molecules

MDPI

Supplementary Materials

Identification of influenza PA$_N$ endonuclease inhibitors via 3D-QSAR Modeling and docking-based virtual screening

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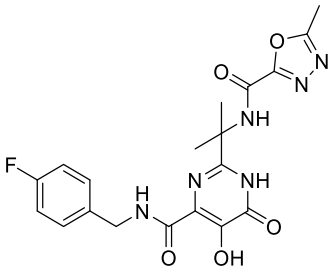
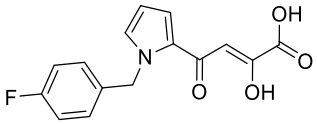
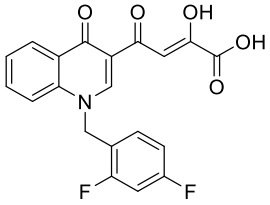
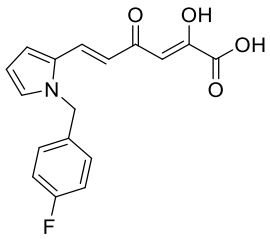
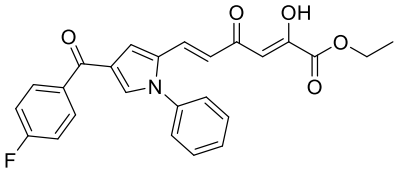
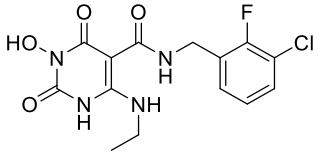
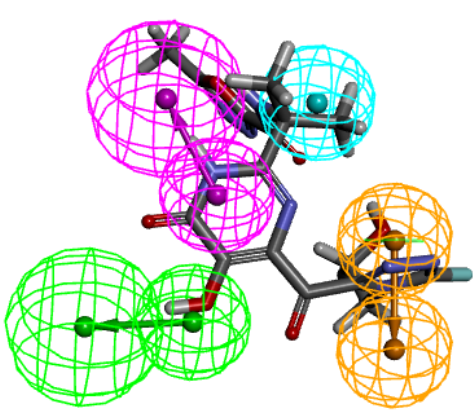
Table S1. Structures of selected candidate compounds (**Hit 1 – Hit 6**) with Estimate activity and Fit value.

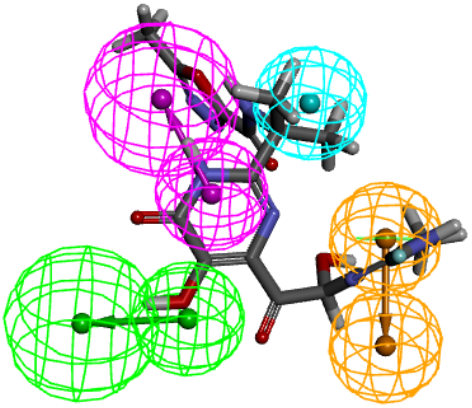
Compound	Structure	Estimated IC_{50} value (μM)	Fit value
Hit01		1.16424	4.56426
Hit02		1.31451	4.51154
Hit03		0.158572	5.43007
Hit04		0.942881	4.65584
Hit05		1.97529	4.33467
Hit06		4.63103	3.96462

We carried out active prediction using the generated Hypo1 pharmacophoric model. It was obviously to see that the novel 6 compounds mapped well with all chemical features (Figure S1), including one hydrogen bond acceptor (HBA), one hydrogen bond

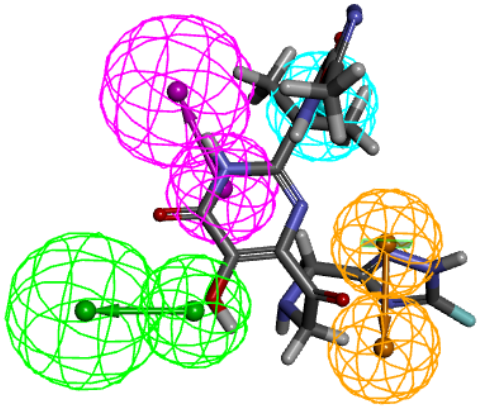
donnor (HBD), one hydrophobic (HYD) and one ring aromatic (RA). And the estimated activities were extremely lower than the lead compounds.



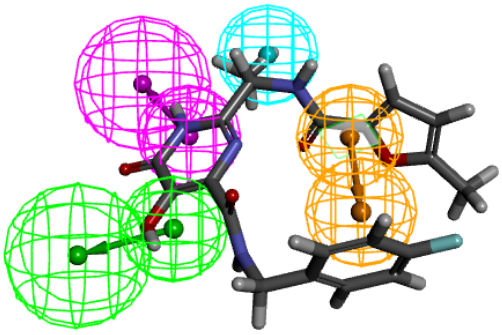
Hit07 – Hypo1



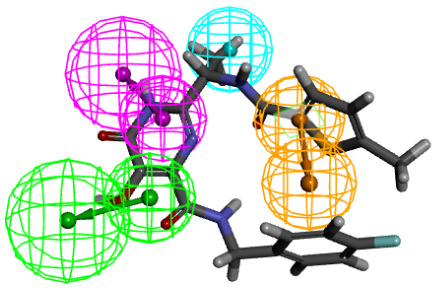
Hit08 – Hypo1



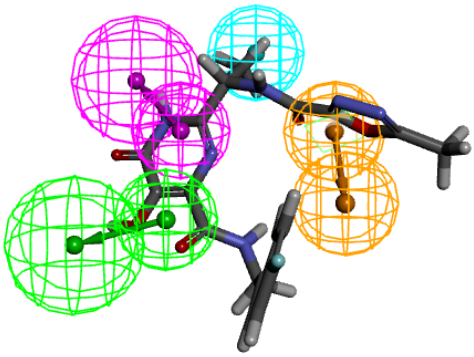
Hit09 – Hypo1



Hit10 – Hypo1



it11 – Hypo1



Hit12 – Hypo1

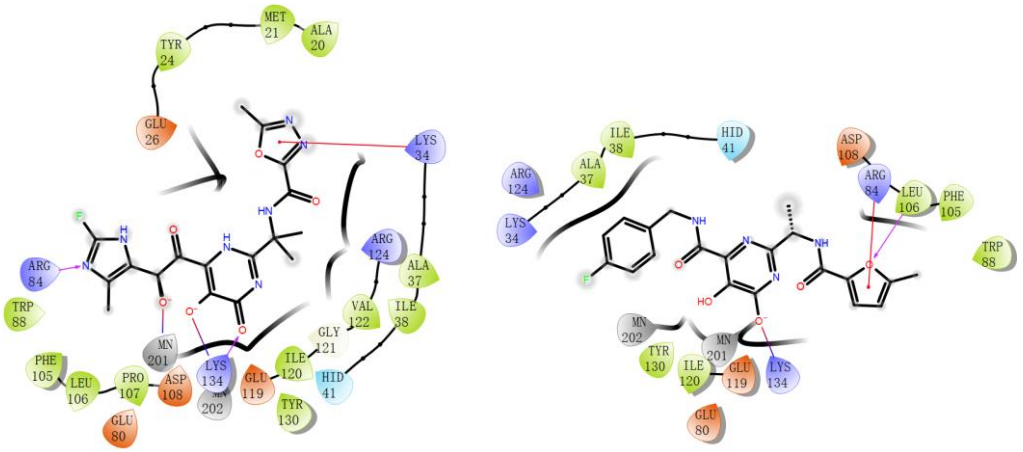
H

Figure S1. Pharmacophore mapping of the six compounds.

Then we selected typical compounds (**Hit08** and **Hit10**) to analyze the docking poses using Glide program in 2015 Schrödinger software package. The specific docking poses were showed in Figure S2.

Compound **Hit08** (N-{2-{4-[2-(2-fluoro-5-methyl-1H-imidazol-4-yl)-2-hydroxyacetyl]-5-hydroxy-6-oxo-1,6-dihydropyrimidin-2-yl}propan-2-yl}-5-methyl-1,3,4-oxadiazole-2-carboxamide) was found to interact with amino acids Lys34 and Lys134, which were all essential binding site residues. The carbonyl oxygen atom in pyrimidinone formed one hydrogen bond interactions with amino acids Lys 134. The 1,3,4-oxadiazole generated Pi-cation bond with amino acids Lys34. Furthermore, the Hydroxyl oxygen atom in pyrimidinone generated salt bridge with amino acids Lys134 (Fig. 10A). The first Mn^{2+} ion of PAN interacts with the oxygen atom of its carboxylate moiety and the α-hydroxyl group while the carboxylate of pyrimidinone moiety chelates the second Mn^{2+} ion.

Compound **Hit10** (N-(4-fluorobenzyl)-5-hydroxy-2-[1-(5-methylfuran-2-carboxamido)ethyl]-6-oxo-1,6-dihydropyrimidine-4-carboxamide) was able to form one hydrogen bond interaction with amino acid Leu106. The furan ring generated Pi-cation bond with amino acids Lys34. Hydroxyl oxygen atom in pyrimidinone also generated salt bridge with amino acids Lys134. The carboxylate of pyrimidinone moiety chelates the first Mn^{2+} ion, while the second Mn^{2+} ion of PAN interacts with the oxygen atom of its amide moiety and the α-hydroxyl group of pyrimidinone moiety.



Hit08 – 6E6W **Hit10**– 6E6W

Figure S2. The binding interactions of **Hit08** and **Hit10** with PAN endonuclease protein (PDB ID 6E6W)