KP204 Virtual screening and structural development for insect molting hormonal agonist

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1. Introduction

Insects grow by repeating molting and metamorphosis, which are regulated by the steroidal molting hormone, 20-hydroxyecdysone (20E; Fig.1). On the other hand, vertebrates do not have such effects, and therefore, 20E and its analogs have become candidates for safe insecticides; however, the low hydrophobicity and the high synthetic cost prevented the development of ecdysteroids for practical use. In 1988, *N-tert*-butyl-*N,N'*-dibenzoylhydrazines (DBHs) were discovered as molting hormonal agonists, which cause incomplete molting in insects leading to death. Then, a number of DBH analogs with various substituents at benzene rings were synthesized and the structure-activity relationship (SAR) studies have been performed. To date, four DBH compounds including tebufenozide, methoxyfenozide, chromafenozide and halofenozide have been commercialized. Even though 20E is commonly used as molting hormone in most of insects and it has similar potency among insects, SARs of non-steroidal ecdysone agonists varied among insect species. The reason for the difference of SARs between ecdysteroids and non-steroidal compounds is disclosed by the three dimensional structure analysis of ligand-bound EcR, showing that ponasterone A (PonA) , one of the most potent ecdysteroids, does not necessarily overlap with a chromafenozide analog (BYI06830) in the binding pocket, and therefore, the interaction between EcR and DBHs can be species-dependent.

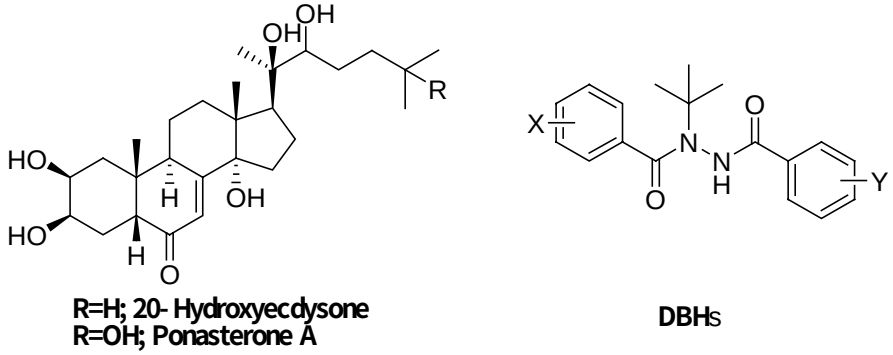

Fig.1 The structures of natural molting hormone and the agonists

In this study, we designed the novel ecdysone agonists based on the ecdysteroid structure, because ecdysteroid-like compounds were supposed to be potent against a broad range of insects. To design the new structures, virtual screening methods were

applied. The target structures were selected from the database by searching the compounds that have similar shape and electric charge distribution to those of PonA.

2. Results and Discussion

Virtual Screening

The molecular modeling softwares package comprised of FILTER, OMEGA, ROCS and EON (OpenEye Scientific Software; Santa Fe) was used for virtual screening. First of all, the structure database of more than 4 million compounds was obtained from ZINC, a free database of commercially-available compounds for virtual screening. In the second step, all structures were screened for the physicochemical parameters such as hydrophobicity. In the third step, all selected compounds were submitted to the conformation search to find the low energy conformations. In the forth step, the structures with similar conformations to that of EcR-bound PonA were selected as candidate compounds. Furthermore, the selected structures were evaluated by the electrostatic similarities to PonA. Finally, the functional groups of the best candidate were changed to maximize the similarities in terms of steric and electrostatic features.

Chemical Synthesis

One of the compounds selected by the virtual screening is compound **1**, and its synthetic method is shown in Fig.2.

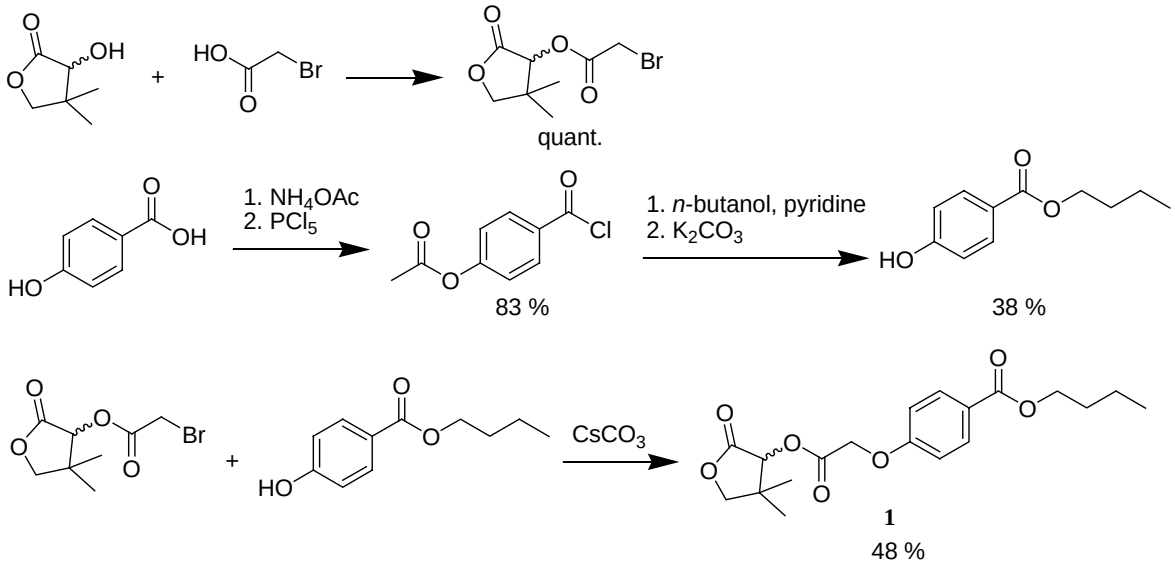

Fig.2 The synthetic method of compound **1**

Bio
logical Test Results

The activity is evaluated by measuring the inhibition of the incorporation of [^{3}H] PonA into Lepidoptera Sf-9 cells. The concentrations required for 50% inhibition of the incorporation of [^{3}H] PonA (IC_{50}) were determined for all compounds. IC_{50} of most potent compound was 17 μM, being 100 times less potent than 20E.