ANNALS OF "DUNAREA DE JOS" UNIVERSITY OF GALATI
MATHEMATICS, PHYSICS, THEORETICAL MECHANICS
FASCICLE II, YEAR XV (XLVI) 2023, No. 1
DOI: https://doi.org/10.35219/ann-ugal-math-phys-mec.2023

Evaluation of physico-chemical parameters of some psychoactive compounds based on molecular modeling

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Abstract
In this paper we have evaluated from a physico-chemical point of view some psychoactive compounds representing substituted phenethylamines which contain methoxy groups on the 2 and 5 positions of a benzene ring. The chemical potential of the investigated compounds was assessed by computing of the main quantum molecular descriptors, such as the dipole moment, the energy of the highest/lowest occupied/unoccupied molecular orbital, the gap energy, the electronegativity, the chemical hardness/softness, the electrophilicity index etc. Also, the presence of the nucleophilic and electrophilic sites was identified by using the molecular electrostatic potential diagram.

Keywords: phenethylamine, drugs of abuse, molecular descriptors, molecular modeling.

1. INTRODUCTION

Quantum molecular descriptors are mathematical representations of molecular properties based on quantum mechanical principles. They provide valuable insights into some important properties of molecules [1] . The molecular electrostatic potential (MEP) diagram is a graphical representation of the distribution of electric charge within a molecule which have been successfully used in the recent years to characterize different substances, including illicit drugs [2, 3].

In order to characterize two of the main classes of compounds abused as recreational drugs, i.e., 2C-x, and NBOMe compounds, a relevant series of quantum molecular descriptors, together with the MEP diagrams were determined. The targeted compounds are 2-(2,5-dimethoxyphenyl)ethanamine (2C-H), 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-B), 2-(4-ethyl-2,5-dimethoxyphenyl)ethanamine (2C-E), 2-(2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25H-NBOMe), 2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25B-NBOMe), and 2-(4-ethyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25E-NBOMe). They represent substituted phenethylamines containing methoxy groups on the 2 and 5 positions of a benzene ring (Fig. 1).

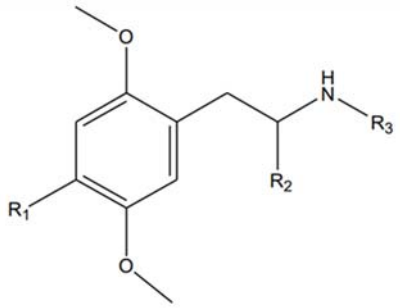

Fig. 1. The parent molecular structure of the investigated compounds

2. EXPERIMENTAL

The 3D structures of the compounds were obtained in .sdf format from the *PubChem* website [4]. The .sdf files were then converted into .hin format by using the *OpenBabel* 2.3.1 software [5]. The .hin files were then loaded into the *HyperChem* 8.0 software, where their geometries were optimized [6].

Using this software, the minimum energy (E_{min}), the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), and the dipole moment (DM) were determined for the targeted compounds. Other important descriptors were calculated using the formulas below:

- The gap energy:

$$E_{gap} = E_{LUMO} - E_{HOMO} \quad (1)$$

- The chemical hardness:

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

where IP (the ionization potential), and EA (the electron affinity) were determined using the formulas:

$$IP = -E_{HOMO} \quad (3)$$

$$EA = -E_{LUMO} \quad (4)$$

- The chemical softness:

$$\sigma = \frac{1}{2 \cdot \eta} \quad (5)$$

- The electronegativity:

$$\chi = \frac{IP+EA}{2} \quad (6)$$

- The chemical potential:

$$\mu = -\chi = -\frac{IP+EA}{2} \quad (7)$$

- The electrophilicity index:

$$\omega = \frac{\mu^2}{2 \cdot \eta} . \qquad (8)$$

In order to identify the distribution of the electrostatic potential for the selected compounds, the molecular electrostatic potential (MEP) diagrams were computed with the *HyperChem 8.0* software.

3. RESULTS AND DISCUSSION

The values of the calculated molecular descriptors are shown in Table 1. The chemical hardness varies from 4.38 to 4.57 eV, while the chemical softness has an approximative value of 0.11 $(eV)^{-1}$ for all the compounds, indicating their good chemical stability. The later property is also highlighted by the values of the energy gap, which vary from 8.75 to 9.15 eV. The calculated electrophilicity indices vary between 1.86 to 2.37, which indicate that all the analyzed compounds are strong electrophiles.

Table 1. Molecular descriptors calculated for the targeted compounds

	E_{min} (kcal/mol)	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{gap} (eV)	η (eV)	σ $(eV)^{-1}$	χ (eV)	μ (eV)	ω (eV)	DM (debye)
2C-H	-2783.23	-8.86	0.29	9.15	4.57	0.11	4.29	-4.29	2.01	2.17
2C-B	-2752.17	-9.00	-0.16	8.85	4.42	0.11	4.58	-4.58	2.37	3.06
2C-E	-3346.64	-8.46	0.31	8.77	4.39	0.11	4.07	-4.07	1.89	1.46
25H-NBOMe	-4634.84	-8.51	0.35	8.86	4.43	0.11	4.08	-4.08	1.88	1.70
25B-NBOMe	-4601.15	-8.97	-0.07	8.90	4.45	0.11	4.52	-4.52	2.30	3.26
25E-NBOMe	-5197.14	-8.41	0.34	8.75	4.38	0.11	4.03	-4.03	1.86	0.73

The computed molecular electrostatic potential (MEP) diagrams are represented in Fig. 2-7. The negative potential regions are displayed in red, the positive potential regions appear in blue, while the neutral potential regions are colored in green.

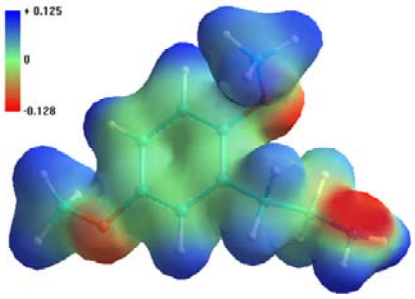

Fig. 2. Molecular electrostatic potential (MEP) of 2-(2,5-dimethoxyphenyl)ethanamine

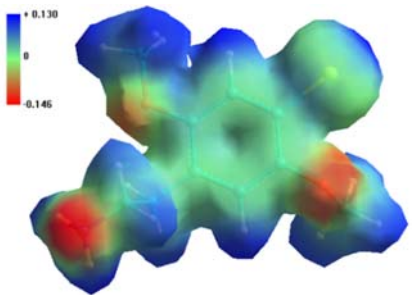

Fig. 3. Molecular electrostatic potential (MEP) of 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine

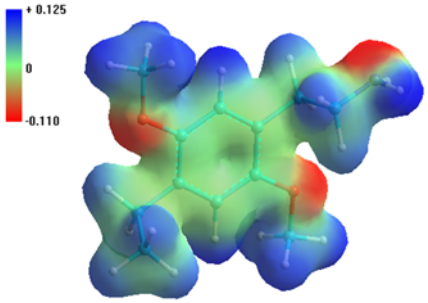

Fig. 4. Molecular electrostatic potential (MEP) of 2-(4-ethyl-2,5-dimethoxyphenyl)ethanamine

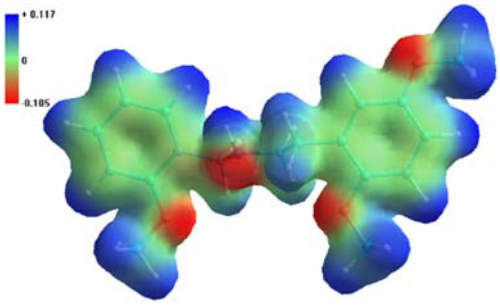

Fig. 5. Molecular electrostatic potential (MEP) of 2-(2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine

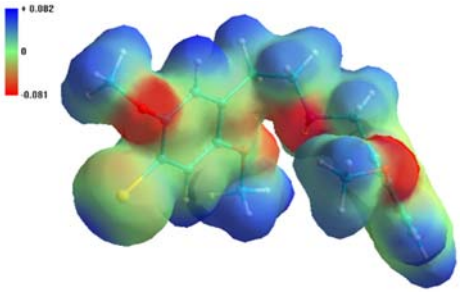

Fig. 6. Molecular electrostatic potential (MEP) of 2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine

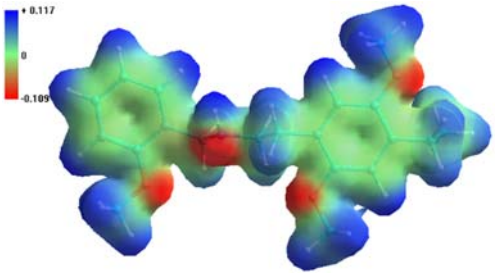

Fig. 7. Molecular electrostatic potential (MEP) of 2-(4-ethyl-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine

4. CONCLUSIONS

Several quantum molecular descriptors regarding the electronic structure, chemical reactivity, and other important properties of a series of 2C-x and NBOMe drugs of abuse have been determined. These compounds have also been characterized by using their molecular electrostatic potential maps. The results constitute valuable information for further modeling.

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