Designing and selecting of novel and safe hypothetical herbicide candidate by computational approach

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Abstract

Herbicides play an important role in the efficient production of crops. However, the improper application causes herbicide residues in the environment. This has become one of the environmental issues in Thailand, which has affected the biota and ecosystems. To solve this problem, an effective new non-environmental toxic herbicide candidate needs to be discovered urgently. This motivated to design a novel herbicide candidate with the desired properties. In this work, a total of 243 hit molecules were generated using LigBuilder. After binding calculation by Audodock, Lig_5 was selected based on the lowest of free binding energy whereas the remaining ligands were chosen based on the least cluster number.

The binding interactions were analyzed via Discovery Studio Visualizer. The interaction patterns of Lig_5 were highly similar to those of glyphosate. It forms multiple hydrogen bonds with conserved residues in the binding site of the enzyme. Moreover, Lig_5 is an herbicide candidate based on herbicide-likeness property scores. In addition, Lig_5 is a non-ecotoxic compound based on computational calculation. The results proposed Lig_5 as a newly potent herbicide candidate which could be as effective as glyphosate for further synthesis and testing for weed control.

Keywords: Bioinformatics tool, *De novo* ligand design, Weed management.

Introduction

Currently, the requirement for food is increasing because the global population is increasing. Thus, farmers inevitably need to use chemical herbicides to control the weeds and increase crop production. This causes herbicide contamination in the environment including soil and water. What happens if Thailand, as an agricultural country, falls into the critical situation of crops and the environment being contaminated with chemical residues? Since these residues are not only dangerous to the environment and ecosystem but also have diverse effects on human health, the economy and society. Moreover, weeds have become widely resistant to traditional chemical herbicides and the resulting decrease in the herbicide discovery[8]. Therefore, there is an urgent need to discovery a novel non ecotoxic herbicide with the desired properties to overcome those problems.

Previously, the discovery of weed killer compounds used diverse techniques including high-throughput screening and optimizing the structure of a moderately active compounds with a novel molecular target to improve their activity[6]. These techniques are slow and expensive. Currently, computational *de novo* design is a popular strategy. This technique aims to generate new molecules with desired properties from scratch without template[23,26]. It is composed of ligand-based and structure-based *de novo* designs[23,26]. However, in order to obtain new molecules, the latter would be appropriate. Among the structural-based *de novo* design program, LigBuilder is well known and successful program[16,24,32]. These successes make it credible that *de novo* molecule design can be used as a tool for creating high-potency herbicides.

However, this technique is not able to predict the binding interaction of hit molecule in the binding site of a target receptor precisely. This can be solved by molecular docking technique. It calculates the free energy of binding between a ligand and a receptor based on Van der Waals, hydrogen bonding, electrostatic interaction and hydrophobic interaction[13]. This technique is performed to identify the most potential molecule with strong ligand binding affinity. The lower free energy of binding values corresponds to more favourable ligand binding[13].

In the design step, the target enzyme, which has to play a vital role in the survival of plants, needs to be selected. In addition, its X-ray crystallography structure is available. Among the biological pathways in plants, the shikimate pathway is very interesting. It is important not only for the synthesis of essential aromatic amino acids, but also for almost all other aromatic compounds[7,30].

Remarkably, the shikimate pathway is exclusively present in plants and microorganisms[2,30] whereas it is not found in mammals[7]. Herbicides inhibiting this biological pathway will have high efficiency for weed control and will be less toxic to animals and humans. There are many enzymes involved in the shikimate pathway.

The enzyme, namely 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase (EC 2.5.1.19), having diverse 3D X-ray crystallography structures complex with its inhibitors, is the sixth enzyme on the shikimate pathway[30]. Therefore, EPSP

synthase should be an attractive target for inhibitor design to develop the new herbicide.

In the selection step, the designed molecule needs to be analysed the binding pattern. Importantly, the herbicide-likeness property needs to be verified to confirm it as an herbicide. Also, the environmental toxicity and enzyme inhibitor need to be analyzed. Finally, the selected herbicide needs to be checked as a novel compound across the famous molecule databases. The objectives of this work were (1) to design a new herbicide candidate, inhibiting the EPSP synthase activity and (2) to filter the desired properties of novel and safe hypothetical herbicide candidate.

Material and Methods

Hardware and Process: All the computational studies were performed on a laptop with the following specifications: Intel (R) CoreTM i7-10750H CPU at 2.60 GHz of processing speed, 16 GB of memory and a 64-bit operating system. The flowchart of this study is shown in fig. 1.

Binding pocket preparation: The X-ray crystallographic structure of EPSP synthase, PDB ID: 1G6S[30], was downloaded from the RCSB Protein Data Bank[3]. This structure complexes with herbicides (glyphosate) and S3P (shikimate 3-phosphate) at a high resolution of 1.50 Å. Discovery studio[4] was used to prepare the binding pocket of EPSP synthase by removing native ligands, water molecules and co-crystal molecules. Then, hydrogen atoms were added to the structure. This pocket was subjected to *de novo* molecule design.

***De novo* design:** The novel molecules were created using LigBuilder, version 3[32]. It is structure - based *de novo* design[26]. The key interaction sites within the binding site of EPSP synthase were analyzed via the cavity module with default parameters. Hit molecules were constructed via the build module. This module is the main function for *de novo* design. Inside this module, hit molecules were designed using normal design mode with an exploring strategy. This strategy is very powerful in *de novo* structure design. The program generates an initial seed and extracts the new seed structures automatically. The search strategy used in LigBuilder is a genetic algorithm to develop and evolve the molecules[26,32]. Almost all parameters were used based on the default values of the tool, except for some values of the chemical viability rules. Molecular weight and LogP were set to 170 g/mol and -2.8 respectively. These values belong to glyphosate to control the molecular size of the compounds designed[26].

Binding energy calculation: Re-docking was performed before the generated molecules were investigated to ensure the accuracy of the docking process. The co-crystalized glyphosate was removed from the receptor and then docked back. The root mean squared deviation (RMSD) is used as a quantitative measure of accuracy by Discovery Studio. For the docking technique, all generated molecules were converted to PDBQT using the in-house batch script in Python[29]. EPSP synthase was converted to PDBQT by adding Kollman charges using AutoDockTool 1.5.6[22]. The size of a gird box was set to 40 x 40 x 40 Å with coordinates X = 60.527, Y = 9.077 and Z = 29.519 and with grid spacing of 0.375 Å.

The Lamarckian Genetic Algorithm was used as a search engine with default parameters. The genetic algorithm was set to 50 runs with energy evaluations of 2500000. Molecular docking was carried out using the in-house batch script for automatic running of the AutoDock 4.2/ADT program[22]. Glyphosate was docked to the same target as the reference inhibitor.

Property evaluation: Enzyme-ligand interactions were analyzed using Discovery Studio. Hydrogen bonding was focused on this study. The herbicide-likeness property was analyzed by HerbiPAD[10]. The bioactivity score of enzyme inhibitors was predicted by the Molinspiration database[21]. Environmental toxicity was also analyzed by ADMETLab 2.0[31]. The novel of the designed molecule was checked across several databases such as PubChem[18], ChemSpider[25] and Zinc20 databases[12].

Results and Discussion

Designed molecules: Using the cavity module of LigBuilder, the key interaction sites in the binding pocket were generated and they were visualized by Discovery Studio (Fig. 2). With the build module application of LigBuilder, 243 molecules were generated. Molecules designed from LigBuilder appear of diverse structure due to the limits of the molecular descriptors[26].

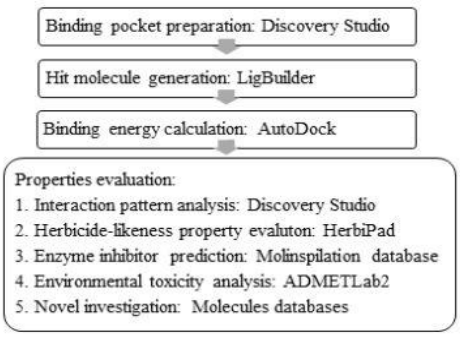


Fig. 1: Methodology of this study

Binding energy of designed molecules: The RMSD value of the overlay structure between the docked pose and the co-crystallized glyphosate was 0.2469 Å (Fig. 3). This indicates that re-docking was successful with the accuracy of the docking due to the RMSD values being less than 2.0 Å[26,27]. The free binding energies of all designed molecules was in the range of +0.69 to -7.65 kcal/mol. The lowest of free binding energy of the top 10 designed molecules and glyphosate is shown in table 1. Considering the binding energy value, the more negative is the free binding energy value, the better and stronger are the binding between enzyme and ligand[14]. Therefore, Lig_5 was selected based on the lowest of free binding energy value of -7.65 kcal/mol. However, Lig_2, 27, 109 and 115 were also selected based on the least number of cluster groups. A total of 5 molecules were selected to analyze binding patterns compared to those of glyphosate.

Binding pattern: The binding mode of re-docked glyphosate in binding site of EPSP synthase is shown in fig. 4. It showed several hydrogen bonds, which bind with the important amino acid residues including Lys22, Gly96, Gln171, Arg124, Arg344, Arg386 and Lys411. This result is in accordance with the previous work. For example, Schönbrunn et al[30] showed that the strictly conserved residues of EPSP synthase are Arg27, Ser23, Ser169, Ser197, Lys340, Asp313 Lys22, Gln171, Arg124, Gly96, Glu341, Arg344 and Arg386. The binding site is dominated by charged residues (Lys22, Arg124 and Lys411) from both domains of the enzyme[30].

Besides, glyphosate interacts with Lys22, Arg124, Arg344, Arg386 and Lys411, which are suggested as an allosteric action of the herbicide via hydrogen bond[30]. The hydrogen bond plays a vital role in adjusting the proper orientation of the molecule in order to form a suitable interaction[28]. In general, a single hydrogen bond is relatively weak and would not be expected to support a drug-receptor interaction alone, but multiple hydrogen bonds can provide a significant amount of stability during the drug-receptor interaction[28].

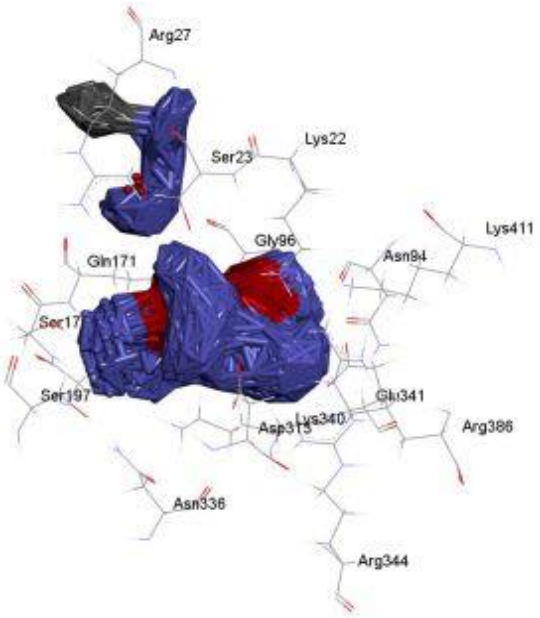


Fig. 2: Key interaction sites of EPSP synthase visualized by Discovery Studio in which nitrogen atoms (blue) represent hydrogen-bond donor sites; oxygen atoms (red) represent hydrogen-bond acceptor sites and carbon atoms (grey) represent hydrophobic sites. Drawn with Discovery Studio[4].

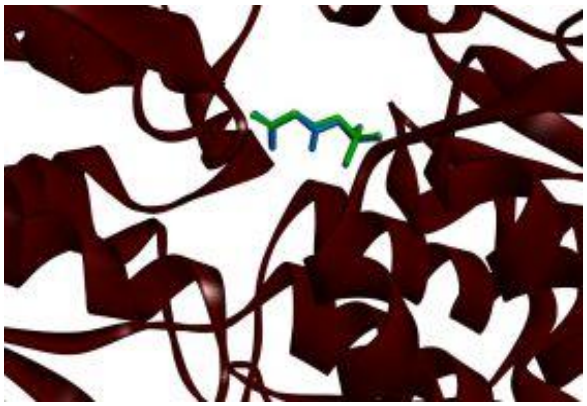


Fig. 3: Re-docked glyphosate (blue) overlay with co-crystallized glyphosate (green) in the pocket (grey). Drawn with Discovery Studio[4].

Table 1
Binding energies of the top ten designed molecules calculated by molecular docking

Ligand No.	Free binding energy (kcal/mol)	Cluster No.
Lig_2	-7.03	**3**
Lig_5	**-7.65**	6
Lig_27	-7.12	**3**
Lig_98	-7.56	7
Lig_109	-7.11	**2**
Lig_115	-7.22	**2**
Lig_129	-7.49	8
Lig_130	-7.56	6
Lig_198	-6.96	7
Lig_231	-7.43	6
Glyphosate	-8.78	1

Bold fonts indicate the selected ligands for binding interaction analysis.

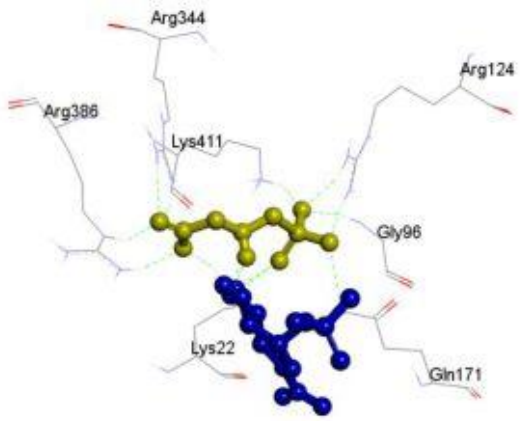


Fig. 4: Binding interactions of re-docked crystallized glyphosate in EPSP synthase. S3P and glyphosate are shown as ball-and-stick models in blue and yellow respectively. Drawn with Discovery Studio[4].

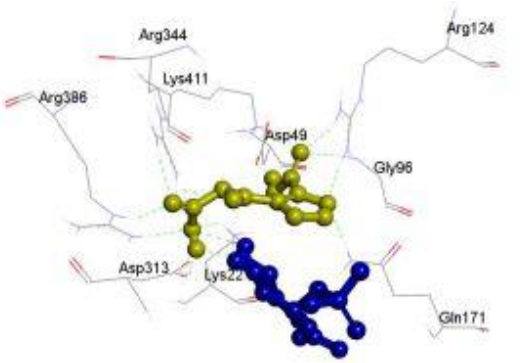


Fig. 5: Binding interactions of Lig_5 in EPSP synthase. S3P and Lig_5 are shown as ball-and-stick models in blue and yellow respectively. Drawn with Discovery Studio[4].

Moreover, Gly96 is essential for the binding of glyphosate[15] and Lys411 has a role in the catalytic efficiency of the enzyme[30]. These indicate that the re-docking was successful and could promote glyphosate as the traditional herbicide. The binding pattern of generated ligands with the lowest of free binding energy (Lig_5) in binding site of enzyme is shown in fig. 5. Lig_5 could form hydrogen bonds with Lys22, Gly96, Gln171, Arg124, Arg344, Arg386 and Lys411. They were most similar to those of glyphosate binding interaction (Fig. 4) compared to those of Lig_2, 27, 109 and 115. Moreover, Lig_5 could bind with Asp313 and Asp49. Asp49 is also highly conserved residue involved in ligand-binding and catalysis of EPSP synthase[19]. The role of Asp313 is unclear[7].

Meanwhile, the interaction pattern of Lig_2, 27, 109 and 115 is shown in fig. 6A-6D respectively. Their interactions were similar. They form hydrogen bonds with Lys22, Thr97, Gln171, Arg124, Arg344, Arg386 and Asp313. However, they could not form hydrogen bonds with important residues such as Gly96 and Lys411. Therefore, they were not selected.

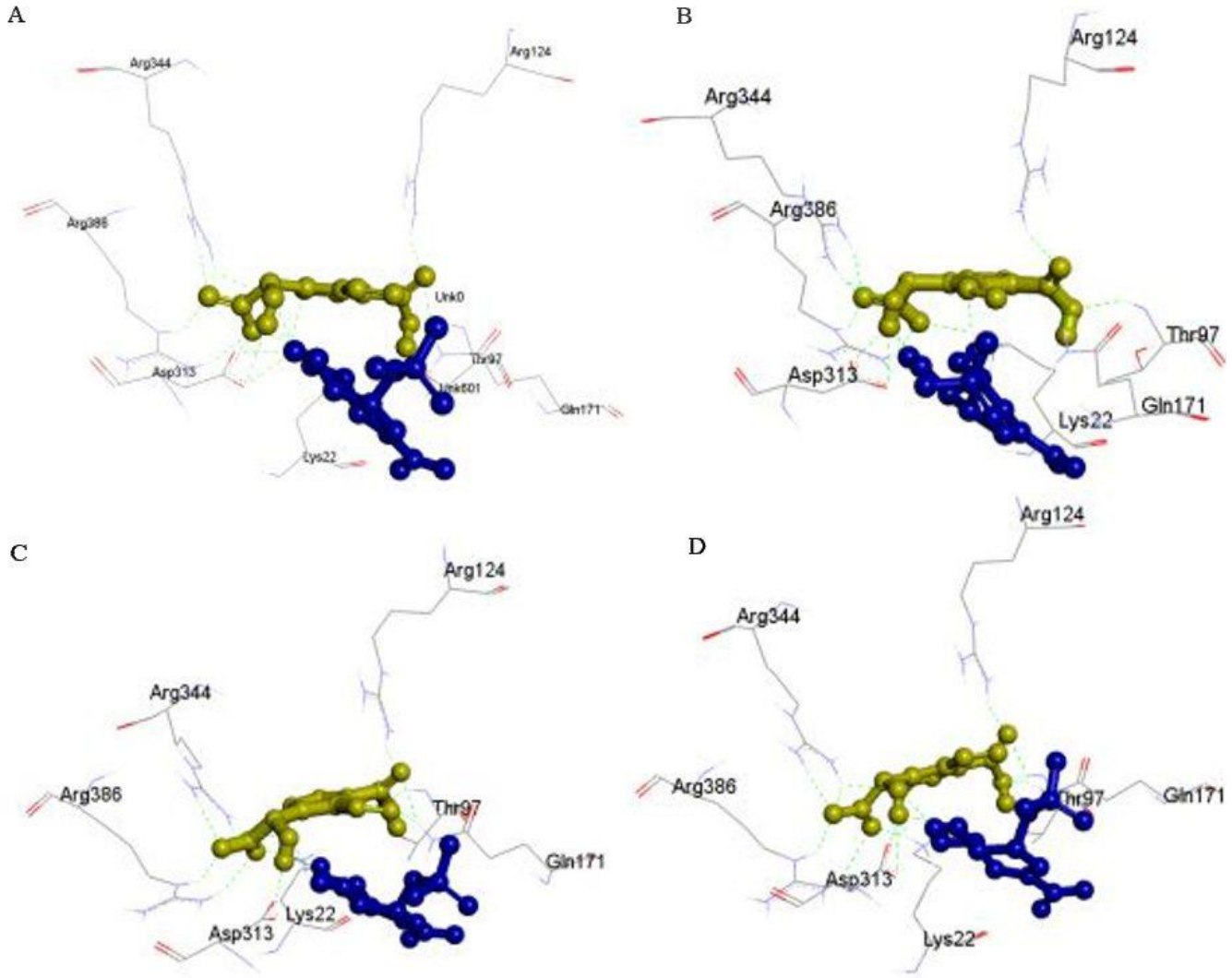


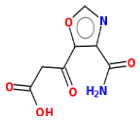
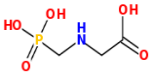
Fig. 6: Binding interactions of (A) Lig_2, (B) Lig_27, (C) Lig_109 and (D) Lig_115 in EPSP synthase binding pocket. S3P and Ligands are shown as ball-and-stick models in blue and yellow respectively. Drawn with Discovery Studio[4].

As mentioned above, Lig_5 was selected as a potent inhibitor against EPSP synthase. It could be as effective as glyphosate based on similar binding patterns and the lowest free binding energy, compared to those of glyphosate.

Lig_5's Properties evaluation: Considering the herbicide-likeness property, Lig_5 was an herbicide compound based on the criteria values of the herbicide-likeness property via HerbiPAD. Three scoring functions are QEH (quantitative estimate of herbicide likeness), RDL (relative drug likelihood) and GAU (Gaussian function). Lig_5 had 0.50 of QEH, 1.58 of RDL and 4.94 of GAU. Those values were higher than those of the HerbiPAD's threshold (QEH > 0.47, RDL > 1.15, GAU > 4.75)[10]. Moreover, the higher is the score, the better is the herbicide-likeness[10]. Almost all the properties of Lig_5 were similar to those of glyphosate (Table 2). The enzyme inhibitor score of Lig_5 was -0.04. The maximum score is 2. The larger is the value of the enzyme inhibitor score, the higher is the probability that the particular molecule will be active[21]. This result is consistent with the study of Husain et al[11] who reported that a molecule with a bioactivity score greater than 0.00 is most likely to exhibit considerable biological activity, while values ranging from -0.50 to 0.00 are expected to be moderately active. If the score is less than -0.50, it is presumed to be inactive[11]. Therefore, Lig_5 could be a moderately active enzyme inhibitor. Importantly, an herbicide candidate has to be a non-toxic compound for the environment. The general indicators of environmental toxicity are listed in table 2. Bioconcentration factor (BCF) is defined as the ratio of the chemical concentration obtained through aqueous exposure in aquatic water-respiring organisms to water in a steady state[9].

It is used for considering secondary poisoning potential and assessing risks to human health via the food chain[1]. This factor is an estimate of the residual organic chemicals used for ranking chemicals as possible hazards to the environment[1]. 50% growth inhibitory concentration (IGC_{50}) for *Tetrahymena pyriformis* has been widely used in ecotoxicology and environmental safety applications[17].

Table 2
Properties of Lig_5 compared to those of glyphosate

Property	Ligand_5	Glyphosate
Formula	$C_7H_6N_2O_5$	$C_3H_8NO_5P$
Molecular weight	198.13	169.07
No. H-bond acceptors	7	6
No. H-bond donors	3	4
No. rotatable bonds	4	4
Enzyme inhibitor	-0.04	1.03
Environmental Toxicity:		
Bioconcentration factor IGC_{50}	0.206	0.151
$LC_{50}FM$	2.548	2.351
$LC_{50}DM$	3.624	3.794
	3.341	3.503
2D-structure		

H-bond stands for hydrogen bond.
2D-structures was drawn by Molinspiration database[21]

Pimephales promelas and *Daphnia magna* are two of the most common aquatic organisms which are useful for testing the ecological toxicities of environmental pollutants[5,20]. A 50% lethal concentration of fathead minnow (*P. promelas*) ($LC_{50}FM$) for 96 h is used as a quantitative toxicity endpoint[5]. Likewise, a 50% lethal concentration of *D. magna* ($LC_{50}DM$) is used as a quantitative toxicity endpoint. Lig_5 had 0.206 of BCF, 2.548 of IGC_{50}, 3.624 of $LC_{50}FM$ and 3.341 of $LC_{50}DM$. This indicates that Lig_5 is a non-ecotoxic herbicide. This is consistent with the study by Ahmad et al[1] who found that 4-hydroxyisoleucine is a non-ecotoxicity compound. Its values including BCF, IGC_{50}, $LC_{50}FM$ and $LC_{50}DM$ are 0.17, 2.43, 2.92 and 2.36 respectively. Finally, none of the compounds in the library of PubChem, ChemSpider and Zinc20 databases has an identity with Lig_5. This confirms that Lig_5 was the new compound.

Conclusion

In this study, a designed molecule, Lig_5, was successfully created by the computational biology method. This study platform provides a strong candidate for the synthesis and development of new and environmentally friendly herbicides. Further, the herbicidal effect of Lig_5 has to be performed under experimental conditions in order to promote its practical applications.

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