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Pseudo-chirality – an issue that should not be misdefined, misinterpreted or treated as a „pseudo-matter" nor in describing stereochemistry neither in drug design☆

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Abstract:
Pseudo-chirality represents a matter that is unfortunately often misdefined, misinterpreted or even neglected, as it is frequently supposed not to be worth mentioning in describing chemical structures; however, it has proven on numerous occasions to be determinant for properties that can affect not only theoretical scientific knowledge but even critical human health situations, as drug design is involved. The present paper aims to draw attention to some common mistakes in understanding the subtle term of pseudo-chirality, starting from its current understanding by four of the most well-known AI chatbots (ChatGPT, Gemini, Copilot and DeepSeek R1) and within open-access web resources that we tested in this regard.

Keywords: pseudo-chirality, chirality, molecular symmetry, stereochemistry, drug design

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1. INTRODUCTION

Pseudo-chirality is a very interesting issue in stereochemistry which is the subject of some current studies, as this concept was also proved to have a practical impact on modern chemical synthesis, including drug design [1-3]; however, this being a subtle term, there are some common mistakes about it, which we intend to draw attention to, in order for the readers to avoid them.

2. TESTING AI CHATBOTS IN THE REGARD OF UNDERSTANDING PSEUDO-CHIRALITY

In testing four of the most well-known AI chatbots (ChatGPT, Gemini, Copilot and DeepSeek R1) in the regard of understanding pseudo-chirality, we were unpleasantly surprised to see that one of them got it all wrong, trying to treat pseudo-chirality as a particular case of chirality, *i.e.*, stating that „*if all four groups bonded to a carbon atom are different from each other, the molecule is chiral, whereas if two of these four are identical, the molecule becomes achiral*"; but, in the case of pseudo-chirality, things are exactly the opposite, meaning that: if two of the four substituents of a carbon atom are in „object/mirror image" relationship with each other (the other two being different from these two and also from each other, not even being in „object/mirror image" relationship with each other), then the molecule becomes achiral as a whole due to an internal compensation (but it can present itself in two diastereoisomeric forms), whereas if two of the substituents, being both chiral, are identical including in terms of chirality, the molecule is chiral as a whole (so that – obviously – it can present itself in two enantiomeric forms).

Moreover, when asked „what is pseudo-chiralitaty?", another one of the tested AI chatbots answered that: „*pseudo-chirality is a concept in stereo-chemistry describing an atom, often a carbon, bonded to four groups where two of the groups are constitutionally identical but configurationally different, making the atom pseudo-asymmetric*"; the third answered the same question that: „*pseudo-chirality describes a point or*

center in a molecule that is not truly chiral but can exist in two enantiomeric forms due to the configuration of its surrounding groups" and the remaining one answered that: „*pseudo-chirality refers to a subtle type of stereochemical configuration that arises when a center in a molecule appears achiral at first glance but actually behaves as if it were chiral due to the spatial arrangement of its substituents*".

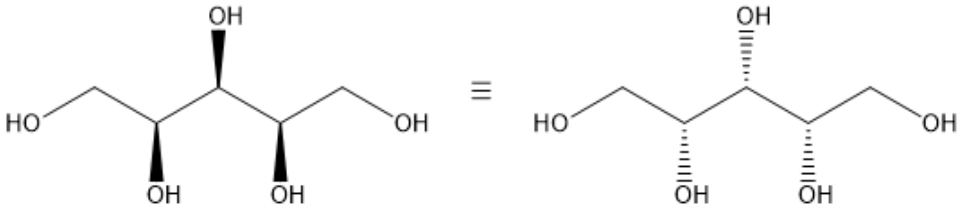
These answers show that, when referring to pseudo-chiralitaty, this term seems to be wrongly „attached" to the idea of a chiral center (usualy a carbon atom), with four groups bonded to it; but – exactly like in „pure chirality" case, this means misdefined the term; the definition should not be limited to this, as there are cases in which the reasons are different (such a case will be referred to in the final part of the paper, within which an example of drug will be given, whose pseudo-chirality is an axial one, being due to a specific 3D-shape of an alkaloid ring exhibiting bridgehead carbon atoms).

3. INVESTIGATING OPEN-ACCESS WEB RESOURCES REGARDING PSEUDO-CHIRALITY

The problem of pseudo-chirality in organic chemistry being extremely subtle, it is often ignored, as it is considered as a „pseudo-matter" by those who do not understand it exactly.

This is why, for example, regarding the IUPAC name of xylitol – a natural sweetener used to replace sugar – at the time of writing this paper (10/10/2025), when consulting Wikipedia in English, we find the correct variant, (2R,3r,4S)-pentane-1,2,3,4,5-pentol, whereas, accessing Wikipedia in Romanian, we encounter the wrong variant: (2R,4S)-pentane-1,2,3,4,5-pentol; even worse, Wikipedia in Portuguese defies any matter related to the chirality of this compound, completely ignoring to mention any stereochemical aspect [4-6}.

A very interesting aspect is that the discused molecule, despite having two chiral centers and a pseudo-chiral one, is achiral in its entirety, due to an internal compensation (like in the cases of classic *meso* forms); however, this aspect is not even mentioned in any of the variant given by Wikipedia.



xylitol – an achiral molecule with two chiral centers and a pseudo-chiral one

Furthermore, we also dived into ones of the most relevant open-access sources for chemists, including databases of publications (such as PLoS, eLife and ACS), open-access journals (such as Chemistry Central Journal), preprint archives (such as ChemRxiv), open educational resources (such as MIT and OpenCourseWare) as well as specific search engines (such as Scifinder/ Reaxys with open-access features).

We found satisfactory results in quite a few situations but, on the other hand, on the contrary, we also encountered mistakes related to the aspect of chirality (which we do not consider ethical mentioning hereby).

Consequently, from all this foundings, we concluded that the subject of pseudo-chirality, although important and interesting, is far from being correctly understood on a large scale; therefore, we thought that perhaps it would be useful to refer to it within the framework of this paper.

4. EXAMPLE OF MODELING IN ORDER TO UNDERSTAND PSEUDO-CHIRALITY

For the sake of consistency, let us give another simple example of molecule exhibiting pseudo-chirality, also presenting the related molecular modeling performed in order to understand chirality and pseudo-chirality.

The molecule chosen for this purpose is 2,4-dichloropentane-3-thiol, in which the second and the penultimate carbon atoms are both

definitely chiral, whereas the central one could be achiral or pseudo-chiral, depending on the concordance/discordance between the configurations of these two.

In case of concordance between them, we can find two enantiomers:

(2*S*,4*S*)-2,4-dichloropentane-3-thiol

(2*R*,4*R*)-2,4-dichloropentane-3-thiol

In case of discordance between them, we can find two diastereoisomers:

(2*R*,3*s*,4*S*)-2,4-dichloropentane-3-thiol

(2*R*,3*r*,4*S*)-2,4-dichloropentane-3-thiol

Another common mistake we draw attention to, in order for the readers to avoid it, is considering such diastereoisomers' pair as „*meso* forms"; indeed, *meso* compounds are classically defined as molecules containing chiral centers, but which, despite this fact, are superimposable on their mirror images, being therefore achiral

overall, *i.e.*, optically inactive (due to an internal symmetry plane that cancels out the optical activity of the individual chiral centers).

However, each classic *meso* compound is unique, unlike the case here chosen, in which molecules exhibiting pseudo-chiral centers appear in pairs of diastereoisomers – so the term *meso* would be unproperly used for them!

On one hand, we have computationally modeled all the four molecules presented above, using specialized software, namely Hyper 8.0.10 [7] (an only ball was used to represent methyl group, for the sake of simplicity and clarity).

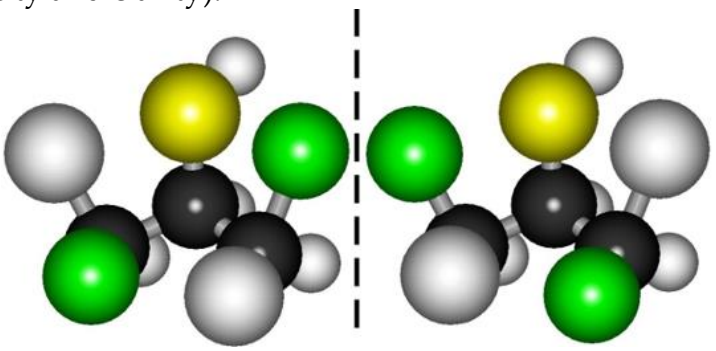


Figure 1. Computational models – enantiomers: (2*S*, 4*S*) – left / (2*R*, 4*R*) – right.

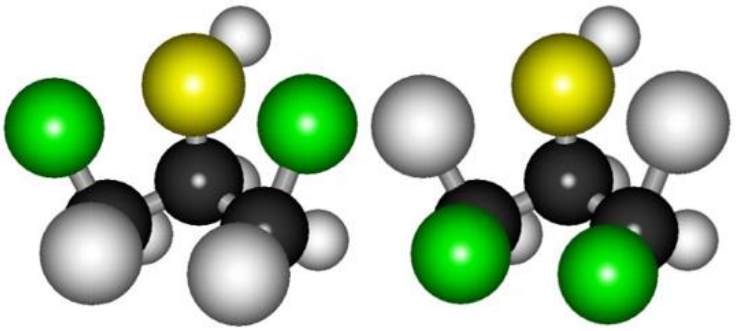


Figure 2. Computational models – diastereoisomers (2*R*, 3s, 4*S*) – left / (2*R*, 3r, 4*S*) – right.

On the other hand, we have also objectually modeled the molecules, by using sticks and balls (again, an only ball was used to represent methyl group).

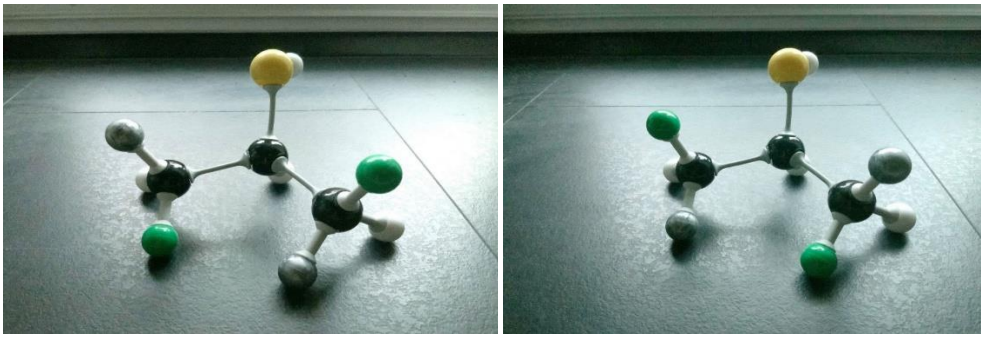


Figure 3. Objectual models – enantiomers: (2S, 4S) – above / (2R, 4R) – below.

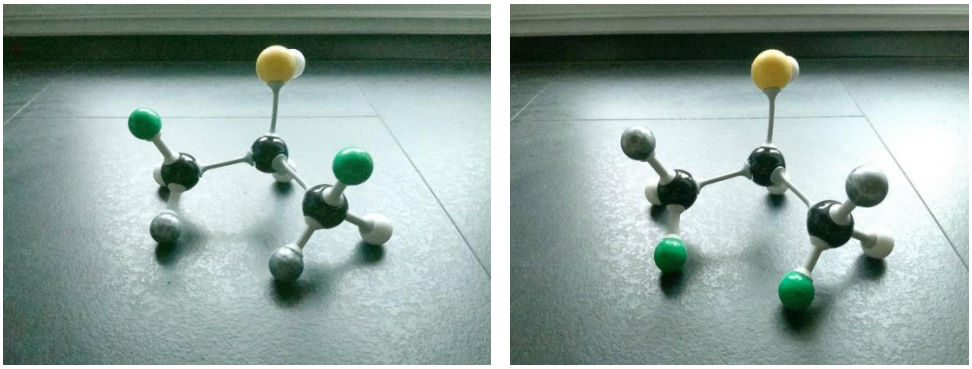


Figure 4. Objectual models – diastereoisomers (2R, 3s, 4S) – above / (2R, 3r, 4S) – below.

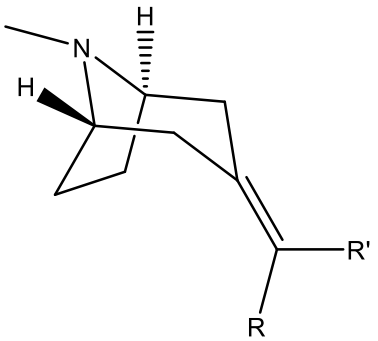
5. EXAMPLE OF PSEUDO-CHIRALITY IN DRUG DESIGN

In drug design, pseudo-chirality could be sometimes important. An example could be represented by certain beta-blockers [1].

Another example could be tropisetron (the ester of indole-3-carboxylic acid and tropine, namely (3-endo)-8-methyl-8-azabicyclooct-3-yl 1H-indole-3-carboxylate, mostly used as its hydrochloride salt) and some other related alkaloids for which binding orientation – that is closely related to its pseudo-chirality (which is an axial one, being due to a specific 3D-shape of an

alkaloid ring system exhibiting bridgehead carbon atoms) – is crucial for drug activity [2].

Very recent research [3] reveals an entire series of newly synthesized drugs: axially pseudo-chiral alkylidene azacycloalkanes (alkylidene tropanes) – more precisely, various three-dimensional nonatropisomeric axially chiral alkylidene N-bridged [3.2.1] and [3.3.1] ring systems.



Structure of axially pseudo-chiral alkylidene tropanes exhibiting drug activity

Despite the fact that pseudo-chiral centers are not truly chiral, they can affect how a substance interacts with different enzymes and/or receptors, such interactions habitually depending on the spatial orientation of atoms, so pseudo-chirality can influence drugs' binding affinity and efficacy.

Moreover, we can bring into discussion an enantiomeric recognition, as many biological systems can distinguish between molecules with pseudo-chiral centers, particularly when the molecules also contain truly chiral centers, therefore leading to different pharmacological effects for each stereoisomer.

Pseudo-chirality can play a key-role in complex drug design, because in order to introduce or to control pseudo-chiral centers during syntheses always requires specific stereoselective techniques, especially when the goal is synthesizing a single stereoisomer which exhibits the best pharmacological activity.

As two groups that are constitutionally identical but stereochemically different are bonded to a pseudo-chiral carbon atom, identifying or separating these groups during synthesis can be very difficult or even impossible, thus affecting purity, yield and – consequently – enhancing cost of synthesis.

Therefore, regulatory consequences follow, since regulatory agencies habitually require detailed stereochemical characterization of drugs, so that pseudo-chirality augments the complexity of quality control and approval procedures.

6. CONCLUSION

Through this paper, we have brought some arguments for the idea mentioned in the title, namely that pseudo-chirality is an issue that should not be misdefined, misinterpreted or treated as a „pseudo-matter", nor in theoretical stereochemical description, neither in drug design.

We have led and finally carried out this approach by focusing on some common mistakes, so as to explain why they should be avoided for a correct understanding and implicitly for a correct use of this subtle notion, as we do consider this aspect as important, especially regarding it from the perspective of drug design (since a series of new drugs can be synthesized, which exhibit this interesting structural property that might affect their therapeutic effects).

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