Molecular Docking on Azepine Derivatives as Potential Inhibitors for H1N1-A Computational Approach

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***Abstract*—Azepine are an important class of organic compounds. They are effective in a wide range of biological activity such as antifeedants, antidepressants, CNS stimulants, calcium channel blocker, antimicrobial and antifungal properties. In our continue efforts to search for a potent inhibitor for H1N1 virus using molecular docking. In this study, 15 azepine (ligands) derivatives were docked to the neuraminidase of A/Breving Mission/1/1918 H1N1 strain in complex with zanamivir (protein). The Cdocker energy was then calculated for these complexes (protein-ligand). Based on the calculation, the lowest Cdocker interaction energy was selected and potential inhibitors can be identified. Compounds MA4, MA7, MA8, MA10, MA11 and MA12 with promising Cdocker energy was expected to be very effective against the neuraminidase H1N1.**

***Keywords*— molecular docking, azepine derivative, H1N1, computational**

I. INTRODUCTION

Azepine are well established in pharmacological and medicinal chemistry. However, limited number of studies had been carried out on the synthesis and structure activity relationship (SAR) for azepine, especially in terms of anti-viral activities. The anti-viral effects of benzodiazepines and benzothiazepines have mainly been focused on HIV and hepatitis viruses. Dibenzothiazepinethione derivatives to have anti-viral activities against Varicella-Zoster virus, hepatitis B and HIV-1 [1]. In another study, Delpa and co-workers showed 1,4- benzothizapines and 1,4-benzodiazepines with a peptide side-chain to have inhibitory effect on hepatitis B, and D viruses by affecting the binding of the hepatitis virus to annexin V [2].

Our recent interest in azepines has been inspired by the anti-viral properties of this class of compounds. Thus, in this study we explored on neuraminidase inhibitory activity. To the best of our knowledge, there are a limited number of reports on the computational approach (i.e. docking) of azepine derivative as H1N1 inhibitors.

II. METHODOLOGY

The docking of these 15 azepine compounds [3] (i.e. general molecular structure as presented in Figure 1) onto the neuraminidase of A/Breving Mission/1/1918 H1N1 strain in complex with zanamivir which downloaded from PDB data bank (www.pdb.org, PDB ID: 3B7E) was achieved using Discovery studio 2.5 software packages (Accelrys). The docking proses were beginning with the preparation of ligand and the protein. Hydrogen atoms were added to the protein and its backbone was minimized. All ligands were minimized before docking.

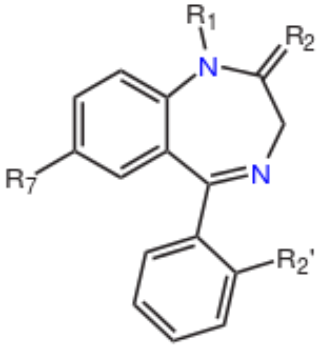

Fig. 1 Molecular structure of benzothiazepine

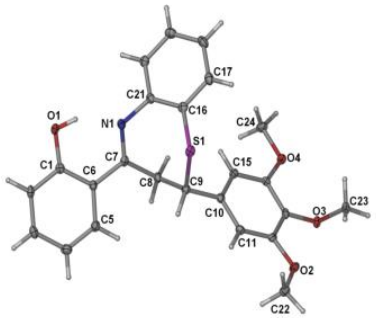

Fig. 2 Xray crystal structure

Docking was performed through the Cdocker protocol. In general, cdocker is a grid based molecular docking method that employs CHARMM forcefields. This protein was firstly held rigid the ligand were allowed to flex during the refinement. Two hundred ligand conformations were then generated from the initial ligand structure though high temperature molecular dynamic followed by random rotation, refinement with grid based (GRID 1) simulated annealing and

a final grid based or full force field minimization. Upon completion of the docking proses, conformations with the lowest cdocker energy were then chosen and compared with DANA (active agents against neuramininidase H1N1 with Cdocker energy equal to -46.11 kcal/mol).

III. RESULT AND DISCUSSION

Docking studies were performed to evaluate the effects of agents against neuraminidase. The Cdocker energy reflects the interaction energy for the ligand-protein complex and the lower energy means the interaction is more stable. The results of Cdocker energy are presented in Table I.

TABLE I
CDOCKER ENERGY OF AZEPINE

No	Compounds	Cdocker energy (kcal/mol)
1	MA1	29.26
2	MA2	27.82
3	MA3	32.81
4	MA4	40.52
5	MA5	28.85
6	MA6	28.75
7	MA7	32.86
8	MA8	35.34
9	MA9	25.63
10	MA10	34.31
11	MA11	36.23
12	MA12	39.08
13	MA13	23.50
14	MA14	29.75
15	MA15	23.26

The cdocker energy of MA4, MA7, MA8, MA10, MA11 and MA12 compounds were relatively close to the active agents (DANA). It indicated that those compounds can be used as new active compounds against neuramininidase H1N1, this observation might be due to the azepine as a ligand is binding well to the active site of the protein.

IV. CONCLUSIONS

Azepines with promising Cdocker energy (compared to DANA with Cdocker interaction energy equal to -46.11 kcal/mol) were expected to be active against neuraminidase. Cdocker energy reflects a logical progression for early stage drug discovery that can be used to successfully identify drug candidates. Further studies are to do the biological test to validate the computational results.

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