Illustrating the Challenge of Medicinal Chemistry Research through an Interactive Activity: The Drug Discovery Game

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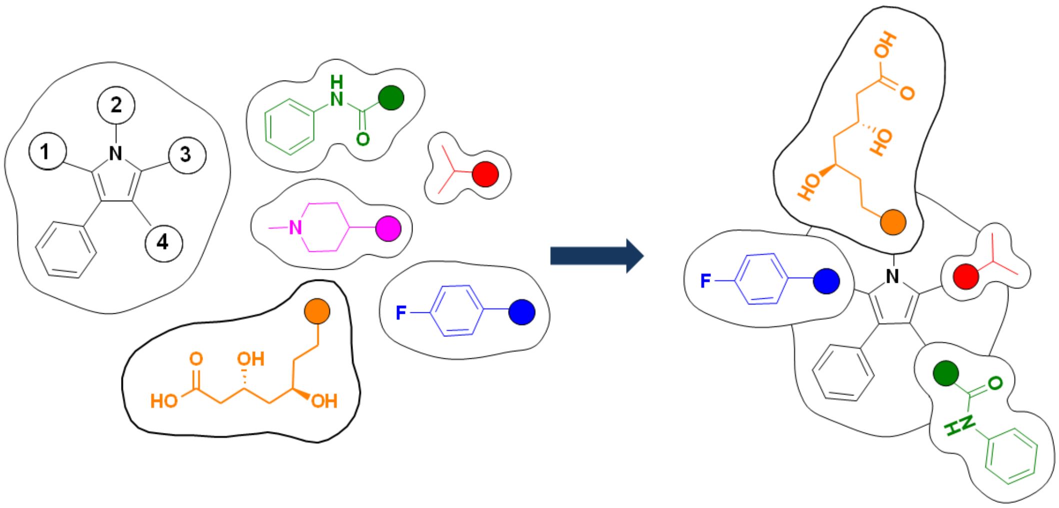
ABSTRACT

The Drug Discovery Game is an engaging, interactive demonstration that serves as a springboard to a discussion of the methods used in modern medicinal chemistry. Students (playing the role of medicinal chemists) are given seed capital money and challenged to invent a small molecule pharmaceutical starting with a Velcro-equipped scaffold and Velcro-equipped molecular fragments. The teacher (playing the role of a biologist running an assay) provides logical feedback after each student's attempt that guides the student toward the solution. The game simulates the workflow of medicinal chemistry research and launches discussions of such topics as the methods of modern drug invention, the cost of pharmaceuticals, molecular structure and design, and structure-activity relationships.

ABSTRACT GRAPHIC



Today's students will face challenges if they begin careers as medicinal chemists in the pharmaceutical/biotech industry. For instance, until 2014 the number of new molecular entities approved by the FDA each year remained mostly flat while the cost of research and development increased tremendously.[1,2] Although FDA approvals increased in 2014 and 2015, a recent estimate of the cost to discover and develop a single new drug exceeded two billion dollars.[3] Furthermore, when the cost of research and development on compounds that fail to gain approval is included, it has been estimated that drug companies are spending at least four billion dollars for each new molecular entity that they take to market.[4] Indeed, today's graduating students will be required to create highly innovative solutions if they wish to cost effectively develop treatments for complex diseases such as Alzheimer's disease or cancer.

Even students who will not enter a career in the pharmaceutical industry will be impacted by the challenges it faces. Current political debate has focused on the price of new, innovative pharmaceuticals.[5,6] Students are ill-equipped to enter such a debate without a general knowledge of the ongoing scientific methods employed in the hunt for new pharmaceuticals and the process by which a new drug is approved by the FDA as safe and effective.

The game described herein aims to educate the student about the modern interdisciplinary approach to pharmaceutical research by presenting the early stage of drug discovery for what it is: a complex but very interesting puzzle. While playing this game, the students take on the role of medicinal chemists and attempt to invent a pharmaceutical compound to treat a particular disease. As chemists, they "synthesize" molecules by combining possible molecular fragments with a molecular scaffold. The teacher takes on the role of the biologist and provides results of a biological assay for the synthesized molecules as feedback to the medicinal chemist students. The feedback loop of design, chemical synthesis, biological testing, and redesign common in pharmaceutical research is thereby demonstrated.

The specific goals of the activity are:

- Simulation of the medicinal chemist's trial and error workflow that leads to the development of structure-activity relationships (SAR). [7]
- Illustration of the challenge of drug discovery by emphasizing the vastness of medicinal chemical space (with estimates as high as 10^{60} possibilities).[8,9]
- Introduction of the concept that drug discovery research requires a significant investment.[4] Currently, it is estimated that the cost to invent and develop a new pharmaceutical treatment is $2.56 billion.[3]

Ultimately, the game serves as a springboard for a discussion of the entire process currently used in modern pharmaceutical drug discovery and highlights how challenging discovering a new, safe, effective drug treatment can be. The game has been employed as an educational outreach activity for high school and middle school students during "Take Your Child to Work Day" at a biotechnology company and utilized during introductory lessons in organic and medicinal chemistry on an undergraduate level.

Games designed to introduce the methods of medicinal chemistry are rare. Indeed, we are aware of only one game, a computer game published in 1982,[10] aimed at introducing the interplay between synthetic chemistry and biological assay results that is essential to the optimization of medicinal compounds.

SET-UP

At the onset of the game, students are given a central molecular scaffold on which to build a new drug (Figure 1). The scaffold consists of a structure cut from cardstock with three or four of the outer molecular functional groups replaced with numerical "blanks". To each "blank" is affixed a small bit of soft Velcro.

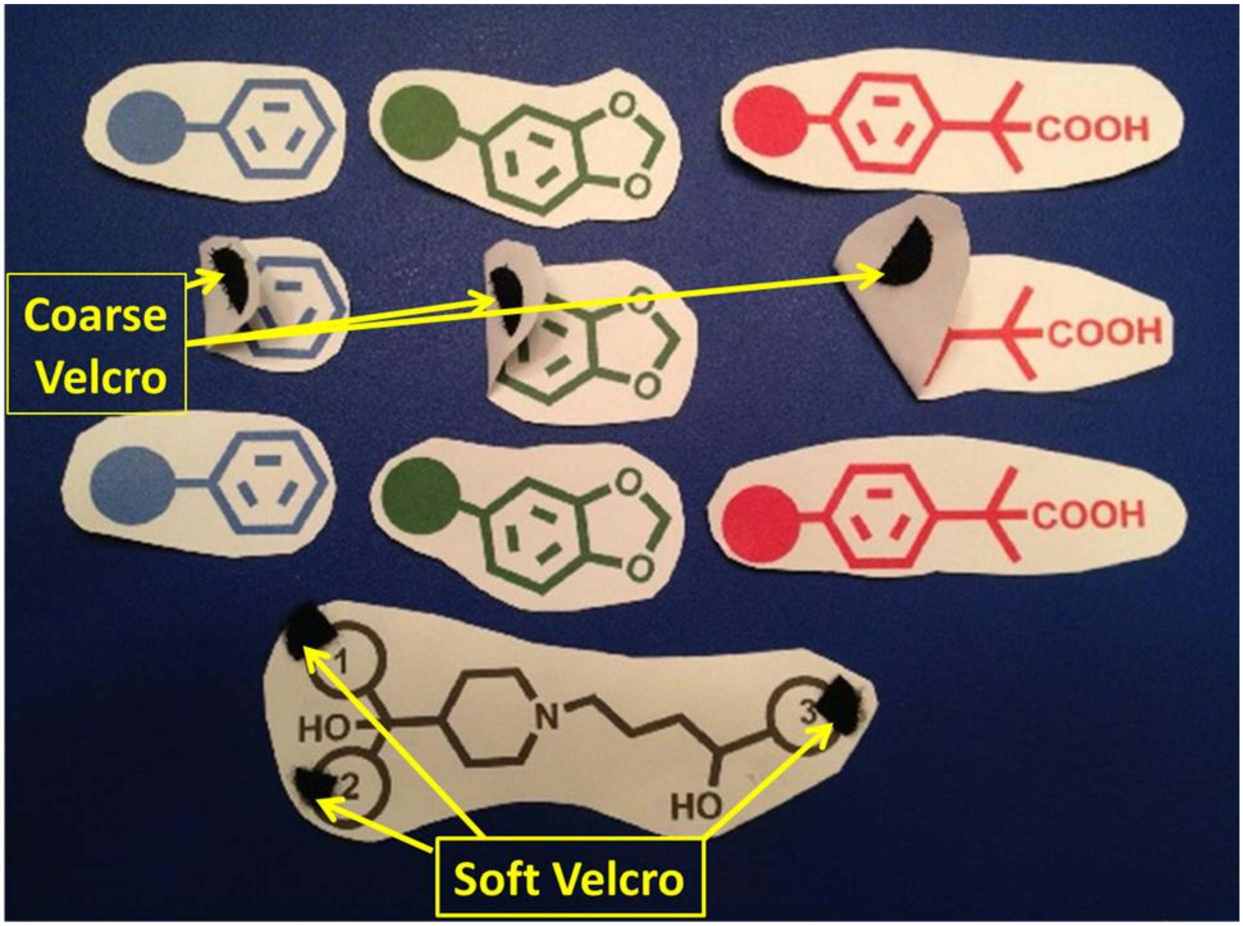


Figure 1. Game Pieces for the Allegra Puzzle. Coarse Velcro is attached to the underside of each of the blue, green, and red molecular fragments. (The molecular fragments on the second row are purposefully bent to show the coarse Velcro underneath.) The molecular scaffold is shown at the bottom in black. Soft Velcro is attached to the three attachment points on the face of the molecular scaffold as shown.

To fill in the blanks, the student is supplied multiple "molecular fragments" or pieces to choose from. To the underside of each "molecular fragment" is affixed a small piece of coarse Velcro (Figure 1). Hence, the "molecular fragment" can be readily attached to the "scaffold" via the Velcro, creating a molecule. Velcro enables quick detachment and exchange of the various functional groups, thereby allowing quick "synthesis" of molecules. Cardstock and Velcro can be obtained at any office supply store.

In addition to the molecular building blocks, the students are also given $700 (7 X $100 bills) in play start-up money. Students are told that they have just started a drug discovery company attempting to find a treatment for a particular disease. The money is needed to complete the drug discovery effort and will be spent on such things as paying scientists, buying equipment, renting laboratory space, etc. Play money can be obtained at any dollar store.

THE RULES

The rules of the game are similar to the popular game “Mastermind”. The teacher plays the role of the biologist conducting an assay and also fills the role of the “Mastermind”: the person who knows the answer to the puzzle. The students will try to solve the puzzle by playing the role of medicinal chemists. The chemist/student assembles a molecule by attaching “molecular fragments” to the Velcro attachment points on the “scaffold”. An assembled molecule is presented to the biologist/teacher for evaluation in the assay. The biologist/teacher tells the chemist/student how many of the “molecular fragments” in the molecule are correct and how many are in the correct Velcro space on the scaffold. (The biologist/teacher does *not* tell the chemist *which* pieces are correct or *which* pieces are in the correct place.) For example, the biologist will say “The assay indicates that your molecule has two correct pieces but only one is in the correct place.” This is the only feedback given to the student/chemist. The chemist/student must use that knowledge (plus his or her skills of logic) to prepare a second guess.

Each piece can be used more than once in the puzzle. Therefore, it is important that each student have access to sufficient copies of each molecular fragment to fill all of the Velcro spots on the scaffold.

Each time the student makes a guess, he/she must pay $100 of the play money. It is explained that drug discovery requires a significant investment. For example, chemicals to synthesize the compounds must be purchased, reagents and robotic instruments are required for the biological assay, laboratory space requires rent payments, and the scientists must be paid. Game play continues in an interactive fashion with the chemists paying $100 per guess, guessing by presenting their designed molecule, and receiving feedback from the biologist until the student logically deduces the correct structure. Each chemist who discovers the drug is rewarded with a $500 payout for his/her discovery and asked to sit quietly until the others finish. Play continues until all the students have the satisfaction of "discovering the drug".

This demonstration has been conducted in a room with ten to fifteen "chemists" (students) and three "biologists" (the teacher with a few student volunteers). In larger classrooms of up to thirty students, the game has been played with students paired into teams of two or three.

GAME PLAY

An example of the game is provided in Table 1. In this example, the students are told their goal is to synthesize a treatment for allergy. The molecule they will discover is fexofenadine sold under the commonly known trade name Allegra. At the start of the game (Game Start in Table 1), the students are provided with a black-colored core scaffold and three each of the green (piperonyl), red (4-(2-carboxypropan-2-yl)phenyl), and blue (phenyl) molecular fragments. A representative interaction between the student and teacher is outlined throughout the body of Table 1. Note that the logical progression of the student's educated guesses is in direct response to the feedback given by the biologist/teacher.

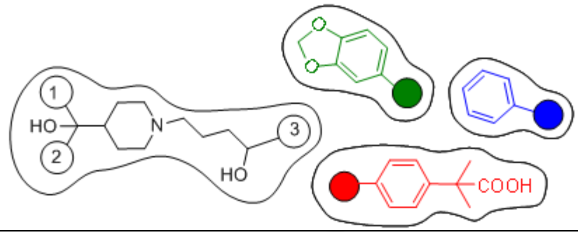
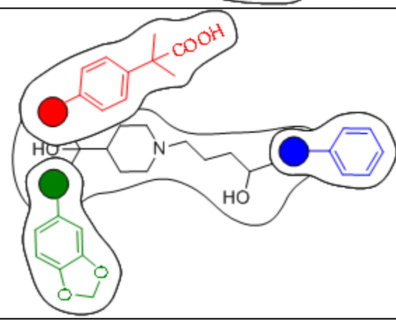
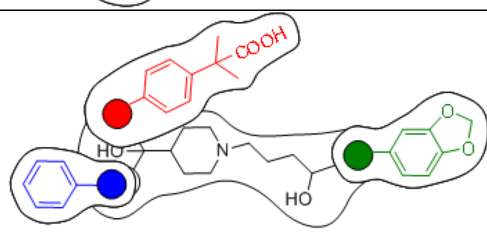
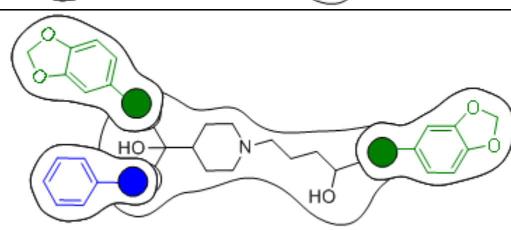
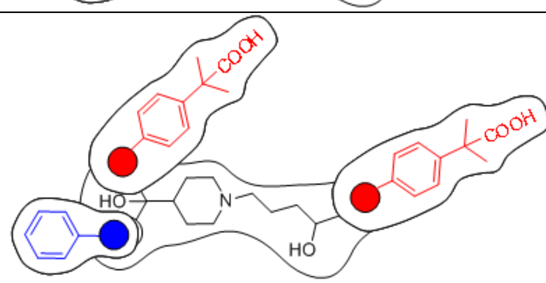
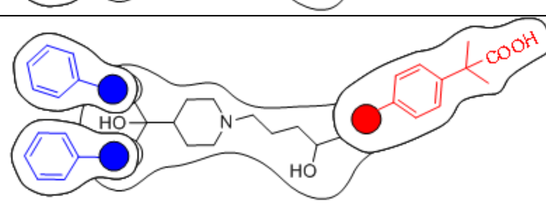
Guess Number	Molecule Presented by Chemist (Student)	Response by Biologist (Teacher)
Game Start		**Scaffold (in black) and unassembled pieces prior to game start. (Three of each of the color pieces are provided.)**
1		**Two pieces are correct. None are in the correct place.**
2		**Two pieces are correct. One is in the correct place.**
3		**One piece is correct. One is in the correct place.**
4		**Two pieces are correct. Two are in the correct place.**
5		**All pieces are correctly placed. The drug "synthesized" is Allegra.**

Table 1. Example of game play using an Allegra puzzle.

To make each of the guesses outlined in Table 1, the chemist paid $100 of the play money. In this example the student guessed five times and therefore spent $500. The reward of $500 for discovering the drug covered the cost of the drug discovery effort and the student broke even.

DISCUSSION

The students usually complete three puzzles of increasing difficulty during this activity. Each puzzle is followed by a discussion to emphasize one of the goals of the lesson. After completion of the first puzzle, Allegra, it is explained to the students that drugs are usually discovered through an interactive exchange between chemists and biologists. Optimization of an initial hit structure follows a trial and error path where chemists submit compounds for biological testing in a similar manner to the game being played. The biologist uses an assay to determine the potency of the compound and feeds that data back to the chemist. With this information, the chemist can redesign the molecule to hopefully synthesize a more potent molecule for a second round of testing. This cycle of "synthesis followed by assay" continues until the optimal compound is obtained as an effective treatment for the disease. The role that molecular structure plays on the observed biological activity is emphasized during this discussion.

A second more difficult puzzle is played next. Again, a scaffold containing three Velcro blanks is employed, but six possible molecular pieces are given out. The number of combinations for this puzzle is 216 (6^3; 6 X 6 X 6). A puzzle of this level of complexity, Amoxicillin, is shown in the top row of Table 2. After completion of the second, more difficult puzzle, the students are prepared for a discussion of the mathematics behind the difficulty of the puzzles. The number of combinations is dictated by the number of pieces and the number of empty slots on the scaffold. The formula for the number of combinations is the number of molecular pieces to the power of the number of Velcro blanks. Once the students understand the limited number of combinations possible in their puzzles, a discussion of the enormous mathematical possibilities facing the medicinal chemist commences. It has been estimated[8] that the possible number of drug-like molecules is somewhere between 10^{23} and 10^{180} with the number 10^{60} often quoted in the literature.[9] Students are usually amazed by the magnitude of the problem facing the medicinal chemist at this point since the puzzles they are struggling with have so few possible solutions in comparison to this large number. Usually, the demonstration ends with a puzzle of higher complexity. The puzzle in the bottom row of Table 2, Lipitor (atorvastatin), is an example with this level of difficulty (625 combinations possible).

After the students solve the most difficult puzzle, a discussion of the cost of drug research begins. Students are asked to review the amount of play money they have at the end of the game and to consider the cumulative cost of each step along the path of developing a new pharmaceutical. It is explained that the game the students have played mimics only one portion of the early stage of drug research. The later steps in drug development are described including animal testing, pre-clinical toxicology, and the three main phases of human clinical trials. The accumulated expenditure of each step of the development pathway leads to a current estimate of the cost to bring a new pharmaceutical to market of $2.56 billion.[3]

The Drug Discovery Game was developed as an outreach activity for middle school and high school students during “Take Your Child to Work Day” at a biotechnology company where it was well received by the student participants. Additionally, adult non-scientists who attended the activity commented that they now understood the workflow ongoing at the company. The game has subsequently been utilized as an activity to accompany an introductory organic chemistry unit within a general chemistry course

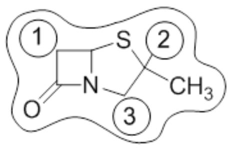
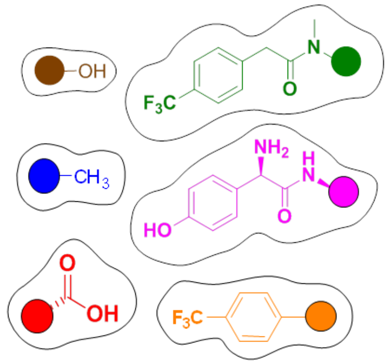
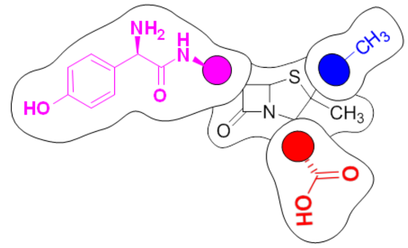
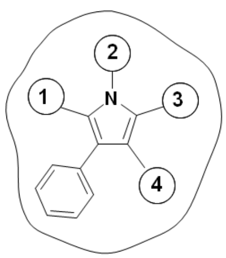
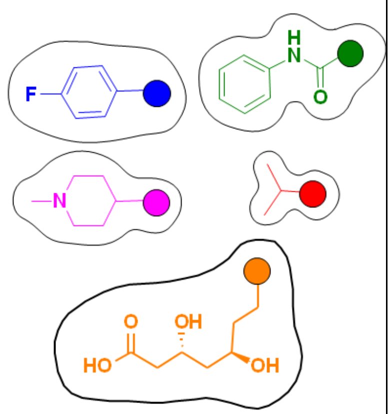
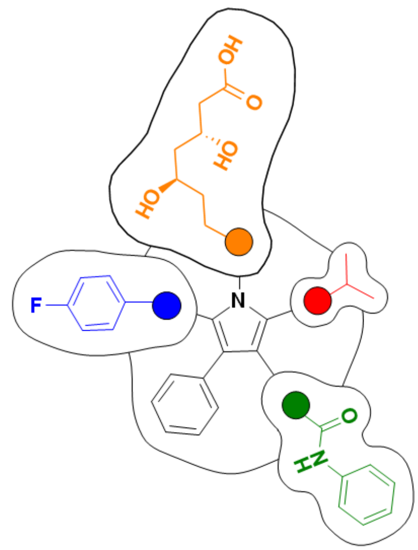
Scaffold	Molecule Fragment Choices	Completed Drug
		 Amoxicillin
		 Lipitor

Table 2: Top Row: Amoxicillin Puzzle with 216 combinations possible (6^3; 6 X 6 X 6). Second Row: Lipitor Puzzle with 625 combinations possible (5^4; 5 X 5 X 5 X 5).

emphasizing the utility of organic chemistry and basic molecular structure. The activity has also been used in conjunction with an introductory medicinal chemistry course. The students remained engaged throughout the entire activity, as the game portion enticed them to listen during the interspersed short discussions on the drug discovery process.

Each time the activity has been performed there have been multiple questions on pharmaceutical research from the students, indicating that the activity enhanced their curiosity about medicinal chemistry.

CONCLUSION

The Drug Discovery Game is an engaging, interactive demonstration that provides a launching point to teach the methods of modern drug discovery. The game focuses on the early stage of drug invention by highlighting the interaction between medicinal chemists and biologists as molecules are designed and assayed. The challenge of synthesizing a properly optimized pharmaceutical is emphasized through a comparison of the vast number (10^{60}) of possible drug-like molecules with the small number of possible combinations (≤625) for solving the simplistic puzzles in the game. The use of play money emphasizes the costs of research and opens a discussion of the increasing cost of pharmaceuticals. Finally, the presentation of drug discovery as a puzzle to be solved will hopefully entice students to take up the challenge and bring fresh innovation to medicinal chemistry.

ACKNOWLEDGMENTS

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