Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Current trends in designing antiviral agents against emerging and re-emerging RNA viruses

RNA viruses have always been a great threat to human civilization, and these have evolved along with humanity's progress. In parallel, this large group of viruses constitutes a great challenge for humankind, which is not yet properly prepared for. The most indisputable proof for this fact is verified in the COVID-19 pandemic (SARS-CoV-2), which resulted in immeasurable economic impacts, as well as thousands of deaths worldwide. Still, other viruses were able to leave their negative marks on the history of our modern society, such as Hepatitis C (HCV), Influenza (INFV), HIV, Ebola (EBOV), Marburg (MARV), Zika (ZIKV), MERS- and SARS-CoV, among others. All these viruses have RNA as genetic material, which may be a single- or double-stranded RNA. Moreover, their viral life cycle exhibits numerous promising targets for designing antivirals, such as RNA-dependent RNA polymerase (RdRp) and diverse proteases. A meaningful number of both on the market and new clinical trials, target different steps of the viral life cycle. In this context, several research groups have dedicated their scientific efforts to discovering new potential biological targets, improving the structural data of known targets, as well as repurposing drugs, develop synthetic and/or natural compounds. Thusly, in the last few decades, great advances have been made in the field of medicinal chemistry focused on the development of new antiviral agents. Then, this special volume was designed to bring some most relevant advances in this field that may inspire researchers around the world.

Regarding the importance of the development of novel antiviral compounds, S. Mahajam, S. Tomar, and co-workers[1] provided a great overview of molecular mechanisms involved in innate/adaptive responses to viral infection caused by ZIKV, HCV, Japanese encephalitis (JEV), Chikungunya (CHIKV), Dengue (DENV), and SARS-CoV-2 (COVID-19), and antiviral strategies targeting host factors. The authors concluded that host-directed antiviral agents might prove to be a rewarding approach in controlling the unprecedented spread of viral infection. However, their side effects on the host cells should not be ignored. In the context of the COVID-19 pandemic, L. Paulsson-Habegger, S.P. Wren, and coauthors[2] elaborated a review highlighting the enzymatic inhibition as a potential therapeutic strategy to combat this RNA virus, in which the authors supported that TMPRSS2 constitutes the most promising target to treat this disease. Besides, J.A. Takahashi, L.P.S. Pimenta, and collaborators[3] produced a review focused on some antiviral fungal metabolites targeting COVID-19. They explored the metabolic adaptability of fungi during fermentation to produce metabolites active against RNA viruses, including also DENV, ZIKV, HIV, H1N1, and Hepatitis. Still, S. Murtuja, V. Jayaprakash, and co-workers[4] wrote a short review on the DENV protease inhibitors in the past 6 years with an emphasis on similarities between DENV and SARS-CoV-2 proteases. They compared the substrate-peptide residue preferences and the residues lining the sub-pocket of the proteases of these viruses, as well as analyzed their similarities.

In recent decades, virtual screening studies have attracted even more attention, mainly after the emergence of SARS-CoV-2. Then, Y. Gupta, P. Kempaiah, and collaborators[5] produced a study focused on a virtual screening involving a library of hydroxyethylamine (HEA) derivatives as $3CL^{pro}$ inhibitors. By using *in silico* approaches the authors found a promising HEA, which posteriorly was screened *in vitro,* and its activity was improved by the application of additional steps involving virtual protocols. Similarly, molecular docking studies were performed by J.L. Vique-Sánchez[6] to identify potential inhibitors interacting in Neuropilin-1 (NRP1) to act as an adjuvant drug against SARS-CoV-2. The author found that some compounds could bind between the S1 region in the spike protein and b1 region in NRP1, acting as a new adjuvant drug against this virus, which could be safe in humans, following its predicted ADMET properties. In contrast, Y.G. Lee, S.C. Kang, and co-workers[7] developed an experimentally evaluated the antiviral activity of two plants and their components against SARS-CoV-2, which were able to strongly inhibit this virus by interfering with multiple steps of the viral cycle, including its host cell entry and replication. Moreover, three phytochemical compounds displayed strong activity. Finally, the authors suggested that the mixture of both vegetal species could be a promising drug candidate against SARS-CoV-2 and its variants.

Still regarding respiratory viruses, J. Xu, J. Zhou, and coauthors[8] reported the development of substituted hydroxybenzamide analogs as potential inhibitors against respiratory syncytial virus (RSV) replication and RSV infection-associated inflammatory responses. The authors identified that six compounds exhibited low cytotoxicity, being selected for further evaluations. All of them suppressed not only the viral replication but also RSV-induced IRF3 and NF-κB activation and associated production of cytokines/chemokines. Still, studies focused on their mechanism of action revealed that the best two compounds decreased RSV-induced IRF3 phosphorylation at both early and late infection phases.

Focusing on the development of synthetic inhibitors against other RNA viruses, J. Li, P. Zhan, and coauthors[9] designed and synthesized phenylalanine analogs and screened them against HIV-1 capsid. Among their compounds, two of them were found to have exceptional anti-HIV-1 activity in the micromolar range, in which surface plasmon resonance (SPR) binding assay revealed that these compounds prefer to combine with capsid hexamer rather than monomer. Still, the research team supervised by P. Zhan reported the discovery of diarylpyrimidines as HIV-1 NNRTIs against wild-type and K103N mutant viruses,[10] as well as, indolylarylsulfones bearing phenylboronic acid and phenylboronate ester groups as potent HIV-1 non-nucleoside reverse transcriptase

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inhibitors.[11] These research articles represent an immense advance in the of anti-HIV inhibitors, showing remarkable results that could inspire new studies against this RNA virus. Targeting this same virus, P.K. Kushwaha, A. Sharon, and collaborators[12] reported some novel isoxazole containing disubstituted 1,2,4-oxadiazole analogs, by applying non-classical isosteric replacement of an amide group from a lead anti-HIV inhibitor belonging to the research team. For the new compounds synthesized in this study, the anti-HIV potential was checked in human $CD4^+$ reporter cell lines. Then, it was verified that two of their compounds significantly inhibit HIV-1 replication and, according to the authors, these analogs could be considered as a new lead candidate against HIV-1. Another anti-HIV-1 study was performed by F. Curreli, A. K. Debnath, and coworkers.[13] They designed and synthesized a series of CD4-mimetic small molecules as potential HIV-1 entry inhibitors. The best thiazole analog displayed the greatest antiviral activity and selectivity against $HIV\text{-}1_{HXB2}$. Also, the authors tested it against a large panel of HIV-1 Env-pseudotyped viruses representing clinical isolates of diverse subtypes. Thusly, it was verified that its activity and selectivity index were ~3-fold improved. Furthermore, the authors concluded that this inhibitor could be optimized to a more potent and clinically relevant HIV-1 inhibitor.

ZIKV and DENV have been responsible for many cases of human illness and deaths worldwide, mainly in tropical and sub-tropical countries. Notwithstanding this fact, several research teams have addressed their efforts to combat these viruses. Based on this, S. Colarusso, J.M. Ontoria, and collaborators[14] synthesized and evaluated potent C-terminal carboxamide peptide inhibitors of ZIKV NS2B/NS3 protease. In this context, the authors reported a structure–activity relationship (SAR) study on a series of substrate-like linear tripeptides that inhibit in a non-covalent manner this protease at a sub-micromolar range. Posteriorly, some structural modifications were performed at the P1 position, increasing the activity of new compounds, reaching a nanomolar range. Also, these compounds presented high selectivity against trypsin-like proteases and the proteases of other flaviviruses, such as DENV-2 and West Nile virus (WNV). In parallel, the research team supervised by T. Schirmeister[15] synthesized and evaluated the activity of novel benzothiazoles targeting an allosteric pocket of DENV and ZIKV NS2B/NS3 proteases, as well as reporting their SAR analyses. Moreover, they developed a new series of Y-shaped inhibitors, which, with their larger hydrophobic contact surface, should bind to previously unaddressed regions of the allosteric NS2B/NS3 binding pocket. By scaffold-hopping, they varied the benzothiazole moiety and identified benzofuran as a new lead scaffold shifting the selectivity of initially ZIKV-targeting inhibitors to higher activities towards the DENV protease. Finally, these authors were able to increase the ligand efficiency for the best inhibitors with great selectivity, and the cell-based assays were capable of proving their antiviral activity *in cellulo*. Providing a new overview about DENV protease assays, T. Dražić, C.D. Klein, and coworkers[16] elaborated a study focused on the binding mode of DENV protease ligands with modulated basicity and hydrophobicity since peptides can be inhibitors and substrates for proteases. This study describes the inhibitor- *vs*. substrate-like properties of peptide ligands of DENV NS2B/NS3 protease which were designed to provide insight into their binding modes. The authors observed a tendency of basic elements to favor a substrate-like binding mode, whereas hydrophobic elements decrease or eliminate enzymatic cleavage. This fact indicates a necessity to include basic elements which closely mimic the natural substrates into covalent inhibitors, posing a challenge from the chemical and pharmacokinetic viewpoint.

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References

1 Mahajan S, Choudhary S, Kumar P, Tomar S. Antiviral strategies targeting host factors and mechanisms obliging +ssRNA viral pathogens. *Bioorg Med Chem.* 2021; 46:116356. https://doi.org/10.1016/j.bmc.2021.116356.
2 Paulsson-Habegger L, Snabaitis AK, Wren SP. Enzyme inhibition as a potential therapeutic strategy to treat COVID-19 infection. *Bioorg Med Chem.* 2021;48:116389. https://doi.org/10.1016/j.bmc.2021.116389.
3 Takahashi JA, Barbosa BVR, Lima MTNS, Cardoso PG, Contigli C, Pimenta LPS. Antiviral fungal metabolites and some insights into their contribution to the current COVID-19 pandemic. *Bioorg Med Chem.* 2021;46:116366. https://doi.org/10.1016/j.bmc.2021.116366.
4 Murtuja S, Shilkar D, Sarkar B, Sinha BN, Jayaprakash V. A short survey of dengue protease inhibitor development in the past 6 years (2015–2020) with an emphasis on similarities between DENV and SARS-CoV-2 proteases. *Bioorg Med Chem.* 2021;49: 116415. https://doi.org/10.1016/j.bmc.2021.116415.
5 Gupta Y, Kumar S, Zak SE, et al. Antiviral evaluation of hydroxyethylamine analogs: Inhibitors of SARS-CoV-2 main protease (3CLpro), a virtual screening and simulation approach. *Bioorg Med Chem.* 2021;47:116393. https://doi.org/10.1016/j.bmc.2021.116393.
6 Vique-Sánchez JL. Potential inhibitors interacting in Neuropilin-1 to develop an adjuvant drug against COVID-19, by molecular docking. *Bioorg Med Chem.* 2021;33: 116040. https://doi.org/10.1016/j.bmc.2021.116040.
7 Lee Y-G, Kang KW, Hong W, et al. Potent antiviral activity of Agrimonia pilosa, Galla rhois, and their components against SARS-CoV-2. *Bioorg Med Chem.* 2021;45:116329. https://doi.org/10.1016/j.bmc.2021.116329.
8 Xu J, Wu W, Chen H, Xue Y, Bao X, Zhou J. Substituted N-(4-amino-2-chlorophenyl)-5-chloro-2-hydroxybenzamide analogues potently inhibit respiratory syncytial virus (RSV) replication and RSV infection-associated inflammatory responses. *Bioorg Med Chem.* 2021;39:116157. https://doi.org/10.1016/j.bmc.2021.116157.
9 Li J, Jiang X, Dick A, et al. Design, synthesis, and antiviral activity of phenylalanine derivatives as HIV-1 capsid inhibitors. *Bioorg Med Chem.* 2021;48:116414. https://doi.org/10.1016/j.bmc.2021.116414.
10 Fu Z, Zhang T, Zhou Z, et al. Exploiting the hydrophobic channel of the NNIBP: Discovery of novel diarylpyrimidines as HIV-1 NNRTIs against wild-type and K103N mutant viruses. *Bioorg Med Chem.* 2021;42:116239. https://doi.org/10.1016/j.bmc.2021.116239.
11 Xu S, Song S, Sun L, et al. Indolylarylsulfones bearing phenylboronic acid and phenylboronate ester functionalities as potent HIV-1 non-nucleoside reverse transcriptase inhibitors. *Bioorg Med Chem.* 2022;53:116531. https://doi.org/10.1016/j.bmc.2021.116531.
12 Kumar Kushwaha P, Saurabh Srivastava K, Kumari N, Kumar R, Mitra D, Sharon A. Synthesis and anti-HIV activity of a new isoxazole containing disubstituted 1,2,4-oxadiazoles analogs. *Bioorg Med Chem.* 2022;56:116612. https://doi.org/10.1016/j.bmc.2022.116612.
13 Curreli F, Ahmed S, Benedict Victor SM, et al. Design, synthesis, and antiviral activity of a series of CD4-mimetic small-molecule HIV-1 entry inhibitors. *Bioorg Med Chem.* 2021;32:116000. https://doi.org/10.1016/j.bmc.2021.116000.
14 Colarusso S, Ferrigno F, Ponzi S, et al. SAR evolution towards potent C-terminal carboxamide peptide inhibitors of Zika virus NS2B-NS3 protease. *Bioorg Med Chem.* 2022;57:116631. https://doi.org/10.1016/j.bmc.2022.116631.
15 Maus H, Barthels F, Hammerschmidt SJ, et al. SAR of novel benzothiazoles targeting an allosteric pocket of DENV and ZIKV NS2B/NS3 proteases. *Bioorg Med Chem.* 2021; 47:116392. https://doi.org/10.1016/j.bmc.2021.116392.
16 Dražić T, Kühl N, Gottscheber N, Hacker CN, Klein CD. The spectrum between substrates and inhibitors: Pinpointing the binding mode of dengue protease ligands with modulated basicity and hydrophobicity. *Bioorg Med Chem.* 2021;48:116412. https://doi.org/10.1016/j.bmc.2021.116412.

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