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BIOTECHNOLOGY

Binding Affinity Analysis of Cinnamanilide and α-Aminophosphonic Acid Derivatives for Acetohydroxyacid Synthase through Molecular Docking

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ABSTRACT

In the present study, the synthesized derivatives of cinnamanilide and α-aminophosphonic acid were used to analyze their binding affinity with acetohydroxyacid synthase (AHAS) (PDB ID: 1YHY) a molecular target for development of herbicide through molecular docking. The result of present studies showed that cinnamanilide derivative 2-nitro cinnamanilide has greatest affinity toward AHAS as compared to other derivatives, which bind at amino acids residue Ile396, Arg246, Ser186 with three hydrogen bonds and -8.5 kcal/mol binding energy. α-Aminophosphonic acid 1-(2,5 dimethoxyphenyl)-1-(phenylamino) methylphosphonic acid exhibited the maximum affinity toward AHAS with four double bonds binding at amino acids Trp267, Arg109 and -5.6 kcal/mol binding energy as compared to other derivatives. This may lead to inhibition of AHAS protein. Further field trial is required to validate its efficacy and potency as herbicide for the protection of crop plants.

Highlights

- Molecular docking studies of cinnamanilide and α-aminophosphonic acid derivatives to search new herbicides have revealed 2-nitro cinnamanilide and 1-(2,5 dimethoxyphenyl)-1-(phenylamino) methylphosphonic acid as potential inhibitor of acetohydroxyacid synthase (AHAS).

Keywords: Cinnamanilide, α-Aminophosphonic acid, Acetohydroxyacid synthase (AHAS), Molecular docking, 2-nitro cinnamanilide, 1-(2,5 dimethoxyphenyl)-1-(phenylamino) methylphosphonic acid

Chemical weed control to reduce the damage due to weeds is essential but herbicide usage has drawbacks including the loss of non-target organisms due to persistence of herbicides in soil and water, which causes indirect ecological problems (Lewis *et al.*, 2009, Wang *et al.*, 2010, Willemsen and Hailey 2001). Herbicide applications also affect human health due to residue in foods exposed to herbicides (Chade *et al.*, 2006, Fantke *et al.*, 2012, Rouimi *et al.*, 2012) and development of herbicide resistants in weeds (Heap 2007). To overcome the problem of persistence and resistant of herbicides, it is necessary to develop new classes of herbicides with novel mode of action and less persistence in environment.

Molecular docking helps in theoretically designing new molecule. This technique has been used widely in pharmaceutical industry (Kuntz 1992, Klebe 2000, Anderson 2003). Structure based design is new approach in the field of agrochemical industry and currently there is no product in the market as a direct result of this approach (Plant 2010, Lamberth *et al.*, 2013).

Cinnamanilide derivatives attract the attention of many researchers as they show activities like fungicidal, insecticidal (Xiao *et al.*, 2011) herbicidal (Vishnoi *et al.*, 2009) and avian repellent (Gill et al, 1998a,b) etc. α-Aminophosphonic acid exhibit various activities like anticancer or antitumor (Lavielle *et al.*, 1990, Kafarski and Lejczak 2001, Djokic *et al.*, 2008, Naydenova *et al.*, 2010), antioxidant (Onita *et al.*, 2010) antimicrobial (Chinnam *et al.*, 2013), plant growth regulator or herbicidal (Sarapuk *et al.*, 2003, Duke and Powles 2008).

The enzyme acetohydroxyacid synthase AHAs catalyzes the biosynthesis of branched chain amino acids (BCAAs) like valine, isoleucine and leucine from their precursor acetohydroxyacid (2-aceto lactate) (Chipman *et al.*, 1998, Duggleby and Pang 2000, Dumas *et al.*, 2001, Mccourt and Duggleby 2006). Therefore, the enzyme involved in biosynthesis of BCAAs is potential target for the development of herbicides (Shaner and Singh 1997, Mccourt *et al.*, 2005). Many chemical classes like sulfonylurea's, imidazolinones (Wang *et al.*, 2005, Wang *et al.*, 2007), triazolopyrimidines, sulfonylaminocarbonyl triazolinones and pyrimidiyloxy benzoates have been developed as herbicides on the basis of studies that reveals that these chemical classes inhibit AHAS (Zabalza *et al.*, 2013). Studies on mechanism of interaction between acetohydroxyacid synthase and different classes of compound have been carried out (Chipman *et al.*, 2005). Continuous increase in efficacy and potency of AHAS inhibitors is bound to replace the traditional herbicides (Cobb and Reade 2010).

Widespread use of AHAS inhibiting herbicides represent the second largest class of active herbicidal products used in weed control for many crops. However, few weeds have also developed resistance against some of the herbicides developed on the basis of AHAS inhibiting activity (Heap 2012). Therefore, new chemical classes may be found out having AHAS inhibiting activity, so that they may be developed as new class of herbicides which may act on resistant weeds (Gerwick 2010, Duke 2012).

In order to find out efficient molecules to be developed as new class of herbicides, cinnamanilide and α-aminophosphonic acid derivatives have been undertaken for molecular docking studies with AHAS as a target molecule.

MATERIAL AND METHODS

Preparation of ligand structure

The cinnamanilide and α-aminophosphonic acid derivatives were docked with acetohydroxy acid synthase (AHAS) as target protein. The three dimensional coordinates of cinnamanilide and α-amino phosphonic acid derivatives were prepared using Marwin sketch (www.chemaxon.com) in .pdb format and these files were used to prepare .pdbqt files by AutoDock (Trott and Olson 2010) for molecular docking studies.

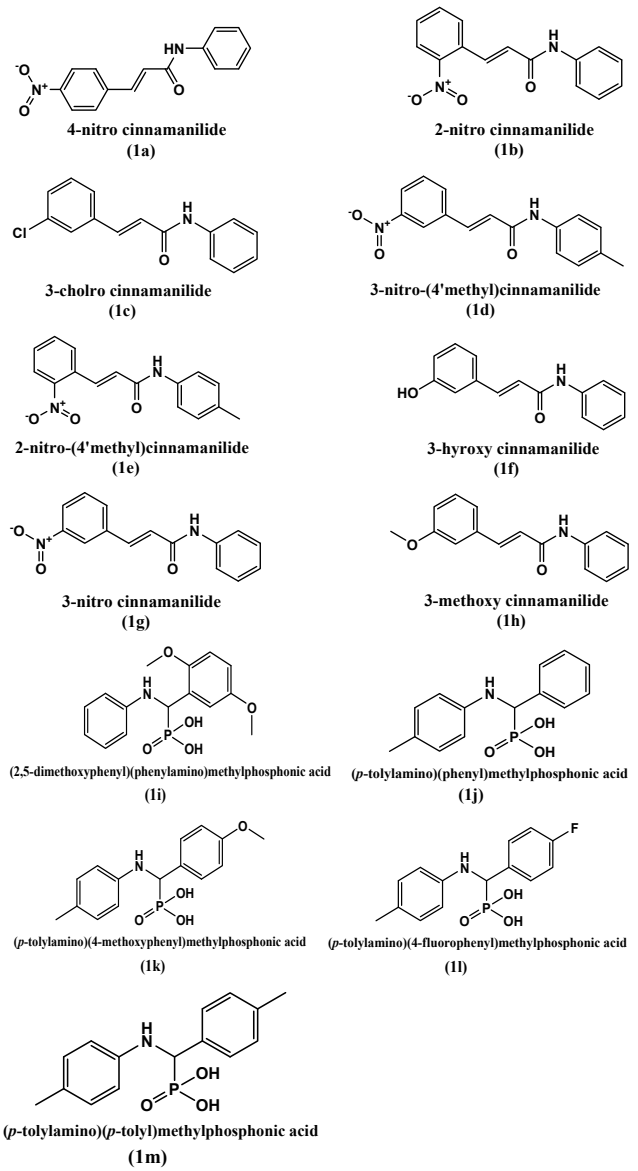

Fig. 1: Structure of all the docked compounds

Preparation of protein structure

Structure of acetohydroxyacid synthase (PDB ID:

1YHY) was downloaded from RCSB protein data bank (http://www.rcsb.org). These structures was analyzed by AutoDock tool (Trott and Olson 2010) and converted into .pdbqt file format after addition of polar hydrogen. The grid map of 1YHY centered at the active pocket of protein (www.scfbio-iitd.res.in) lies in the center x 62.341, center y 67.09, center z 58.697 with size are 86, 90, 110.

Molecular docking and analysis

Molecular docking studies were performed by AutoDock vina using the synthesized derivatives at the active site pocket of receptor for the analysis of interactions. For each ligand, all the conformers with their best interaction on the basis of their docking energy and number of hydrogen bonds were selected for analysis. Ligplot were used for the analysis and visualization of protein ligand interaction.

RESULTS AND DISCUSSION

AHAS protein catalyzes the biosynthesis of BCAA in plants (Ray 1984, Duggleby and Pang 2000). So, AHAS protein is a major target for the development of new herbicides (Wang *et al.*, 2011, Pang et al 2002**).** Moreover, AHAS protein is not present in human and other animals, so if such compounds are searched which inhibit AHAS protein, they will be having no harmful effect in animals and humans being sulfonylurea derivatives, a potent class of herbicides, also show same mode of action as they inhibit AHAS protein enzyme.

In the present studies we utilized the power of computational chemistry and bioinformatics tools for identification of agriculturally important molecules. All the previously designed compounds in our lab were docked with AHAS protein to investigate its binding affinity. Derivative 1a showed binding energy -8.3 Kcal/mol with AHAS protein, it binds at amino acid residue Thr331with one hydrogen bond; 1b showed binding energy -8.5 Kcal/mol and binds at Ser186, Arg246, Ile396 with three hydrogen bonds (Fig. 2a); 1c showed binding energy -6.8 but no hydrogen bond was observed; 1d showed binding energy -7.4 Kcal/mol and bind at His567, Arg583, His643 with three hydrogen bonds;

Table 1: Molecular docking parameter of cinnamanilide and α-amino phosphonic acid derivatives with AHAS

Compound code	Docking energy (Kcal/mol)	No. of H-bond	H-bond length	Interacting amino acid residue
1a	-8.3	1	2.69	Thr331
1b	-8.5	3	2.93 3.11 3.10	Ile396, Arg246, Ser186
1c	-6.8	—	—	—
1d	-7.4	3	3.26 2.80 3.15	His643, His567, Arg583
1e	-6.5	—	—	—
1f	-6.7	—	—	—
1g	-7.1	3	3.25 3.07 3.02	His643, His567, Arg583
1h	-6.8	1	3.17 3.25	Asn582
1i	-5.6	4	3.35 3.17 3.17	Trp267, Arg109
1j	-6.0	—	—	—
1k	-6.0	—	—	—
1l	-6.2	2	3.13 3.07	His643, His643
1m	-6.5	—	—	—

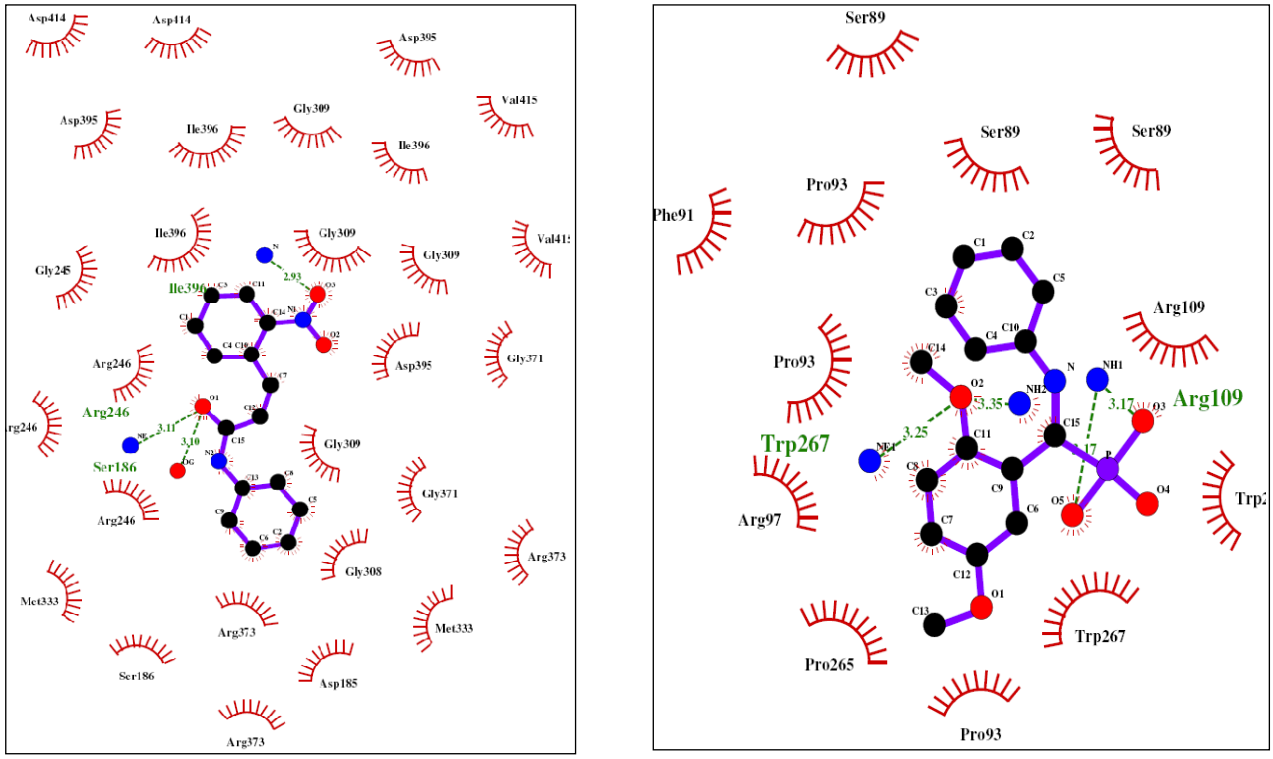

Fig. 2: 2D representation of 3D docked structure of AHAS (a) 1b derivative of cinnamanilide in active site of enzyme and (b) 1i derivative of α-Amino phosphonic acid in active site of enzyme

1e and 1f showed binding energy -6.5 and -6.7 Kcal/mol but no hydrogen bond was observed; 1g showed binding energy -7.1 Kcal/mol and binds at Arg583, His567, His643 with three hydrogen bonds; 1h showed binding energy -6.8 Kcal/mol and bind at Asn582 with one hydrogen bond; 1i showed binding energy -5.6 Kcal/mol and binds at Try267, Arg109 with four hydrogen bonds (Fig. 2b); 1j and 1k showed binding energy -6.0 Kcal/mol but no hydrogen bond was observed; 1l showed binding energy -6.2 Kcal/mol with two hydrogen bonds and 1m showed the binding energy -6.5 Kcal/mol but no hydrogen bonding was observed.

The different parameters such as docking energy, number of hydrogen bonds, hydrogen bond length and amino acid interacting sites of all the docked compounds are shown in Table 1. The designed derivative 2-nitro cinnamanilide and 1-(2,5 dimethoxy phenyl)-1-(phenyl amino) methyl phosphonic acid were found as inhibitor for AHAS and may be developed as potential herbicide.

CONCLUSION

The cinnamanilides and α-amino phosphonic acids were identified as herbicidal agents. 2-nitro cinnamanilide and 1-(2,5 dimethoxy phenyl)-1-(phenyl amino) methyl phosphonic acid exhibit comparable docking energy and number of hydrogen bonds clearly indicating that the cinnamanilide and α-aminophosphonic acid may be developed new type of herbicides for herbicide resistant weeds.

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