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Molecular Modelling Analysis of the Metabolism of Eszopiclone

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Abstract: Eszopiclone (ESZ) is a recently introduced drug to treat insomnia. In this study, molecular modelling analyses based on molecular mechanics, semi-empirical (PM3) and DFT (at B3LYP/6-31G* level) calculations have been carried out to obtain insight into toxicity of ESZ and its metabolites. The results of the study show that both ESZ and its metabolites NDMESZ and ESZNO have small LUMO-HOMO energy differences, indicating that the compounds would be kinetically labile with ESZNO being most reactive. The molecular surfaces of ESZ, NDMESZ and ESZNO are found to posses significant amounts of electron-deficient regions so that the compounds, especially ESZNO, can react readily with cellular nucleophiles such as glutathione and nucleobases in DNA thus causing depletion of glutathione and oxidation of nucleobases. The former would induce cellular toxicity due to oxidative stress and the latter would cause DNA damage associated with oxidation of nucleobases.

Key words: Eszopiclone, insomnia, hypnotics, GABBA, molecular modelling

INTRODUCTION

Insomnia is a common subjective complaint of inadequate sleep that affects 15 to 40% of the general population (Walsh and Ustun, 1999). However, less than 15% of patients with insomnia receive treatment (Mellinger *et al*., 1985). Women have about 1.5 times higher risk of insomnia than men and the overall prevalence increases with age (Weyerer and Darling, 1991). There is compelling evidence to suggest that insomnia is underrecognized, underdiagnosed and undertreated (Najib, 2006). Insomnia has health, social and economic consequences. Untreated insomnia is also a risk factor for the development of psychiatric illness, particularly depressive and anxiety disorders. Benzodiazepines have been used to treat insomnia over the last three decades. However, benzodiazepines have numerous side effects including amnesia, respiratory depression, cognitive and psychomotor impairment, rebound insomnia, physical dependence and withdrawal reactions on discontinuation. Eszopiclone (ESZ), the S-enantiomer of racemic zopiclone is a pyrrolopyrazine derivative of the cyclopyrrolone class recently introduced to treat insomnia-to induce sleep and to maintain sleep. Its chemical name is (+)-(5S)-6-(chloropyridine-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo (3,4-b) pyrazin-5-yl 4-methyl-piperazine-1-carboxylate. The precise mechanism of sedative action of ESZ remains unknown. What are known are that ESZ and other members of its class act as agonists at the type A GABA (german butyric acid) receptor. ESZ has approximately 50-fold higher binding affinity than its antipode R-zopiclone for GABA-A receptor (Hegde and Schmidt, 2006). The two most frequent side effects associated with ESZ therapy are unpleasant taste and headache. Other less frequent side effects include dry mouth, nausea and somnolence.

About 50% of ESZ is bound to plasma proteins. It is metabolized in the liver through oxidation and demethylation by CYP3A4 and CYP2E1. The primary metabolites are (S)-eszopiclone-*N*-oxide (ESZNO) and *N*-desmethyl-(S)-eszopiclone (NDMESZ). ESZNO is found to be inactive (Hedge and Schmidt, 2006).

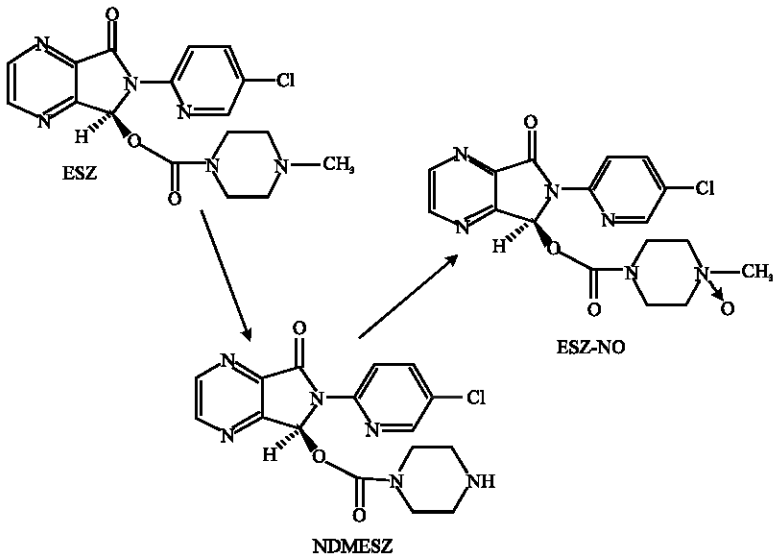

Fig. 1: Metabolic pathways for ESZ in rats and humans based on Shams *et al*. (Hedge and Schmidt, 2006)

In this study, molecular modelling analyses have been carried out using the program Spartan '02 (2002) to provide information on the relative toxicity of ESZ and its metabolites. To my knowledge no prior theoretical study has been done on the metabolism of ESZ.

Computational Methods

The geometries of ESZ and its metabolites ESZNO and NDMESZ (Fig. 1) have been optimised based on molecular mechanics, semi-empirical and DFT (density functional theory) calculations, using the molecular modelling program Spartan '04. Molecular mechanics calculations were carried out using MMFF force field. Semi-empirical calculations were carried out using the routine PM3. DFT calculations were carried at B3LYP/6-31G* level. In optimization calculations, a RMS gradient of 0.001 was set as the terminating condition. For the optimised structures, single point calculations were carried out to give heat of formation, enthalpy, entropy, free energy, dipole moment, solvation energy, energies for HOMO (Highiest Occupied Moleculer Orbital) and LUMO (Lowest Unoccupied Moleculer Orbital). The order of calculations: Molecular mechanics followed by semi-empirical followed by DFT ensured that the structure was not embedded in a local minimum. To further check whether the global minimum was reached, some calculations were carried out with improvable structures. It was found that when the stated order was followed, structure corresponding to the global minimum or close to that could ultimately be reached in all cases. Although RMS gradient of 0.001 may not be sufficiently low for vibrational analysis, it is believed to be sufficient for calculations associated with electronic energy levels.

RESULTS AND DISCUSSION

Table 1 gives the total energy, heat of formation as per PM3 calculation, enthalpy, entropy, free energy, surface area, volume, dipole moment and energies of HOMO and LUMO as per both PM3 and DFT calculations for ESZ and its metabolites NDMESZ and ESZNO. Figure 2-4 give the regions of negative electrostatic potential (greyish-white envelopes) in (a), HOMOs (where red indicates

Table 1: Calculated thermodynamic and other parameters of ESZ and its metabolites

Molecule	Calculation type	Total energy (kcal mol^{-1}/ atomic unit*)	Heat of formation (kcal mol^{-1})	Enthalpy (kcal mol^{-1} K^{-1})	Entropy (cal mol^{-1} K^{-1})	Free energy (kcal mol-1)	Solvation energy (kcal mol^{-1})
ESZ	PM3	-50.36	-35.69	221.94	168.46	171.71	-14.68
	DFT	-1640.30		223.08	167.44	173.18	-14.06
NDMESZ	PM3	-34.14	-19.94	219.59	161.59	171.42	-14.19
	DFT	-1600.99		220.76	160.37	172.97	-13.60
ESZNO	PM3	-42.00	-19.54	225.13	170.37	174.34	-22.46
	DFT	-1747.57		226.37	169.24	175.94	-21.23

Molecule	Calculation type	Area (Å^2)	Volume (Å^3)	Dipole moment (debye)	HOMO (eV)	LUMO (eV)	LUMO-HOMO (eV)
ESZ	PM3	382.96	358.47	1.4	-9.30	-1.32	7.98
	DFT	380.59	367.30	6.3	-6.07	-2.45	3.62
NDMESZ	PM3	367.17	350.70	4.2	-9.37	-1.13	8.24
	DFT	360.88	348.16	6.7	-6.06	-2.43	3.63
ESZNO	PM3	388.26	366.18	4.8	-9.35	-1.44	7.91
	DFT	386.15	367.24	5.5	-5.17	-2.48	2.69

*In atomic units from DFT calculation

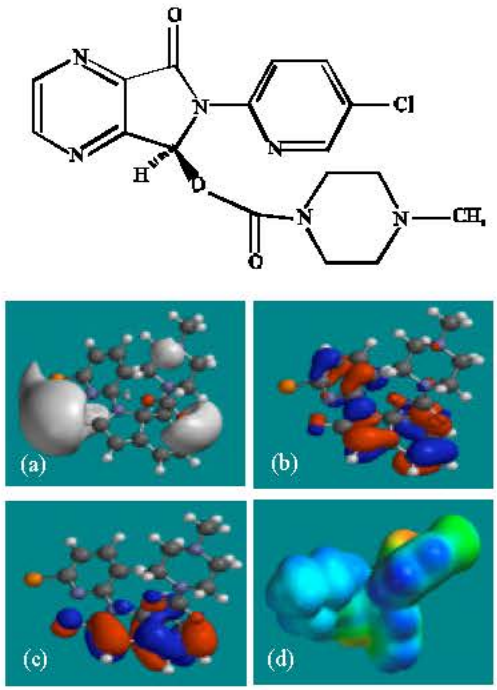

Fig. 2: Structure of ESZ giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

HOMOs with high electron density) in (b), LUMOs in (c) and density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral) in (d) as applied to optimised structures of ESZ and its metabolites NDMESZ and ESZNO.

The LUMO-HOMO energy differences for ESZ and its metabolites NDMESZ and ESZNO from DFT calculations are found to be 3.62, 3.63 and 2.69 eV, indicating that the compounds would be kinetically labile with ESZNO being the most reactive compound.

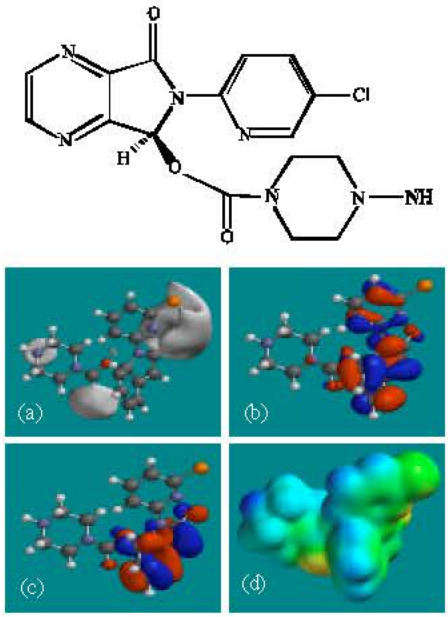

Fig. 3: Structure of NDMESZ giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

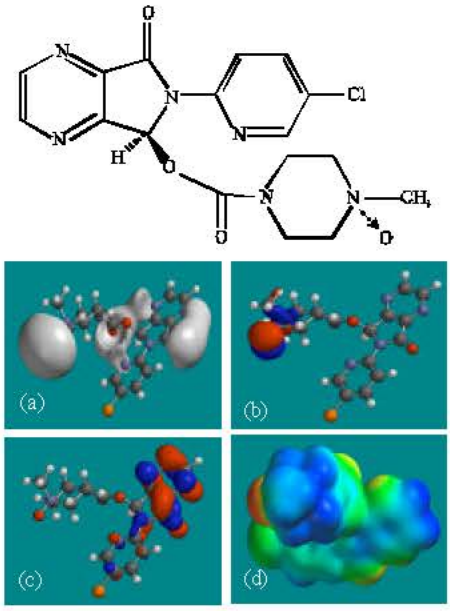

Fig. 4: Structure of ESZNO giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

In the case of ESZ, NDMESZ and ESZNO, the electrostatic potential is found to be more negative mainly around the oxygen atoms, indicating that the positions may be subject to electrophilic attack.

In the case of ESZ and NDMESZ, the HOMOs with high electron density are found to be more widely distributed localised than the LUMOs whereas in the case of ESZNO, the reverse is found to be true.

The overlap of HOMO with high electron density and region of negative electrostatic potential at some positions, gives further support to the idea that the positions may be subject to electrophilic attack.

The molecular surfaces of ESZ, NDMESZ and ESZNO are found to posses significant amounts of electron-deficient regions so that the compounds, especially ESZNO, can react readily with cellular nucleophiles such as glutathione and nucleobases in DNA thus causing depletion of glutathione and oxidation of nucleobases. The former would induce cellular toxicity due to oxidative stress and the latter would cause DNA damage associated with oxidation of nucleobases.

The solvation energies of ESZ, NDMESZ and ESZNO in kcal $mol^{-1}$from PM3 calculations are respectively -14.68, -14.19 and -22.46, indicating that among the three compounds ESZNO would have the highest solubility in water. The greater solubility in water of ESZNO would serve to increase its ease of excretion via the urine.

CONCLUSION

Eszopiclone is a recently introduced drug to treat insomnia that is a common subjective complaint of inadequate sleep that affects 15 to 40% of the general population. Molecular modelling analyses show that both ESZ and its metabolites NDMESZ and ESZNO have small LUMO-HOMO energy differences, indicating that the compounds would be kinetically labile with ESZNO being most reactive. The molecular surfaces of ESZ, NDMESZ and ESZNO are found to posses significant amounts of electron-deficient regions so that the compounds, especially ESZNO, can react readily with cellular nucleophiles such as glutathione and nucleobases in DNA thus causing depletion of glutathione and oxidation of nucleobases. The former would induce cellular toxicity due to oxidative stress and the latter would cause DNA damage associated with oxidation of nucleobases.

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