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A Novel Small-Molecule Inhibitor of Influenza a Virus Acts by Suppressing PA Endonuclease Activity of the Viral Polymerase

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Abstract : The RNA-dependent RNA polymerase of influenza a virus comprises conserved and independently folded subdomains with defined functionalities. The N-terminal domain of the PA subunit (PAN) harbors the endonuclease function so that it can serve as a desired target for drug discovery. To identify a class of anti-influenza inhibitors that impedes PAN endonuclease activity, a screening approach that integrated the fluorescence resonance energy transfer based endonuclease inhibitor assay with the DNA gel-based endonuclease inhibitor assay was conducted, followed by the evaluation of antiviral efficacies and potential cytotoxicity of the primary hits in vitro and in vivo. A small-molecule compound ANA-0 was identified as a potent inhibitor against the replication of multiple subtypes of influenza A virus, including H1N1, H3N2, H5N1, H7N7, H7N9 and H9N2, in cell cultures. Combinational treatment of zanamivir and ANA-0 exerted synergistic anti-influenza effect in vitro. Intranasal administration of ANA-0 protected mice from lethal challenge and reduced lung viral loads in H1N1 virus infected BALB/c mice. Docking analyses predicted ANA-0 bound the endonuclease cavity of PAN by interacting with the metal-binding and catalytic residues. In summary, ANA-0 shows potential to be developed to novel anti-influenza agents.

Keywords : anti-influenza, novel compound, inhibition of endonuclease, PA
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