Received: 18 February 2017 | Revised: 1 May 2017 | Accepted: 9 May 2017

DOI: 10.1002/jmr.2644

WILEY Journal of Molecular Recognition

RESEARCH ARTICLE

# Computational modeling of the bat HKU4 coronavirus 3CL$^{pro}$ inhibitors as a tool for the development of antivirals against the emerging Middle East respiratory syndrome (MERS) coronavirus

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**Funding information**
CRDF Global, Grant/Award Number: 61556 and 61557; National Science Foundation, Grant/Award Number: OISE-9531011; US Civilian Research & Development Foundation (CRDF Global), Grant/Award Number: 61556 and 61557

## Abstract

The Middle East respiratory syndrome coronavirus (MERS-CoV) is an emerging virus that poses a major challenge to clinical management.

The 3C-like protease (3CL$^{pro}$) is essential for viral replication and thus represents a potential target for antiviral drug development. Presently, very few data are available on MERS-CoV 3CL$^{pro}$ inhibition by small molecules. We conducted extensive exploration of the pharmacophoric space of a recently identified set of peptidomimetic inhibitors of the bat HKU4-CoV 3CL$^{pro}$. HKU4-CoV 3CL$^{pro}$ shares high sequence identity (81%) with the MERS-CoV enzyme and thus represents a potential surrogate model for anti-MERS drug discovery. We used 2 well-established methods: Quantitative structure-activity relationship (QSAR)-guided modeling and docking-based comparative intermolecular contacts analysis. The established pharmacophore models highlight structural features needed for ligand recognition and revealed important binding-pocket regions involved in 3CL$^{pro}$-ligand interactions. The best models were used as 3D queries to screen the National Cancer Institute database for novel nonpeptidomimetic 3CL$^{pro}$ inhibitors. The identified hits were tested for HKU4-CoV and MERS-CoV 3CL$^{pro}$ inhibition. Two hits, which share the phenylsulfonamide fragment, showed moderate inhibitory activity against the MERS-CoV 3CL$^{pro}$ and represent a potential starting point for the development of novel anti-MERS agents. To the best of our knowledge, this is the first pharmacophore modeling study supported by *in vitro* validation on the MERS-CoV 3CL$^{pro}$.

### Highlights:

- MERS-CoV is an emerging virus that is closely related to the bat HKU4-CoV.
- 3CL$^{pro}$ is a potential drug target for coronavirus infection.
- HKU4-CoV 3CL$^{pro}$ is a useful surrogate model for the identification of MERS-CoV 3CL$^{pro}$ enzyme inhibitors.
- dbCICA is a very robust modeling method for hit identification.
- The phenylsulfonamide scaffold represents a potential starting point for MERS coronavirus 3CL$^{pro}$ inhibitors development.

KEYWORDS

3CL$^{pro}$ inhibitors, coronavirus, dbCICA, MERS, pharmacophore modeling

  