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NeuroClick: software for mimicking click reaction to generate drug-like molecules permeating the blood–brain barrier

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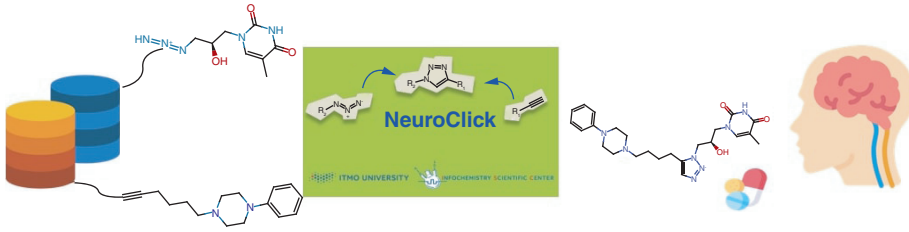
Background: Traditional methods for chemical library generation in virtual screening often impose limitations on the accessible chemical space or produce synthetically irrelevant structures. Incorporating common chemical reactions into generative algorithms could offer significant benefits. **Materials & methods:** In this study, we developed NeuroClick, a graphical user interface software designed to perform in silico azide–alkyne cycloaddition, a widely utilized synthetic approach in modern medicinal chemistry. **Results & conclusion:** NeuroClick facilitates the generation and filtering of large combinatorial libraries at a remarkable rate of 10,000 molecules per minute. Moreover, the generated products can be filtered to identify subsets of pharmaceutically relevant compounds based on Lipinski's rule of five and blood–brain barrier permeability prediction. We demonstrate the utility of NeuroClick by generating and filtering several thousand molecules for dopamine D3 receptor ligand screening.

Graphical abstract:



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Keywords: blood–brain barrier • chemoinformatics • click chemistry • library design • virtual screening

In silico organic synthesis and virtual screening of novel drug-like molecules comprise a vast and rapidly developing area seeking alternatives to time-consuming and resource-intensive experimental screening. A particular task within rational drug design and discovery is the generation of large libraries of chemical compounds comprising hundreds of thousands or even millions of small organic molecules. However, the libraries for *in silico* drug discovery are mainly obtained from existing libraries of synthesized or hypothetical compounds and with the help of generative models and other artificial intelligence methods [1,2]. Indeed, the application of existing libraries can limit the chemical space available for screening, and generative models are prone to yielding synthetically irrelevant compounds. A better solution can be found in the transfer of combinatorial organic synthesis of a chemical library into a virtual environment. This allows one to create libraries of compounds that are relevant to a specific screening task while maintaining the synthetic availability of the compounds under study [3].

In this work, we focus on the azide–alkyne cycloaddition reaction, one of the most famous and most important click reactions. In chemical synthesis, click chemistry refers to a class of straightforward atom economy reactions that are frequently employed to combine two preferred molecular entities. Click reactions have a number of

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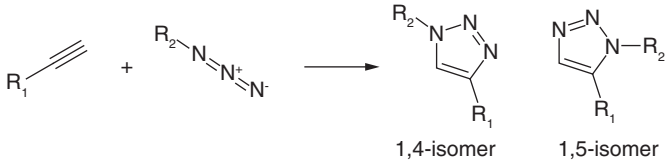


Figure 1. The versatile regioselectivity of azide–alkyne cycloaddition click reaction. A temperature-driven reaction usually yields a mixture of regioisomers, whereas a copper-catalyzed reaction controls for 1,4-isomer and ruthenium catalysis leads to the primary formation of 1,5-isomer. Visualized based on [5].

advantages and are widely recognized as a prominent synthetic approach in modern medicinal chemistry. They are fast, highly selective and easily performed and can lead to great structural diversity in high yields [4]. Although azide–alkyne cycloaddition has numerous variations and applications, we focus on intramolecular reaction, as a process limited within the structure of a single molecule, with controlled regioselectivity to merge reagents featuring diverse functionalities, which is particularly relevant in the context of combinatorial synthesis (Figure 1) [5].

Our research was aimed at finding new drug-like molecules that could permeate the blood–brain barrier (BBB). The BBB is a semipermeable barrier that keeps undesirable substances out of the CNS and controls the flow of chemicals, metabolites and biologically active substances from the blood to the brain. Chemical compounds that overcome the BBB have potential applications in the treatment of diseases of the CNS and brain, including neurodegenerative diseases, addictions of various kinds, depression and brain cancer [6]. A recent study has shown that compounds obtained in the click reaction of azide–alkyne cycloaddition (1,2,3-triazoles) have great potential as inhibitors of the dopamine receptor [7].

The 1,2,3-triazoles are heterocyclic molecules with a five-membered unsaturated ring system with six electrons comprising two carbon atoms and three nitrogen atoms [8]. When employing azide–alkyne cycloaddition in library design, it is important to keep in mind certain issues, such as alkyne homocoupling [9], copper toxicity *in vivo* [10], triazoles acting as inhibitors or substrates of CYP isoenzymes with particular side effects [11] and association of triazoles with hepatotoxicity [12]. Regardless of these negative aspects, click chemistry is still a powerful tool for drug design, and rational use of triazoles provides promising compounds for medicinal chemistry as a result of their antimicrobial, antiviral, antitubercular, anticancer, anticonvulsant, analgesic, antioxidant, anti-inflammatory and antidepressant activities [13–18].

Experimentally, the click chemistry approach offers a convenient combinatorial synthesis method by employing alkyne and azide molecules, resulting in the generation of a wide array of highly diverse chemical structures. Our objective was to develop an innovative algorithm, serving as standalone software, leveraging the click reaction. This algorithm translates click chemistry into virtual screening protocols by generating 1,2,3-triazole compound libraries from a specified set of reagent Simplified Molecular Input Line Entry System (SMILES) [19]. The SMILES notation allows a user to represent a chemical structure in a computer-readable way. Atoms are represented by the standard chemical element abbreviation, and single, double and triple bonds are represented by the symbols -, = and #, respectively (more details regarding SMILES rules can be obtained from the US Environmental Protection Agency [20]). In addition, the program was enhanced with druggability and BBB permeation analyzer modules based on Lipinski's rule of five [21] and blood–brain partitioning coefficient (logBB) to assess compound pharmacokinetics. The logBB is the logarithmic ratio of the total concentration of a compound in the brain and in plasma or whole blood

$$logBB = lg\frac{C_{brain}}{C_{plasma}}$$

where C_{brain} is the drug concentration in the brain and C_{plasma} is the drug concentration in blood plasma.

Our unique software is the only program available for the scientific community that can perform click chemistry with subsequent druggability and BBB permeation analysis. NeuroClick data processing is extremely fast and efficient because of the highly optimized novel algorithm designed by our group [22]. The AutoClickChem program, originally developed by Durrant and McCammon, is now considered outdated for performing click reactions [23]. However, this tool has a number of significant drawbacks and is considered outdated (Table 1). AutoClickChem does not provide a user-friendly graphical interface, which may limit users to researchers familiar with terminal tools. The application is also written in Python 2, which stopped being supported 1 January 2020 [24]. Last but not least, AutoClickChem lacks the option to filter reaction products by drug-likeness or physicochemical parameters. As for

Table 1. Comparison of AutoClickChem and NeuroClick.

Application	Free†	Python version	Data format	Reaction type	Convenient distribution	Lipinski filter	logBB filter	GUI	Built-in library visualization
AutoClickChem	+	2	PDB	Multiple click reactions	-/+	-	-	-	3D
NeuroClick	+	3	SMILES	Azide–alkyne cycloaddition only	+	+	+	+	2D

†Software is available free of charge.
GUI: Graphical user interface; PDB: Protein Data Bank; SMILES: Simplified Molecular Input Line Entry System.

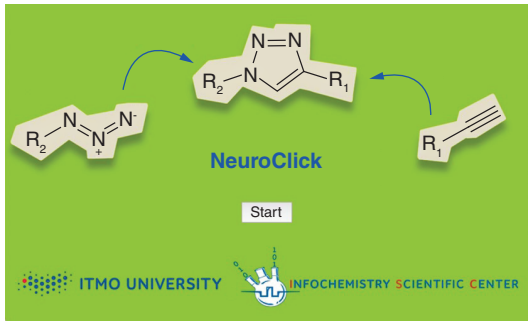


Figure 2. Home screen of the NeuroClick application.

NeuroClick, we aimed to equip the application with an intuitive graphical user interface, which makes it convenient to use without any special instructions or skills. For ease of distribution, an executable program file has been compiled, which allows one to run NeuroClick without any extra installations or builds. Unlike AutoClickChem, which works with Protein Data Bank files and provides 3D visualization of molecules, NeuroClick was designed to work with data in the SMILES format, increasing the computational speed exponentially. The SMILES string format is considered to be more convenient in the context of large chemical libraries, as it is lightweight and supported by most modern chemical databases [25–27]. SMILES data can be easily copied or downloaded from databases and pasted into NeuroClick without any preprocessing. In addition, data in SMILES format can be easily converted to Protein Data Bank or other 3D formats using free applications (e.g., Open Babel [28]).

It is also noteworthy to mention other software tools like the SmiLib graphical user interface application. Specifically designed to work with the SMILES format, SmiLib is tailored for generating virtual libraries through combinatorial enumeration, with applications beyond just click chemistry [29]. However, the compounds for the reaction must be prelabeled by users manually, which limits the performance and convenience of this program.

Design & implementation

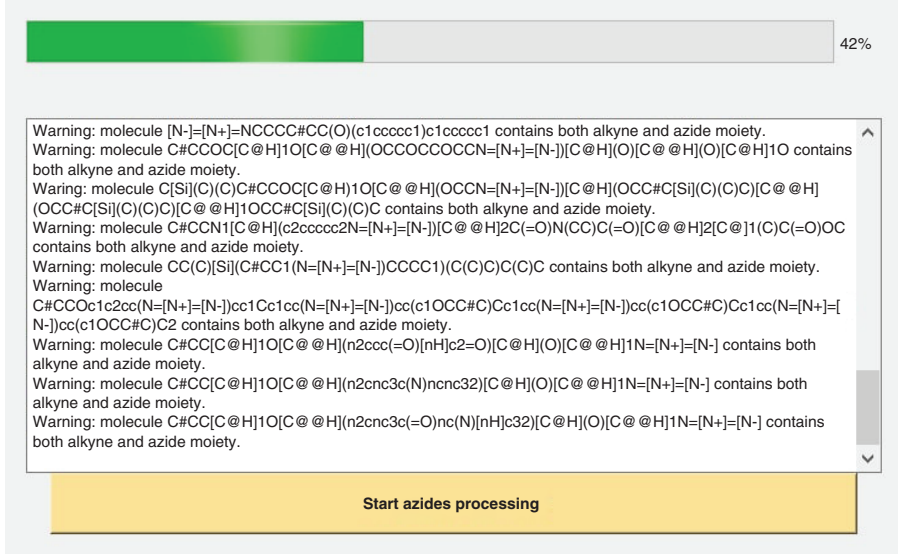
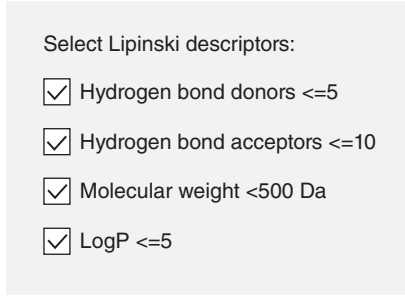
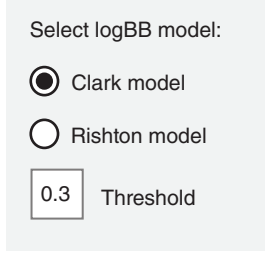
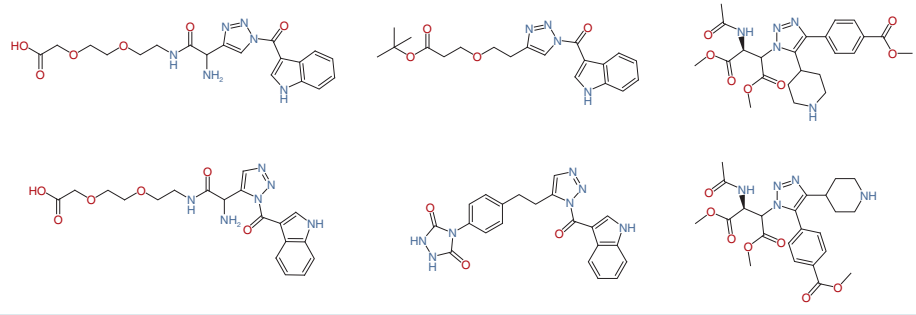
The main functionality of the program was written using the RDKit 2022.3.1 library of the Python programming language. The library provides a wide range of features for handling chemical data, including checking the correctness of entered formulas, calculating various chemical and physicochemical parameters and drawing molecules [30]. For representation of molecules, we chose a widely utilized SMILES notation that is conveniently handled by RDKit. The graphical interface was implemented using the Python library PyQt5 v5.15.6. The home screen of the application is shown in Figure 2.

First, the user uploads the azides. Data can be entered from the keyboard or uploaded from a file on the local computer. The program processes the input by filtering out the molecules that do not contain an azide group, have damaged SMILES not recognized properly by RDKit, as well as the molecules that contain both azide and alkyne moiety (for those an oligomerization occurs and no clear product can be provided). SMILES containing multiple molecular species are also discarded as they are irrelevant for virtual screening.

In the second step, the user does the same with alkynes, which are processed by similar rules. The logs are provided to describe which compounds were successfully processed and which were filtered out and why. The program rejects molecules containing more than one functional (i.e., azide or alkyne) group because in this case the generation of reaction products can take a long time, significantly slowing down the library generation process.

The following options are provided for click reaction: generation of 1,4- or 1,5-isomers or both and processing of internal alkynes (since the triazole products for internal alkynes cannot be assigned 1,4- or 1,5-isomers, it is logical

Table 2. Different stages of NeuroClick molecur processing performance.

Stage	Illustration
Azide processing	
Lipinski selection	
logBB selection	
Visualization	

to either generate or ignore both). Various stages of NeuroClick molecular processing performance are presented in Table 2.

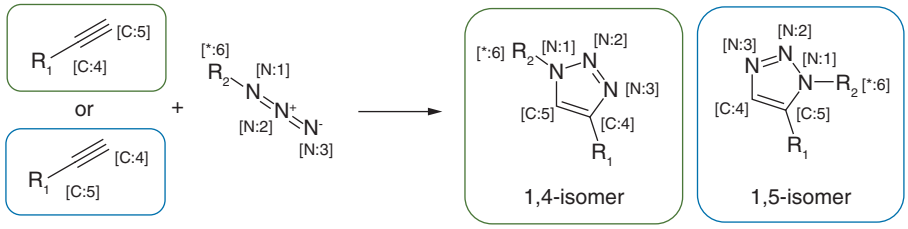


Figure 3. Reaction scheme illustrating Simplified Molecular Input Line Entry System arbitrary target specification pattern for click reaction producing both isomers. Atom tags from the pattern are placed near the respective atoms to illustrate the pattern logic.

Table 3. Simplified Molecular Input Line Entry System arbitrary target specification patterns and isomers generated from them.

Pattern	Product isomer
[*:6][N:1]=[N:2]=[N:3].[#6:7][C:4]#[C:5]>>[*:6][N:1]([N:2]=[N:3]1)[C:5]=[C:4]1[#6:7]	1,4
[*:6][N:1]=[N:2]=[N:3].[#6:7][C:4]#[C:5]>>[*:6][N:1]1[N:2]=[N:3][C:4]=[C:5]1[#6:7]	1,5
[*:6][N:1]=[N:2]=[N:3].[C:4]#[C:5]>>[*:6][N:1]1[N:2]=[N:3][C:4]=[C:5]1	Both

The user can optionally select Lipinski descriptors based on which reaction products will be filtered. Relevant pharmaceuticals tend to satisfy four criteria: molecular weight of less than 500 Da, octanol–water partition coefficient (ClogP) that does not exceed 5, hydrogen bond donors of no more than five and hydrogen bond acceptors of no more than ten.

Additionally, there is an option for molecule filtering by the logBB value, which is a measure of permeability through the BBB [31,32]. Additionally, users have the option to filter molecules based on their logBB value, a measure of permeability through the blood-brain barrier (BBB) [31,32]. A higher logBB value indicates easier diffusion through the BBB. By default, the threshold for logBB is set to 0.3, although users can customize this threshold based on relevant research findings [33,34]. All molecules that have a logBB value below the specified threshold are filtered out. For the logBB calculation, one can specify the models from Clark [35] or Rishton *et al.* [36]. The total polar surface area (TPSA) of a compound is a measure of its polar surface area, representing the sum of the contributions of polar atoms (typically oxygen and nitrogen) and their attached hydrogen atoms.

$$logBB_{Clark} = 0.152 \cdot \mathrm{ClogP} - 0.0148 \cdot \mathrm{TPSA} + 0.139$$

$$logBB_{Rishton} = 0.155 \cdot \mathrm{ClogP} - 0.01 \cdot \mathrm{TPSA} + 0.164$$

The *in silico* click reaction is implemented through SMILES arbitrary target specification reaction patterns in RDKit (Figure 3 & Table 3). SMILES arbitrary target specification is an extension of SMILES that is used for substructure search and definition of molecular patterns. With differing levels of specificity and generality, SMILES arbitrary target specification can characterize structural patterns and incorporate logical operators and extra molecular descriptors [37].

The library generation statistics regarding the number of constructed molecules and species filtered by Lipinski and logBB filters are provided in the log file. The generated library can be saved in TXT format (SMILES notation of triazole products only) or as a CSV table, including the calculated Lipinski descriptors, logBB values and respective reagent azides and alkynes (which may be important for subsequent laboratory synthesis).

The application includes an option to draw molecules, which makes it easier for users to understand the molecular structures compared to deciphering SMILES representations. The user can draw five randomly selected triazoles from either the generated library or the entire library. Needless to say, rendering the entire library may require a fairly large amount of memory and time, and users will be warned about this.

Finally, NeuroClick has a number of additional features that make it even more convenient to use. At the end of the library generation, users are suggested to save a file with all of the program logs so that they can explore the statistics at each stage in more detail later. During the molecule loading and generation, a progress bar is shown to

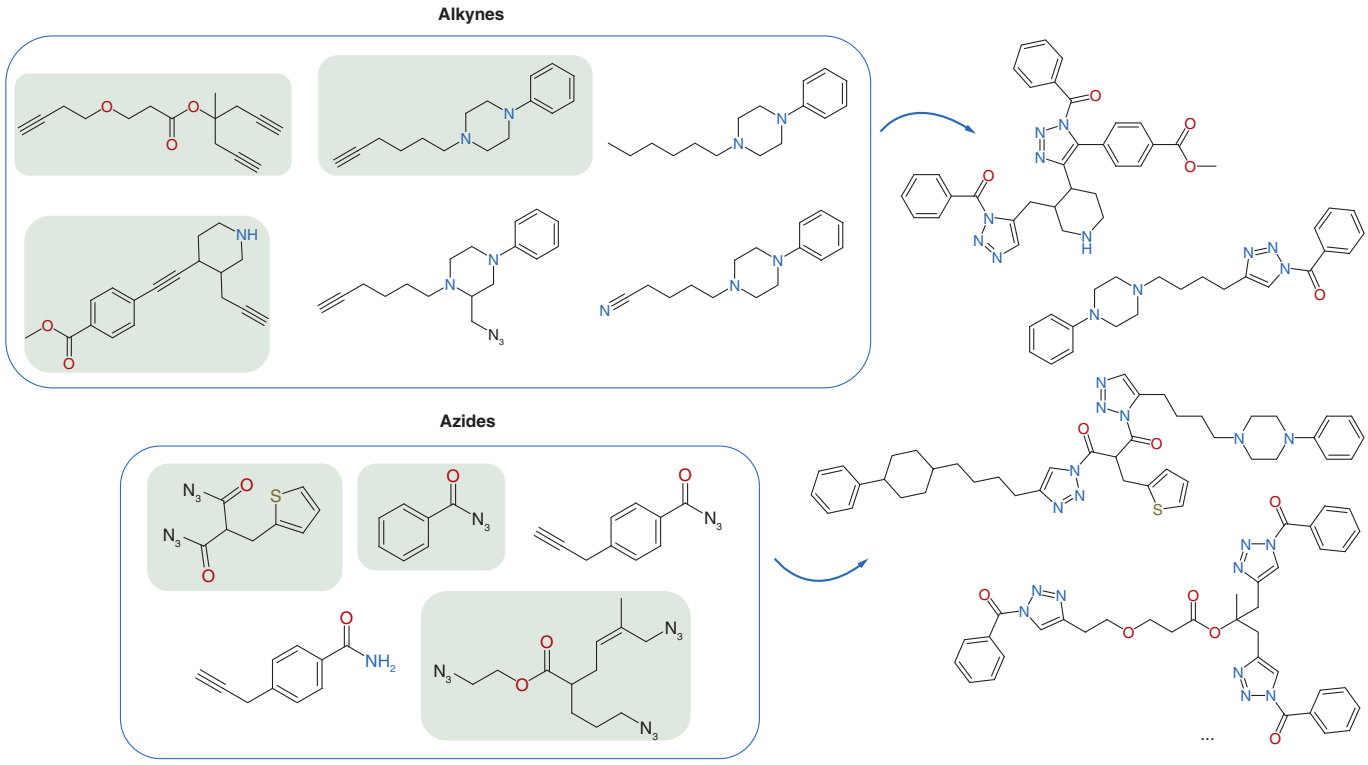


Figure 4. Illustration of a test run for NeuroClick. Test sets of azides and alkynes are displayed on the left within blue frames. NeuroClick identifies relevant reagents highlighted in green. On the right, examples of products demonstrate the fulfillment of requirements for both isomers and the handling of internal alkynes.

monitor the process. Using a 'Back' button users can always return to the previous stage, and using a 'Next' button they can always go to the next one.

Results & discussion

The primary objective of NeuroClick is to facilitate intermolecular click reactions for generating combinatorial libraries intended for virtual screening. Therefore, the algorithm isn't tailored for intramolecular click reactions or managing reactants featuring multiple azide/alkyne moieties. To validate its accuracy and efficiency, the software underwent rigorous testing across various applications. Initially, it was tested with a small dataset comprising seven alkyne records and six azide records, the file for which is provided in the Supplementary Material. These SMILES encompass diverse molecule types likely encountered during algorithm execution, including damaged SMILES, molecules containing both alkynes and azides, and instances of multiple alkyne or azide moieties within a single molecule (Figure 4). NeuroClick successfully processed all of these molecules, leaving three correct azides and three correct alkynes. These reagents were tested under varying reaction options. For example, with requirements of both generating isomers and processing internal alkynes, the reagents yielded 23 products, as expected. It is important to note that the reagent with three azide groups shown in Figure 4 includes an allylic azide, which can undergo sigmatropic rearrangement, leading to a complicated mixture of products [38]. NeuroClick is exclusively designed for azide–alkyne cycloaddition and does not accommodate any other chemical routes. Hence, a user would have to control for potential instability of the reagents supplied for combinatorial processing.

We utilized NeuroClick to replicate the synthesis of dopamine D3 receptor ligands as described by Keck *et al.*, resulting in two sets of products consisting of 10 and 12 molecules each [7]. These products were generated based on the azide and alkyne reactants outlined in the article (refer to the Supplementary Material for the file containing the SMILES of reagents and products). In order to test the application for large library production, we utilized it to generate compounds for the screening of dopamine D3 receptor inhibitors based on a molecular template containing 1,2,3-triazoles. The algorithm was supplied with a set of 143,075 azides sourced from various databases (such as ZINC and PubChem) along with an alkyne, namely 1-(hex-5-yn-1-yl)-4-phenylpiperazine

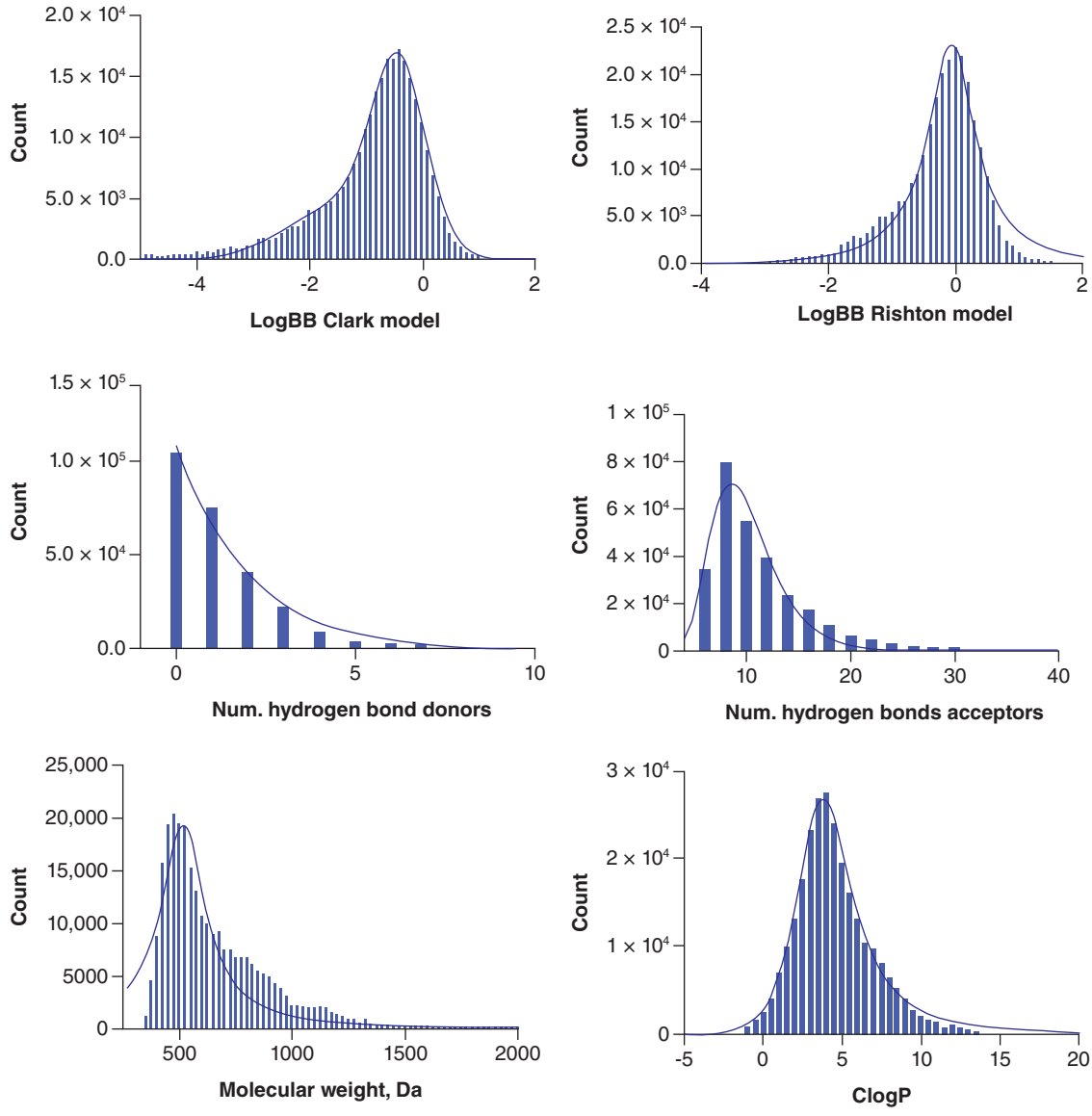


Figure 5. Distributions of Lipinski and logBB descriptors in the experiment with 143,075 azides and one alkyne.

(C#CCCCCN2CCN(c1ccccc1)CC2). The correction processing of azide SMILES resulted in a reduction of the library size to 133,632 unique molecules, retaining 93% of the initial data. In particular, 1116 of 143,075 molecules were filtered out as containing more than three azide groups (0.78% of the initial data). The process of loading and filtering went at a speed of approximately 30,000 molecules per min (approximately 6 min to load the test azide library).

The virtual click reaction yielded 284,770 triazoles in approximately 17 min. In our experiment, both 1,4- and 1,5-isomers were generated. The process of triazole library generation went at a speed of approximately 9000 molecules per minute, but this value may vary depending on the available computational resources. Distributions of the Lipinski and logBB parameters for the yielded molecules are shown in Figure 5. Of the generated molecules, 75,190 passed five Lipinski filters (26% of generated triazoles), 1056 passed the default logBB Clark filter (1.4% of Lipinski-filtered, 0.37% of generated) and 9132 passed the default logBB filter from Rishton *et al.* (12% of Lipinski-filtered, 3.2% of generated). An important factor in the design of CNS-targeted molecules is the possibility of their being substrates for P-glycoprotein (Pgp), which is an efflux transporter expressed at the BBB that restricts the brain distribution of many drugs [39]. We evaluated the probability of the filtered molecules being Pgp substrates using ADMETlab 2.0 [40]. Among the molecules passing the Clark filter, 95% demonstrated low

probability of being Pgp substrates (<0.1), 4% showed a probability of 0.1–0.5 and only 1% could be considered Pgp substrates (probability >0.5). A similar pattern was shown for molecules filtered by the logBB from Rishton *et al.* (91, 5 and 4% in the respective probability groups). The probability distribution of molecules being Pgp substrates is illustrated in Supplementary Figure 1.

Conclusion

We introduced the NeuroClick graphical user interface application for performing intermolecular azide–alkyne cycloaddition reaction to generate combinatorial triazole libraries. Currently, the application is ready for use and available in the GitHub repository as open source software (https://github.com/Anaiya798/NeuroClick). It can be executed in all of the most popular modern operating systems (Windows, Linux, MacOS). Other key software features are processing of large input files, saving of chemical libraries in TXT/CSV format, visualization of molecules and convenient distribution as an EXE file.

In silico drug design is one of the most important trends in modern medicinal chemistry. Over the next several years, there will be more and more computational tools that help make this process faster and more reliable and user-friendly. As for our application, further development of NeuroClick will be undertaken to maintain software functionality and to implement additional physicochemical property predictions (logD, Pgp efflux, etc.) as well as other types of click reactions (intramolecular azide–alkyne cycloaddition, reaction scenarios with multiple active sites, inverse electron demand Diels–Alder reaction between alkynes and tetrazines) and other chemical reactions widely used for combinatorial chemistry.

Summary points

- *In silico* methods for drug molecule screening have had a growing impact on medicinal chemistry. Design of chemical libraries in this field could benefit from transferring common organic reactions into generative algorithms to sample synthetically achievable compounds.
- In this work, we focus on azide–alkyne cycloaddition (also known as click reaction), which is a timely tool in drug molecule design. Currently available tools producing molecular libraries based on azide–alkyne cycloaddition are outdated or lack user-friendly functionality.
- In order to bridge this gap, we developed the Python 3 graphical user interface application NeuroClick. The NeuroClick cross-platform application is freely available via the GitHub repository (https://github.com/Anaiya798/NeuroClick).
- NeuroClick provides an intuitive interface for combinatorial generation of 1,2,3-triazoles from Simplified Molecular Input Line Entry System representations of alkyne and azide reactants. Users can specify preferred regioselectivity and filter compounds based on Lipinski descriptors (hydrogen bond donor/acceptor count, molecular weight and ClogP) and logBB values indicating the molecule's permeability through the blood–brain barrier, which is an important metric in the design of drugs targeted toward the CNS.
- NeuroClick was tested using a generic sample of molecules as well as a panel of reactants from a publication describing synthesis of dopamine D3 receptor inhibitors. The panel was extended using a single template alkyne and a library of 143,075 azides collected from various databases. Library generation went at a speed of approximately 9000 molecules per minute, and final filtering by Lipinski rules and logBB values allowed us to subset several thousand drug-like compounds.
- We look forward to maintaining NeuroClick functionality and expanding it to other azide–alkyne cycloaddition scenarios and more types of click reactions as well as evaluation of other physicochemical parameters.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.4155/fmc-2023-0017

Author contributions

Conceptualization, supervision, project administration, data curation and writing of original draft: S Shityakov. Methodology and writing of original draft: AA Kovalenko. Funding acquisition and review: EV Skorb. Methodology, data curation, software implementation and writing of original draft: AM Isakova.

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Competing interests disclosure
The authors have no competing interests or relevant affiliations with any organization or entity with an interest in or conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

Writing disclosure
No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors did not use any materials or data from human and/or animal studies; therefore, ethical approval based on institutional review boards and guidelines was not required.

Availability of data & materials
The NeuroClick application is openly available via the GitHub repository (https://github.com/Anaiya798/NeuroClick). As mentioned, the application is platform-independent and was written using the Python 3 programming language. Azide molecules for library construction were collected from the PubChem and ZINC databases. Python 3 packages, including RDKit, are openly available via the Python Package Index.

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