging with a sulfonylurea group and is used for the treatment of type π diabetes mellitus in adults when not complicated[1-5] .Along-acting first generations sulfonylurea with hypoglycemic activity[6-7].Compared to other sulfonylureas, Chlorpropamide has an increased risk of prolonged hypoglycemic because of its long half – life [8]. Therapy with sulfonylurea drugs was instituted in type n diabetic patients at the beginning of the 1950, Chlorpropamide, is sulfonylurea derivative presenting prolonged pharmacological action[9]. Chlorpropamide belongs to class n of the biopharmaceutical classification exhibiting poor solubility which causes problems during absorption. The polymorphic character of Chlorpropamidum was first reported by Simmons [1]. However, in the medicinal chemistry literature Chlorpropamide derivatives (Fig-1) are always presented as structure which leads to a misleading perception [8-10].

Especially when molecular modeling – based studies are being increasingly employed for the study of theoretical computational. It is important to identify the appropriate structures and the detailed electronic charge distribution. Dipole moment, total energy and other properties in Chlorpropamide and derivatives. Amide bonds are indeed pre sent in a huge array of molecules, including major marketed drugs [11-13]. Hence amides and their derivatives have attracted continuing interest over the years.

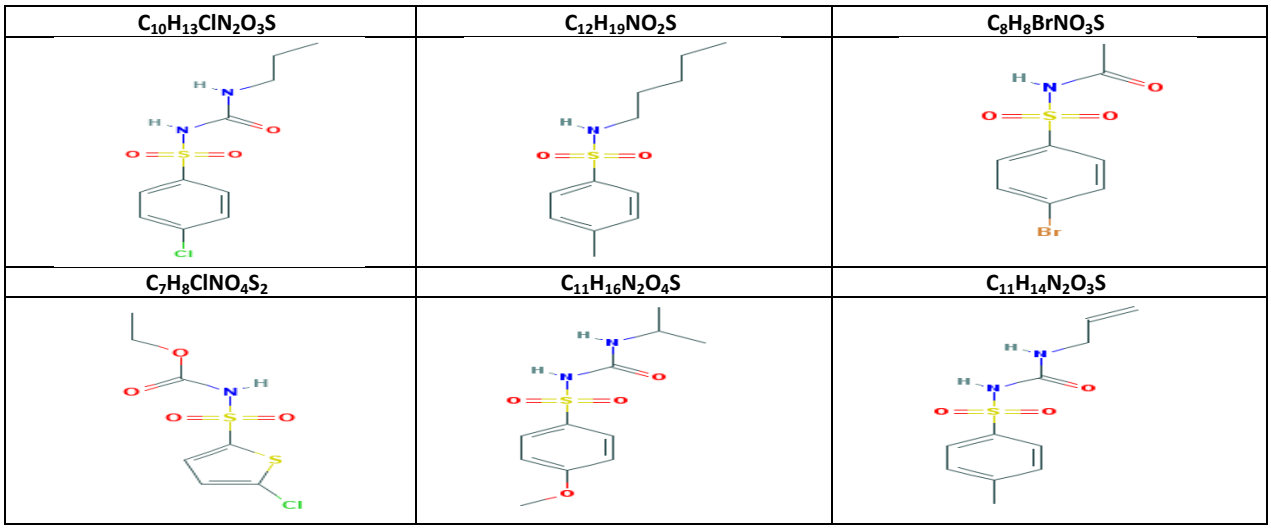


Figure 1: Structure of Chlorpropamide drugs and its derivatives.

MATERIALS AND METHOD

(Fig 2) shows the structural formula, and the atomic position numbers assigned in this work, the molecular structures of Chlorpropamide and derivatives are presented in (fig 2) and Table 1 respectively.

Table 1: Chlopropamide data with its derivatives.

Name	Formula	Molecular Weight	IUPAC Name
Chloroproamide	$C_{10}H_{13}ClN_2O_3S$	276.735 g/mol	1-(4-chlorophenyl)sulfonyl-3-propylurea
Patent 1	$C_{12}H_{19}NO_2S$	241.349 g/mol	4-methyl-N-pentylbenzenesulfonamide
Patent 2	$C_8H_8BrNO_3S$	278.1 g/mol	N-(4-bromophenyl) sulfonylacetamide
Patent 3	$C_7H_8ClNO_4S_2$	269.71 g/mol	ethyl N-(5-chlorothiophen-2yl) sulfonylcarbamate
Patent 4	$C_{11}H_{16}N_2O_4S$	272.319 g/mol	1-(4-methoxyphenyl)sulfonyl-3-propan-2-ylurea
Patent 5	$C_{11}H_{14}N_2O_3S$	254.304 g/mol	1-(4-methylphenyl)sulfonyl-3-prop-2-enylurea

The program that used in the search

Gaussian 09

An electronic structural package capable of predicting many properties of atoms, molecules, reactive system[14], 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[15, 16]
- Sketch molecules
- Setup Gaussian 09 input files
- Graphically examine results

Molden

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

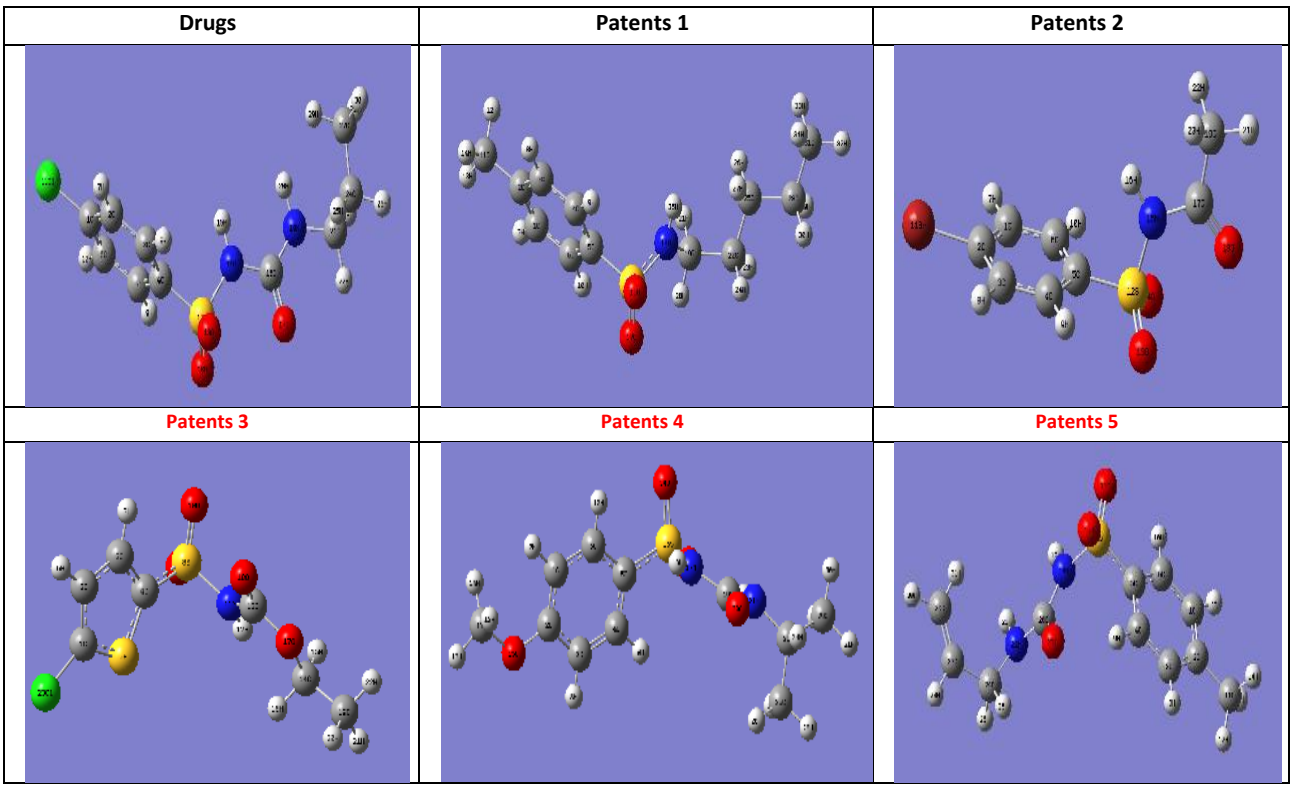


Figure 2: 3D Structure of various of Chlorpropamidum and its derivatives in Gaussian 09 program.

Computational details

The molecular geometry optimization, calculations of total energy, Vibration frequencies ,IR intensities, dipole moment, charge distribution, bond length, and HOMO- LUMO energy for Chlorpropamide and its derivatives by Gaussian 09 software package[17] using (HF,DFT/B3LYP functional ,AM1, PM3) method[17. 18].

The first step of the calculation, of the total energy of drug at (AM1, PM3), (HF /6-3IG level of theory and (DFT/B3lyp/6-31G) methods. For the lowest energy conformer, the geometric structure was optimized at the four methods [19, 20.] Then the vibrational frequencies, IR intensities were also calculated at the four methods [21, 22]. The vibrational frequency calculations at the same methods of theory revealed no imaginary frequencies, indicating that an optimal geometry at this level of approximation was found for the title compound[23].

The electronic properties: HOMO – LUMO energies are calculated by four methods, based on the optimized structure for soluble in water solvent. Thermodynamic properties of the little compound at 310k temperature have been calculated using four methods, moreover, the dipole moment, and Milliken atomic charge have also been studied.

RESULTS AND DISCUSSION

Molecular structure

The schematic depiction of the drug with its derivatives by structure optimization are shown in fig.2 and the optimized bond length of Chlorpropamide 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 bond length shows a good relationally agreement for the different methods[24, 25].

The geometry optimization of bond length for the derivatives shows a slightly difference from the drug bond lengths table -2-. Due to the fact that the theoretical calculation deals with an isolated molecule in water solvent and 310k temperature. The mean values of (S- O), (S- N), (C- S), bond length which calculate by (AM1, PM3) were shorter than that of (HF, DFT) which used force field theory. It's not possible to predict the activity of a compound depending on the bond length character alone, on other bond derivatives (2, 3) give the most similarity in bond length with drug for four methods.

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

			Bond Length(G 09)									
Bond	**Drug 1**		**Patent 1**		**Patent 2**		**Patent 3**		**Patent 4**		**Patent 5**	
	AM1	**PM3**	**AM1**	**PM3**	**AM1**	**PM3**	**AM1**	**PM3**	**AM1**	**PM3**	**AM1**	**PM3**
$S_{12} = O_{13}$	1.40	1.45	1.42	1.48	1.41	1.45	1.41	1.45	1.41	1.46	1.41	1.46
$S_{12} = O_{18}$	1.40	1.45	1.42	1.48	1.41	1.46	1.45	1.40	1.41	1.46	1.41	1.46
$S_{12} – N_{14}$	1.64	1.76	1.59	1.75	1.64	1.76	1.63	1.74	1.63	1.76	1.64	1.76
$C_4 – S_{12}$	1.67	1.76	1.67	1.76	1.67	1.76	1.64	1.73	1.65	1.75	1.66	1.75
$C_{16} = O_{17}$	1.26	1.23	….	…..	1.24	1.22	1.24	1.22	1.25	1.22	1.26	1.23
$C_1 - Cl_{11}$	1.69	1.68	….	…..	….	….	1.67	1.65	…..	….	….	….
$C_{16} – N_{14}$	1.41	1.42	1.43	1.48	1.39	1.42	1.38	1.41	1.38	1.43	1.40	1.42
			Bond Length(G 09)									
Bond	**Drug 2**		**Patent 1**		**Patent 2**		**Patent 3**		**Patent 4**		**Patent 5**	
	HF	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**	**HF**	**DFT**
$S_{12} = O_{13}$	1.64	1.63	1.64	1.64	1.64	1.63	1.64	1.63	1.63	1.63	1.63	1.63
$S_{12} = O_{18}$	1.64	1.63	1.64	1.64	1.64	1.63	1.64	1.63	1.64	1.65	1.64	1.64
$S_{12} – N_{14}$	1.72	1.75	1.72	1.81	1.73	1.81	1.78	1.82	1.72	1.81	1.72	1.80
$C_4 – S_{12}$	1.82	1.86	1.82	1.85	1.82	1.86	1.79	1.80	1.82	1.85	1.82	1.86
$C_{16} = O_{17}$	1.23	1.25	…..	….	1.86	1.79	1.22	1.24	1.23	1.25	1.23	1.25
$C_1 - Cl_{11}$	1.80	1.82	….	….	1.22	1.24	1.76	1.78	….	….	….	…..
$C_{16} – N_{14}$	1.40	1.40	1.47	1.48	1.37	1.38	1.36	1.38	1.33	1.34	1.38	1.39

Thermodynamic parameters and molecular properties

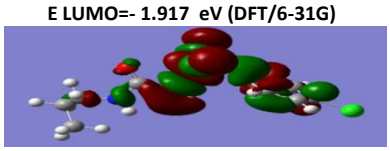
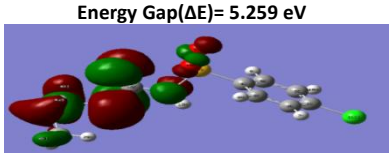
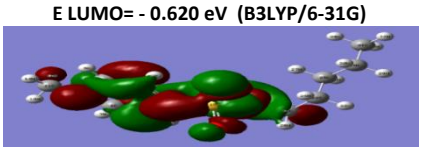
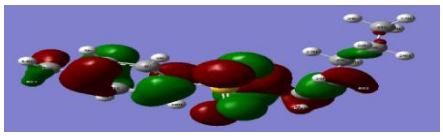
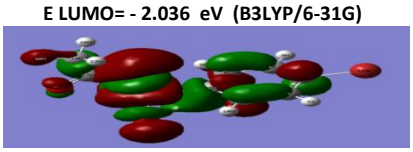
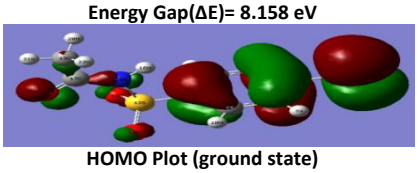
To evaluate the energetic behavior of the title compound in water solvent media theoretical calculations were Carried out at 310 k. Total energies and dipole moments have been calculated in solvent media with (AM1,PM3) and (HF,DFT/B3LYP/6-31G) level for Chlorpropamide drug and its derivatives. Table (3, 4) lists 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) of Chlopropamide and its derivatives. Were obtained using (AM1, PM3) methods, showed that the patent 1,4 have higher energy which that both compounds were than the drug, on other hand patent 2,3 is less stable due to lower energy, the only patent has similar energy is patent 5. The result obtained using (HF.DFT) method predicts the same evaluation. The value of dipole moment (D.M) for drugs was also calculated in Tables (3, 4). Dipole moment is a measure of the molecular charge distribution. 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 drug in HF/6-31G (13.0890) whereas the smallest one was

observed for drug in PM3 (10.1718) 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 characters for the polarity of the compounds mostly, the higher the compound polarity the higher that activity of it. As Tables (3, 4) shows that Patent 2 was the only derivative has a (D.M) similar to that of the drug.

Tables (5, 6) shows 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. Mulliken charge distributions were calculated by determining the electron population of each atom as defined by the four methods. The results in the (AM1, PM3, HF, and DFT) were in Tables (5,6) . The charge change with method, basis set presumable occurs due to polarization. In the atomic charge calculation O_{12}, O_{13}, N_{14}, and C_{26} atoms exhibit a substantial negative charge, which are donor atom. S_{11} and C_{16} atoms exhibit a positive charge, which is an acceptor atom (see Tables 5, 6). These atoms 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 have been given the biggest value for Chlorpropamide for vibrational entropy (69.482) (Cal/mole-Kelvin) and the biggest vibrational C_V (61.430) (Cal/mole-Kelvin) value whereas the five derivatives have been given the more stability for patents 2 and 3. Mostly,(DFT) method is more professional way to evaluate the methods characters due to its modern and complex calculations , there its results more reliable that other method . DFT method give a relatively similar results for the energy evaluations but not for the HOMO,LUMO energies and the Dipole moment which give relativity different results as Tables(3,4) shows. Because the study is correlation study, there the different in results will not affect the study. Tables (3, 4) shows that all the methods evaluate D.M results, and patent 2 has D.M in a good agreement with drug.

HOMO and LUMO analysis

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 Eigen values 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]. Relatively large LUMO-HOMO energy gap of the studied molecule indicates that it can be considered as kinetically stable. In addition, energy of the HOMO is directly related to the ionization potential, while 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 Chlopropamide and its derivatives are calculated by four methods and various levels which are given in Tables (3, 4) and Figs. (3). As a result, at biggest HOMO energy value for Chlorpropamide is (-7.177 eV) calculated at DFT/B3LYP/6-31G whereas the smallest one is (-10.753 eV) calculated at AM1. The biggest LUMO energy value is (-1.011 eV) obtained using PM3, band energy gap (E*g*) value is (5.525 eV) 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 (Tables 3,4 and Figs. 3).

Drug 1(DFT)	Patent 1 (DFT)	Patent 2 (DFT)
LUMO Plot(first excited state) E LUMO=- 1.917 eV (DFT/6-31G)  Energy Gap(ΔE)= 5.259 eV  HOMO Plot (ground state) E HOMO =- 7.177 eV (B3LYP/6-31G)	LUMO Plot(first excited state) E LUMO= - 0.620 eV (B3LYP/6-31G)   Energy Gap(ΔE)= 9.441 eV HOMO Plot (ground state) E HOMO =- - 10.061 eV (B3LYP/6-31G)	LUMO Plot(first excited state) E LUMO= - 2.036 eV (B3LYP/6-31G)  Energy Gap(ΔE)= 8.158 eV  HOMO Plot (ground state) E HOMO =- 10.195 eV (B3LYP/6-31G)
Patent 3(DFT)	Patent 4 (DFT)	Patent 5 (DFT)

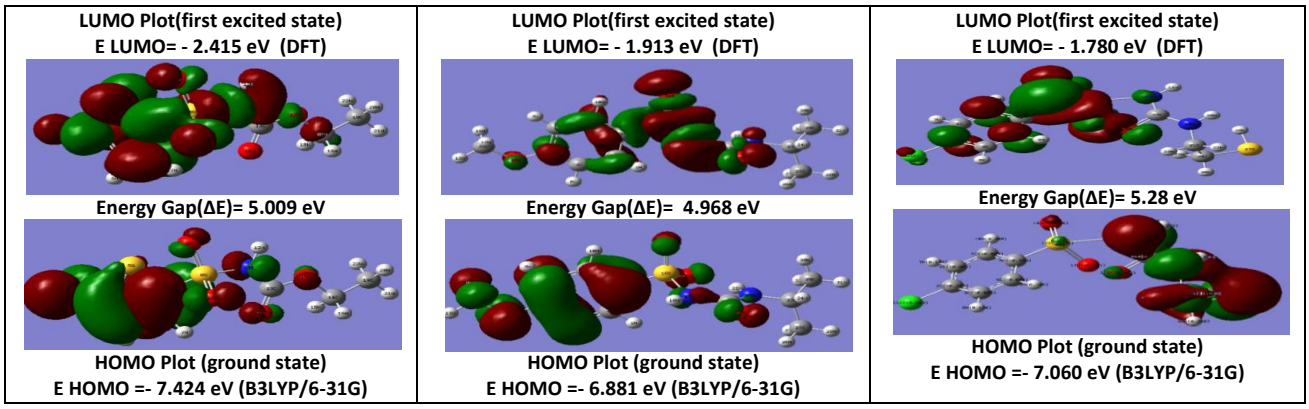


Figure 3: HOMO- LUMO plot and energy orbital and its energy using (DFT) method, red values represent negative drug and green values represent positive charge.

Assignment of vibration spectra

The observed and calculated frequencies using four methods (AM1, PM3, HF/6-31G, DFT/B3LYP/6-31G) with their absolute intensities were shown in Tables (7.8). In order to facilitate assignment of the observed peaks we have analyzed some vibrational frequencies, and compared our calculated results of the Chlopropamide with their five derivatives which shown in Tables (7, 8). In present study, theoretical calculations of vibrational spectra using different methods and different basis sets were compared drugs with the derivatives to obtain a com. The best frequencies calculated by DFT which was in a good agreement with drug frequencies results.

N–H Vibrations

Stretching type vibrations of amine functional group has 3300 – 3500 cm^{-1} characteristic IR absorption frequencies. N–H stretching modes have been calculated as (3343 -3393) cm^{-1} (AM1, PM3) and (3588 – 3787) cm^{-1}(HF, DFT) .We have assigned the N–H stretching modes to the frequency of the (3371cm^{-1})[1] in the experimental spectra. The high wavenumber fundamental vibrations for Chlorpropamide, N– H stretching modes, the longer NH… intermolecular hydrogen bonds because of some interesting effect, such as , the temperature and water solvent and different theoretical methods.

CH3, CH2 -Vibrations

In the frequency range (2800- 3000) [1] cm^{-1} .As shown in Table 7,8 ,calculated CH_2 have been assigned at (3260-3390) cm^{-1} in (AM1,PM3) and (3183-3390) cm^{-1} in (HF,DFT) are observed in the IR-spectra of the Chlorpropamide . It can be interpreted as a consequence of the Fermi-resonance between the fundamental vibrations (CH_2) and (CH_3), combination frequencies, as well as of the factor-group splitting. The frequency vibrational band at four methods are observed, which can be assigned to the stretching vibrations of theCH_3- and CH_2- groups(derivatives), in a good agreement with the theoretical calculation for chloropropamide ,the disappearance of the resonance condition.

SO_2 Vibrations

The observed bands at (1358- 1130) cm^{-1} in IR spectrum. We have assigned the SO2 –group as stretching ant symmetric and symmetric vibrations, but it is necessary to take into account, that these vibrations affected by the CH2, CH3, C6H4 and amide groups .The S– C stretching vibration is assigned at (AM1, PM3, HF, DFT) (606, 722, 590, 743) and the S–N stretching modes at (AM1,PM3,HF) (820,779, 811) in our present study, the very strong band observed in FT-Raman at 721 by B3LYP/6-31G method which is in good agreement with the recorded spectral data.

C–N Vibrations

In our present work , theoretical high values in IR spectrum have been assigned to C– N stretching vibrations of Chlorpropamide (1329, 1320, 1380, 1333) 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[1].

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 2.3 similarities with the Chlorpropamide.

C = O Vibrations

The C =O stretching modes are generally stronger absorption bands within the range of (1715 – 1680) [25] cm^{-1} and strong absorption or high intensity in these modes can be caused by the formation of hydrogen bonds for carbonyl group. Frequency of 1700cm^{-1} (IR) as a very strong band has also been assigned to C=C stretching vibration in the present work. Theoretical wavenumbers for C=O mode in chlorpropamide are (1888 -1697) cm^{-1} in (AM1, PM3) and (1987 – 1883) cm^{-1} in (HF, DFT). It is the drugs in frequency are very high according to experimental result because the results can be attributed strong intermolecular hydrogen bonding on N – H structure[28].

Table 3: Selected thermodynamic parameters for AM1, PM3, DFT and HF of the drug and its derivatives.

Thermodynamic Parameter	Drug 1		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})	143.38	139.12	187.14	181.45	97.82	93.95	98.79	93.50	171.88	165.05	154.07	147.41
Thermal Correction to energy (Kcal.mole^{-1})	152.58	148.51	199.09	193.65	106.66	103.64	109.14	104.66	181.26	178.27	165.78	159.86
Thermal Correction to enthalpy (Kcal .mole^{-1})	153.20	149.12	199.70	194.27	107.27	104.25	109.75	105.27	181.88	178.89	165.78	160.48
Thermal Correction to Gibbs Free Energy (Kcal .mole^{-1})	116.76	111.98	153.63	148.71	69.49	63.45	68.28	61.93	138.65	132.41	121.56	113.75
CV(Cal/mole-Kelvin)												
Total	57.474	58.75	65.86	68.78	48.84	54.15	55.55	59.70	70.48	74.68	64.86	68.91
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	51.51	52.78	59.90	62.82	42.88	48.19	49.58	53.74	64.52	68.72	58.90	62.95
S(Entropy) (Cal/mole-Kelvin)												
Total	117.54	119.80	148.63	146.96	121.88	131.60	133.77	139.81	139.72	141.66	151.01	153.48
Translation	42.93	43.93	42.53	42.53	42.94	42.94	42.86	42.86	42.97	42.97	42.91	42.90
Rotational	34.17	34.17	33.72	33.66	33.50	33.62	33.58	33.75	34.75	34.76	34.39	34.51
Vibrational	40.43	42.68	72.37	70.76	45.42	55.03	57.32	63.20	62.005	63.94	73.70	76.06
E_{Homo}(eV)	-10.372	-9.895	-10.119	-10.061	-10.379	-10.362	-9.959	-9.828	- 9.906	-9.782	- 10.169	- 9.835
E_{Lumo} (eV)	-1.1447	-1.0119	-0.6917	-0.6206	-1.173	-1.002	-1.288	-1.408	- 1.006	- 0.820	- 0.975	- 0.871
E *g* =E_{Lumo} –E_{Homo}(eV)	9.2272	8.8833	9.474	9.4411	9.206	9.361	8.671	8.419	8.899	8.962	9.194	8.963
Ionization Potential (IE = - E_{HOMO}) eV	10.37	9.895	10.119	10.061	10.379	10.362	9.959	9.828	9.906	9.782	10.169	9.835
Electron affinity (EA = - E_{LUMO}) eV	1.1447	1.0119	0.6917	0.6206	1.173	1.002	1.288	1.408	1.006	0.820	0.975	0.871
Dipole moment (Debye)	10.233	10.171	7.153	6.043	9.642	9.508	8.221	5.752	6.202	6.089	7.5400	7.916

Table 4: Selected thermodynamic parameters for AM1, PM3, DFT and HF of the drug and its derivatives.

Thermodynamic Parameter	Drug 1		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})	153.75	143.25	198.62	185.96	103.28	96.93	103.15	95.33	181.89	169.79	163.39	151.82
Thermal Correction to energy (Kcal.mole^{-1})	162.12	155.48	210.26	189.22	112.41	103.89	113.58	106.54	194.17	182.77	174.76	164.05
Thermal Correction to enthalpy (Kcal .mole^{-1})	162.73	155.47	210.87	189.83	113.02	104.51	114.20	107.15	194.79	183.39	174.76	164.67
Thermal Correction to Gibbs Free Energy (Kcal .mole^{-1})	127.41	110.54	164.99	153.12	74.96	71.95	72.79	63.23	149.76	137.03	131.60	119.10
C_V (Cal/mole-Kelvin)												
Total	50.67	67.39	63.76	68.17	49.67	41.32	55.57	59.38	68.73	73.16	62.67	67.63
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	44.71	61.43	57.80	62.21	43.71	35.35	49.61	53.42	62.77	67.21	56.72	61.67
S (Entropy) (Cal/mole-Kelvin)												

Total	113.94	146.93	148.01	147.45	122.76	105.04	133.57	141.70	145.24	149.55	141.23	146.99
Translation	42.93	42.93	42.53	42.53	42.94	42.94	42.86	42.86	42.89	42.89	42.69	42.69
Rotational	34.17	34.51	33.65	33.76	33.63	33.44	33.84	33.90	34.30	34.14	33.70	33.79
Vibrational	36.83	69.48	71.82	71.16	46.18	28.65	56.87	64.92	68.04	72.52	64.83	70.50
E_{Homo}(eV)	-10.408	-7.177	-9.9028	-7.208	-10.228	-10.195	-10.366	-7.424	- 9.588	- 6.881	- 9.926	- 7.060
E_{Lumo} (eV)	1.9189	-1.9172	-2.4612	-1.377	1.8949	-2.0364	1.3888	-2.415	- 2.393	- 1.913	2.258	- 1.780
$E g = E_{Lumo} - E_{Homo}$(eV)	12.326	5.2597	12.364	5.8309	12.122	8.0586	11.754	5.0087	11.981	4.9683	12.184	5.2797
Ionization Potential ($IE = - E_{HOMO}$) e.V	10.408	7.1774	9.9028	7.2081	10.228	10.195	10.366	7.424	9.588	6.881	9.9265	7.0607
Electron affinity ($EA = - E_{LUMO}$) e .V	-1.9189	1.9172	2.4612	1.377	-1.8949	2.0364	1.3888	2.415	2.303	1.913	2.258	1.780
Dipole moment (Debye)	13.089	11.888	9.4777	8.4868	12.649	11.429	8.1009	7.3654	11.421	8.2847	10.502	9.2131

Table 5: Selected atomic charges of drugs with its derivatives in AM1, PM3.

NO	Atoms	Drugs		Patents 1		Patents 2		Patents 3		Patents 4		Patents 5	
		PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1
1	C	-0.082	-0.004	-0.136	-0.166	-0.107	-0.132	-0.320	0.412-	-0.210	-0.233	0.138-	-0.169
2	C	-0.132	-0.153	-0.136	-0.166	-0.072	-0.108	-0.161	-0.182	0.157	0.157	-0.137	-0.168
3	C	0.035	0.007	0.008-	0.004	-0.107	-0.131	0.062	-0.012	-0.182	-0.197	-0.004	0.014
4	C	-0.573	-0.852	-0.548	-0.854	-0.563	-0.838	-0.802	-1.284	-0.616	-0.911	-0.577	-0.873
5	C	0.035	0.008	0.010	0.009	-0.028	-0.002	.....	.....	0.030	0.026	0.020	-0.001
6	C	-0.131	-0.153	-0.136	-0.166	-0.029	-0.002	.....	.....	0.061	0.038	0.020	0.001
7	H	0.133	0.169	0.123	0.153	0.138	0.169	0.152	0.183	0.138	0.166	0.124	0.154
8	H	0.126	0.166	0.121	0.155	0.138	0.169	0.144	0.186	0.133	0.166	0.124	0.154
9	H	0.126	0.167	0.120	0.153	0.127	0.167	.....	.....	0.131	0.161	0.122	0.162
10	H	0.133	0.169	0.123	0.153	0.127	0.167	.....	.....	0.122	0.162	0.120	0.158
11	S	2.318	2.907	2.217	2.893	2.307	2.888	2.376	2.951	2.308	2.905	2.363	2.900
12	O	-0.867	-0.967	-0.884	-0.987	-0.868	-0.968	-0.844	-0.959	-0.865	-0.978	-0.866	-0.965
13	O	-0.866	-0.970	-0.881	-0.986	-0.867	-0.968	-0.854	-0.961	-0.862	-0.966	-0.866	-0.968
14	N	-0.474	-0.853	-0.469	-0.896	-0.486	-0.852	-0.468	-0.841	-0.471	-0.861	-0.466	-0.848
15	H	0.144	0.277	0.134	0.263	0.146	0.278	0.152	0.280	0.149	0.277	0.194	0.276
16	C	0.312	0.422	.....	.....	0.354	0.359	0.440	0.444	0.326	0.436	0.312	0.422
17	O	-0.472	-0.458	.....	.....	-0.434	-0.402	-0.459	-0.403	-0.445	-0.445	-0.467	-0.449
18	N	-0.022	-0.329	.....	.....	.....	.....	.....	.....	-0.080	-0.353	-0.034	-0.336

19	H	0.090	0.242	……	……	……	……	……	……	0.106	0.250	0.099	0.242
20	C	-0.074	-0.036	0.024-	-0.008	……	……	0.061	-0.027	-0.043	0.019	-0.041	-0.013
21	H	0.064	0.113	0.069	0.104	……	……	0.054	0.103	0.079	0.116	0.071	0.116
22	H	0.056	0.106	0.060	0.086	……	……	0.052	0.101	……	……	0.069	0.125
23	C	-0.114	-0.907	-0.129	-0.175	……	……	……	……	……	……	-0.151	-0.198
24	H	0.061	0.090	0.064	0.096	……	……	……	……	……	……	0.108	0.137
25	H	0.059	0.098	0.063	0.089	……	……	……	……	……	……	……	……
26	C	-0.114	-0.219	-0.106	-0.162	-0.136	-0.242	-0.123	-0.221	-0.137	-0.221	-0.162	-0.217
27	H	0.042	0.079	0.055	0.083	0.077	0.128	0.050	0.091	0.048	0.084	0.090	0.121
28	H	0.040	0.075	0.053	0.081	0.070	0.120	0.059	0.106	0.053	0.092	0.088	0.116
29	H	0.080	0.080	……	……	0.078	0.127	0.050	0.091	0.050	0.084	……	……
30	Cl	0.093	0.008	……	……	……	……	0.209	0.082	……	……	……	……
31	C	……	……	-0.096	-0.160	……	……	……	……	……	……	……	……
32	H	……	……	0.055	0.083	……	……	……	……	……	……	……	……
33	H	……	……	0.053	0.081	……	……	……	……	……	……	……	……
34	O	……	……	……	……	……	……	-0.247	-0.255	-0.196	-0.214	……	……
35	S	……	……	……	……	……	……	2.376	2.951	……	……	……	……
36	C	……	……	-0.110	-0.213	……	……	……	……	-0.125	-0.242	……	……
37	H	……	……	0.038	0.073	……	……	……	……	0.053	0.083	……	……
38	H	……	……	0.038	0.073	……	……	……	……	0.047	0.084	……	……
39	H	……	……	0.039	0.073	……	……	……	……	0.049	0.092	……	……
40	C	……	……	-0.080	-0.200	……	……	……	……	-0.048	-0.085	-0.082	-0.202
41	H	……	……	0.059	0.103	……	……	……	……	0.042	0.093	0.060	0.097
42	H	……	……	0.054	0.095	……	……	……	……	0.057	0.119	0.056	0.099
43	H	……	……	0.055	0.098	……	……	……	……	0.040	0.092	0.056	0.105
44	Br	……	……	……	……	0.018	0.074	……	……	……	……	……	……

Table 6: Selected atomic charges of drugs with its derivatives in HF, DFT.

NO	Atoms	Drugs		Patents 1		Patents 2		Patents 3		Patents 4		Patents 5	
		HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT	HF	DFT
1	C	-0.293	-0.225	-0.224	-0.156	-0.146	-0.083	-0.641	-0.565	0.238	-0.131	-0.230	-0.160
2	C	-0.154	-0.090	-0.111	-0.090	-0.361	-0.287	-0.076	-0.008	0.438	0.306	0.021	0.118
3	C	-0.091	-0.066	-0.235	0.157	-0.146	-0.083	0.014	0.022	-0.241	-0.128	-0.238	-0.164
4	C	-0.530	-0.342	-0.509	-0.313	0.533-	-0.347	-0.836	-0.639	-0.515	-0.316	-0.501	-0.301
5	C	-0.091	-0.066	0.017	0.115	-0.091	-0.064	.....	.....	-0.072	-0.080	-0.082	-0.063
6	C	-0.154	-0.090	-0.105	-0.082	-0.091	-0.064	.....	.....	-0.101	-0.092	-0.107	-0.085
7	H	0.281	0.202	0.244	0.165	0.274	0.197	0.296	0.231	0.263	0.185	0.245	0.167
8	H	0.301	0.216	0.243	0.164	0.274	0.197	0.315	-0.609	0.254	0.178	0.245	0.166
9	H	0.301	0.216	0.285	0.194	0.300	0.215	.....	.....	0.286	0.205	0.283	0.198
10	H	0.281	0.202	0.285	0.196	0.300	0.215	.....	.....	0.289	0.207	0.283	0.201
11	S	1.816	1.332	1.758	1.245	1.807	1.326	1.822	1.353	1.820	1.292	1.819	1.326
12	O	-0.744	-0.595	-0.786	-0.624	-0.744	-0.593	-0.742	-0.571	-0.795	-0.568	-0.758	-0.602
13	O	-0.744	-0.595	-0.775	-0.633	-0.744	-0.593	-0.726	-0.790	-0.776	-0.587	-0.775	-0.635
14	N	-1.128	-0.846	-0.985	-0.707	-1.081	-0.792	-1.081	0.411-	-1.119	-0.814	-1.117	-0.824
15	H	0.472	0.299	0.427	0.360	0.475	0.404	0.485	0.766	0.469	0.385	0.470	0.395
16	C	1.147	0.779	.....	.....	0.795	0.559	1.141	0.182	0.150	0.715	1.141	0.767
17	O	-0.684	-0.523	.....	.....	-0.622	-0.478	-0.618	-0.472	-0.692	-0.514	-0.682	-0.522
18	N	-0.894	-0.638	.....	.....	.....	.....	.....	.....	-0.894	-0.642	-0.816	-0.639
19	H	0.419	0.359	.....	.....	.....	.....	.....	.....	0.414	0.375	0.420	0.358
20	C	-0.073	-0.096	-0.104	-0.149	.....	.....	.....	.....	0.045	0.049	-0.102	-0.142
21	H	0.205	0.171	0.219	0.185	.....	.....	.....	.....	0.212	0.164	0.214	0.179
22	H	0.197	0.162	0.217	0.187	.....	.....	.....	.....	.....	.....	0.223	0.194
23	C	-0.300	-0.232	-0.320	-0.257	.....	.....	0.017	-0.022	.....	.....	-0.142	0.065
24	H	0.171	0.142	0.174	0.144	.....	.....	0.210	0.182	.....	.....	0.195	0.142
25	H	0.168	0.140	0.176	0.153	.....	.....	0.210	0.182	.....	.....	.....	.....
26	C	-0.463	-0.415	-0.298	-0.239	-0.538	-0.475	-0.470	-0.422	-0.432	-0.391	-0.376	-0.308
27	H	0.154	0.137	0.156	0.131	0.230	0.201	0.182	0.162	0.169	0.147	0.178	0.139
28	H	0.159	0.139	0.155	0.124	0.226	0.191	0.183	0.163	0.160	0.141	0.177	0.136
29	H	0.162	0.141	.....	.....	0.230	0.201	0.182	0.162	0.165	0.144	.....	.....
30	Cl	0.109	0.081	.....	.....	.....	.....	0.171	0.155	.....	.....	.....	.....
31	C	.....	.....	-0.299	-0.238	.....	.....	.....	.....	.....	.....	.....	.....
32	H	.....	.....	0.154	0.129	.....	.....	.....	.....	.....	.....	.....	.....
33	H	.....	.....	0.154	0.129	.....	.....	.....	.....	.....	.....	.....	.....
34	O	.....	.....	.....	.....	.....	.....	-0.736	-0.519	-0.795	-0.568	.....	.....
35	S	.....	.....	.....	.....	.....	.....	0.694	0.218	.....	.....	.....	.....
36	C	.....	.....	-0.457	-0.412	.....	.....	.....	.....	-0.456	-0.418	.....	.....
37	H	.....	.....	0.154	0.133	.....	.....	.....	.....	0.174	0.150	.....	.....

38	H	.....	.....	0.151	0.134	.....	.....	.....	.....	0.176	0.152	.....	.....
39	H	.....	.....	0.152	0.134	.....	.....	.....	.....	0.165	0.146	.....	.....
40	C	.....	.....	-0.480	-0.483	.....	.....	.....	.....	-0.146	-0.191	-0.479	-0.483
41	H	.....	.....	0.194	0.177	.....	.....	.....	.....	0.187	0.178	0.198	0.178
42	H	.....	.....	0.191	0.165	.....	.....	.....	.....	0.209	0.189	0.188	0.164
43	H	.....	.....	0.185	0.163	.....	.....	.....	.....	0.187	0.178	0.187	0.165
44	Br	.....	.....	.....	.....	0.186	0.155	.....	.....	.....	.....	.....	.....

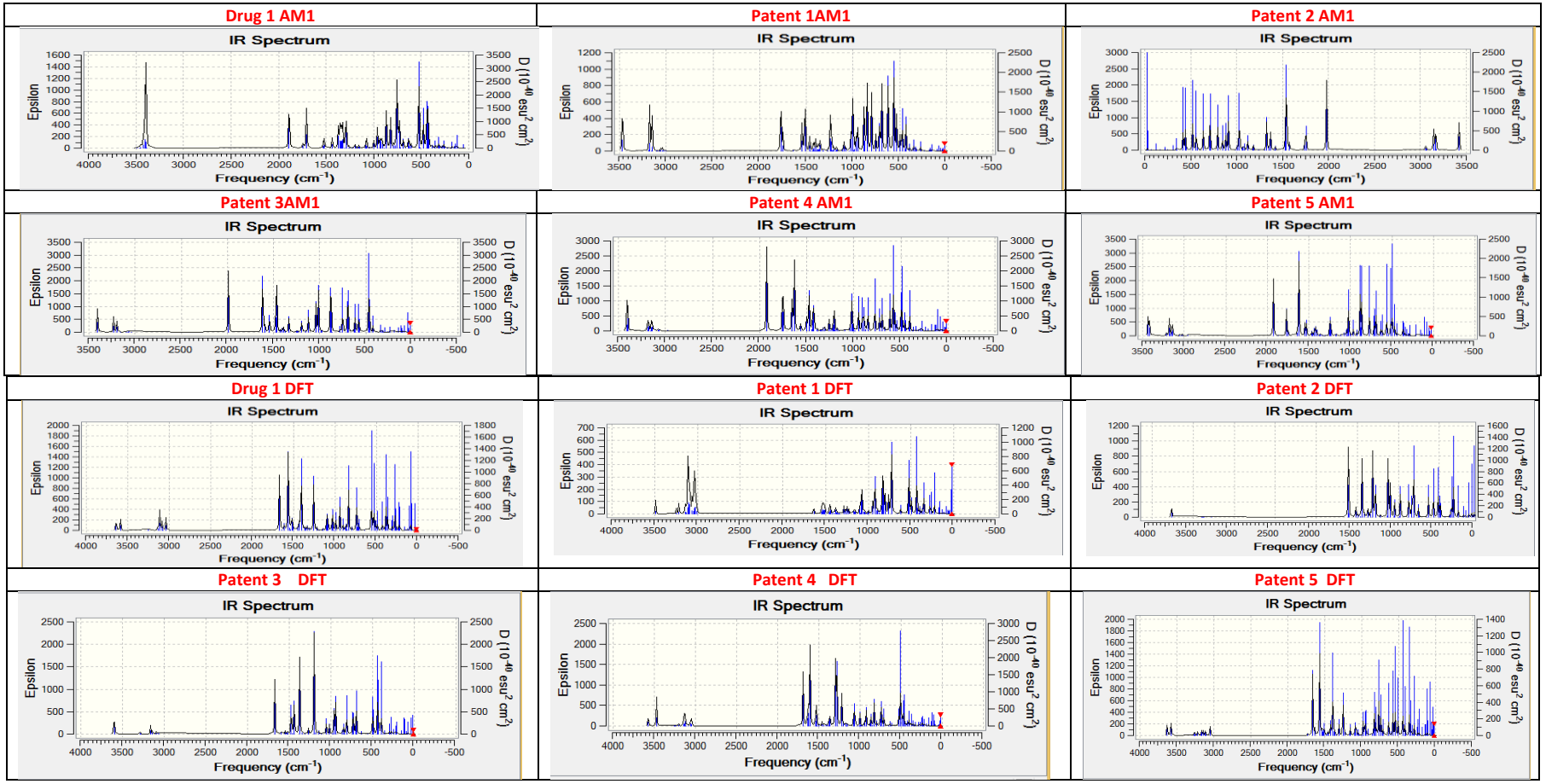


Figure 4, 5: Calculated theoretical IR- spectra of the chloropropamide in two methods (AM1, DFT).

Table 7: Theoretically calculated spectra of Chloropropamide and its derivatives.

	Drugs				Patents 1				Patents 2			
	AM1		PM3		AM1		PM3		AM1		PM3	
	Freq.Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq.Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity
N– H	3393.40	202.0977	3343.82	80.2085	3468.11	245.6302	3277.65	74.9742	3422.31	296.4491	3346.59	82.7006
C– N	1329.01	92.1944	1320.44	94.7916	1327.95	1.3894	1320.40	1.5256	1420.99	36.6588	1414.08	601.6077
C = O	1888.53	359.4753	1697.42	429.0126	……..	……..	…….	……..	1980.30	632.7590	1894.24	710.7302
C– H	3390.45	8.8893	3260.75	4.4339	3156.60	0.0187	3181.43	0.0579	3150.52	19.9937	3173.46	14.2641
C– C- C	1157.16	14.7559	1036.88	5.4682	1094.36	32.5492	1099.87	16.4129	……..	……..	,…….	……..
O– S- O	856.40	217.9865	825.00	386.2771	847.52	289.9918	794.62	143.2229	845.21	134.8347	816.66	359.7331
C– Cl	624.65	10.9073	620.46	14.8829	…….	…….	…….	…….	……..	……..	……..	……..
C– Br	……..	……..	……..	……..	…….	…….	…….	…….	521.31	233.9864	491.42	148.6819
	Patents 3				Patents 4				Patents 5			
	AM1		PM3		AM1		PM3		AM1		PM3	
	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}.	Intensity	Cm^{-1} Freq.	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity
N–H	3406.08	316.0213	3324.86	104.6239	3402.60	352.2987	3337.26	83.9163	3414.90	176.3652	3331.97	74.0871
C–N	1331.81	203.3212	1310.12	252.5419	1475.21	498.6459	1359.36	79.4946	1432.53	67.9083	1414.61	322.9437
C = O	1987.37	744.9715	1883.37	758.5241	1924.30	818.5657	1868.62	837.9493	1942.84	629.2322	1837.69	694.0399
C–H	3160.72	4.7687	3086.00	1.4821	3160.56	1.7978	3180.34	1.7825	3023.37	20.9511	3146.83	19.1782
C–C	1150.92	10.2005	1130.71	0.1304	1194.66	3.7538	1104.64	1.1794	1108.93	10.2528	1131.17	35.2838
O–S–O	883.00	205.7082	866.02	242.0960	848.95	236.9109	812.56	264.3213	862.30	390.8311	811.63	280.2826
C– Cl	569.87	72.9348	515.25	195.5309	……	…..	…….	……..	…….	…….	…….	……..

Table 8: Theoretically calculated spectra of Chloropropamide and its derivatives.

	Drugs				Patents 1				Patents 2			
	HF		DFT		HF		DFT		HF		DFT	
	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity
N–H	3787.42	149.6406	3588.58	74.6492	3803.96	96.4482	3488.12	32.7179	3825.02	212.0573	3762.19	66.3300
C–N	1380.59	5.0912	1333.76	26.1999	1372.50	3.5982	1348.15	2.1728	1368.61	316.5109	1311.31	251.3526
C = O	1578.44	176.0314	1671.21	369.6602	……..	……..	…….	…….	1844.76	426.3639	1607.91	225.1931
C–H	3390.40	8.9051	3138.58	24.5106	3247.64	94.6769	3110.93	70.3687	3342.00	5.1816	3393.48	1.5316
C–C-C	1062.43	22.8549	1040.71	31.1336	1082.54	36.5944	1074.74	54.3393	……..	……..	……..	……..
O–S–O	828.68	208.6544	943.30	135.0268	897.92	47.9022	833.34	81.4290	917.75	118.4002	870.26	125.3671
C– Cl	590.93	36.4020	509.76	20.7474	…….	…….	…….	…….	……..	……..	…….	…….
	Patents 3				Patents 4				Patents 5			
	HF		DFT		HF		DFT		HF		DFT	
	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity	Freq. Cm^{-1}	Intensity
N–H	3824.05	289.4414	3600.72	185.3288	3826.41	193.4604	3573.00	105.6804	3821.03	177.3851	3579.99	96.8023
C–N	1092.72	87.3133	1055.12	89.6906	1171.83	70.5023	1063.37	175.8425	1037.97	48.2199	1068.03	19.0120
C = O	1813.71	515.0656	1673.36	355.8406	1789.93	355.2876	1691.17	413.0281	1797.13	338.0368	1662.32	328.4727
C–H	3210.02	21.6884	3063.28	17.8498	3254.34	24.5695	3138.85	49.2040	3231.25	37.8669	3161.37	28.2907
C–C	1244.21	11.5196	1185.66	10.3347	1261.58	28.0951	1170.17	28.1498	1169.30	27.2615	1152.91	38.1636
O–S–O	901.38	26.6141	962.21	138.7098	925.55	14.7846	924.57	123.4727	944.83	56.4334	946.96	72.2048
C– Cl	562.98	167.5488	500.62	103.8890	……	……	……	……	……	……	……	……

CONCLUSION

From theoretical studies method (AM1, PM3, HF, DFT) were used to measure the physical and chemical characters of the drug chloropropamide and its five derivatives.

The characters stability, activity and the polarity were used as correlation factors for the drug and its derivatives to choose the best derivative as drug. The evaluation of the different kind of energy point to the patents which has similar stability to the drug. By comparing the energy gap which is the character four activities, patent 2 has an activity close to the one of the drug. The calculation was done using high value solvent (water) then the polarity is an important factor. By compare the (D.M) for the drug and its derivatives, patent 2 is the only derivative which has an (D.M) similar to that of drug. From above results its can said that patent 2 are the only derivatives which ability to be a possible drug.

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Source of Support: Nil, **Conflict of Interest:** None.