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# LigBRs: Automated Software for the Creation of Chemical Libraries.

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## ABSTRACT

**Background:** Molecular and computational modeling play a crucial role in designing new drug candidates and optimizing treatments for neglected diseases such as Chagas disease and leishmaniasis. Among these strategies, Ligand-Based Drug Design (LBDD) uses known bioactive compounds as starting points for creating novel candidates, while Fragment-Based Drug Design (FBDD) assembles simple molecular fragments to construct more complex bioactive molecules. A key approach within FBDD is fragment growing, where fragments are modified to enhance interactions with biological targets. This work introduces "Ligands by Brute Force Substituent Replacement" (LigBRs)—software developed in Python that generates new molecules by systematically combining a core structure with various fragments. LigBRs replaces hydrogen atoms with these fragments at different positions, ensuring the three-dimensional integrity of the resulting molecules is preserved.

**Objectives**: The main objective of this work was to develop software with a graphical user interface (GUI) for constructing chemical libraries of ligands using the Fragment Growing approach to generate molecules while preserving conformational integrity. The software aims to provide an intuitive and user-friendly interface for end users. It employs Fragment-Based Drug Design (FBDD) methodologies and supports the processing of Structure-Data Files (SDF) and Tripos Mol2 Files. Additionally, it allows users to perform hydrogen substitutions systematically or selectively during molecule construction. The program generates high-precision 3D molecular structures and optimizes the resulting compounds for energetically favorable conformations.

**Methodology:** The project was developed in Python (version 3.11.4) using a combination of object-oriented and structured programming to create the LIGBRs software. Molecular editing utilized the Open Babel and RDKit libraries, with RDKit generating 2D representations of the molecular core and indicating positions for hydrogen substitution. NumPy was used for numerical data manipulation, and the graphical interface was designed with Tkinter, while development was conducted in VSCode and IDLE.The software supports both .mol2 and .sdf files, organizing molecular fragments into lists for easy manipulation. The core and fragments are aligned using iterative loops to connect structures via hydrogen atoms. Bond creation is managed by the AddBond() function from Open Babel, while the DeleteAtom() function removes central hydrogen atoms. Molecular conformations are optimized with RDKit's Merck Molecular Force Field (MMFF) for stability. Users run the program by inputting files for the core and fragment library, defining combination parameters, and saving the generated molecules in a specified folder.

**Results and discussion**: Scientific research underscores the vital role of molecular modeling in predicting the pharmacological properties and toxicities of bioactive compounds. This approach facilitates structural analysis of drug candidates and predicts the intermolecular interactions crucial for developing new compounds. The Ligands by Brute Force Substituent Replacement (LigBRs) software employs this methodology, allowing the creation of chemical libraries with three-dimensional bioactive molecules without quantity limits. It does this by substituting hydrogens at specific positions and linking molecular fragments to a core from a pre-existing library.With multiple user-friendly interfaces, LigBRs simplifies the selection and handling of .mol2 and .sdf files, ensuring intuitive and efficient user interaction.

**Conclusion:** Developed in Python using structured and object-oriented programming, the software generates new molecules by combining molecular fragments with core structures, ensuring conformational integrity within the Fragment-Based Drug Design (FBDD) framework. Future studies may explore further optimizations to enhance conformational quality.