IJPSR (2014), Volume 5, Issue 10 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 March 2014; received in revised form, 19 June 2014; accepted, 09 July 2014; published 01 October 2014

AVERTING CANCER EFFECT OF PARACETAMOL AND PHENACETIN BY N-ACETYLCYSTEINE AND ITS ANALOGUES

Anwar El-Shahawy *, Nagwa Abo El-Maali and Hassan H. El-Hawary

Department of Chemistry, Faculty of Science, Assiut University 71516, Egypt.

Keywords:

DFT, TD-DFT, PA, PH, NAC, NAM,NAGA, E_{et}

Correspondence to Author:
Anwar El-Shahawy

Department of Chemistry, Faculty of Science, Assiut University 71516, Egypt.

E-mail: anwarshahawy@yahoo.com

ABSTRACT: Comparative DFT calculations have been studied for Paracetamol (PA) and its analog Phenacetin (PH) to verify their electronic resemblance. DFT studies concluded that PA and PH have the lower energy predominant trans conformers with respect the cis-conformers. From TD-DFT studies, the electronic transition energies between the ground state and singlet excited states for the two conformers have been done. The metabolized product of PA or PH, *i.e*., m-PA in the liver of the human being is N-acetylimidoquinone. The electron affinity, Ea, of metabolized Paracetamol (m-PA) is sufficient to interact with the nucleic acid bases in the liver. So long as the m-PA product is produced in the liver and the electron transfer energy, E_{et}, between m-PA and nucleic acid bases has very small energy value with guanine, *i.e.*, 0.382 eV, from the nucleus of the cell in the liver producing a spontaneous electron transfer from the nucleus to m-PA producing cationic nucleus leading to the carcinogenic behavior of the cell in the liver. The presence of glutathione in the liver prevents the formation of m-PA *via* proton transfer, avoiding the carcinogenic effect of PA and PH. Repetitive usage of PA or PH drug consumes the glutathione in the liver, permitting the interaction between m-PA and guanine in the liver. Addition of N-acetylcysteine (NAC), N-acetylmethionine (NAM) or N-acetylglucoseamine (NAGA) prevents the formation of m-PA, *i.e*., cancer effect. Therefore PA and PH can be used as safe drugs after mixing with the pharmacological dose of N-acetylcysteine, N-acetylmethionine or N-Acetylglucoseamine.

INTRODUCTION: Paracetamol instead of Phenacetin is worldwide use as analgesic, and antipyretic drug [1] not as anti-inflammatory and literature including 93 references reported the clinical side effects of Paracetamol in terms of the following system processes: allergic and skin; hematol; renal diseases; pregnant lactation; cancer effect [2]. Availability effect of EtOH with PA was studied by Wojcicki *et al*., [3] in healthy man.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(10).4159-69

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(10).4159-69

Goto *et al*., had studied the charge transfer energy values for some pyridines and pyrimidines by CNDO/2 [4].

Charge transfer complex formation between nucleic acid bases and isoproterenol has been studied using UV spectrophotometer measurement by Taha *et al*. [5] Tautomeric structures of uracil and its electrochemical corrosion behavior of mild steel in the acidic medium were studied using CNDO calculations by Makhlouf and El-Shahawy [6]. The interaction of hydrogen bonding studies in drug-receptor has been performed by Ghafourian *et al*. [7] Severe hepatotoxicity and nephrotoxicity as a reason for the accumulation of toxic metabolites of Paracetamol were studied by Moffat [8]. The CT-complex formation between cytoseine, thymine adenine, and uracil with catechol in acidic medium

has been studied by Al-Obeidi *et al.* [9] The formation of charge transfer complex between oxytetracycline and tetracycline with purines, pyrimidines, and amino acids was studied by Lahiri [10]. El-Shahawy *et al*., have studied the formation of CT- complex between 4, 4'-dimethoxydiquinone with uracil using CNDO calculations [11]. Paracetamol toxicity is manifested primarily in the liver. Hepatic damage from PA can be treated with N-Acetylcysteine (NAC) if started within 10 h from ingestion [12].

The rheumatism therapy has been known since many years ago with the usage of extracts of plants such as willow bark or leaves, most of which contain salicylates. Bayer Company in Germany made the acetylsalicylate form salicylic acid in 1897. This drug has been named ‘‘Aspirin’’ and became the most worldwide use medicine of all time. In 1971, Vane found out the mechanism by which aspirin makes its anti-inflammatory, analgesic and antipyretic effects

He proved that aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) prevent the enzyme activity which is now called cyclooxygenase (COX) producing prostaglandins (PGs) that cause inflammation, swelling, pain, and fever. However, by inhibiting this key enzyme in PG synthesis, the aspirin-like drugs also prevented the production of physiologically important PGs which save the mucosa of the stomach from damage by HCl.

This conclusion provided an explanation for the therapeutic actions and accompanied side effects of the aspirin-like drugs. Twenty years later, with the discovery of a second COX gene, it was clear that there are two forms of the COX enzyme. The constitutive form, COX-1 which supports the beneficial homeostatic functions, whereas the second inducible form, COX-2, is unregulated by inflammatory mediators and its products lead to many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis [13].

Experimental Work:

Materials: Paracetamol (Chem. Pharm. Works, Dupnitsa) was recrystallized from water to show a melting point of 168°. The ethyl alcohol solvent was extra pure Prolabo and Merk grades.

Instrumentation: The UV-visible spectra of some of the studied compounds had been scanned by UV-2101 PC UV-vis scanning spectrophotometer Shimadzu.

The temperature effect on the PA spectrum has been scanned by Perkin Elmer Lambda 35 UV/V is spectrophotometer USA.

Method of Calculations:

Computational Studies: Computational study on an isolated gaseous molecule was done by the aid of DFT-method. Minimizing structures energies have been achieved using B3LYP with 6-31**G basis set.

Calculations were performed on the minimum energy structures using the closed shell Hartree-Fock, Becke's three parameters density functional theory, DFT, [14] in combination with the Lee, Yang and Parr correlation functional B3LYP [15] with basis set 6-31**G. The differentiation between the conformers' cis and trans was based on the total energy difference which has been calculated via SCF using RHF for these types of molecules and UHF for the molecular ions (cations and anions).

With respect to DFT calculations, it has been performed as B3LYP/6-31**G and the energy of the density function theory can be represented as follows [16, 17].

$$E|\rho| = \frac{-\hbar^2}{2m_e}\sum_{i=1}^{n}\int \psi_i^*(r_1)\nabla^2\psi_i(r_1)dr_1 - \sum_{i=1}^{n}\int \frac{z_r e^2}{4\pi\varepsilon_o r_{11}}\rho(r_1)dr_1 + \frac{1}{2}\int \frac{\rho(r_1)\rho(r_2)e^2}{4\pi\varepsilon_0 r_{12}}dr_1 dr_2 + E_{xc}|\rho|$$

Where ρ is the electron density.

$$\rho = \sum_{i=1}^{n}\left|\psi_{i(r)}\right|^2 = \sum_{i}^{n} C_{i(r)}^2$$

Where C_i is the eigenvectors and

$$\hat{H}_i = \frac{-\hbar^2}{2m_e}\nabla_i^2 - \sum_i^n \frac{z_1 e^2}{4\pi\varepsilon_0 r_{12}} + \int \frac{\rho(r_2)e^2}{4\pi\varepsilon_0 r_{12}} + V_{xc}(r_1)$$

Where $\hat{H}_i$ is the Hamiltonian of the total energy.

Electron Transfer Studies: The electron transfer energy in the CT–complex between the donor and the acceptor (cation and anion) was calculated according to the following equation [18].

$$E_{CT} = I_D - E_A - (C^+ + C^-)$$

Where I_D is the ionization potential of the donor and E_A is the electron affinity of the acceptor. C^+ is the columbic potential energy of the donor as a cation, and C^- is the columbic potential energy of the acceptor as an anion. The columbic potential energy can be calculated, according to the following equation [18].

$$C = 14.4 \sum_{i=1}^{N} \sum_{j \neq i}^{N} \frac{Z_i Z_j}{r_{ij}} \quad eV$$

Where Z_i and Z_j are the charge densities and r_{ij} is the distance between two atoms in the molecule of N atoms. The ET-band position in nm can be obtained by dividing 1240.824 by the electron transfer energy in electron volts.

$$\lambda \times E = 1.241 \times 10^3 \text{ nm eV}$$

RESULT AND DISCUSSIONS:

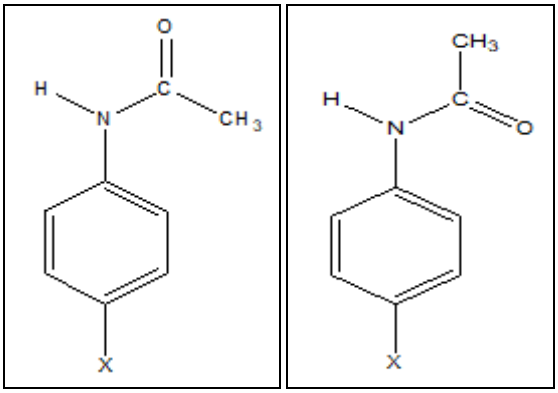
Conformational Studies: Also, it is necessary to compare the conformers of PA with its analog PH. The cis-conformer is the structure in which the amino hydrogen atom and the carbonyl group are on the same side.

TABLE 1: DFT (B3LYP/6-31G) PARAMETERS OF THE STUDIED COMPOUNDS**

Compound	TE au	I_p ev	E_a ev
PA-cis	-515.3532	6.1634	0.9162
PA-trans	-515.3591	5.8374	0.6640
PH-cis	-593.9488	5.8105	0.9265
PH-trans	-593.9606	5.7106	0.5712
m-PA	-514.0887	7.3112	4.2400
N-acetylcysteine	-799.2027	7.2159	1.8585
Glutathione	-1404.793	6.9944	0.0559
ADENINE	-467.1749	6.4061	1.2672
GUANINE	-542.3770	6.1879	1.2828
CYTOSINE	-394.8229	6.5819	1.4768
URACIL	-414.7031	7.3316	1.8626

TE is the total energy in au unit.
I_p is the ionization energy in eV unit.
E_a is the electron affinity in eV unit

The trans-conformer is the structure in which the amino hydrogen atom and the carbonyl group are in opposite sides, **Fig. 1**.



Cis-Form **Trans-Form**

FIG. 1: THE CONFORMERS OF X= OH OR OEt

The existence of conformers cis and trans, **Fig. 1**, is probably due to the small energy difference between them in Paracetamol and Phenacetin. The ratio of the existence of the two conformers depends on the energy difference between them and the temperature, 27 ºC, according to Boltzmann equation [19].

TABLE 2: B3LYP/6-31G ENERGY DIFFERENCE BETWEEN THE CONFORMERS AT 27 º**

Compound	Δ E eV	N/N_0	N
PA cis/trans	0.16055	2.00404×10^{-3}	1.207037×10^{21}
PH cis/trans	0.27211	2.67×10^{-5}	106135×10^{19}

Δ E is the energy difference between the two conformers.
N/N_o is the ratio between the two conformers.
N is the number of the cis-conformer molecules of the higher energy in one mole.

From the previous **Table 2**, it is clear that the trans-conformer has the lower energy in PA as the situation in PH molecules abundance. The energy difference between the two conformers is a fraction of electron volt; therefore their abundance is probably in the normal temperature, especially the transforms.

Regarding the existence of the two conformers in the room temperature in solutions [20], it is probable to change the temperature of the UV-spectra of PA solution in ethyl alcohol, **Fig. 2**, to find out duplicity relative intensity change in the UV-band at different temperatures.

In realty, there isn't observable duplicity at the top of the UV-band of PA, and hence there isn't any change in the relative intensity change indicating to

the absence of the conformers. Using TD-DFT calculations, the electronic spectra have been studied for both conformers cis and trans, to find out the electronic transitions between the ground state and the excited singlet states as follows in the following **Table 3** and **4**.

TABLE 3: ELECTRONIC TRANSITION ENERGIES BETWEEN THE GROUND STATE AND THE SINGLET EXCITED STATES OF TRANS-PARACETAMOL

Excited State 1:	**Singlet-A**	
40 -> 42	0.69844	4.5698 eV 271.31 nm f=0.0001
Excited State 2:	**Singlet-A**	
38 -> 41	0.23477	4.6453 eV 266.90 nm f=0.0428
38 -> 46	-0.11219	
40 -> 41	0.18160	
40 -> 43	0.61001	
Excited State 1:	**Singlet-A**	
40 -> 44	0.70111	4.7303 eV 262.11 nm f=0.0001

TABLE 4: ELECTRONIC TRANSITION ENERGIES BETWEEN THE GROUND STATE AND THE SINGLET EXCITED STATES OF CIS-PARACETAMOL

Excited State 1:	**Singlet-A**	
38 -> 42	0.21497	4.5836 eV 270.49 nm f=0.0442
40 -> 41	0.63233	
40 -> 42	-0.13652	
Excited State 2:	**Singlet-A**	
40 -> 42	0.18779	4.7849 eV 259.11 nm f=0.0033
40 -> 43	0.66942	
Excited State 3:	**Singlet-A**	
39 -> 41	-0.18640	
39 -> 42	-0.40338	
39 -> 45	0.10294	
39 -> 46	-0.19266	
40 -> 42	0.38604	
40 -> 43	-0.16222l	

f is the oscillator strength.

From the previous **Table 3** and **4**, it is clear that the allowed transition energies for cis and trans conformers lie at 254nm and 267nm respectively which they are very near to each other, then the expected duplicity can't be observed by the temperature effect at 248 nm in the UV spectrum in ethyl alcohol [21] as shown in the following **Fig. 2**.

The experimental λ_{max} of Paracetamol lies at 261 nm in chloroform solvent[21] over broadband including the λ_{max} at positions 254 nm and 267 nm for cis and trans conformers respectively.

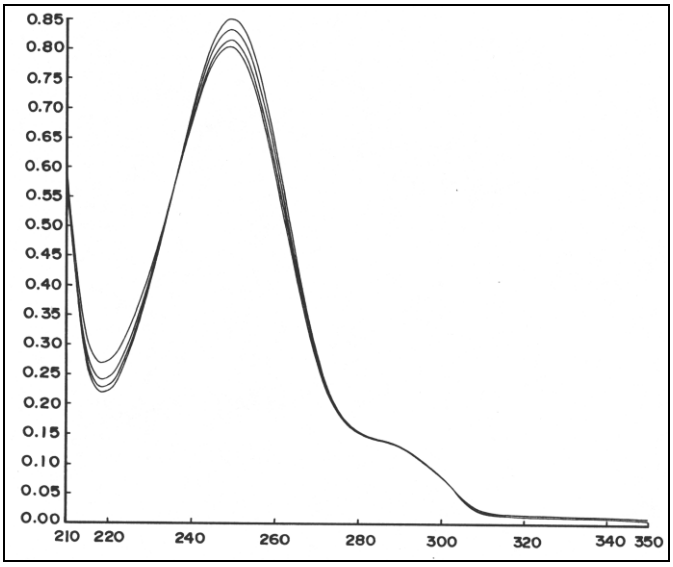


FIG. 2: THE HEAT EFFECT ON THE ELECTRONIC SPECTRUM OF PA MOLECULE IN EtOH. (a) at (45 °C), (b) at (35 °C), (c) at (25 °C), (d) at (15 °C)

Electron Transfer Studies: PA and PH are metabolized primarily in the liver [22-24], into toxic and non-toxic products **Fig. 3, 4,** and **9**. Three metabolic pathways are notable, **Fig. 4**, and **9**. The hepatic enzyme system metabolizes Paracetamol, producing the toxic product as N-acetylimidoquinone, which has the symbol (m-PA) for simplicity, **Fig. 4**.

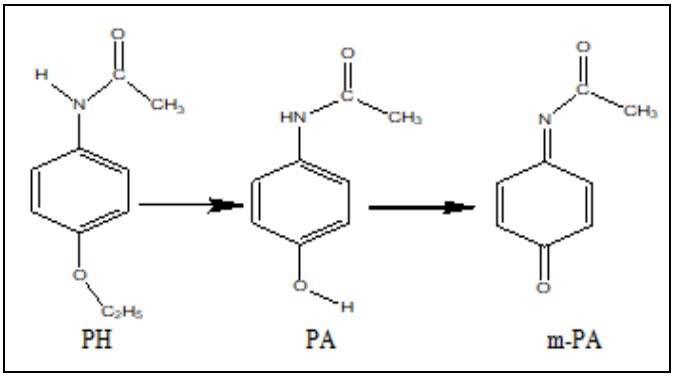


FIG. 3: METABOLIZED PRODUCT, m-PA FROM PA, AND pH

All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidneys. The intermediate product m-PA is also produced via the metabolism of PH in the liver, **Fig. 3** and **4**. This means that m-PA is primarily responsible for the toxic effects of PA and PH. Then it is interesting to use quantum mechanical DFT (B3LYP/6-31**G) calculations to study the interaction between this product, m-PA, and the nucleic acid bases in the nucleus in the liver cell.

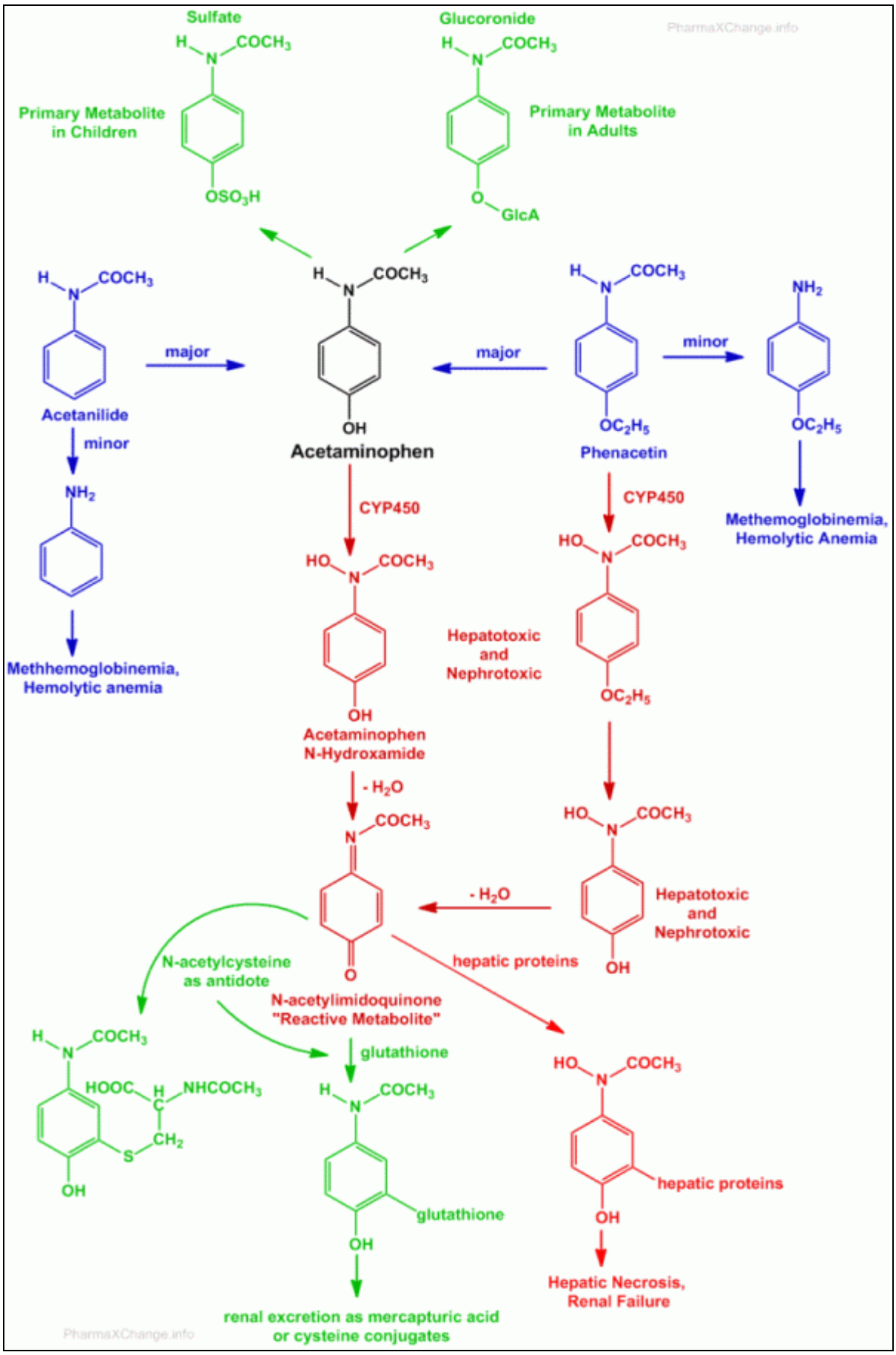


FIG. 4: SCHEME OF METABOLISM OF PA AND pH TO FORM m PA

These studies deal with the electron transfer energy of the metabolized product, m-PA with the nucleic acid bases (NAB), **Fig. 5,** in the liver, to acquire the liver cell the carcinogenic nature via the electron transfer between them. The electron transfer energy depends mainly on the ionization potential of the donor, the electron affinity of the acceptor, and the columbic potential energies of the cation of the donor, and the anion of the acceptor. The ionization potential and the electron affinity were calculated via DFT/B3LYP-6-31**G method for these molecules and their ions. Also, the columbic potential energies of the cation (donor) and the anion (acceptor) were calculated using the Cartesian coordinates of the optimized molecular ions and the Mulliken charge densities of the molecular ions using the output data coming out from the DFT method using the equation 2 in the 3.2-electron transfer section.

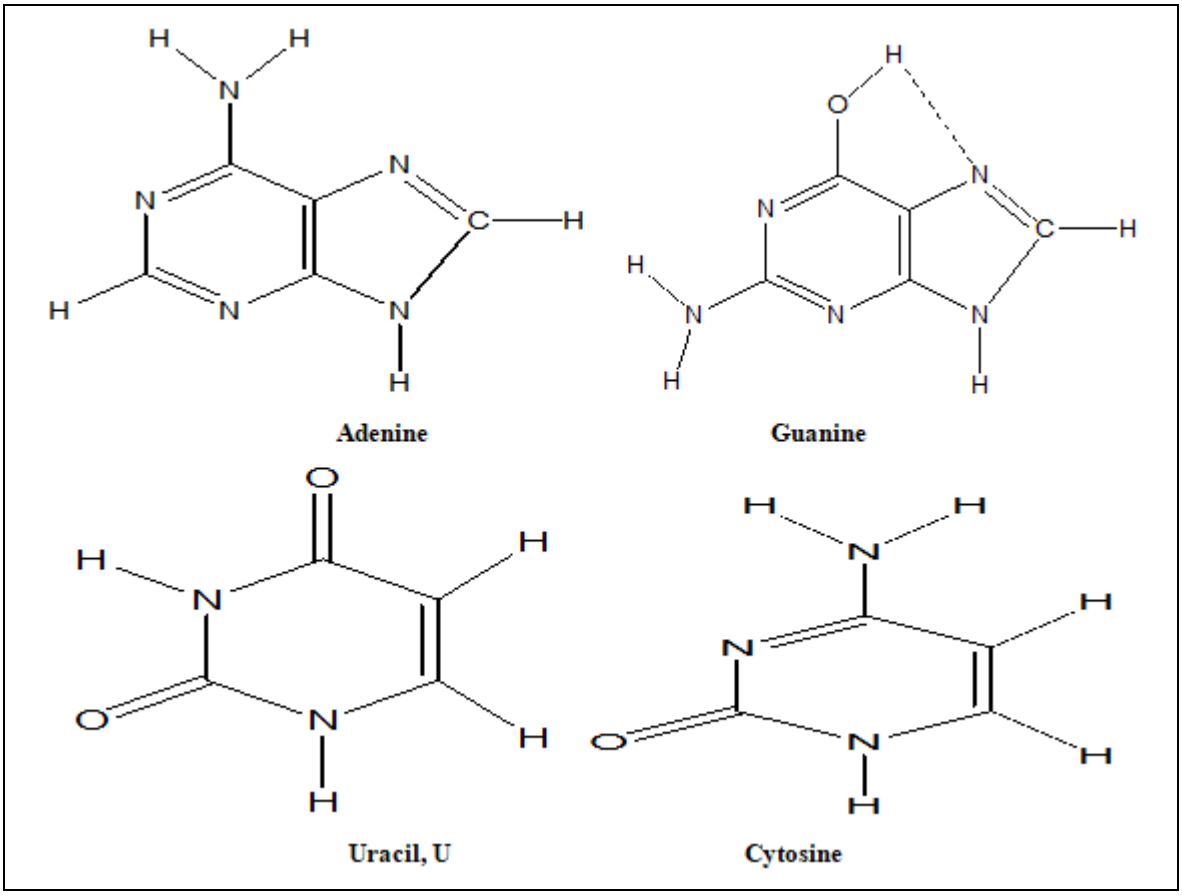


FIG. 5: NUCLEIC ACID BASES (NAB)

The acceptor and the donor can be defined by the relative values of the ionization potential energy and the electron affinity of the two interacting molecules. The molecule having higher electron affinity and high ionization potential acts as an acceptor to form an anion in the ct-complex. The molecule has lower electron affinity, and lower potential ionization acts as a donor to form a cation in the ct-complex.

Since the electron affinities of PA and PH are lower than those of nucleic acid bases, **Table 1**, therefore they act as a donor to produce charge transfer complex in which these molecules are cationic and the nucleic acid bases are anionic. In contrary, the metabolized product, m-PA, has much higher electron affinity than those of the nucleic acid bases, **Table 1**, therefore m-PA is anionic, and the nucleic acid bases are cationic in the ct-complex.

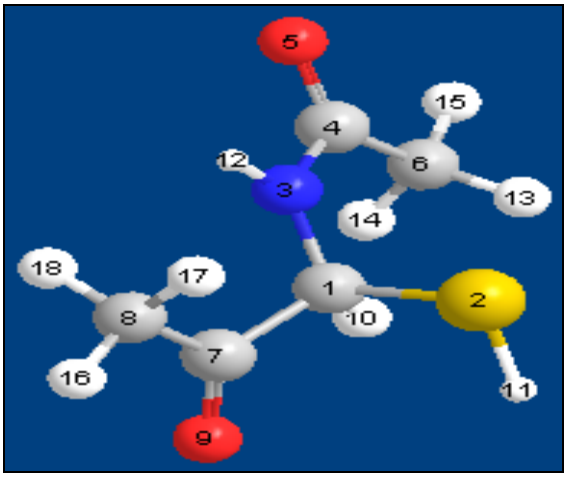
After calculation of the columbic potential energies of PA, PH, and m-PA with the nucleic acid bases using equation 2 in the 3.2-electron transfer section, the total columbic potential energies with the nucleic acid bases have been obtained in the following **Table 5**.

TABLE 5: THE COLUMBIC POTENTIAL ENERGIES (C= C^+ + C^-) of PA, PH, and m-PA WITH THE NUCLEIC ACID BASES IN eV

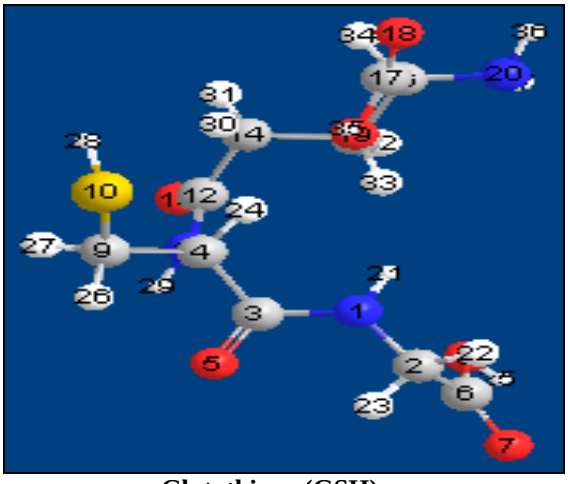
Compound	C, eV adenine	C eV guanine	C eV, cytosine	C eV, uracil
PA cis	0.2857	0.8655	0.7938	0.1989
PA trans	0.1493	0.7293	0.6574	0.0618
PH cis	1.7553	0.7553	0.6836	0.0887
PH trans	0.0887	0.7556	0.6838	0.1782
m-PA	0.3255	1.5617	1.2384	0.5025

Using the ionization potential energies, the electron affinities of the studied molecules from **Table 1** and the columbic potential energies from the previous **Table 5**, to calculate the electron transfer energies which can be illustrated as cancer energy barrier. When it has a small value, it means the electron transfer being easy to produce the carcinogenic effect.

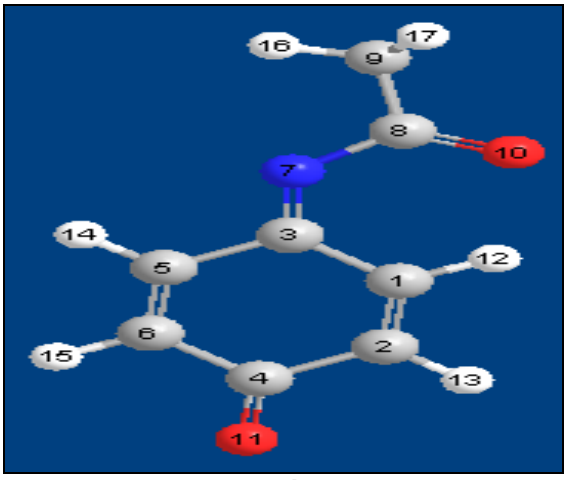
In contrary, the high value of the cancer energy barrier indicates to the arduousness of the electron transfer to render the drug being safe from the cancer effect. The values of the cancer energy barriers E_{et} of the studied compounds have been obtained in the following **Table 6**.



N-Acetylcysteine (NAC)



Glutathione (GSH)



m-PA

FIG. 6: THE OPTIMIZED STRUCTURES OF NAC, GSH, AND m-PA.

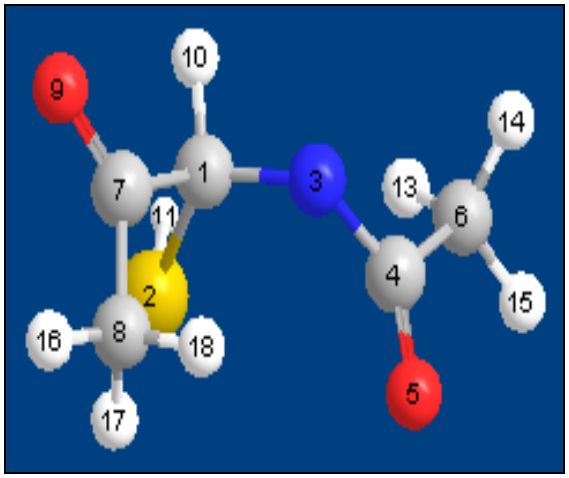
TABLE 7: DFT/B3LYP-6-31G CHARGE DENSITIES OF GSH, NAC AND m-PA MOLECULES**

N.A.B	m-PA Eet eV	Ph.ci Eet eV.	Ph.tr Eet eV	Pa cis Eet eV	Pa.tr Eet eV
Adenine	1.811	3.484	4.355	4.611	4.421
Guanine	0.382	3.772	3.672	4.015	3.825
Cytosine	1.104	3.650	3.550	3.893	3.703
Uracil	2.589	3.859	3.670	4.102	3.975

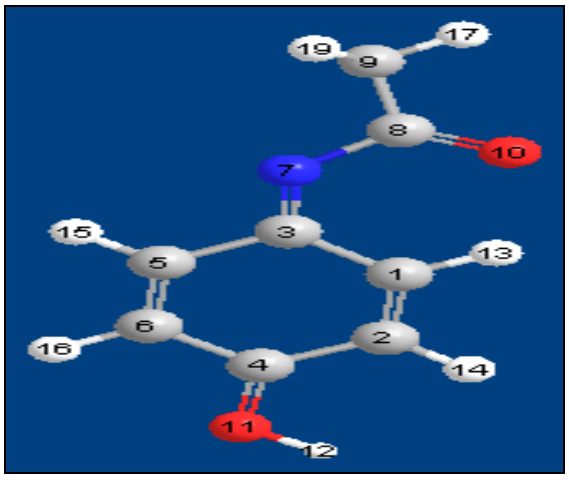
TABLE 8: THE CHARGE DENSITIES OF THE FREE RADICALS OF NAC AND m-PA

S. no.	GSH	NAC	m-PA
1	N -0.057143	C -1.003289	C 0.285352
2	C -0.615967	S0.397550	C 0.492989
3	C -0.196757	N -0.206871	C -0.84676
4	C -0.373881	C 0.540236	C -0.45967
5	O -0.456866	O -0.465326	C-0.24005
6	C 0.355514	C -0.746486	C 0.182835
7	O -0.402651	C 0.338204	N -0.10934
8	O -0.482321	C -0.820600	C 0.652457
9	C -1.163754	O -0.388053	C -0.919709
10	S 0.383267	H 0.335015	O -0.413230
11	N -0.190125	H 0.068367	O -0.451106
12	C -0.140436	H 0.462384	H 0.316077
13	O -0.421302	H 0.244840	H 0.260896
14	C -0.121432	H 0.248682	H 0.280168
15	C -0.454235	H 0.254663	H 0.257812
16	C -0.605286	H 0.242716	H 0.225737
17	C 0.360928	H 0.236793	H 0.242777
18	O -0.380013	H 0.261176	H 0.242759
19	O -0.435481		
20	N -0.421719		
21	H 0.614308		
22	H 0.279929		
23	H 0.306883		
24	H 0.183612		
25	H 0.496271		
26	H 0.351963		
27	H 0.287111		
28	H 0.030564		
29	H 0.477789		
30	H 0.371327		
31	H 0.262664		
32	H 0.255370		
33	H 0.367222		
34	H 0.231998		
35	H 0.517138		
36	H 0.409611		
37	H 0.37590		

From **Table 8, Fig. 7**, it clear that the high negative carbon atom at position 1 in the free radical of NAC will be attached to the higher positive charged carbon atom at position 2 in the benzene ring of the free radical of m-PA. The N-acetylcysteine will be attached at position 2 in the ring since the hydrogen atom attached this carbon atom at position 14 has less positive charge, therefore, there is a competitive attraction between H 14 in the ring of m-PA and the highly negative C1 in NAC. Hence C1 in NAC will be attached with the ring of m-PA at position 2. The positive hydrogen atom at position 14 will be attracted with the negative nitrogen atom at position 7 producing amino-hydrogen at this position, and the quinoide structure of m-PA will disappear producing another molecule preventing the formation of the quinoide structure as in m-PA which is responsible for the cancer effect. The hydrogen atom at position 10 in NAC free radical has a high positive charge which will be attracted to high negative charge, therefore, proton transfer from C1 to N3 to permit the attachment between C1 in NAC to C2 in the m-PA free radical



NAC Free Radical



m-PA Free Radical

FIG. 7: THE MINIMUM ENERGY STRUCTURES OF THE FREE RADICALS OF NAC AND m-PA

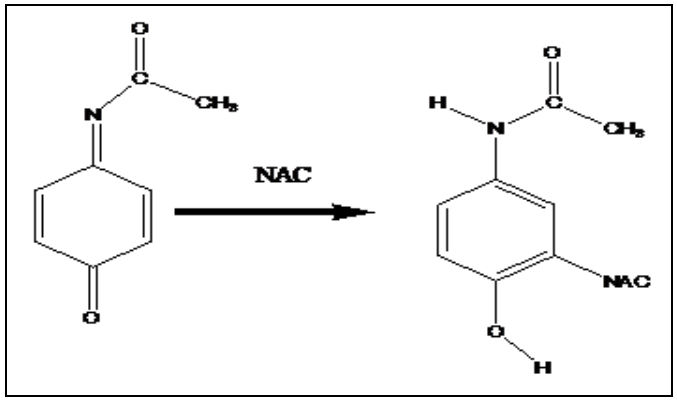


FIG. 8: THE INTERACTION BETWEEN m-PA AND NAC

June 2009, an FDA advisory committee recommended that new restrictions should be placed on Paracetamol usage in the United States to help protect people from the potential toxic effects. The maximum dosage to be consumed at any given time would be decreased from 1000 mg to 650 mg, while combinations of Paracetamol and narcotic analgesics would be prohibited. Committee members were particularly concerned by the fact that the present maximum dosages of Paracetamol had been shown to produce alterations in hepatic function. The FDA has not implemented its recommendations as of October 2010.

TABLE 8: THE CHARGE DENSITIES OF THE FREE RADICALS OF NAC AND m-PA

S. no.	N-Acetylglucosamine	NAC	N-Acetylmethionine
1	C 0.044547	C -1.003289	C 0.012310
2	O -0.145295	S 0.397550	C -0.600503
3	C -1.320108	N -0.206871	O -0.343951
4	C -0.227236	C 0.540236	N -0.361189
5	C -0.224849	O -0.465326	C -0.069797
6	C -0.079104	C -0.746486	C 0.378164
7	O -0.403142	C 0.338204	O -0.470179
8	O -0.576282	C -0.820600	C -0.628453
9	O -0.346952	O -0.388053	C -0.786407
10	O -0.484174	H 0.335015	S 0.447818
11	N -0.061105	H 0.068367	C -0.923976
12	C 0.614239	H 0.462384	H 0.184305
13	O -0.459002	H 0.244840	H 0.233699
14	C -0.781099	H 0.248682	H 0.464186
15	H 0.226279	H 0.254663	H 0.215990
16	H 0.268590	H 0.242716	H 0.234493
17	H 0.232670	H 0.236793	H 0.240787
18	H 0.260592	H 0.261176	H 0.249389
19	H 0.256456		H 0.238037
20	H 0.461922		H 0.266902
21	H 0.484443		H 0.286863
22	H 0.501197		H 0.240635
23	H 0.474750		H 0.243739
24	H 0.528768		H 0.247138
25	H 0.251994		
26	H 0.253578		
27	H 0.248321		

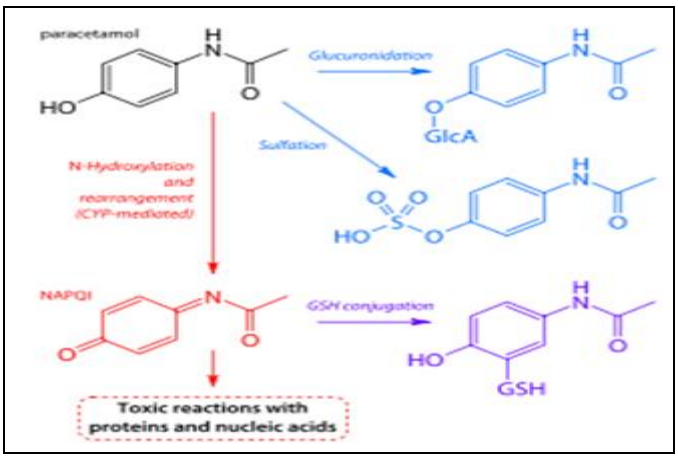


FIG. 9: THE THREE PATHWAYS OF PARACETAMOL IN THE LIVER

TABLE 9: DFT/6-31G.CHARGE DENSITIES OF THE N-ACETYLMETHIONINE AND N-ACETYLGLUCOSAMINE WITH RESPECT TO N-ACETYLCYSTEINE**

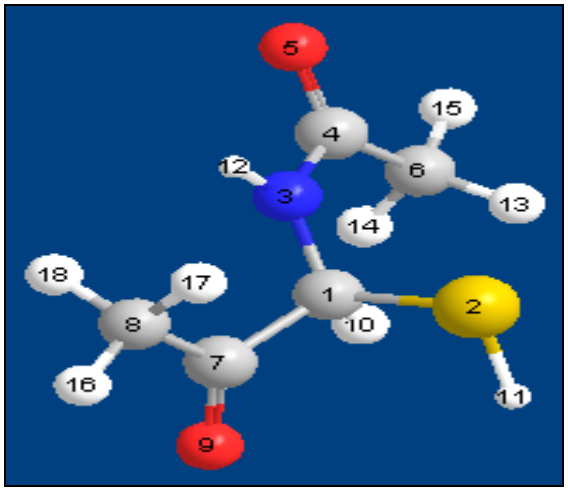
No. of atom	NAC free radical	m-PA free radical
1	C -1.006906	C 0.349037
2	S 0.430132	C 0.384714
3	N 0.239680	C -0.906151
4	C 0.100551	C -0.002261
5	O -0.363729	C -0.271942
6	C -0.598040	C -0.298343
7	C 0.340232	N -0.160492
8	C -0.670558	C 0.689206
9	O -0.372600	C -0.914644
10	H 0.375061	O -0.448519
11	H 0.071781	O -0.581359
12	H 0.220141	H 0.293696
13	H 0.253135	H 0.211427
14	H 0.242265	H 0.259567
15	H 0.237844	H 0.244277
16	H 0.211060	H 0.217471
17	H 0.289948	H 0.238823
18		H 0.238836
19		H 0.456656

N-Acetylmethionine has charge density 0.464186, **Table 9**, at amino-hydrogen atom at position 14, **Fig. 10,** which isn't far from the charge density value of amino-hydrogen atom at position 12 in NAC molecule, **Fig. 10**, therefore, they behave similarly toward N-Acetyliminoqunone (m-PA).

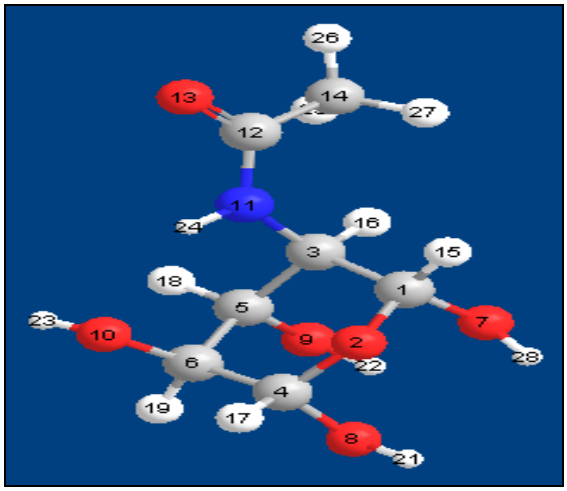
N-Acetylglucosamine (NAGA) has higher charge density, 0.528768, **Table 9**, in the amino-hydrogen atom at position 24, **Fig. 10**, therefore it is expected that NAGA is more efficient to remove the carcinogenic effect of Paracetamol than NAC and NAM from the charge density point of view.

From **Table 10**, it is obvious that the studied molecules (NAC, NAM, and NAGA) and their free radicals, **Fig. 11**, have small comparative Ea and Ip values with respect to those of nucleic acid bases, therefore, there is not apprehension to make an electron transfer with them, **Table 1**. From **Table 10**, it clear that the energy barrier ΔE between NAM molecule and its free radical (F.R.), **Fig. 11**, has the lowest value, 18.89 eV.

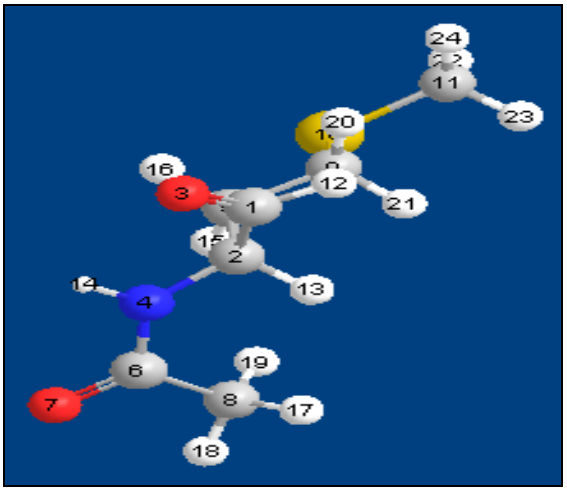
This means the alteration of the NAM molecule is easier to be free radicals which combine with N-Acetyliminoquinone (m-PA) to remove its quinoide structure. Hence the removal of m-PA means the removal of the carcinogenic effect of Paracetamol drug.



N-Acetylglucosamine (NAGA)

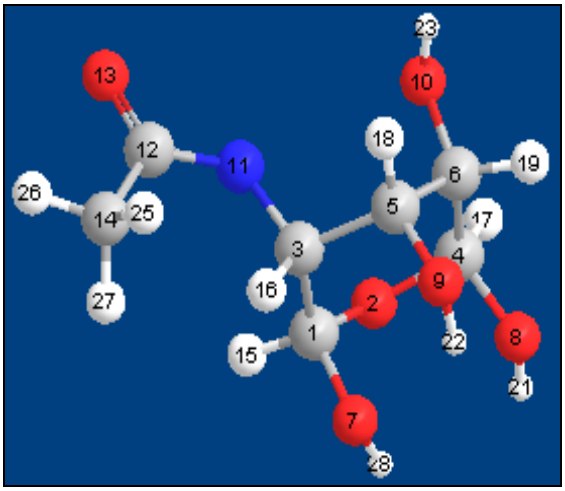


N-Acetylcysteine (NAC)

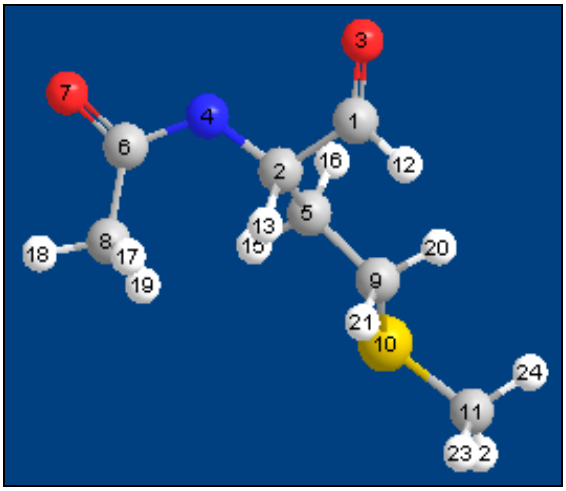


N-Acetylmethionine (NAM)

FIG. 10: THE OPTIMIZED STRUCTURE OF NAGA, NAC AND NAM MOLECULES



NAGA (F.R)



NAM (F.R)

TABLE 10: DFT PARAMETERS OF NAC, NAM AND NAGA

Molecule	E au	Ip au	eV	Ea au	eV	ΔE eV	Dip. D
NAC	-799.20269	0.26518	7.21592	0.06830	1.85854		1.7519
NAC(FR)	-798.49508	0.26225	7.13619	0.05783	1.57364	19.25506	2.5736
NAM	-877.79130	0.24309	6.61482	0.07564	2.05827		6.9543
NAM(FR)	-877.09702	0.24669	6.71278	0.07008	1.90698	18.89233	7.7958
NAGA	-780.41870	0.25486	6.93510	0.03600	0.97961		3.9933
NAGA(FR)	-779.72201	0.26682	7.26055	0.03540	0.96328	18.95791	3.5941

CONCLUSION: Paracetamol and Phenacetin as drugs are safe from the cancer effect in the presence of N-acetylcysteine, N-acetylmethionine, or N-Acetylglugosamine.

ACKNOWLEDGEMENT: This work has been supported by the Egyptian Ministry of Higher Education, Management of Supporting Excellence, Competitive Excellence Project of Higher Education Institutions, (project: CEP1-043-ASSU), Grant 2014.

CONFLICT OF INTEREST: Nil

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How to cite this article:
El-Shahawy A, El-Maali NA and El-Hawary HH: Averting cancer effect of paracetamol and phenacetin by n-acetylcysteine and its analogues. Int J Pharm Sci & Res 2014; 5(10): 4159-69. doi: 10.13040/IJPSR.0975-8232.5(10).4159-69.