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Dopamine antagonists for the treatment of drug addiction: PF-4363467 and related compounds

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RESEARCH ARTICLE

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ABSTRACT

Drug addiction refers to an out-of-control and compulsive use of substances, which can reach epidemic magnitudes. It is a health concern throughout the world and has major economic impact. Dopamine receptor agonists and antagonists have been cited as molecular targets for the treatment of drug addiction. In this report, the main idea is to analyze the new D3R/D2R ligands that are proposed for the treatment of drug abuse, in terms of their electron donor/acceptor properties. Substances catalogued as agonists represent good electron donors, whereas antagonists represent good electron acceptors. HOMO and LUMO eigenvalues indicate that more energy is necessary to remove an electron from the antagonists, and likewise more energy is gained when antagonists accept an electron. The combination of two molecules (PF-592379 and PNU-177864) produces a new compound (PF-4363467) with properties that are intermediate. Irrespective of the characteristics of the receptor, the classification of ligands is important, in order to further understanding of the reaction mechanism of these compounds. This may help in the design of new molecules for the treatment of drug addiction.

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1. Introduction

Drug addiction refers to an out-of-control and compulsive use of substances, regardless of any negative effects on health. Substance abuse has reached epidemic magnitudes and is a health concern throughout the world with major economic impact [1-3]. In particular, opioid dependency mainly affects young people and there is an ongoing increment in opioid addiction. This is the reason why it is important to develop new medicines that treat dependency and deter relapse.

Dopamine receptor agonists and antagonists have been used as molecular targets for the treatment of drug addiction, for example, in order to curtail opioid-seeking behavior in rodents that consumed fentanyl out of choice [4]. For more than a decade, the dopamine D3 receptor (D3R) has been considered as a potential target for the treatment of substance disorders [5-13]. The first clinical evidence corroborating the hypothesis of the importance of D3R in the treatment of drug addiction was the discovery of a selective D3R antagonist, known as GSK598809 [10,11]. Since then, several investigations have focused on the study of D3R and also of the dopamine D2 receptor (D2R) for the treatment of substance dependence. Recent literature suggests that D3R/D2R ligands show potential for curtailing drug-seeking behavior [7,12,13] pointing out that cariprazine (a 10-fold selective D3R/D2R partial agonist) is able to reduce the rewarding effect of cocaine and thus attenuates relapse into cocaine seeking behavior among rats [14]. Agonists and antagonists of dopamine are also used as antipsychotics [15-19]. Cariprazine [14,20-22], the same substance used to treat drug addiction, is also an antipsychotic. Among atypical antipsychotics, cariprazine displays greatest D3R binding affinity and a predisposal towards D3R as opposed to D2R.

Ligands used to prevent dependency consist of both agonists and antagonists, and they also have the potential to engage D3R at high occupancy levels, while simultaneously interacting with D2R at a wide range of occupancies. The hypothesis is that this dual pharmacological strategy modulates the cue-reward processing pathway. Concurring with this idea, a structurally unique D3R/D2R antagonist was reported recently [23]. This drug is known as PF-4363467 and attenuates the opioid drug-seeking behavior of animals trained to self-administer fentanyl. This compound is obtained from two pharmacophore elements, one agonist and the other antagonist; known as PF-592379 (D3R agonist) and PNU-177864 (D3R antagonist).

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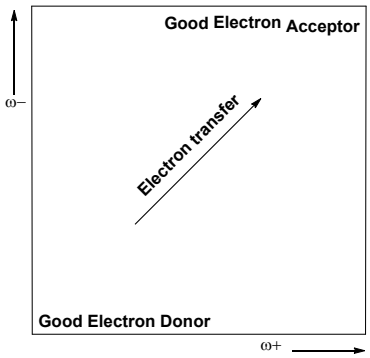

Figure 1. Donor-Acceptor Map (DAM).

The classification of these substances as agonists or antagonists is not always straightforward. In previous investigations, agonists and antagonists of dopamine were classified by applying quantum chemical calculations [18,19], in conformity with electron donor-acceptor properties. Antagonists are categorized as electron acceptors, whereas agonists and dopamine are good electron donors. This categorization also provides some insight into the action mechanisms of these drugs.

In spite of all these previous investigations, few theoretical studies exist which help us better understand the electronic properties of these molecules. In this report, the main idea is to analyze the new D3R/D2R ligands proposed for the treatment of drug abuse, in terms of their electron donor acceptor properties. Irrespective of the characteristics of the receptor, the classification of the ligands is important for elucidating the reaction mechanism of these compounds, as this may help in the design of new molecules for the treatment of drug addiction.

2. Theory/Calculations

Gaussian09 was used for all electronic calculations [24] Geometry optimizations without symmetry constraints were implemented at M06/6-311+G(2d,p) level of theory [25-29] while applying the continuum solvation model density (SMD) with water and benzene, in order to mimic polar and non-polar environments [30]. Harmonic analyses were calculated to verify local minima (zero imaginary frequencies). All molecules have chemical properties that can be described in terms of response functions. These response functions refer to modifications in the electronic states of one molecule due to the presence of other molecules [31,32]. In this context and in order to analyze the electron-donor acceptor properties, vertical ionization energy (I) and vertical electron affinity (A) were obtained from single point calculations of the corresponding cationic and anionic molecules, using the optimized structure of the neutrals. The same level of theory was used for all computations. These values were used to obtain the electrodonating (ω–) and electroaccepting (ω+) powers, previously reported by Gázquez *et al.* [33,34]. These authors defined these two quantities as follows:

$$\omega- = (3I + A)^2 / 16 (I-A) \quad (1)$$

$$\omega+ = (I + 3A)^2 / 16 (I-A) \quad (2)$$

Lower values of ω– imply greater capacity for donating charge. Higher values of ω+, imply greater capacity for accepting charge. In contrast to I and A, ω– and ω+ refer to partial charge transfers, not necessarily from one electron. This definition is based on a simple charge transfer model expressed in terms of chemical potential and hardness. The Donor-Acceptor Map (Figure 1) previously defined [35] is a useful graphic tool that has been used successfully in many different chemical systems [18,19,36-39]. Electrons are transferred from good donor systems (down to the left of the map) to good electron acceptor systems (up to the right of the map).

3. Results and discussion

As pointed out in the introduction, it has been reported recently that some D3R/D2R ligands are able to curb drug-seeking behavior [6,20-22,40-43]. This action mechanism is not completely understood, although previous reports have indicated that both agonists and antagonists are useful for treating substance addictions. Former investigations have focused on receptor occupancy, but electronic properties were not assessed. In this investigation, we present an analysis of D3R/D2R agonists and antagonists. We intend to reveal more information concerning the electronic properties of these substances, in order to classify them from a quantum chemical point of view. This may help expound the action mechanism.

Figure 2 reports the schematic representation of molecules being studied. Cariprazine is a partial agonist that reduces the rewarding effect of cocaine and attenuates relapse to cocaine seeking among rats [21]. It is also administered as an antipsychotic. PF-592379 is a full agonist that has affinity for and will select D3R over D2R. BP897 is a D3R partial agonist that reduces cocaine-seeking behavior in rats, but further studies have shown that this compound also exhibits antagonism to D3R [40-43]. GSK598809 is a selective D3R antagonist, which attenuates addiction among rats that are dose-dependent on nicotine. This was the first compound to provide clinical evidence corroborating the idea that D3R antagonists are effective for the treatment of substance abuse [10,11]. NGB2904 is a selective D3R antagonist that inhibits self-administration of cocaine [44]. PNU-177864 represents a structurally unique D3R antagonist scaffold. It exhibits moderate affinity for D3R with clear preference in comparison to D2R, and is considered a functional antagonist. PF-4363467 was recently reported [23] as an excellent preclinical tool to test for D3R and D2R antagonist action.

Optimized structures for all these compounds are presented in Figure 3. First, it is evident that some of the structures are not linear. They are bent by approximately 85 degrees (BP897, NGB 2904, PNU-177864 and PF-4363467). Optimization was undertaken in water and benzene, and under both conditions, the optimized structures are practically the same. PF-502379 is a small molecule, which cannot be bent. The other two molecules, cariprazine and GKS598809, are quasi linear.

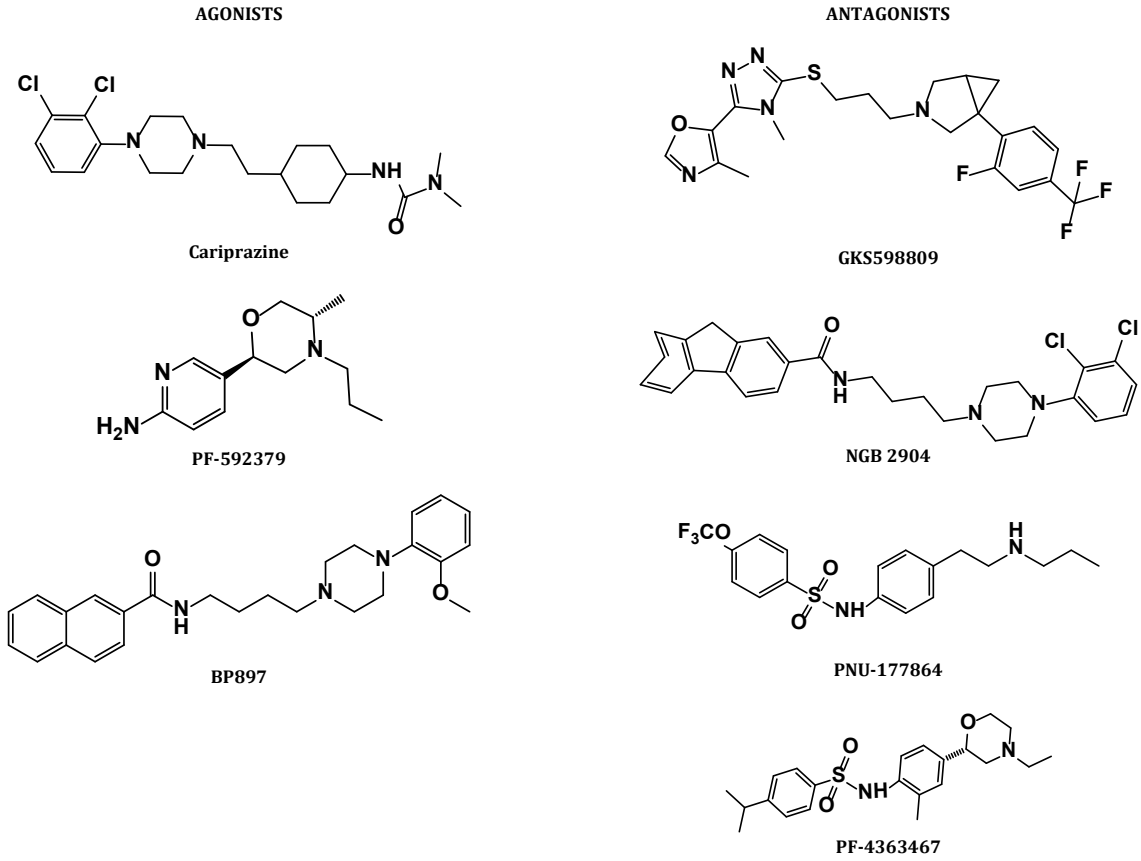

Figure 2. Schematic representation of the molecules under study.

These structures cannot easily be shown to relate to the activity of these molecules, as D3R/D2R agonists or antagonists. These molecules are quite different; all of them contain nitrogen and oxygen and some contain halogens and/or sulfur. They should bind to the receptor in different positions or to distinct amino acids, but albeit they were proved as efficient molecules to control drug seeking in rats. Because the molecular structure does not provide much information, we need to analyze electronic structure. Antagonists occupy the receptors but do not activate them, in contrast to agonists, which bind to the receptors and activate them.

The hypothesis here, previously reported for the study of antipsychotics, is that those molecules acting as agonists to D3R and D2R must have electron transfer properties similar to dopamine, a neurotransmitter that also binds to these receptors and activates them. Agonists will therefore interact with the receptors and activate them (as dopamine does). Molecules that are antagonists must have a different capacity to transfer charge. They must be different to the electron-donor acceptors of dopamine, which explains why they interact with the receptors but do not activate them. We should remember that cariprazine is an agonist, but in the presence of high extracellular concentrations of dopamine, these drugs compete with dopamine and act as antagonists. Nonetheless, the principal role played by these drugs is as agonist.

To analyze electron-donor acceptor properties, Figure 4 presents the DAM in water and benzene for all molecules being studied. Dopamine is included for comparison. Under both conditions; water and benzene, agonists are more like dopamine than antagonists. This means that they are good electron donors. Antagonists are up to the right of the map, meaning they represent better electron acceptors than dopamine. BP897 also appears at the top right of the map, and accordingly, it is a good electron acceptor. It is important to remember that BP897 was reported to be a partial agonist, but also similar to antagonists of D3R. As pointed out previously in the introduction, it is difficult to determine experimentally, whether substances are agonists or antagonists. The classify-cation reported here, based on quantum chemistry calcula-tions proves that BP897 is as good an electron acceptor as the other antagonists.

Experimentally, it was reported that PF-5923790 (an agonist) combines with PNU-177864 (an antagonist) to yield the novel PF-4363467 that is also an antagonist. The DAM indicates that the values for PF-4363467 fall between the values of the reactants from which it comes. It is not as good an electron donor as PF-592379 or as good an electron acceptor as PNU-177864. This might explain the excellent properties of this new antagonist, reported previously [23]. Among all the antagonists, GSK598809 is the best electron donor. This may be important for effective control of drug abuse.

Figure 5 reports the eigenvalues (absolute values) of the Highest Occupied Molecular Orbitals (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO), whereas Figure 6 presents their molecular orbital surfaces. In the case of the DAM, analysis assesses partial charge transfer process, whereas eigenvalues enable us to consider a single electron transfer process. Antagonists have higher values for HOMO and LUMO than agonists and dopamine. More energy is necessary to remove an electron from the antagonists, and likewise more energy is gained when antagonists accept an electron. The exception is BP897, but as explained before, this compound is both agonist and antagonist.

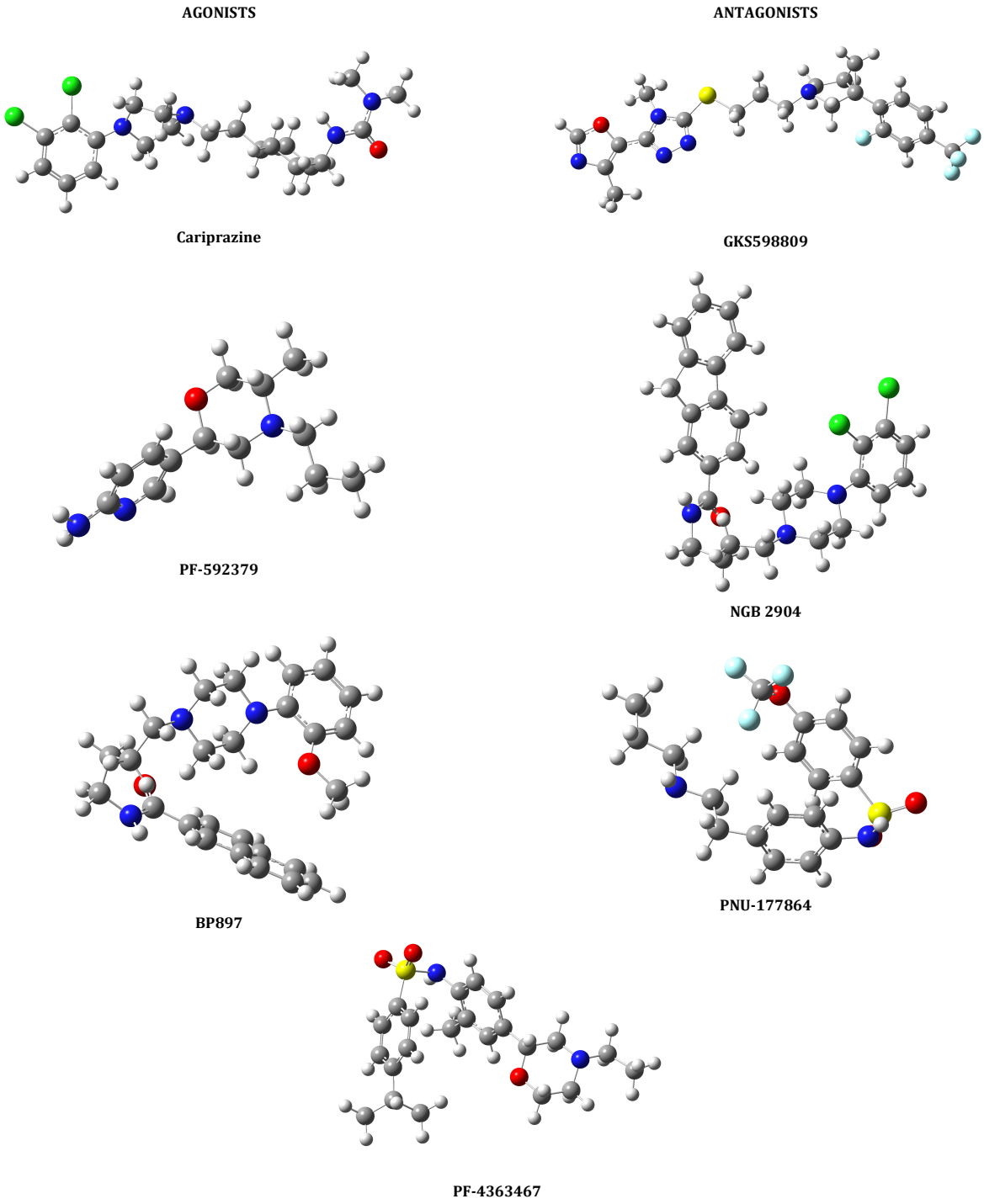

Figure 3. Optimized structures of the molecules under study.

BP897 is interesting because it manifests the lowest value for HOMO and the highest for LUMO. We need less energy to remove one electron from the HOMO and it is also energetically more favorable that BP897 accepts one electron in the LUMO, rather than the others. Evidently the values for PF-4363467 fall between the values for PF-592379 and PNU-177864. Combining these two molecules produces a new compound with properties that are intermediate. Figure 6 indicates that all frontier molecular orbitals are π-bonding orbitals. HOMO and LUMO of the agonists are located in the same atoms of the molecules, whereas when the molecules are antagonists, they are located in different atoms. The orbitals of PF-4363467 are situated in different regions of the molecule, in comparison to PNU-177864 and PF-592379. These results elucidate the electronic properties of agonists and antagonists, providing us with greater insight in relation to the characteristics of these molecules, which manifest particular activity.

4. Conclusions

The molecular structures of the compounds reported here cannot easily be shown to relate to the activity of these molecules, as D3R/D2R agonists or antagonists, as the optimi-

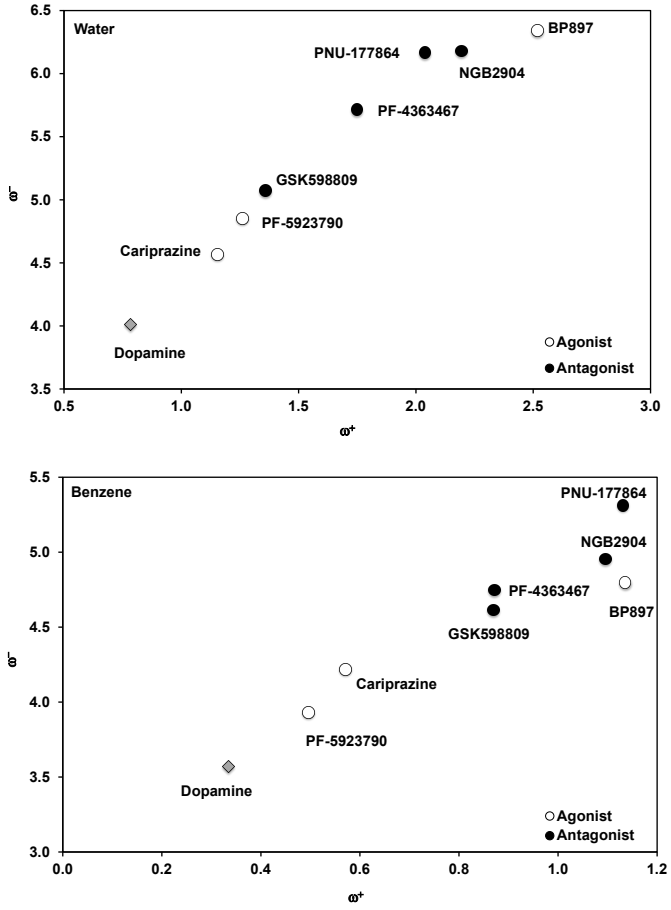

Figure 4. DAM of the compounds under study, in water and benzene.

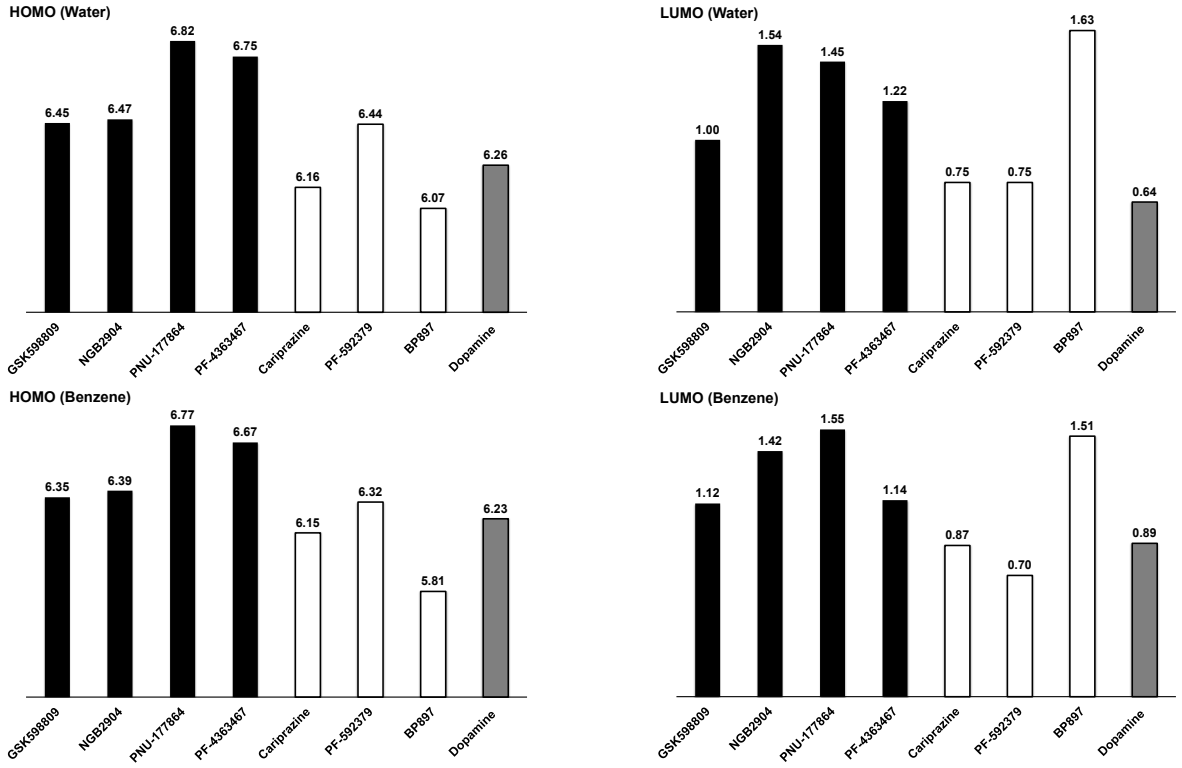

Figure 5. Eigenvalues (absolute values) of the Highest Occupied Molecular Orbitals (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO).

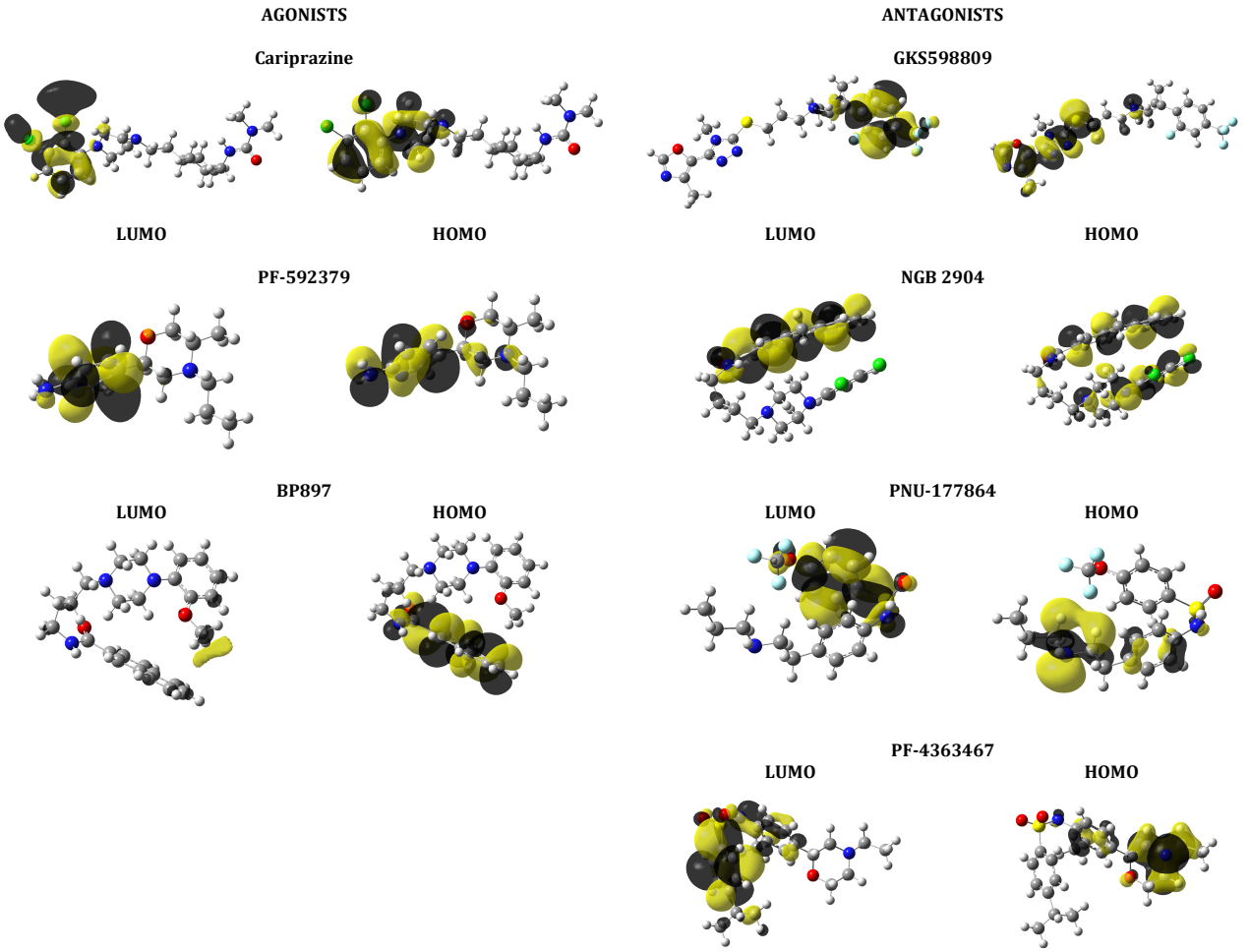

Figure 6. HOMO and LUMO.

zed structures of some of these compounds are bent by approximately 85 degrees (BP897, NGB 2904, PNU-177864 and PF-4363467) and the others (cariprazine and GKS598809) are quasi linear. PF-502379 is a small molecule, which cannot be bent.

The DAM indicates that agonists and dopamine are good electron donors. Antagonists are up to the right of the map, and therefore they are good electron acceptors. The quantum chemistry classification reported here indicates that BP897 is as good an electron acceptor as the other antagonists.

HOMO and LUMO eigenvalues indicate that more energy is necessary to remove an electron from the antagonists, but that more energy is gained when antagonists accept an electron. BP897 is interesting because it manifests the lowest value for HOMO and the highest for LUMO. The combination of two molecules (PF-592379 and PNU-177864) produces a new compound (PF-4363467) with properties that fall in between. All frontier molecular orbitals are π-bonding orbitals. HOMO and LUMO of the agonists are located in the same atoms of the molecules, whereas they are located in different atoms, when the molecules are antagonists. All these characteristics may be useful for the design of new molecules that are helpful for the control of drug abuse, related to D3R.

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Disclosure statement

Conflict of interests: The author declares that she has no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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