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Design, synthesis and biological evaluation of novel oseltamivir derivatives as potent neuraminidase inhibitors

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ABSTRACT

Neuraminidase (NA) is one of the particular potential targets for novel antiviral therapy. In this work, a series of neuraminidase inhibitors with the cyclohexene scaffold were studied based upon the combination of 3D-QSAR, molecular docking, and molecular dynamics techniques. The results indicate that the built 3D-QSAR models yield reliable statistical information: the correlation coefficient (r^2) and cross-validation coefficient (q^2) of CoMFA (comparative molecular field analysis) are 0.992 and 0.819; the r^2 and q^2 of CoMSIA (comparative molecular similarity analysis) are 0.992 and 0.863, respectively. Molecular docking and MD simulations were conducted to confirm the detailed binding mode of enzyme-inhibitor system. The new NA inhibitors had been designed, synthesized, and their inhibitory activities against group-1 neuraminidase were determined. One agent displayed excellent neuraminidase inhibition, with IC_{50} value of 39.6 μM against NA, while IC_{50} value for oseltamivir is 61.1 μM. This compound may be further investigated for the treatment of infection by the new type influenza virus.

As worldwide epidemic strains, influenza can cause acute respiratory diseases and annual influenza pandemic. The swine-origin H1N1 influenza virus unleashed a severe public panic in 2009.[1] It is reported that highly pathogenic influenza virus H5N1 can lead to an alarming life threatening (60% mortality),[2,3] and recent studies have raised a major concern on possible transmission of avian influenza virus H5N1 to humans. A lethal avian influenza H7N9 has evolved to influence human since 2013, endemic to China.

Neuraminidase (NA), a membrane-bound glycoprotein, playing a dominant role in the viral life cycle.[4] The phylogenetic tree divides all neuraminidase subtypes into two groups,[5] there exists a large cavity (termed 150-cavity) in group-1 NAs, adjacent to the active site of proteins, whereas that is not found in group-2 NAs.[6] Neuraminidase inhibitors (NAIs) had been regarded as the most potent agents to cure influenza disease. Up to now, four NA inhibitors have been developed as efficacious treatment of influenza infections: oseltamivir (1), zanamivir (2), peramivir (3), and laninamivir (4) (Fig. 1).[7] Among these, orally administered oseltamivir (OS) has been posed to treat broader cases since its approval in 1999, while recently, several reported oseltamivir-resistant strains have seriously limited the drug's clinical application.[8–12] Zanamivir is primarily administered by inhalation via a nebulizer or intravenous channels.[13] Peramivir has been authorized in the Republic of Korea and China, and laninamivir have to date been approved as antiviral drugs in Japan.[14,15] Nevertheless, variant strains that are against these drugs are also continuously been discovered.

Recent papers have reported some progresses in NA and its inhibitors in theoretical and experimental studies. For instance, Chen et al.[16] discovered a series of crenatoside analogs as novel influenza neuraminidase inhibitors, identified by biological evaluation. Hoffmann et al.[17] developed a platform for determining the inhibition profile of NAIs in the N1 background. In addition, Xie et al.[18] had designed and synthesized two series of oseltamivir derivatives. Of these, two compounds obtained by introduction of biphenyl substituents into the C-5 NH_2 position exhibited comparable or even better inhibitory activities relative to the OS carboxylate against N1.

In this work, 65 oseltamivir analogs were selected as dataset.[18,19] Some studies were employed using computational methods including 3D-QSAR, molecular docking and MD simulations. The results of CoMFA and CoMSIA supply insights into key structural factors required for the neuraminidase inhibition.[20,21] Molecular docking and MD simulations were performed to validate the 3D-QSAR models and quantify the interactions of NA-ligand.[22–27] Previous studies showed that the biphenyl substituents introduced into C5-NH_2 of ligand could improve compound's biological activity.[28–30] In terms of substituent's structure, the chemical bonds between the biphenyl groups can be freely rotated, this increases

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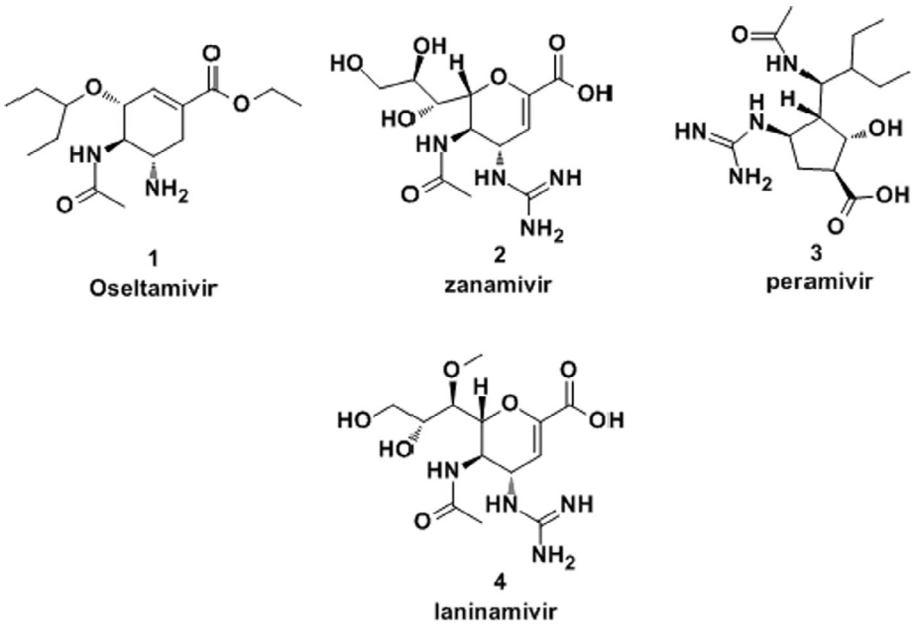

Fig. 1. Structures of the approved NA inhibitors 1–4.

the opportunity to interact with neighbouring amino acid residues. Accordingly, some new oseltamivir derivatives were designed by introduction of biphenyl substitutes into the C5 NH_2 position based on the built 3D-QSAR contour maps. Finally, the new designed molecules were further confirmed by experimental synthesis and biological evaluation.

The 65 oseltamivir derivatives in this paper randomly divided into 55 training set compounds (84.6%) for model generation and 10 test set compounds (15.4%) for model validation. The chemical structures, active values against neuraminidase subtype 1 are listed in Supplementary Information (Table S1). To build more reliable and statistical 3D-QSAR models, we corrected the active data originating in two independent documents to eliminate errors. The specific method is as follows: the IC_{50} active values were converted into the corresponding pIC_{50} ($-\log IC_{50}$) values, then the pIC_{50} values were transformed into superior pIC_{50} values ($pIC_{50}c$), used as dependent variables to build molecular models. $pIC_{50}c$ values were obtained according to the following formula[31]:

$$pIC_{50}c = pIC_{50}/pIC_{50}(\text{OS-C}) \quad (1)$$

Where pIC_{50}, pIC_{50}(OS-C) represent the experimental bioactive data of the data set compounds and oseltamivir carboxylate (OS-C), respectively.

In this study, the ligand-based alignment rule was used. The alignment result is shown in Fig. 2. We performed regression analysis using partial least squares (PLS) to evaluate and judge merits or demerits of the model with some statistical parameters, including r^2, q^2, standard error of estimate (SEE) and F-test values. The best optimal value of CoMFA and CoMSIA models are listed in Table 1. From this, we observed both models show satisfactory predictive capability, with q^2, r^2, and SEE are 0.819, 0.992, 0.013 for CoMFA model, and 0.863, 0.992, 0.014 for CoMSIA model. In Fig. 3, the linear fit between actual and predicted activity of the best optimal CoMFA and CoMSIA model is described, the residual values of drugs between the predicted and actual pIC_{50} exceeded 1 logarithm unit is treated as outliers (compounds **56** and **60**).[32] Actually, when the classical internal validation parameter q^2 is greater than 0.5, a model is reassuring and predictive.[33,34] Determined by leave-one-out validation, the optimal principal components of CoMFA and CoMSIA are 8 and 9, respectively. The F-test

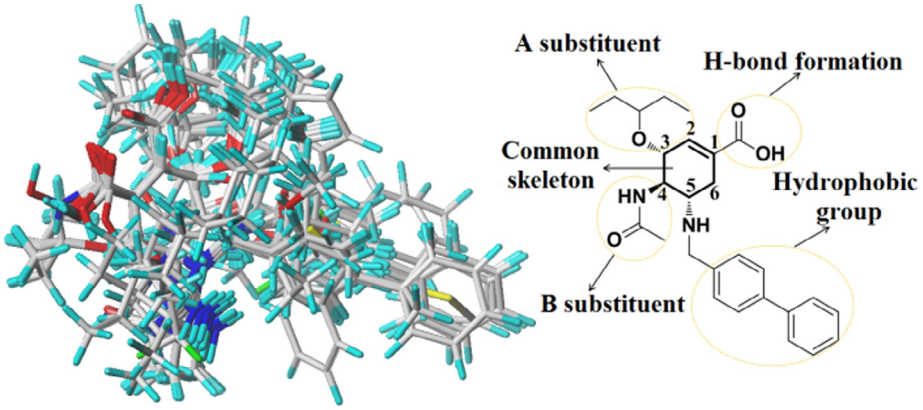

Fig. 2. Superimposition of the training set and compound **25** used as a template for alignment. Molecules are colored in white for common C, cyan for H, red for O, blue for N, yellow for S, green for F, Cl & Br, respectively. The common substructure is cyclohexene (shown in bold), and other important substituents involving A, B, H-bond formation substituent and hydrophobic groups, shown in dashed orange frame.