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# Escape from PharmaZ: a Game to Boost Pharmacophore Learning through Immersive Augmented Reality

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**Abstract.** Pharmacophores are abstract descriptions of the properties of drug-like molecules that are necessary to understand how they interact with their biological target and hence, characterize their medical action. Mastering pharmacophores is essential for pharmaceutical science but this concept is very hard to grasp. This is mainly due to the difficulty of perceiving the three-dimensional aspect of pharmacophore models but also their combinatorial nature. We therefore designed *Escape from PharmaZ*, a hybrid serious game for undergraduate students. It is composed of a collaborative board game and a dedicated Augmented Reality (AR) smartphone application that allows the students to visualize and manipulate 3D molecular structures. The preliminary tests of this game, with 24 volunteers, show that it helps understand the pharmacophore concept, especially for novices in chemistry. The results also show that the game mechanics and the AR rendering help players better understand the nature of pharmacophore features and the importance of their spatial and combinatorial positioning.

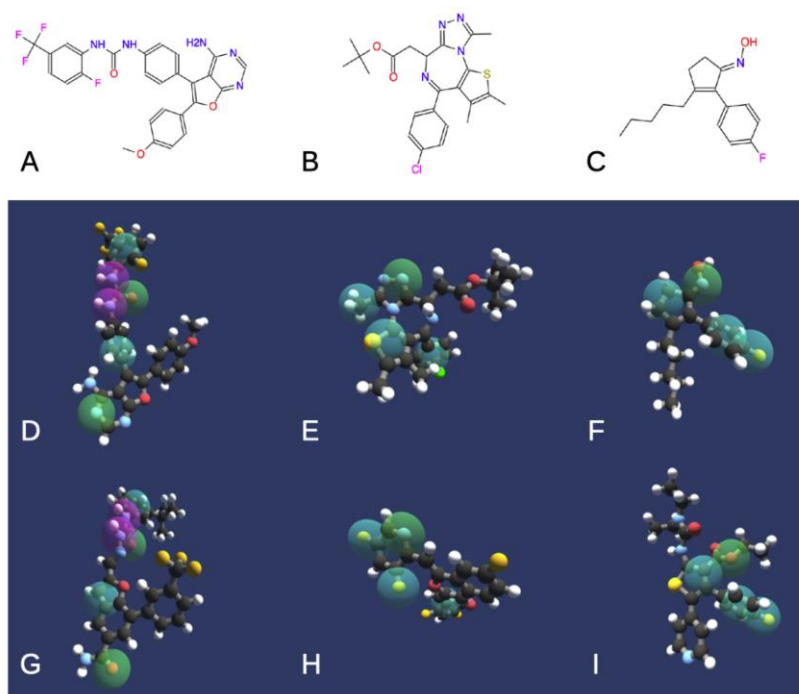
**Keywords:** serious games, molecules, pharmacophores, *in silico* drug design, collaborative games, augmented reality

## 1 Introduction

According to the International Union of Pure and Applied Chemistry, “a **pharmacophore** is an ensemble of steric and electronic features that are necessary to ensure the optimal supramolecular interactions with a specific biological target to trigger or block its biological response”. In other words, pharmacophores play a key role in the discovery of new active molecules for *in silico* drug design and is therefore taught in Pharmacy undergraduate curriculums. Yet, learning pharmacophores is very challenging for students. This is mainly due to two reasons.

The first is related to the difficulty to **identify the relevant combinations of pharmacophoric features** [1]. The main features are Aromatic, Hydrophobic, Negative Ionizable, Positive Ionizable, Hydrogen Bond Donor and Hydrogen Bond Acceptor, and are usually represented as colored spheres [2]. For example, in Figure 1, the representation of the F molecule shows that it bears three Hydrophobic features (cyan spheres) and one Hydrogen Bond Acceptor (green sphere).

The second challenge, related to mastering pharmacophores, is to **perceive their spatial dimension** [1]. Molecules are usually represented with schematic formulas (A, B and C in Figure 1). However, these formulas need to be mentally pictured as 3D models (D, E, F in Figure 1) to fully understand their molecular structure. Indeed, it is the combination of pharmacophoric features and their 3D position on the molecule that characterize the way this molecule interacts with its biological target, and hence, its action as a drug. For example, G shares the same therapeutic properties as D, because they present the same 3D arrangement of pharmacophoric features, even though they do not have the same formula. On the other hand, the molecules F and E have the same pharmacophoric features (three Hydrophobic features and one Hydrogen Bond Acceptor) but their relative positioning is different and they therefore differ in terms of pharmaceutical action. Visualizing the spatial distribution of pharmacophoric features is therefore particularly important to understand therapeutic equivalences.



**Fig. 1.** Molecule formulas (A-C) with their 3D representation (D-F, respectively). Other molecules that share the same pharmacophore model but not the same formula (G-I). Equivalences are shown in columns (D is equivalent to G, E to H and F to I).

In order to make pharmacophores easier to master, we designed a serious game, called *Escape from PharmaZ*. Our objective is to help undergraduate students learn how to identify the pharmacophoric features and practice mentally visualizing them in 3D with the help of a dedicated Augmented Reality (AR) smartphone application. This study aims to address the following key research question:

- RQ1: Can the game help understand the main pharmacophoric features and the fact that they need to be combined in a specific way to build a pharmacophore model?
- RQ2: Does the use of AR help understand the three-dimensional nature of pharmacophores and hence, their possible variability through molecular structures and dynamics?

To this end, the next section begins with a brief review of the current serious games and AR applications to teach molecular concepts. Section 3 presents *Escape from PharmaZ*. Section 4 discusses the preliminary study, the data collection method, the initial results and limitations. Finally, section 5 will conclude our research.

## 2 State of the Art

The use of **serious games** in education is becoming increasingly widespread, with applications in many fields. Their interest and added value have recently been the subject of a systematic literature review [3]. In the field of human health, many serious games are used for training, for informing the general public about common illnesses, motor rehabilitation, etc [4]. Chemistry and pharmacology are no exception, and there are many serious games applied to these fields [5, 6]. However, chemistry games are usually focused on combining atoms to create molecules, and rarely on 3D molecular structures themselves. For instance, recent games such as *Molecular Builder Laboratory* [7] and *Elementium* [8] use 2D visualizations. Nevertheless, other recent games address biomolecular interactions with physical or virtual 3D molecular representations: *Pangu* [9], *DocMolecules* that aims at teaching antihistamine drug action [10] and a Virtual Reality simulation dealing with enzyme catalysis [11]. However, to our knowledge, no serious game proposing a three-dimensional approach of the pharmacophore concept has yet been developed, even if the software developed by Frey [12] could be seen as a 2D premise to pharmacophores.

The use of **AR** has proven its effectiveness for STEM learning, particularly in the fields that need 3D representations such as anatomy [13]. Concerning Molecular Science and Chemistry, several research projects have recently shown that the use of 3D digital models that students can explore in AR, is a good way to help them understand complicated concepts [14]. In particular, tools such as the web platform *MoleculARweb* [15] propose AR illustrations of a wide range of chemistry concepts. This platform uses letters or QRcodes as markers for displaying the 3D models.

## 3 Serious Game Escape from PharmaZ

*Escape from PharmaZ* is a **collaborative game** for three groups of two players (students). The game also needs a game master, played by the teacher or a student,

## Escape from PharmaZ

with the help of an answer booklet. The game is intended to be used during a lab session, with approximately 16 students, followed by a debriefing session.

The game proposes a sci-fi setting in which the players are astronauts that have just crashed on an unknown planet (PharmaZ). Several of the crew members are gravely injured or sick because of the air breach. The players impersonate three healthy crew members (the astronaut pawns) that need to explore the planet to find local plants, animals or minerals that provide the right type of molecules for curing their fellow astronauts. The goal is to find molecules that are equivalent to terrestrial drugs (with an equivalent pharmacophore model). Players need to collaborate to find the appropriate molecules and bring them back to the spaceship, before the sun storms hit the planet in 40 minutes.

### 3.1 Game Material

*Escape from PharmaZ* is a **hybrid game**, composed of a **board game** (Figure 2) and a dedicated **smartphone application called *Nanoscope*** (Figure 3). The board game is shown in Figure 2 (A). It has 12 tiles (B) that represent the land of the planet PharmaZ that needs to be explored. Each team has a pawn (C) that shows the position of their astronaut and a control panel (D), placed in front of them. This control panel helps them remember the right terms for the pharmacophoric features and holds the two goal molecule cards (E) they are looking for.



**Fig. 2.** Escape From PharmaZ game material

The *Nanoscope* smartphone application is used to show the 3D pharmacophores, in AR. As shown in Figure 2, the tiles are initially placed with the landscape face up. During the game, the players can turn over the tile, on which their pawn is, to scan the resource face with *Nanoscope* and view the 3D pharmacophore (Figure 3).



**Fig. 3.** Nanoscope: dedicated smartphone application that shows the 3D pharmacophore model

### 3.2 Game Rules

At the beginning of the game, each team (two players per astronaut pawn) gets two goal cards that are placed on the control panel. These cards show the 2D molecular formulas of a terrestrial drug. Their objective is to find the alien molecule that shares an equivalent pharmacophore model. Before the first turn, they are encouraged to identify possible pharmacophoric features and mark them, with translucent tokens, on the goal molecule formulas (figure 2, E).

During their turn, players first move their pawn one or two spaces to an adjacent tile. They then turn the tile over, on its resource face, and scan it with *Nanoscope*. The AR technology enables the players to view the 3D pharmacophore model from all angles by simply turning the tile or moving their smartphone like a virtual magnifying glass. As show in the state of the art, this interaction should be very useful to understand the spatial distribution of the pharmacophoric features.

Once they have analyzed the 3D model, the players need to decide if this alien pharmacophore corresponds to one of the terrestrial molecules they are looking for. Remember, these goal molecules are only shown as a 2D molecular formula and the players will therefore have to imagine them in 3D. During this step, verbal exchanges are crucial within the team (Figure 4). If they decide that it does not correspond to one of their goal molecules, they place the tile back on the board. If they decide that it does correspond, they keep the tile and, during their next turn, must go back to the center of the board, where the spaceship crashed. Indeed, it is the central computer of the spaceship, personified by the game master, which will validate the correspondence with the help of the answer booklet. If the players are right, they validate their goal card. If the players are wrong, the game master can either reveal the exact pharmacophore model of the goal molecule or give them clues, like the number of a specific feature they should be looking for, depending on their level of expertise.

Note that if two or more astronauts are in the spaceship at the same time, they can argue if a proposed molecule is relevant or not and switch to another correspondence with their own goal molecules. The game ends after the 40 minutes limit or once the players have validated all their goal molecules.



Fig. 4. First test of Escape from PharmaZ

### 3.3 Important Game Mechanics

The game integrates several game mechanics to reach the target educational goals.

First of all, players are encouraged to **learn and use the appropriate vocabulary to designate pharmacophoric features**. The names of the main features are printed on the control panel (Figure 2, D) that is in front of them during the entire game. In addition, each team needs to name the right features and represent them with translucent tokens they place on a goal card (Figure 2, E) at the beginning of the game. Furthermore, each time they turn a tile and discover an alien molecule and its pharmacophore, team members should use the vocabulary again to decide whether the pharmacophore model could correspond to one of their goal molecules.

Secondly, the molecules used in the game were carefully selected to illustrate the fact that several 3D pharmacophore models could correspond to the same molecule. This should **encourage debate among the players and mobilize their knowledge about chemistry**. Furthermore, all the molecules in the game come from real scientific studies that are referenced in the answer booklet in the hopes that the players would want to learn more about them.

Thirdly, *Escape from PharmaZ* **encourages collaboration** between players. Indeed, in the game scenario, the radio system is broken and two teams can only communicate if their pawns are in the spaceship (center of the board) at the same tile. Since the objective of the game is for all the teams to find their goal molecules in less than 40 minutes, the players need to pay attention to the tiles turned by other teams and, if they believe the tile corresponds to one for their goal cards, they should meet up to discuss further similarities. These verbal exchanges should also help the teacher identify the difficulties students might still have to help them immediately or during the debriefing session. In an advanced version of the game, each crew member has specific skills (*e.g.* move faster, excavate faster) which encourages players to collaborate even more to take advantage of these skills.

Finally, the game is designed so that learners constantly need to compare 3D pharmacophore models to 2D molecular formulas. This should **train them to imagine molecules in 3D** and understand the three-dimensional specificity of pharmacophore models.



### 3.4 Game Design and Development

The game was designed by one pharmacy teacher and two chemistry experts with the help of one educational engineer, one graphic designer, one developer and two serious game experts who animated a professional training course [16]. The game design also relied on the expertise and experience of previous projects [9, 10].

The game material was made in the university fablab. The tiles were produced by laser etching on a cardboard-wood material and the pawns were made with the same technique on translucent plexiglass. Only the tokens were commercially purchased.

The *Nanoscope* application was developed with the *UnityMol* [10] software that displays molecules using *Unity 3D*. This solution allows high performance rendering. *Vuforia* was also used for the image recognition and AR rendering. It offers fast and efficient image recognition and allows to associate any mesh (in our case the 3D molecule computed by *UnityMol* from coordinates in the standard Protein Data Bank format) with any picture. This technology avoids using QRcodes that would have altered the game's esthetics and immersion.

## 4 Preliminary Experiment

### 4.1 Experimental Protocol

This preliminary experiment aimed at measuring the effectiveness of the game with a selection of volunteers and improving it before use in class planned next year.

Before the players tested the game, they were asked to answer a **questionnaire to determine their profile** (age, degree of expertise in pharmacophores, experience with games and technological devices and ease with tridimensional visualization) and **eight course questions** to measure their knowledge of pharmacophore concepts. These course questions could be answered by "yes", "no" or "I don't know" (examples in figure 5 and 6) for a maximum score of 8. After the game session, participants were asked the exact same course questions to measure if they had progressed. The participants also provided **written feedback** after the game, related to the rules, the control panel and AR.

**24 subjects participated**, in 5 sessions. They were between 15 and 57 years old with 15 males and 9 females. Their profiles varied: 6 university professors and/or researchers, 3 engineers or technicians, 8 master's degree or PhD students and postdoctoral fellows and 7 high-school students. The players' ease with tridimensional visualization of molecules is well distributed and a large majority are novices with pharmacophore concepts. Half of them frequently play board games and more than half are familiar with advanced technologies such as AR.

### 4.2 Results

A majority of players considered the rules of *Escape from PharmaZ* easy (67%) or very easy (21%) to understand. The duration of a game (40 minutes) was perceived as just right (71%) or rather short (17%).

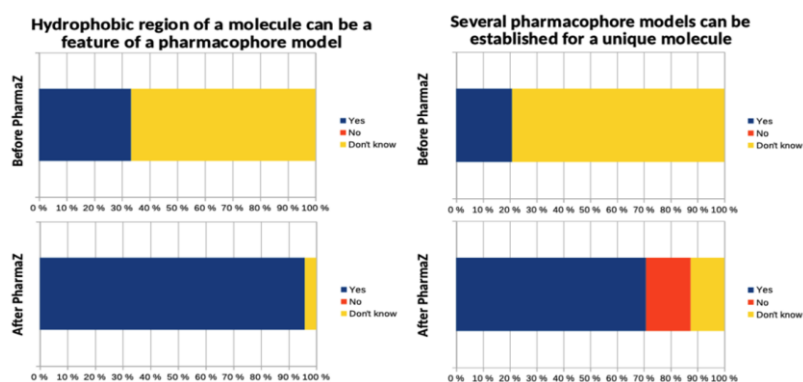
Furthermore, all the participants progressed on their knowledge score after the game with a final average score of 4.96/8 points with p-value<0.01 for high-school



## Escape from PharmaZ

students and  $p$ -value $<0.001$  for the older profiles. More interestingly, while there is a significant difference in the score between novices versus non-novices in chemistry before the game ( $p$ -value $<0.01$ ), no significant difference is measured between these populations after the game ( $p$ -value $>0.05$ ). This could show that *Escape from PharmaZ* is effective for learning pharmacophore because novices have reached a similar score to experts. In addition, by distinguishing the questions related to concepts that were directly integrated in the game (vocabulary of pharmacophoric features, geometry) from the questions related to concepts less frequently mobilized in the game, the progression is only clear for the first type of questions ( $p$ -value $<0.001$ ) while it seems less pronounced for the second type ( $p$ -value $>0.03$ ).

This preliminary study also provides some answers for the two research questions. For instance, the study shows a significant improvement of the rate of correct responses for questions related to **RQ1: Can the game help understand the main pharmacophoric features and the fact that they need to be combined in a specific way to build a pharmacophore model?** (Figure 5). In addition, players state that they used the vocabulary on the control panels always (25%) or frequently (54%). This points to the fact that the game helped them mobilize the right terms to describe pharmacophoric features during their verbal exchanges.



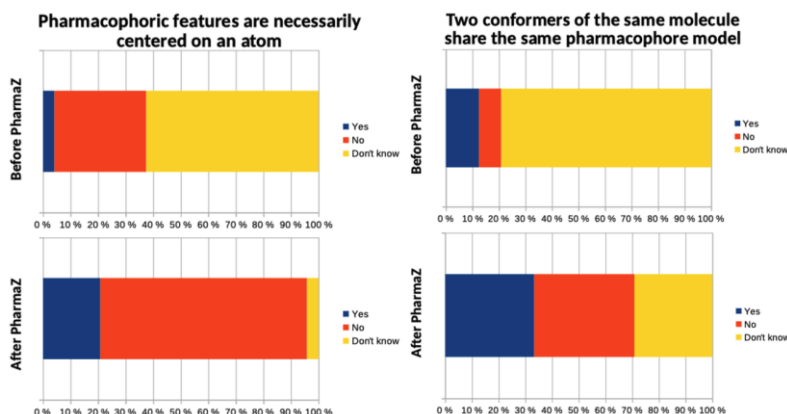
**Fig. 5.** Graph showing results for two questions related to RQ1 before and after the game. For both questions, the expected response was “yes” (in dark blue).

Concerning **RQ2: Does the use of AR help understand the three-dimensional nature of pharmacophores and hence, its possible variability through molecular structures and dynamics?**, this first study shows that 38% of players frequently described relative positions of features with geometric marks and also 38% did it a bit. In addition, the players clearly understood that a pharmacophoric feature can involve a group of atoms (Figure 6, left). However, the game did not seem to help understand the effect of dynamic geometrical changes of a molecule (Figure 6, right).

### 4.3 Limitations and Discussion

This preliminary experiment has several limitations. First of all, 24 participants are hardly enough to determine if the game is effective and to answer the research questions. In addition, classes had already finished at the time of the experiment so

the game was tested with volunteers that are not representative of the undergraduate students and the class setting the game will be used in. Nevertheless, this first experiment provided valuable feedback to improve the game. For example, we changed the colors of the spheres representing the pharmacophore features because they were too hard to distinguish and we added a “flip” button to the *Nanoscope* application that allows players to better view the 3D molecule from all sides.



**Fig. 6.** Graph showing results for two questions related to RQ2 before and after the game. For both questions the expected response was “no” (in red).

## 5 Conclusion

We designed *Escape from PharmaZ*, a hybrid serious game to familiarize undergraduate students with the concept of pharmacophores. The game exploits both the advantages of a classic multiplayer board game to provide a collaborative learning context, and the advantages of an Augmented Reality (AR) smartphone application to visualize and manipulate 3D molecules. The preliminary experiment, with 24 volunteers, shows that it helps them practice mentally visualizing 3D molecules to better understand the three-dimensional aspect of pharmacophores and helps them develop knowledge about pharmacophoric features. In particular, the comparison of answers to course questions shows that players, who were initially novice in pharmacophore concepts, could not be distinguished from experts after the game.

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