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L-Ornithine and its Analogues as Inhibitors of Ornithine Decarboxylase: From Rational Drug to Specifically Devised Drugs

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Difloromethyl ornithine (DFMO) is the first effective, rationally designed antiproliferative drug aimed at depleting polyamines from cells. Polyamines are considered critical regulators of cell growth, differentiation and cell death. The polyamine concentration is found increased in cancer cells. The diflouromethyl ornithine analogues may prove to be useful agents in the chemoprevention of cancer. These interact electrostatically and covalently with various macromolecules such as ornithine decarboxylase (ODC). Since the drug acts by electrostatic and covalent interactions a detailed study is made with various analogues of ornithine, including difloromethyl ornithine at the DFT and MP2 level of theory. The optimised parameters were used to compute reactivity parameters such as softness and electrophilicity index. The optimized geometry was used for docking with ornithine decarboxylase using genetic algorithm. The results are revealing as they help establish a drug with least toxicity in a quantitative approach unlike the rationally devised drug. The dockings interactions have been visualized and the interactions have been correlated with binding energy and electrophilicity concept.

Key Words: L-Ornithine, Difloromethyl ornithine, Ornithine decarboxylase, Toxicity, Electrophilicity, DFT and MP2.

INTRODUCTION

Based on density functional theory (DFT) several global chemical reactivity descriptors of molecules such as hardness, chemical potential, softness, electronegativity and electrophilicity index and local reactivity descriptors such as the Fukui function and the philicity have been defined[1]. Electrophilicity index (ω) is defined within a density functional theory framework by Parr *et al.*[2] as a measure of energy lowering due to maximal electron flow between a donor and an acceptor. They defined electrophilicity index as

$$\omega = \frac{\mu^2}{2\eta}$$

where $\mu \approx -\left(\frac{1+A}{2}\right)$ and $\mu \approx -\left(\frac{1-A}{2}\right)$.

Here μ and η are the electronic chemical potential[3] and the chemical hardness[4] of the ground state of atoms or molecules, respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A). This provides the direct relationship between the reaction rates and the ability to identify the function of the electrophile and the electrophilic capacity of the inhibitors[5]. Using a finite difference method the working equations for the calculation of chemical potential and chemical hardness can be given by:

$$\mu = -\left(\frac{IP + EA}{2}\right)$$

$$\eta = \left(\frac{IP - EA}{2}\right)$$

where IP is ionisation potential and EA is electron affinity.

This can also be defined using Koopmans' theorem[6] as follows:

$$\mu \approx -\frac{1}{2}(E_{HOMO} + E_{LUMO})$$

and

$$\eta \approx \frac{1}{2}(E_{LUMO} + E_{HOMO})$$

where $I \approx E_{HOMO}$ and $A \approx E_{LUMO}$.

Alternatively, using the self consistent field (SCF) finite difference approach, the IP and EA can be calculated for the N-electron system with total energy as follows:

$$IP \approx E(N-1) - E(N)$$

$$EA \approx E(N) - E(N+1)$$

The condensed Fukui functions are calculated as follows:

$f^+ = q(No + 1) - q(No)$ for nucleophilic attack

$f^- = q(No) - q(No-1)$ for electrophilic attack

where q denotes the electronic population of the atom. These were computed using Lowdin, Mulliken and Natural Population Analysis Schemes (LPA, MPA and NPA, respectively).

The reactivity index gives the stabilization in energy when the system acquires an additional electronic charge from the environment. One of the significant applications has been demonstrated with the use of this index in defining the toxicity of a large number of small molecules[7]. It was established here that the interaction between the molecule and the biosystem occurred through a charge transfer process over π stacking. The importance of global and local electrophilicities would therefore help us in providing the toxicities of certain ligands which bind with receptors.

Ornithine decarboxylase (ODC) plays an important role in biological systems and this enzyme is important in drug design[8]. It has been mentioned earlier that electron withdrawing groups increase the ODC inhibitory effects considerably[9]. A chloro substituent has been tested by Jose Correa Basurto *et al*.[10] where they found that this analogue was not toxic. The study was based on the results of several compounds that were tested for their medicinal properties without many side effects due to chloride substituent[11].

Some iodide substituted compounds were tested for biological activity as ODC inhibitors[12]. But these showed hepatotoxic effects. The docking process showed that the compound had an affinity with co-enzyme and interacted with pyridoxal 5' phosphate (PLP) (*ca.* 4º) and with Cys 328 (*ca.* 3º) by electrostatic interactions of iodide with the aromatic ring and phosphate group of PLP and by hydrogen bond interaction between the δ-amino group and Cys328 backbone.

Another important study was done using α-hydrazine ornithine as ODC inhibitor[13]. It was found that the fluoro moieties may have an electron withdrawing effect on the thiol group from Cys360 and this could explain their high affinity observed experimentally and by docking stimulation[10].

Quantum chemical calculations have been done for a series of compounds in order to explore their recognition by some amino acids involved in the binding sites of cholinesterases (AChE)[14]. The electronic effects were related to HOMO-LUMO energies and Hammett effects. Other chemical properties such as partition coefficient and steric effects were considered. It was concluded that compounds with smaller size, low HOMO or high LUMO energies, low optimized energy values of the ligands as well as an electron withdrawing group in aromatic ring showed a better recognition for the receptors (AChE) active site through a π-π interaction and hydrogen bonds. This was evident from the previous work where interaction between AChE and ligand was found due to HOMO-LUMO energies[15]. The unequal distribution of the electron density in bonds (resulting in dipole moments) was also considered under this study. If the ligands were poor in electrons *i.e.*, having high LUMO energy they easily interacted with receptors that had high HOMO energies in certain pockets.

Difloromethyl ornithine (DFMO), a rationally designed anticancer agent[16] first provided the proof of concept that influence polyamine metabolism[17] and content within tumour cells to prevent tumour growth. Targeting polyamine pathway, using DFMO, has been one of the methods to treat cancer[18]. DFMO has been successfully tested[19] only for the treatment of recurrent gliomas (type of tumor that starts in the brain or spine). The polyamine analogues were found to be similar in structure to the parent compound that allowed their recognition and subsequent uptake by the polyamine transporter in regulating the ODC negatively[20]. Hence some more analogues can be tested in this case as the DFMO is a rationally devised drug, whose uptake has been reported to be considerable slow and is rapidly excreted from the body[21]. This suggested that high doses of DFMO were required to maintain the inhibition of ODC. Thus DFMO may not be an efficient drug[22], which has led to studies of some polyamine analogues as useful agents in the chemoprevention of cancer.

The polyamines carry a positive charge on each nitrogen atom at a particular pH and it has been suggested that the polyamines are simply supercations, equivalent to 1 to 2 calcium or magnesium molecules. The positive charge on the polyamines enables them to interact electrostatically with polyanionic macromolecule within the cell. Structural studies have indicated that polyamines interact with individual rather than multiple DNA molecules[23]. Polyamines can also interact with acidic phospholipids in membranes[24]. New strategies should aim at achieving maximum interaction with the ODC and polyamine depletion, as inhibition of polyamines production prevents the growth of tumour cells. This would require methods that look into all aspects of the molecule as interactions take place at the molecular level. The chemical reactivity descriptors would provide an insight into these aspects. Fukui functions and related descriptors such as local softness and local electrophilicity index have been used to assess the reactivity pattern of many molecules at the molecular level[25-29].

Polychloro compounds have been recognized for toxicity in certain studies[30]. Hence an electrophilicity study was carried out as this would suggest whether the ligand exhibits electrophilic effect on the receptors. The electrophilicity has been considered as a descriptor of reactivity for quantitative classification of the global electrophilic nature of the molecule.

For the discovery of novel small molecule drugs that target proteins or enzymes, molecular docking techniques have proved very useful[31,32]. The use of molecular docking might shed light on the important implications for the synthesis and development of small molecule drugs that selectively target the enzymes[33]. The synthesis and *in vitro* evaluation of an ornithine analogues as an ODC inhibitor was reported along with docking studies of ornithine and some of its derivatives was shown by Correa-Basurto *et al.*[10]. They concluded that the iodo derivative of ornithine favoured affinity for ODC than the chloro or flouro derivative[12]. They showed that interactions existed between the ligands and the ODC cofactors such as PLP and Cys 360. A comprehensive DFT study using NPA was done by Carlos *et al*.[34], for the investigation of ligand interaction using electrostatic behaviour of the ligands to conclude drug efficiency of three ligands. Another concept that polarization has the opposite effect in dissimilar environment and that it was critical to treat polarization explicitly to achieve chemical accuracy in predicting the binding affinity of charged system was suggested by Dian Jiao *et al*.[35]. As a good study for drug should have small changes in the substituents covering a range of free energy values within 2.5 kcal/mol,

about 24 chemically important derivatives that would conform to this fact were selected and their binding energy evaluated for further study[36].

COMPUTATIONAL METHOD

The Moeller-Plesset second order (MP2) quantum chemical calculations and density functional theory (B3LYP) methods have been used to evaluate the global and local reactivity descriptors, including electrophilicity. Both the finite and Koopmans' methods were used to arrive at the best possible results. The amino acid was first optimised at the RM1 level using MOPAC[37] and then using the GAMESS[38] program. The optimization was done at the standard split valence basis set 6-311 G (dp). The restricted HF method was used for energy calculations and for the corresponding anionic and cationic systems the restricted open shell HF method was employed. The condensed Fukui function and Softness for all the systems have been achieved using Natural Population Analysis (NPA) scheme[39]. Other schemes such as Lowdin and Mulliken Population have also been used as reference.

The optimized geometry using DFT was used for docking purpose. The crystal structure of human ODC (PDB code: 1D7K) was used as the receptor macromolecule for docking stimulations. Water molecules that were co-crystallized with the ODC were removed from the original structure. Pyridoxal 5' phosphate (PLP) was not removed as it was one of the co-factor where docking was found to take place. By using AutoDock Tools 4.2[40] all possible rotatable bonds of the ligands (flexible) and Kollman charges on ODC were assigned. Docking stimulation were carried out by using the hybrid Lamarckian genetic algorithm with an initial population of 150 randomly placed individuals and a maximum number of 250,000 energy evaluations. The resulting docked orientations within a root-mean-square deviation of 2.0 Å were clustered together. The lowest energy cluster was located using the AutoDock tools and used for analysis like evaluating the interactions. All other parameters were set as default. For the visualisation of the complexes and the interactions Discovery Studio Visualizer[41] was used. The simplification of the docked visualisation was done using Ribbon[42].

RESULTS AND DISCUSSION

The general structure of ornithine is given in the Fig. 1. The global hardness values at the DFT level are noted against the lowest binding energy in Table-1. There are two binding energies given in Table-1 (vide column 3 and 6). To find out the energy of the single isomer, the number of runs was set to 1 as this gave the precise meaning of feeding optimized geometry for docking. Contrary to this, col. 3 has lowest binding energy values for 25 isomers that were changed by the program during docking. It can be seen from the Table that submitting optimized geometry for a single isomer docking produces binding energy that does not match with the other conformer's energy. Hence use of optimized geometry using ab-initio methods does not necessarily produce desired results as obtained by Trujillo *et al.*[12].

TABLE-1
ORNITHINE ANALOGUES STUDIED IN THE ORDER (2) WITH THE LOWEST BINDING ENERGY (3) AND THE MEAN BINDING ENERGY (4) ALONG WITH FREE ENERGY (5) AND SINGLE ISOMER DOCKING ENERGY (6). THE LAST TWO COLUMNS REPRESENT THE GLOBAL HARDNESS VALUES AT DFT USING FINITE (7) AND KOOPMANS' METHOD (8), RESPECTIVELY

S. No. (1)	R = (2)	Lowest binding energy (kcal/mol) (3)	Mean binding energy (kcal/mol) (4)	Free energy (kcal/mol) (5)	Binding energy (single isomer) (kcal/mol) (6)	Hardness (DFT) (IA-EA)/2 (7)	Hardness (DFT) $(E_H-E_L)/2$ (8)
1	H	-5.23	-4.51	-1911.28	-5.65	0.1962	0.1203
2	CH_3	-6.02	-5.02	-1911.47	-3.89	1.0321	0.1230
3	CH_2F	-5.19	-4.40	-1910.63	-2.79	0.1903	0.1110
4	CHF_2	-4.86	-4.16	-1910.69	-4.71	0.1928	0.1096
5	CF_3	-4.94	-4.16	-1778.44	-4.19	0.1985	0.1151
6	CH_2Cl	-5.49	-5.23	-1910.83	-4.98	0.1890	0.1168
7	$CHCl_2$	-4.73	-4.37	-1910.57	-4.28	0.1838	0.1106
8	CCl_3	-5.10	-4.30	-1607.81	-4.69	0.1709	0.0956
9	OCH_3	-5.17	-4.81	-1910.66	-5.04	0.1926	0.1218
10	OCH_2F	-4.08	-3.50	-1607.67	-4.52	0.1978	0.1177
11	$OCHF_2$	-3.86	-3.86	-1607.26	-4.10	0.1964	0.1125
12	OCF_3	-4.57	-3.82	-1777.95	-2.95	0.1952	0.1115
13	CH_2OH	-5.37	-3.89	-1910.36	-4.32	0.1992	0.1213
14	CH_2SH	-5.42	-4.11	-1778.45	-4.45	0.1910	0.1212
15	CH_2NCO	-5.50	-4.67	-1778.80	-5.11	0.1865	0.1150
16	CH_2NCS	-5.44	-4.39	-1911.08	-5.61	0.1693	0.1040
17	CH_2CN	-5.30	-5.30	-1911.31	-4.00	0.1956	0.1191
18	$CH=CH_2$	-5.39	-4.47	-1910.99	-5.72	0.1865	0.1113
19	CH=CHF	-4.93	-4.14	-1910.81	-5.47	0.1840	0.1087
20	$CH=CF_2$	-4.75	-4.22	-1910.80	-3.30	0.1861	0.1114
21	CP*	-5.27	-3.95	-1835.01	-4.35	0.1841	0.1119
22	CPF	-5.11	-4.56	-1835.34	-4.35	0.1908	0.1233
23	CPF_2	-4.88	-4.40	-1835.22	-3.93	0.1911	0.1256
24	CH_2CONH_2	-5.06	-4.21	-1910.89	-4.37	0.1877	0.1177

*CP = Cyclopropene.

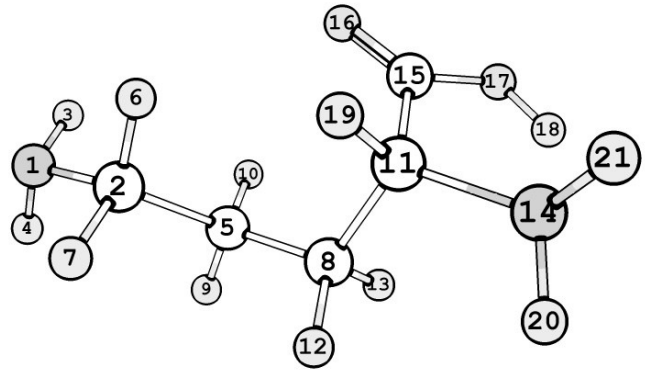


Fig. 1. General structure of ornithine. The substituents are at position 19 on C-11

The global hardness value through Koopmans' method-which is almost the same for the finite method (col. 7 and 8)-is least for the CCl_3 substituted analogue. This would mean the high reactivity of this ligand. The diflorometlhyl ornithine occupies the fourth place after R = CCl_3, CH_2NCS, CH=CHF. As higher hardness values present the resistivity to change, these analogues can be considered as the ones that will interact with other molecules for a change. Only hardness values cannot be considered for the reactivity of the molecule. With three chlorine atoms, the possibility of toxicity effect of this molecule has to be looked into and hence toxicity evaluation has been done using electrophilicity index. It will be noted later that CH=CHF also offers to be a good analogue after the philicity calculations.

The atoms chosen for local property studies were N-14, O-16, O-17 and C-11 as substitution effects can be felt directly on these atoms apart from N-1 the other hetero N-atom in the molecule. The local softness of these atoms was considered against the lowest binding energy (LBE) values of the various substituents under the study. They are presented in the graph (Figs. 2-4).

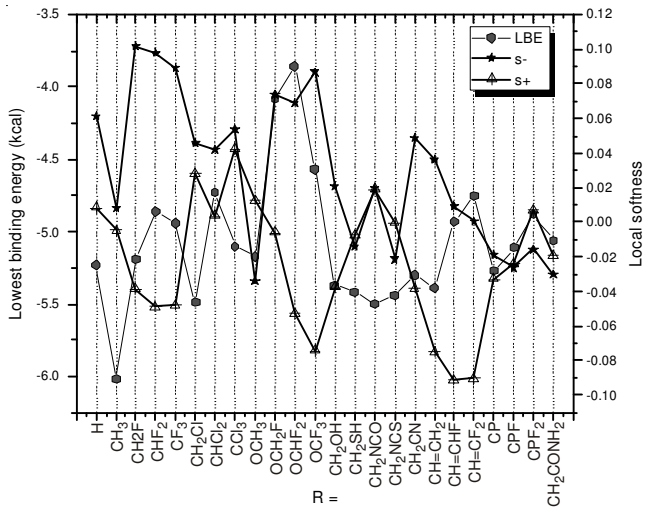


Fig. 2. Local softness values against lowest binding energy for C-11 atom, at DFT-NPA

It can be found from the Figs. 5 and 6 that there is some relationship with the s^- values of α-nitrogen atom (N-1) with the LBE as R is varied. Where there is a decrease in the LBE

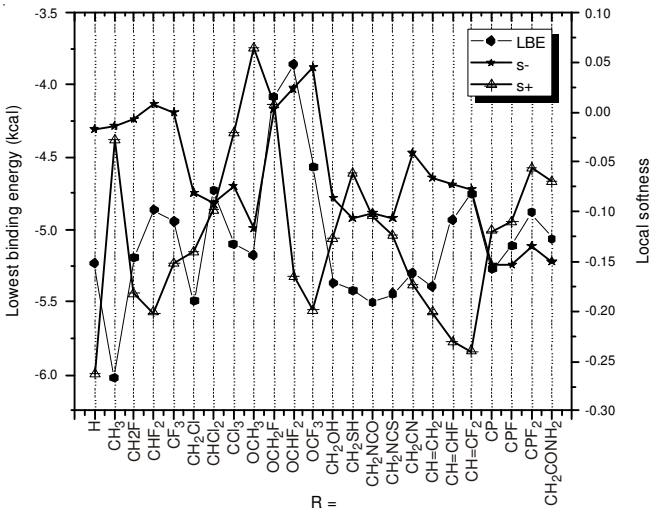


Fig. 3. Local softness values against lowest binding energy for C-11 atom, at DFT-MPA

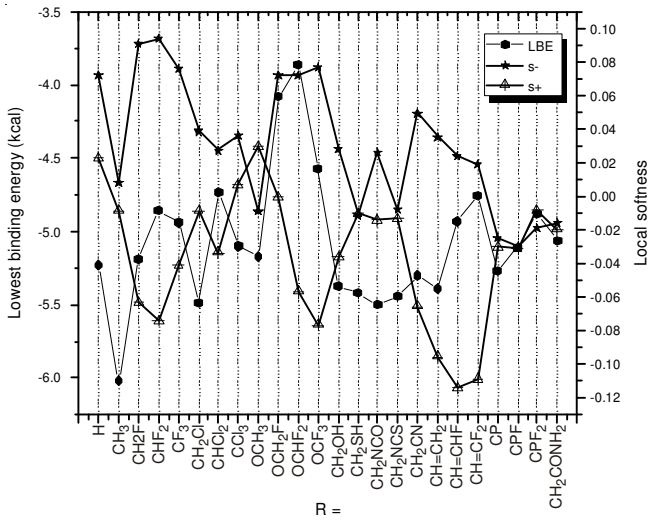


Fig. 4. Local softness values against lowest binding energy for C-11 atom, at DFT-LPA

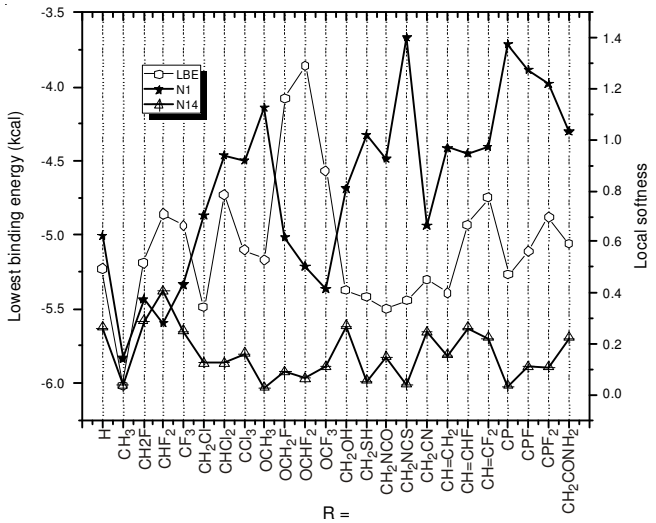


Fig. 5. Local softness (s^-) against lowest binding energy for N-1 and 14 atoms, at DFT-NPA

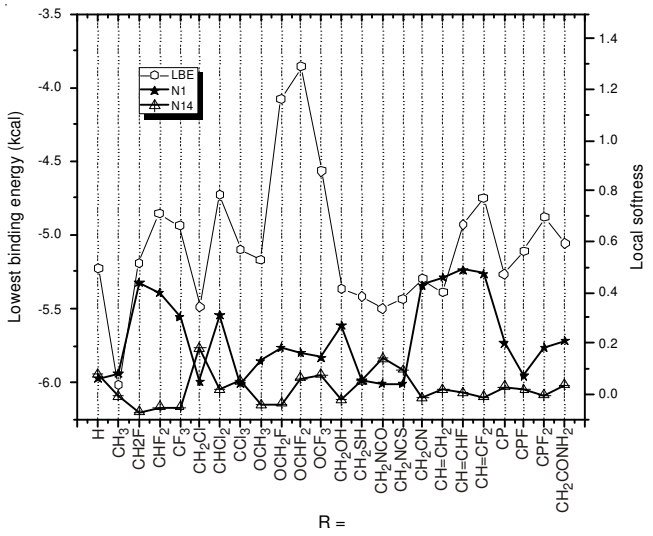


Fig. 6. Local softness (s^+) against lowest binding energy for N1 and N14 atom, at DFT-NPA

there is an increase in the s^- values at the DFT level using NPA scheme. This is not the case with N-14 atoms, which is true for s^+ values too. This would mean that s^- values of the N-1 atoms can be held accountable for binding to the receptor. The lower is the LBE the higher is the s^- value. If DFMO is taken as standard the substituents having higher s^- values include R = CH_2OH, CH_2SH, CH_2NCO, CH_2NCS, $CH{=}CH_2$. There is no consistence with the MP2 values. The DFT level of theory suffices in correlating the local softness values. To see if there was any reactivity centre in the molecule global softness values were explored. Not much information could be derived from the local softness values of the oxygen atom (Figs. 7 and 8).

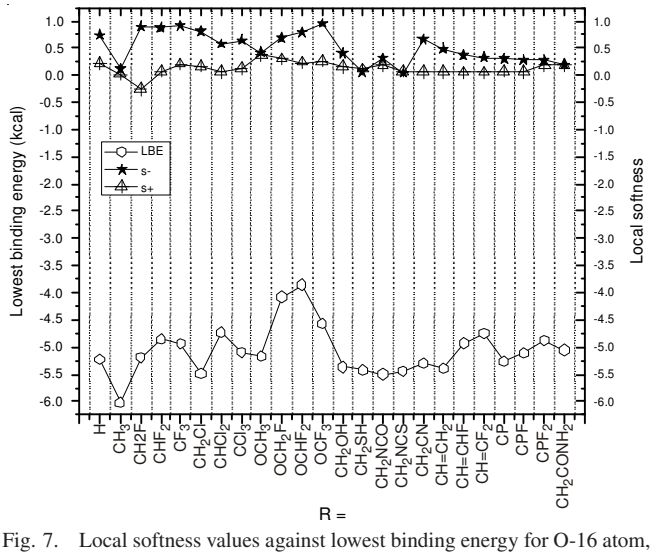


Fig. 7. Local softness values against lowest binding energy for O-16 atom, at DFT-MPA

The global softness (GS) values for the derivatives 13-18 are higher at the DFT level and there is some trend found with regard to LBE values. The highest LBE is found for R=CH_3 and this has the lowest S values. This would suggest that the unsubstituted amino acid would not be a good derivative for reactivity with the receptor. The highest LBE is shown for R =OCH_2F and this has lower S value at the DFT level.

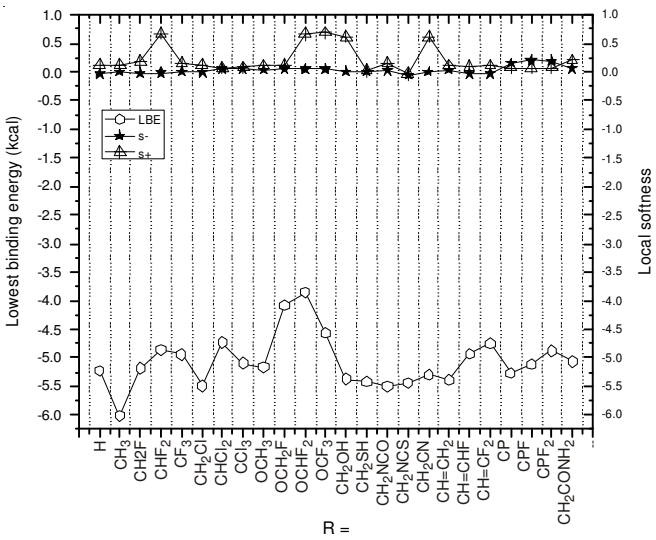


Fig. 8. Local softness values against lowest binding energy for O-16 atom, at DFT-NPA

The global softness value for the Koopmans' level calculation presented a different picture for the same range of derivatives (13-18) which has the lowest values of LBE. The GS values are greater at the DFT level. No such trend was found at MP2 level. The highest GS value is shown by R = CCl_3 which had a moderate LBE value. This would present a molecule with more reactivity. From the docking studies this molecule was found away from the PLP and there was no indication of docking as found for other derivatives with the receptor.

As there is a good trend for the global softness values using Koopmans' method it may be concluded that the HOMO, LUMO levels of molecule can be considered for the reactivity studies of the ligands. It has been already suggested that docking of the ligands can be influenced by high LUMO energies and electronic effects[17] on ligand recognition over the macromolecule.

The local softness values were considered to find out if there was any reactive/interactive center within the molecule. As a first measure the N-1 atom was considered. The derivatives with R = CH_2OH, CH_2SH, CH_2NCO, CH_2NCS, CH_2CN, $CH{=}CH_2$, CH_2Cl, showed higher s^- values, while N-14 atom did not present any reactivity trend with regard to LBE. This should suggest that the N-1 has a good position for electrophilic interactions. This goes well with the chemical intuition that nitrogen atom is a very good sigma donor. The s^- values are less for N-14 atoms as substituents are attached to the carbon atom (C-11) to which this nitrogen atom is attached. This is evident from the fact that the terminal nitrogen atom (N-1) shows more interactions with the receptor molecule and with derivatives R = CH_2SH, CH_2NCS, showing closer interactions with PLP. There are many more interactions apart from these with the molecules mentioned above. These molecules show a very good fit into the gorge of the receptor near PLP and gave a favourable LBE value upon docking.

The s^+ values do not show any good trend for both N-1 and N-14 atoms at the DFT and MP2 level. The LPA and MPA schemes also do not present any significant evidence for the number of interactions found with respect to the docking studies.

The electrophilicity index at the DFT and MP2 level using Koopmans' method is shown in the graph (Figs. 9 and 10). The electrophilicity values at the DFT level present a significant trend. The values are lesser than DFMO and hence the LBE is lowest (R = CH_2SH and CH_2OH). The highest electrophilicity value is shown by the molecule when R = CCl_3. Hence this molecule can be considered as toxic. The next electrophilicity value is shown by R = CH_2NCS, which has a favourable LBE. Hence local electrophilicity values were considered to find out the effect of the substituent. The electrophilicity index using finite method did not show any significant trend with respect to LBE.

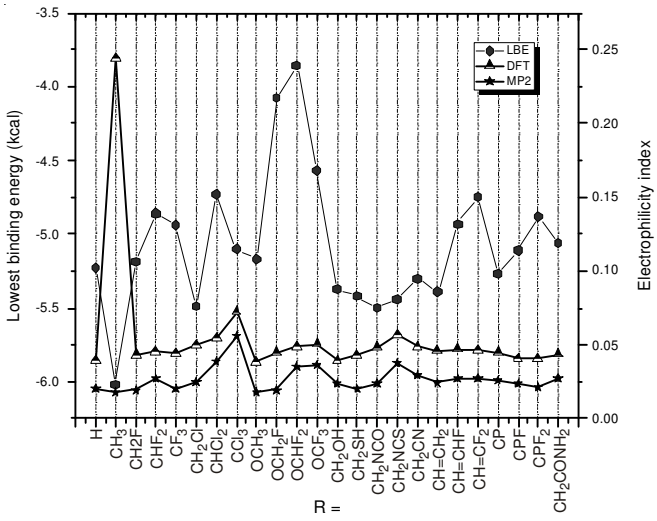


Fig. 9. Electrophilicity index against lowest binding energy at DFT and MP2 using NPA

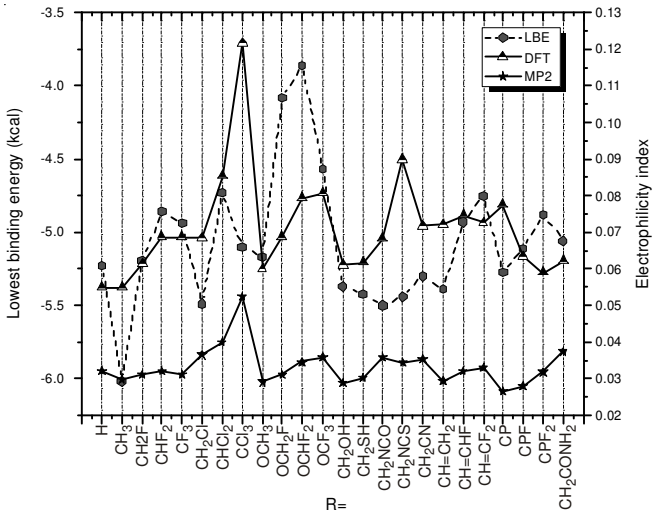


Fig. 10. Electrophilicity index (Koopmanns') against lowest binding energy at DFT and MP2 (NPA)

If the ω^- values are considered for the C-11 atom (Figs. 11 and 12), the highest value is shown by R = OCF_3 and R = CHF_2. If ω^- is considered for the toxicity measure then these two molecules may not be good candidate for drug as they have higher LBE too. CH_2OH and CH_2NCS show very low ω- values which have been considered as good derivatives when the docking score is considered. R = CCl_3 and CF_3 also show

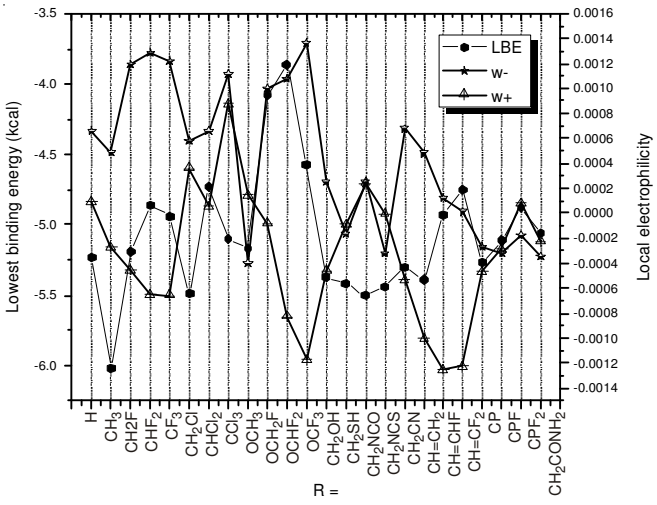


Fig. 11. Local electrophilicity against lowest binding energy for C-11, at DFT using NPA

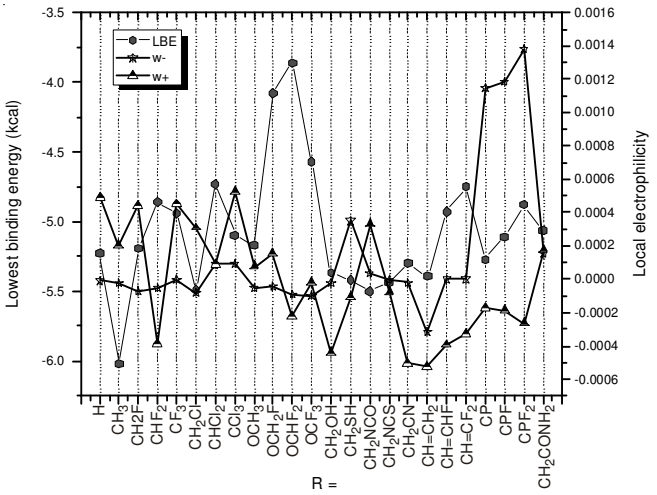


Fig. 12. Local electrophilicity against lowest binding energy for C-11, at MP2 using NPA

high ω^- values and hence are not good ligands for docking. The lower s^- values are shown by R = CH_2CONH_2, CP, CPF but they may not be good candidate for drug as they have higher LBE and show very less interactions. As there is not much resolution among ω^- values against the LBE values at the MP2 level using NPA, we can conclude that the DFT level calculations should suffice in describing the docking behaviour and interactions of the chosen ligands for favourable docking with low toxicity effects.

The ω^- values of N-14 atoms were considered simply because they lie in the region of high local softness or reactivity centre (Figs. 13 and 14). For the compounds 13-18 the ω^- values at the DFT increase and then decrease. For R = CH_2NCO, the ω^- values is greater among the series, while the greatest values is shown by DFMO. These values are least when R = CP and OCH_3 but they have higher LBE relatively and hence the derivative with R = CH_2OH, CH_2SH, CH_2NCS, CP and CPF stand out as good analogues if the toxicity due to N-14 atom is established experimentally. At the MP2 level the ω^- values do not vary over a large scale so that a decisive trend is not evident from these calculations throughout the study.

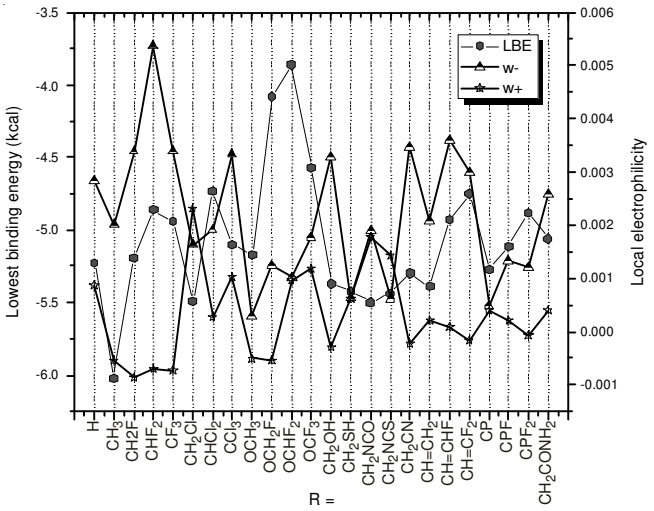


Fig. 13. Local electrophilicity against lowest binding energy for N-14, at DFT using NPA

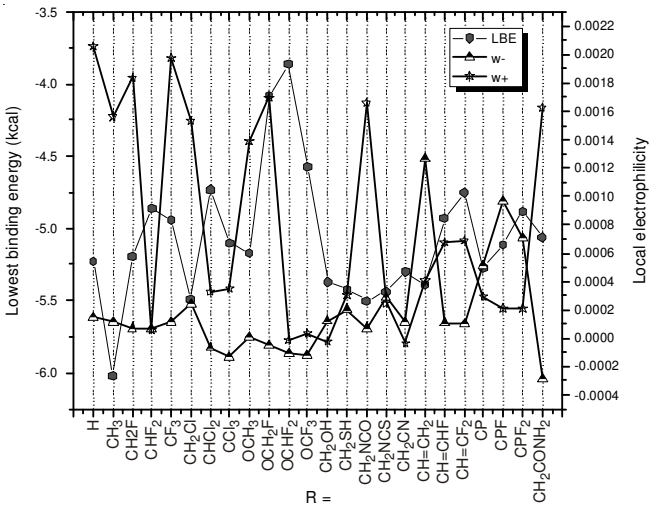
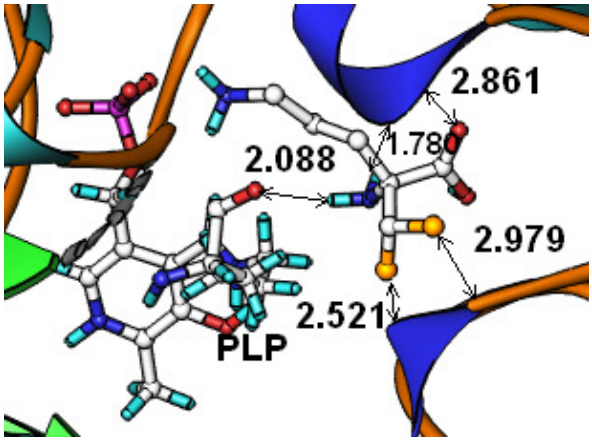
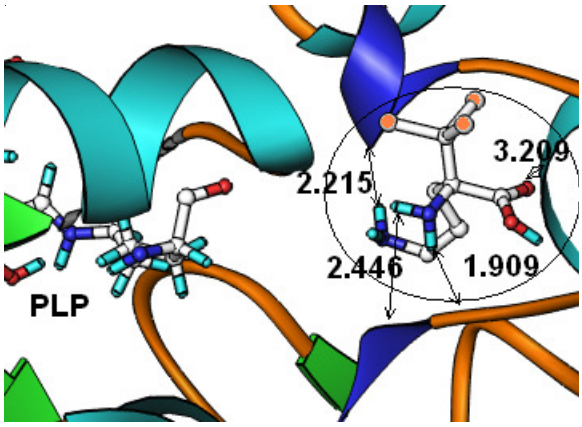


Fig. 14. Local electrophilicity against lowest binding energy for N-14, at MP2 using NPA

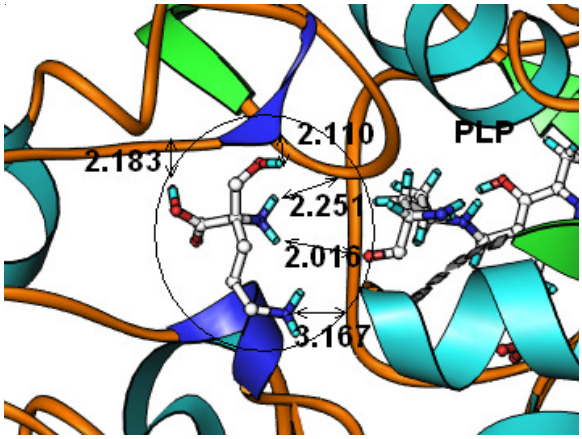
A brief interaction study from Fig. 15 is significant in the context of reactivity studies. In these figures DFMO is encircled. The keto group in Fig. 15. A is found interacting with the PLP chain. This kind of interaction was also found for R = CH_3, CH_2F but with DFMO a closer interaction of α amino H's and F atoms interaction was found. With the substitution of one and two chlorine atoms less interaction of the keto group was found. But the $CHCl_2$ analogue's terminal amino H was found interacting with PLP. With CCl_3, there were interactions but away from the PLP gorge where interactions have been previously found to take place[12]. Even though this analogue had several interactions but they were not significant in the light of docking at the specific site for drug activity. This was so with other analogues such as R = OCH_2F, $OCHF_2$, OCF_3 where very low interactions were found. With R = CH_2OH, CH_2SH, CH_2NCS several interactions were found. The hydroxyl group of the compound was also found interacting at about 2.183 Å with a side chain. With R = CH_2SH and CH_2NCS there was interaction of sulphur atom with the receptor sites at about 2.947 and 3.118 Å (Fig. 15D-E). In



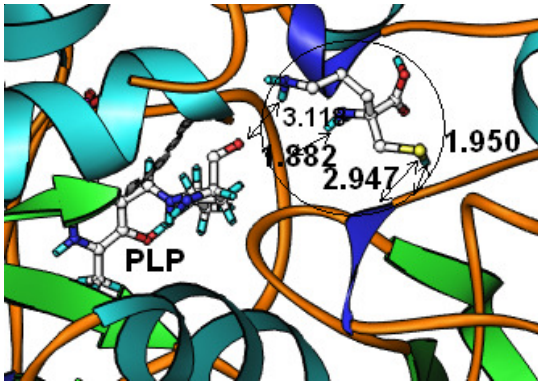
(A) R = CHF_2



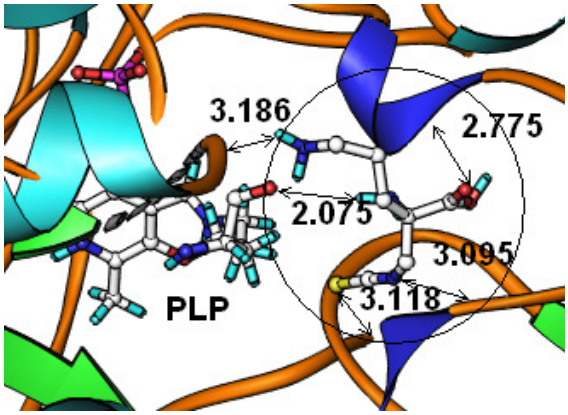
(B) R = CCl_3



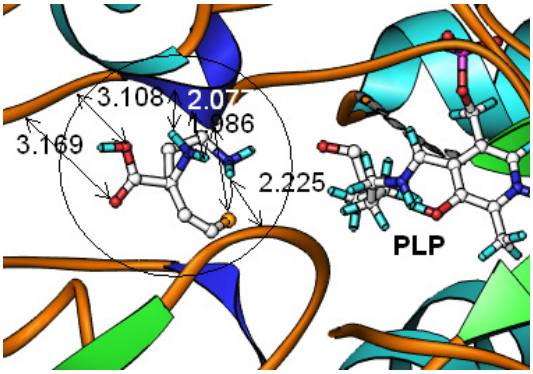
(C) R = CH_2OH



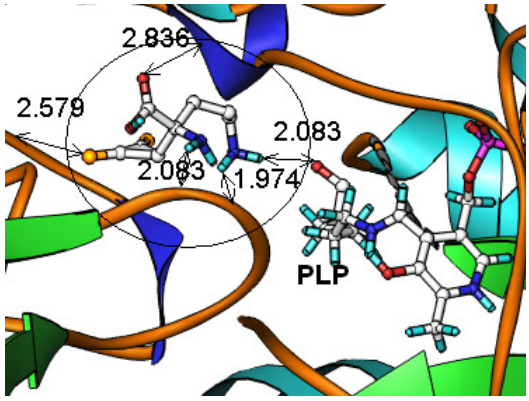
(D) R = CH_2SH



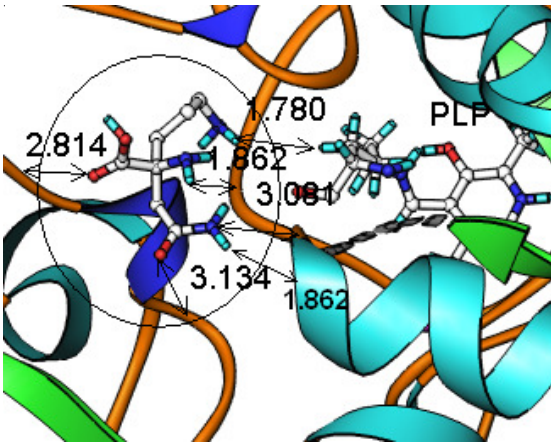
(E) R = CH_2NCS



(F) R = CH=CHF



(G) R = R=CPF_2



(H) R = CH_2CONH_2

Fig. 15. Interacting distances in A of various analogues visualized after the docking studies were completed

both the cases terminal amino group interactions was found closer than other types. These type of interactions (with PLP in particular) were also found for R = CH=CH_2 and CH=CHF. The latter was close to PLP but no interaction could be detected. However its fluorine atom was interacting with the side chains. With the cyclopropene analogues it was nearly the same as with the former series. The CPF and CPF_2 showed more interactions with the PLP (Fig. 15G). The last derivative (R = CH_2CONH_2, Fig. 15H) gave the picture of perfect docking with several closer interactions. α-Amino H was found to interact both with PLP and the side chain as well as the keto O. The molecule was more drifted towards PLP. Perhaps due to the nature of the substituent the molecule is 'allowed' for more penetration towards the binding site. These interactions very well agree with the descriptive properties carried out locally and globally. Certainly the compounds from 13-18, 20 and 22 can prove to be better drugs as they have less toxicity values based on electrophilicity studies.

Conclusion

From the above analysis it can be concluded that electrophilicity studies can be used at the DFT level of theory to establish the toxicity level of a ligand. As DFMO is a rationally designed drugs, it is acceptable here that use of CH_2OH, CH_2SH, CH_2NCS and $CH=CH_2$ can be prepared as analogues of ornithine as a chemopreventive drug. Also it may be noted that optimised geometry when fed for docking changes when the number of runs are put to more than one. A single conformer belonging to optimised geometry yields binding energy values which are not desirable for docking studies. New drugs may be prepared based on the above suggestion. Of all the population analysis NPA analysis at the DFT level gave very significant results.

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