



The Open Medicinal Chemistry Journal

Content list available at: <https://openmedicinalchemistryjournal.com>



EDITORIAL

In Search of Antiviral Metal-Based Drugs

Manos Vlasiou^{1,*}

¹Department of Life and Health Sciences School of Sciences and Engineering P.O.Box 24005, CY-1700, Nicosia, Cyprus

Article History

Received: October 5, 2021

Revised: October 10, 2021

Accepted: October 12, 2021

Even though several vaccines have been developed against several infectious diseases (antiviral included), we still need efficient drugs that can be active against virus mutations in cases when the disease develops and overpass the vaccine strategy. Some infections such as influenza, HIV, or SARS Cov-2 can be lethal if left untreated and it is not necessary to mention the importance of the antiviral drugs.

Important protein targets that need inhibition and are responsible for viral diseases are for example the viral polymerase enzyme, which performs transcription and replication of the RNA genome for influenza [1]. Additionally, the influenza virus genome consists of eight single-stranded (-) RNA segments, which are transcribed and replicated by the viral RNA-dependent RNA polymerase [2]. Moreover, the Human immunodeficiency virus (HIV) encodes four essential enzymes: protease, integrase, reverse transcriptase (RT)-associated DNA polymerase, and RT-associated ribonuclease H (RNase H) [3, 4]. SARS-CoV-2, a positive-strand RNA virus encodes four structural proteins, namely the matrix (M), small envelope (E), spike (S), and nucleocapsid phosphoprotein (N) [5].

Having in mind the resistivity in inhibition for already approved drugs, we know that we have to examine different possibilities in drug discovery. A very promising area and relatively non-discovered is the development of metal-based antiviral drugs. We now have cisplatin which is an anticancer drug in use, showing that metals are very promising for the development of drugs additionally to the organic ones. The different oxidation states of the metals alongside their existence in the active sites of the enzymes justify their need in use [6].

Recently, due to the covid pandemic, more and more researchers are trying to discover and develop metal-based factors with antiviral activity [7, 8]. Although there are limited the efforts compared to the solely organic small molecules,

some of them have shown promising results [9]. The use of computer-aided drug discovery, which was previously limited to organic molecules, has started to be used to metal complexes, opening new opportunities and examples [10].

Overall, more research should be done in this promising area of metal-based drugs, not just for antiviral therapies, but also for other areas where small inhibitors of target proteins are needed.

CONFLICT OF INTEREST

Dr. Manos Vlasiou is the Editorial Board Member for the The Open Medicinal Chemistry Journal.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Bergstrom, D.E.; Lin, X.; Wood, T.D.; Witvrouw, M.; Ikeda, S.; Andrei, G.; Snoeck, R.; Schols, D.; De Clercq, E. Polysulfonates derived from metal thiolate complexes as inhibitors of HIV-1 and various other enveloped viruses *in vitro*. *Antivir. Chem. Chemother.*, **2002**, *13*(3), 185-195. [<http://dx.doi.org/10.1177/095632020201300305>] [PMID: 12448691]
- [2] Kowalinski, E.; Zubieta, C.; Wolkerstorfer, A.; Szolar, O.H.J.; Ruigrok, R.W.H.; Cusack, S. Structural analysis of specific metal chelating inhibitor binding to the endonuclease domain of influenza pH1N1 (2009) polymerase. *PLoS Pathog.*, **2012**, *8*(8)e1002831 [<http://dx.doi.org/10.1371/journal.ppat.1002831>] [PMID: 22876177]
- [3] Himmel, D.M.; Myshakina, N.S.; Iliina, T.; Van Ry, A.; Ho, W.C.; Parniak, M.A.; Arnold, E. Structure of a dihydroxycoumarin active-site inhibitor in complex with the RNase H domain of HIV-1 reverse transcriptase and structure-activity analysis of inhibitor analogs. *J. Mol. Biol.*, **2014**, *426*(14), 2617-2631. [<http://dx.doi.org/10.1016/j.jmb.2014.05.006>] [PMID: 24840303]
- [4] Carcelli, M.; Rogolino, D.; Bacchi, A.; Rispoli, G.; Fiscaro, E.; Compari, C.; Sechi, M.; Stevaert, A.; Naesens, L. Metal-chelating 2-hydroxyphenyl amide pharmacophore for inhibition of influenza virus endonuclease. *Mol. Pharm.*, **2014**, *11*(1), 304-316. [<http://dx.doi.org/10.1021/mp400482a>] [PMID: 24206028]
- [5] Kankanala, J.; Kirby, K.A.; Liu, F.; Miller, L.; Nagy, E.; Wilson, D.J.; Parniak, M.A.; Sarafianos, S.G.; Wang, Z. Design, Synthesis, and Biological Evaluations of Hydroxypyridonecarboxylic Acids as Inhibitors of HIV Reverse Transcriptase Associated RNase H. *J. Med. Chem.*, **2016**, *59*(10), 5051-5062. [<http://dx.doi.org/10.1021/acs.jmedchem.6b00465>] [PMID: 27094954]

* Address correspondence to this author at Department of Life and Health Sciences School of Sciences and Engineering P.O.Box 24005, CY-1700, Nicosia, Cyprus; Tel: +357 22 841500; Fax: +357 22 357481; E-mails: vlasiou.m@unic.ac.cy

- [6] Dick, B.L.; Cohen, S.M. Metal-binding isosteres as new scaffolds for metalloenzyme inhibitors. *Inorg. Chem.*, **2018**, *57*(15), 9538-9543. [<http://dx.doi.org/10.1021/acs.inorgchem.8b01632>] [PMID: 30009599]
- [7] Ivashchenko, A.A.; Mitkin, O.D.; Jones, J.C.; Nikitin, A.V.; Koryakova, A.G.; Karapetian, R.N.; Kravchenko, D.V.; Mochalov, S.V.; Ryakhovskiy, A.A.; Aladinskiy, V.; Leneva, I.A.; Falynskova, I.N.; Glubokova, E.A.; Govorkova, E.A.; Ivachtchenko, A.V. Synthesis, inhibitory activity and oral dosing formulation of AV5124, the structural analogue of influenza virus endonuclease inhibitor baloxavir. *J. Antimicrob. Chemother.*, **2021**, *76*(4), 1010-1018. [<http://dx.doi.org/10.1093/jac/dkaa524>] [PMID: 33367751]
- [8] Pérez-Sánchez, H.; Thirumal Kumar, D.; George Priya Doss, C.; Rodríguez-Schmidt, R.; Cerón-Carrasco, J.P.; Peña-García, J.; Ye, Z.W.; Yuan, S.; Günther, S. Prediction and characterization of influenza virus polymerase inhibitors through blind docking and ligand based virtual screening. *J. Mol. Liq.*, **2021**, *321* [<http://dx.doi.org/10.1016/j.molliq.2020.114784>]
- [9] Karges, J.; Stokes, R.W.; Cohen, S.M. Photorelease of a metal-binding pharmacophore from a Ru(II) polypyridine complex. *Dalton Trans.*, **2021**, *50*(8), 2757-2765. [<http://dx.doi.org/10.1039/D0DT04290K>] [PMID: 33564808]
- [10] Vlasίου, M.C.; Pafiti, K.S. Screening possible drug molecules for Covid-19. The example of vanadium (III/IV/V) complex molecules with computational chemistry and molecular docking. *Comput. Toxicol.*, **2021**, *18100157* [<http://dx.doi.org/10.1016/j.comtox.2021.100157>] [PMID: 33553857]

© 2021 Manos Vlasίου

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: <https://creativecommons.org/licenses/by/4.0/legalcode>. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.