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Molecular descriptors - a mathematical approach to characterize psychedelic substances

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Abstract

Molecular descriptors convert the chemical and structural information into mathematical language. They allow the description of physical and chemical properties in numerical format. An important role of this transformation is to provide an easier identification of related substances, based on the similarities between their molecular descriptors. This paper analyses different molecular descriptors determined for the main 2C-x and DOx psychedelic phenethylamines.

Keywords: psychedelic phenethylamines, 2C-x, DOx, molecular descriptors.

1. INTRODUCTION

New representation techniques have been developed in recent years to characterize chemical compounds. Molecular descriptors express mathematically the proprieties of the substances by using numerical representations. Molecular descriptors are generated by algorithms and play an important role in determining molecules' chemical and physical information [1, 2].

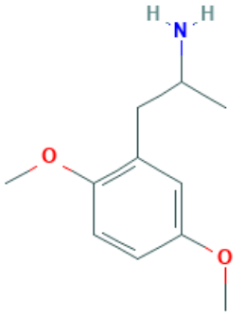
Theoretical descriptors are molecular descriptors calculated based on the structural formula or the molecular representation of the compound. Theoretical descriptors can be divided into five main categories: 0D-descriptors, 1D-descriptors, 1D-descriptors, 2D-descriptors, 3D-descriptors, and 4D-descriptors [3].

2C-x and DOx hallucinogenic drugs are two important classes of psychedelic phenethylamines that appeared on the black market in the last decades. To avoid legal consequences, new synthetic compounds, similar in structure to 2C-x and DOx substances, are produced on the black market. Molecular descriptors may be a powerful tool for their detection, as they encapsulate important chemical and physical information about the substances.

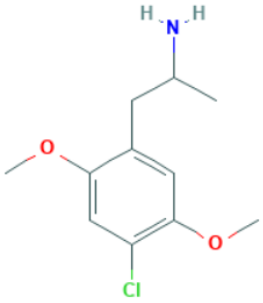
This paper presents a series of important molecular descriptors computed for six representative 2C-x and DOx hallucinogenic drugs. Their names and acronyms are listed in Table 1, while their molecular structures are presented in Figure 1.

2. EXPERIMENTAL

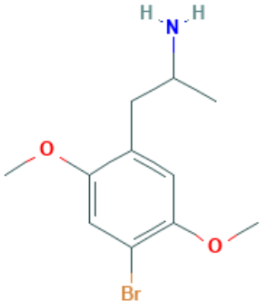
The 3D representations of the compounds were exported from the *PubChem* website in .sdf format [10]. The .sdf files were converted into .hin files by using the *OpenBabel 2.3.1* software [11]. The .hin files were then imported into the *HyperChem 8.0* software. The optimization of the substance geometries was performed by using the AM1 semi-empirical method and the *HyperChem 8.0* software [12].



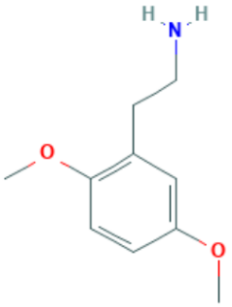
1-(2,5-dimethoxyphenyl)propan-2-amine (2,5-DMA) [4]



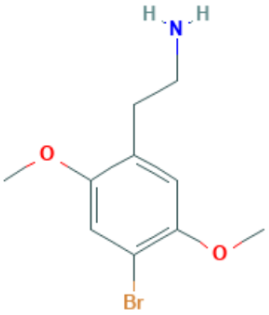
1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine (DOC)[5]



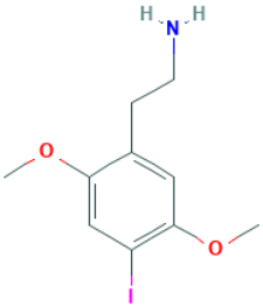
1-(4-bromo-2,5-dimethoxyphenyl)propan-2-amine (DOB) [6]



2-(2,5-dimethoxyphenyl)ethanamine (2C-H) [7]



2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-B) [8]



2-(4-iodo-2,5-dimethoxyphenyl)ethanamine (2C-I) [9]

Fig. 1. Molecular structures of the analysed 2C-x and DOx compounds

3. RESULTS AND DISCUSSIONS

Molecular descriptors play an important role in the chemical and physical characterization of the compounds. An important series of the topological, geometrical and functional group counts descriptors were calculated with the *Dragon 5.5* software [13]. The results are shown in Table 1.

Functional group counts are one-dimensional descriptors based on the number of functional groups present in the chemical structure of the compound [14]. More specifically, we have calculated for each of the targeted substances the nCaR (number of substituted aromatic C(sp2)), nCbH (number of unsubstituted benzene C(sp2)), nCb- (number of substituted benzene C(sp2)), nHAcc (number of acceptor atoms for H-bonds (N, O, F)).

Topological descriptors belong to the two-dimensional class of descriptors and are related to the topological representation of the compounds, namely to molecular graphs [14, 15]. We have calculated the following topological descriptors: ZM1 (The first Zagreb index), ZM2 (The second Zagreb index), Qindex (The quadratic index), SNar (Narumi simple topological index), and Gnar (Narumi geometric topological index).

Geometrical descriptors are three-dimensional descriptors calculated based on the 3D representation of molecules [14]. From this category, the calculated descriptors are HOMA (Harmonic Oscillator Model of Aromaticity index), AROM (The aromaticity index), and HOMT (The HOMA total).

Table 1. Topological, geometrical and functional group counts descriptors calculated for the analyzed 2C-x and DOx compounds

	Topological descriptors				
	ZM1	ZM2V	Qindex	SNar	GNar
2C-B	64	159.037	7	8.553	1.842
2C-H	58	151	6	8.148	1.872
2C-I	64	158.622	7	8.553	1.842
DOB	70	167.037	8	8.959	1.817
DOC	70	169.111	8	8.959	1.817
DOH	64	159	7	8.553	1.842

	Functional group counts			
	nCar	nCbH	nCb-	nHAcc
2C-B	12	6	6	4
2C-H	6	2	4	3
2C-I	6	3	3	3
DOB	6	2	4	3
DOC	6	2	4	3
DOH	6	2	4	3

	Geometrical descriptors		
	HOMA	AROM	HOMT
2C-B	0.955	0.986	11.461
2C-H	0.943	0.988	5.656
2C-I	0.952	0.988	5.715
DOB	0.935	0.986	5.611
DOC	0.94	0.987	5.642
DOH	0.94	0.987	5.643

In the case of the topological descriptors, we can observe that the ZM1 descriptor varies from 58, obtained for 2C-H, to 70 for the DOB and DOC compounds. ZM2 ranges between 151, recorded for 2C-H, and approximately 169 for DOC. The Qindex has values between 6, for 2C-H, and 8, obtained for the DOB and DOC compounds. The smallest SNar, 8.148, was also obtained for the 2C-H compound, whereas the largest value, 8.959, corresponds to DOB and DOC compounds. We observe that the topological descriptors have higher values for the DOx compounds than for the 2C-x compounds. Thus, topological descriptors can be useful in the discrimination of the two classes.

The table displaying the values obtained for the functional group counts descriptors indicates that 2C-B has the largest values for all the descriptors (nCaR, nCbH, nCb-, nHAcc). The lowest values of nCar correspond to five of the substances, both from 2C-x and DOx groups, namely 2C-H, 2C-I, DOB, DOC and DOH. The highest value is attributed to 2C-B. Four of the substances have the lowest value

obtained for nCbH, namely 2C-H and the three DOx compounds, while the highest value corresponds to 2C-B. The nCb- descriptor varies from 3, obtained for 2C-I to 6, obtained for 2C-B. For nHAcc, almost all the analyzed compounds have a value equal to 3, the only substance with a different value (4) being 2C-B. In general, we can observe that the values obtained in the case of the functional group counts for the DOx compounds were the same among all the group members, while the 2C-x members have different values. Thus, the functional group counts descriptors calculated may be a useful tool for the discrimination among the 2C-x group members.

In the case of the geometrical descriptors, we may notice that the HOMA descriptor has the largest value (0.955) obtained for 2C-B, while the lowest value (0.935) corresponds to DOB. For the AROM geometrical descriptor, very close values (around 0.98) were obtained for all of the compounds. The largest value of the HOMT descriptor (11.461) was obtained for 2C-B. This value is significantly larger than the HOMT values obtained for the rest of the compounds, the rest of the 2C-x compounds included. The other compounds have values between 5.61 and 5.71. We can notice that the topological descriptors for the DOx compounds have higher values than those computed for the 2C-x compounds. Consequently, geometrical descriptors can be used for the discrimination of the substances belonging to the two classes.

4. CONCLUSIONS

The results obtained highlight the similarities and differences between the analyzed compounds. In general, the 2C-x compounds present higher values for the topological, functional group counts, and geometrical descriptors, in comparison with DOx compounds. Thus, the molecular descriptors calculated in this work can be a useful tool for identifying the class membership of the 2C-x and DOx psychedelic drugs of abuse.

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