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PREDICTION OF BIOLOGICAL ACTIVITY OF 1,4-DISUBSTITUTED 1*H*-1,2,3-TRIAZOLE DERIVATIVES BY MOLECULAR DOCKING

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Abstract

In accordance with rational drug discovery methodologies, the antiproliferative activity of 1,4-disubstituted 1*H*-1,2,3-triazole derivatives was investigated utilizing an in-house prediction algorithm for molecular docking. This prediction algorithm, implemented in existing software to automate routine stages using Python, is designed for universal application, enabling its use with a diverse array of ligands and targets.

Introduction

The development of novel biologically active compounds is currently undergoing significant advancements, both within the scientific community and the pharmaceutical industry, through the application of rational design strategies. Central to this approach is molecular modeling, which aims to minimize the resource and temporal expenditure associated with the discovery of new biologically active compounds.

Beyond molecular modeling, it is prudent to conduct a rigorous filtration of the chemical compound space, prioritizing structures with the highest potential to evolve into viable drug candidates. The paradigm of click chemistry advocates for the initial exploration of compounds that can be synthesized from simple and readily accessible precursors via reactions characterized by high yields and favorable conditions.

Accordingly, the objective of this study is to harness the synthetic capabilities of our research laboratory, grounded in the principles of click chemistry, to perform molecular modeling of chemical compounds for anticancer activity. The aim is to identify and select hit compounds from the resulting data, thereby advancing the discovery of promising therapeutic candidates.

Materials and Method

The objects of this study are: 1) a set of 1,4-disubstituted 1,2,3-triazoles (see Figure), which can be synthesized in our research laboratory (acting as ligands), and 2) proteins that are directly or indirectly responsible for the development of cancer, serving as biological targets.

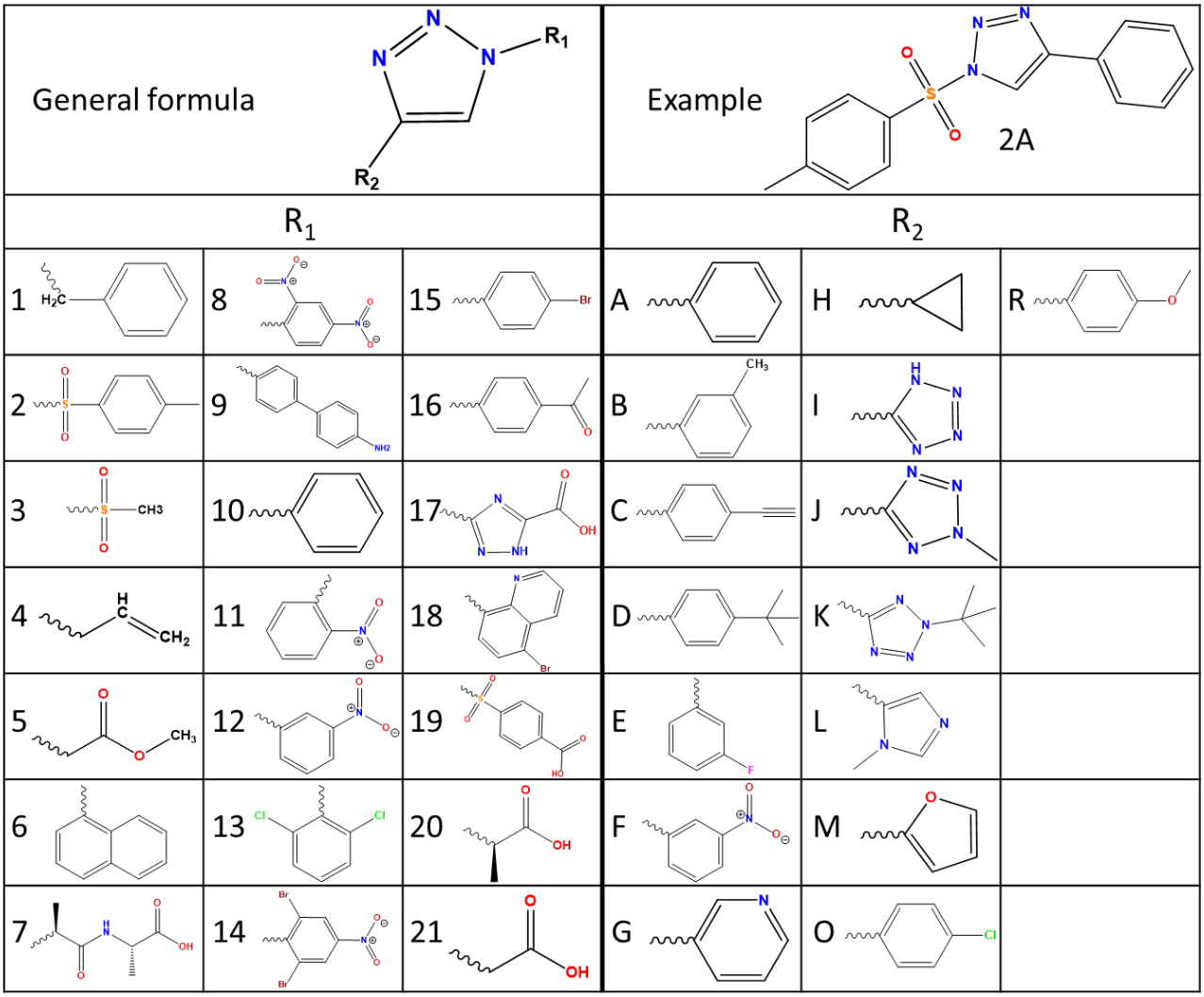
For molecular modeling, we employed the molecular docking method to predict the most favorable conformation and orientation of the ligand molecule within the active site of the macromolecule. The Glide 7.8 program [2–4], along with other utilities from the Schrödinger 2018-1 software package [5], was used for docking. The OPLS 3 force field [6] and the GlideScore scoring function were utilized.

Given the extensive computational volume and significant time requirements, it is more efficient to implement the research algorithm in software to expedite and automate routine stages. This was achieved using Python 3.11.8, as described elsewhere [7]. Molecular docking was performed in two modes: first, the SP mode, which is less accurate but faster; and then the XP mode, which is more accurate but more time-consuming.

Results and Discussions

As a result of molecular docking, GlideScore values were obtained for each ligand, which correspond to the predicted binding energies of ligand-protein complexes. Lower values indicate more stable complexes. Based on these values, compounds can be ranked from best to worst. The first iteration of docking was performed in SP mode, filtering out compounds with scores greater than −8 kcal/mol. The remaining compounds proceeded to the second iteration in XP mode. For the selection of the best compounds, or hits, it is common practice to take the top 10 % for further studies. In our case, compounds with scores greater than −10 kcal/mol were filtered out, and the remaining compounds were accepted as hits, which constituted about 10% of the total.

The hit compounds identified through molecular modeling will be synthesized in the near future and experimentally tested for biological activity against the corresponding biological targets.



The set of 1,4-disubstituted 1*H*-1,2,3-triazoles available in our laboratory

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