Point-by-point responses to the comments of the Editor and reviewers, and a list of changes are:

Editor and Reviewer comments:

Thank you for the evaluation of our manuscript and we appreciate the reviewers' constructive criticism that helped us significantly improve the quality of our manuscript.

Please find below our point-by-point response to the comments.

Reviewer #2:

1. The manuscript should be seriously improved prior to publication. The main drawback is the lack of principal characteristics of viruses used. The only results of the study are values of synergistic effect for various combinations of antivirals. Authors postulate that they used baloxavir- and NAI-resistant viruses. However, no indications are presented to resistance or susceptibility of viruses to specific drug, viruses are marked by amino acid substitutions only. Is PR8-R292K virus resistant to baloxavir? Resistant to NAI? Susceptible to both? If resistant to NAI, what specific drug(s) of NAI class it is resistant to? The same questions should be answered about all other viruses used in the study.

Response: We are grateful that this comment is very important to improve the quality of the manuscript, so we added the relevant information as suggested by the reviewer. Please refer to page 2, lines 19-27. Briefly, the R292K substitution in neuraminidase led to a reduction in or even the complete loss of influenza inhibitory activity of almost all neuraminidase inhibitors (oseltamivir acid, zanamivir, and peramivir), while exhibiting no effect on baloxavir, a drug that acts on the influenza PA protein. The I38T substitution in PA protein resulted in a notable reduction of influenza inhibitory activity observed in baloxavir while exhibiting no discernible effect on NAIs.

2. Why authors selected influenza B virus for the study? What are its main differences from other viruses? Is it susceptible or resistant to the drugs under investigation?

Response: We are very grateful for the questions raised by the reviewer. Both influenza A viruses and B viruses circulate and cause local outbreaks or seasonal epidemics in the world and pose a serious threat to public health and health. According to the Global Influenza Surveillance and Response System (GISRS) data published by WHO, of those infected with influenza, 84.2% were typed as influenza A and 15.8% were typed as influenza B [1]. Baloxavir marboxil was approved as a single-dose treatment for influenza A and B, and neuraminidase inhibitors (NAIs) including oseltamivir acid, zanamivir, laninamivir, and peramivir are effective against influenza A and B virus, so we selected also influenza B virus for the study at the same time.

According to our previous experimental results, several of the drugs involved in the study are susceptible to influenza B virus.

3. How was the baloxavir- and NAI-resistance confirmed phenotypically? What is the value of IC_{50}'s for sensitive viruses and mutants used in the study against the drugs used?

Response: Thank you for your insightful question. Baloxavir and NAIs resistant phenotypes were

confirmed by Cytopathic Effect (CPE) Reduction Assay. Based on previous research findings [2], the average EC_{50} values for oseltamivir against A/WSN/33 strain and WSN-I38T strain were 0.02 μM and ＞10 μM, respectively. The average EC_{50} values for oseltamivir against the PR/8 strain and PR/8-R292K strain were 3.58 μM and ＞100 μM, respectively. The average EC_{50} value for oseltamivir against influenza B virus was 3.08 μM. By using the MacSynergy II program, the three-dimensional peaks above and below the plane were represented as quantitated synergy and antagonism of the interaction of both indicated drugs. These results indicated that the combination of drugs could improve the antiviral effect of resistant strains.

4. The extent of synergy regarding combination of baloxavir with different NAI's appeared different. How authors explain this?

Response: Based on the literature and our previous research, NAIs have different structures and exhibit varying sensitivities to the R292K mutant strain, leading to differences in the synergistic effects when baloxavir is combined with different NAIs.

5. Stronger conclusion for practical use of antivirals should be done. For instance, what is optimal combination of drugs?

Response: Thank you for your suggestion. We have added some stronger conclusions to the manuscript, please refer to page 9, lines 30-35.

6. Comments on the Quality of English Language

p.1. Change to read "four classes of drugs"

p.2. "…protected them from severe pathogenesis". Please re-phrase to avoid protection from pathogenesis, not disease.

Page 3, first line. Change to read "…with influenza virus baloxavir-resistant…"

Page 8. Change to read "…found that viruses bearing I38T and I38S mutations were less sensitive…"

Response: Thank you for highlighting the grammatical and technical errors in our manuscript. We have corrected these errors in our revised manuscript. Please refer to Pages 1, 2, 3, 8, 9.

1. World Health Organization. Influenza Update N° 463 (who.int)

2. Zhao, L.; Yan, Y.; Dai, Q.; Li, X.; Xu, K.; Zou, G.; Yang, K.; Li, W.; Guo, X.; Yang, J.; Li, Y.; Xia, Q.; Cao, R.; Zhong, W., Development of Novel Anti-influenza Thiazolides with Relatively Broad-Spectrum Antiviral Potentials. Antimicrobial agents and chemotherapy 2020, 64 (7).