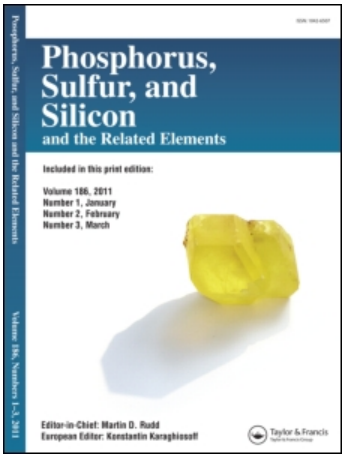

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High Throughput Screening Under Zinc-Database and Synthesis a Dialkylphosphinic Acid as a Potential Kari Inhibitor

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High Throughput Screening Under Zinc-Database and Synthesis a Dialkylphosphinic Acid as a Potential Kari Inhibitor

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A novel phosphorus derivative was synthesized through HTVS. The title compounds were confirmed by MS, ^{1}H *NMR,* ^{31}P *NMR. The DOCK was also studied.*

Keywords DOCK; KARI; phosphorus derivatives; synthesis

1. INTRODUCTION

Ketol-acid reductoisomerase (KARI; EC 1.1.1.86)[1] is an attractive target for argochemical discovery because it catalyzes the second important step in the biosynthesis of the branched chain amino acids that exist in higher plants only and not in animals. Thus, it is an ideal target from which to design nontoxic KARI-inhibitors as potential novel herbicides. The reaction catalyzed by KARI is shown in Figure 1.

In particular, as high throughput screening considerably increased the numbers of new chemical entities to be studied, the expectations to find new bio-active molecules among these compounds were high at the beginning. However, high throughput screenings (HTS) yielded so far the expected success, and therefore virtual screening approaches emerged and largely evolved. Today, high throughput virtual screening (HTVS) is useful in argochemical innovation.

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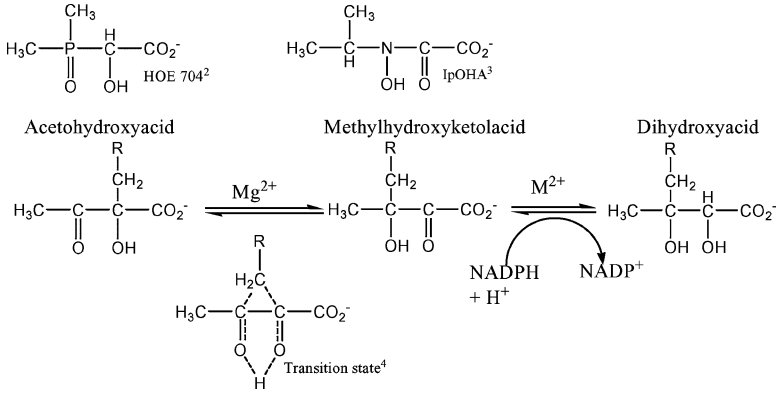


FIGURE 1 Reaction catalyzed by KARI.

2. METHODS AND EXPERIMENTS

2.1. HTVS

Based on the reported crystal structure of complexes of the enzyme KARI, 1000 new molecules were predicted with high affinity for KARI from ZINC-database (Drug-Like) searching, using program eHiTS.[5] The computational flow chart for this study was shown as in Figure 2. Among them, many compounds contain phosphorus structures. A dialkylphosphinic acid was noticed which is analogy of HOE 704 (Figure 1).

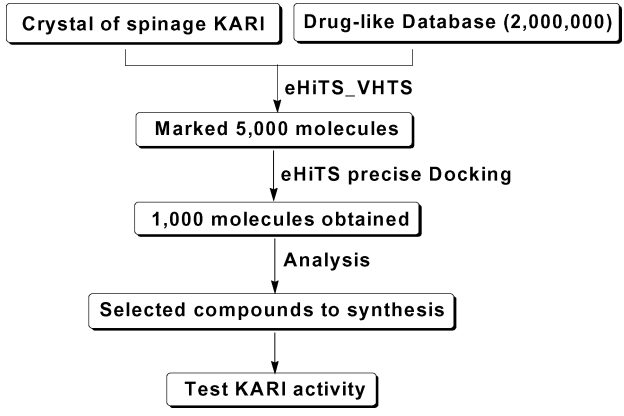
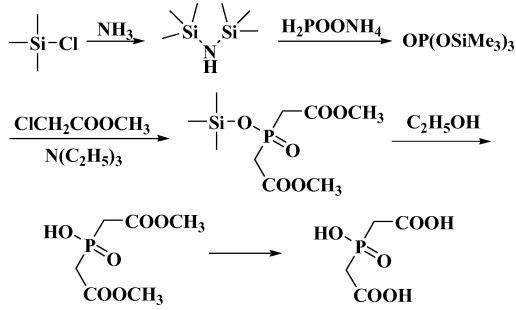


FIGURE 2 Computational and experimental flow chart for this study.

2.2. Synthesis

The dialkylphosphinic acid was synthesized according the reference[6] (Scheme 1). The physical chemistry data were accordance with the reference.



SCHEME 1 The synthesis route of the title compound.

3. RESULTS AND DISCUSSION

3.1. HTVS

A dialkylphosphinic acid was docked with KARI and estimated the pKi = −5.235. The interaction pattern (Figures 3 and 4) between the titled compound and KARI was same as IpOHA (Figure 1). The Mg2+ ions and the crystal water molecules, inhibitor in the active site are necessary for constructing and maintaining the conformation of the active

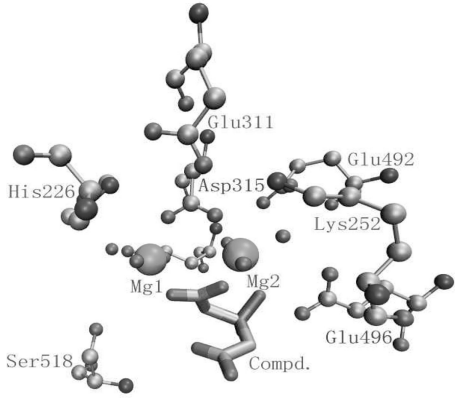


FIGURE 3 Spinage KARI active site with title compound.

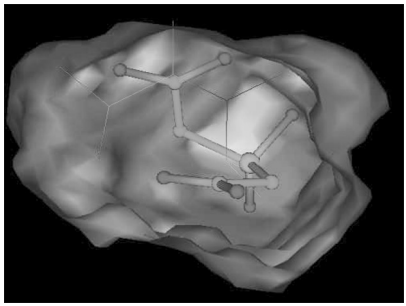


FIGURE 4 Superimposition of the docked modeled into the binding pocket conformation.

site and thus the binding affinity of ligand or the enzymatic activity of title compound and IpOHA in complex with spinage KARI.

3.2. Synthesis and Biological Activity

The synthesis route of the title compound is shown in the Scheme 1. The method was not modified. The dialkylphosphinic acid was synthesized for further bioassay experiments.

4. CONCLUSION

A new potential lead compound of KARI inhibitor was found by virtual and laboratory screening for further optimization.

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