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SUBSTITUENT EFFECT ON THE BINDING MODE AND TOXICITY OF SELECTED 1,4-BENZODIAZEPIN-2-ONE

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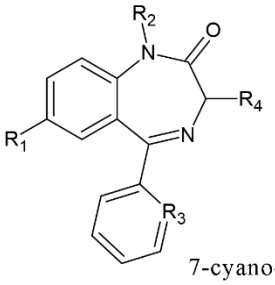
Extended abstract:

1,4-benzodiazepin-2-ones (BZ) are effective in the treatment of depression, anxiety, epilepsy, insomnia, etc [1]. The structural modifications of 1,4-benzodiazepin-2-ones allow new areas of application due to the change in reactivity, potential binding modes, and stability. A series of eight BZs (Figure 1) has been selected to examine the effect of substituents on the binding energy towards μ-opioid receptor, Lipinski's rules, and toxicity. Out of many available structures, the selected BZs have four positions in which the substituents were changed [2]. In position R1 an electron-withdrawing (NO_2, CN) and electron-donating groups (Cl) are present [2]. The positions R2 and R3 contain H, OH, and CH_3 groups. Only bromazepam, a commonly used drug, has nitrogen atom in the second aromatic ring.

The structures of selected benzodiazepines were optimized in the Gaussian 09 Program Package at the M06-2X/6-311++G(d,p) level of theory. The molecular docking studies were performed on the μ-opioid receptor (PDB: 4DKL) in AutoDOCK 4.0. The binding site of protein was determined by the presence of morphinan antagonist in the crystal structure. For the toxicity evaluation, the ProTox-II was used.

All of the investigated compounds meet Lipinski's rules of five: the molecular weight below 500 Da, the logP lower than 5, the number of H-bond donors lower than five, and H-bond acceptors lower than 10. When the toxicity is concerned, the selected BZs fall within several categories. Nordiazepam and diazepam have the lowest predicted LD50 dose of 48 $mgkg^{-1}$, and they belong to the class II compounds which are fatal if swallowed. 7-cyano-1,4-benzodiazepin-2-one has lower toxicity with an LD50 value of 290 $mgkg^{-1}$ (class III compounds: toxic if swallowed). The ciano group in structure is probably responsible for the hydrogen bond formation with the neighboring amino acids, as examined below. The rest of the compounds belong to the class IV: harmful if swallowed, with LC50 values ranging from 550 (nitrazepam) to 2000 (clonazepam) $mgkg^{-1}$. The substituent effect on the toxicity is very complex, as all of the investigated compounds have several active positions. The values of binding energies range from -29.3 (bromazepam) to -22.8 (nordiazepam) $kJmol^{-1}$. Due to the similarity in structure, all of the investigated compounds have similar values of the binding energies and in all cases, this is a favorable process. The presence of an N atom in the second ring structure is an important structural moiety as this is the only feature that differentiates bromazepam from other compounds. The importance of electronegative groups in position R1 is proven in the case of 7-

cyano-1,4-benzodiazepin-2-one and nitrazepam. In general, compounds with two electronegative substituents (Cl, NO_2, and OH) have higher binding energies. Further research is needed to obtain a detailed structure-activity relationship model that will correlate the substituent properties with toxicity/protein binding affinity.



	R1	R2	R3	R4	ΔG_{bind} (kJmol^{-1})
bromazepam	Br	H	H	N	-29.3
clonazepam	NO2	H	H	C-Cl	-26.0
diazepam	Cl	CH3	H	C-H	-26.0
nitrazepam	NO2	H	H	C-H	-27.1
nordiazepam	Cl	H	H	C-H	-22.8
oxazepam	Cl	H	OH	C-H	-23.6
tempazepam	Cl	CH3	OH	C-H	-28.1
7-cyano-1,4-benzodiazepin-2-one	CN	H	H	C-H	-27.3

Fig. 1. The Structures and binding energies towards μ-opioid receptor of selected benzodiazepines.

Keywords: 1,4-benzodiazepin-2-one, DFT, ADME, toxicity evaluation

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References

[1] Pluskal T., Weng, J-K., *Natural product modulators of human sensations and mood: molecular mechanisms and therapeutic potential,* Chemical Society Reviews, Vol. 47, 1592, 2018.

[2] Pem B., Vrčekm V., *Substituent effects on the stability of 1,4-benzodiazepin-2-one tautomers: A density functional study*, International Journal of Qunatum Chemistry, Vol. 118, e25523, 2017.

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