Current Chemistry Letters 13 (2024) 445–450

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

Synthesis of some ribonucleosides derivatives and molecular docking analysis against variant corona virus omicrone

Driss Ouzebla[a], Najia Ourhriss[b], Aslı Eşme[c], Mohamed El idrissi[d*] and Abdellah Zeroual[e]

[a]*Department of chemistry, Faculty of Science, Chouaïb Doukkali University, P.O. Box 20, 24000, El Jadida, Morocco*
[b]*Laboratory of Biomolecular Chemistry, Natural Substances and Reactivity, URAC 16, Faculty of Sciences Semlalia, Cadi Ayyad University, P.O. Box 2390, Marrakech, Morocco*
[c]*Department of Elementary Science Education, 41380, Umuttepe, Kocaeli, Turkiye*
[d]*Team of Chemical Processes and Applied Materials, Polydisciplinary Faculty, Sultan Moulay Slimane University, Beni-Mellal, Morocco*
[e]*Molecular Modeling and Spectroscopy Research Team, Faculty of Science, Chouaïb Doukkali University, P.O. Box 20, 24000, El Jadida, Morocco*

C H R O N I C L E

Article history:
Received March 20, 2023
Received in revised form
June 17, 2023
Accepted October 9, 2023
Available online
October 9, 2023

Keywords:
Catalyze heterogene
Phosphate Naturel
SnCl4
Molnupiravir
Omicron variant

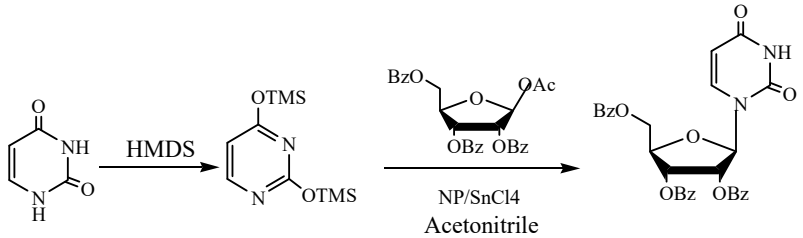
A B S T R A C T

In this work, ribonucleoside products have been prepared by employing stannic tetrachloride ($SnCl_4$) and natural phosphate as catalysts. The obtained result suggests that this catalyst facilitates the reactions of ribonucleoside-like products in a stereo-controlled manner, exhibiting β-selectivity when reacting with trimethylsilyl uracil, the ribonucleosides derivatives were obtained in suitable yields. In addition, we have performed the molecular docking analysis, demonstrated that the synthesized compounds have potential for antiviral activity against the omicron variant of coronavirus, and the D3, D4, E and F products have a higher binding energy than the molnupiravir drug, indicating that these products may be a probable drugs for the omicron variant.

1. Introduction

Nucleotides are precursors to DNA and RNA, they help to explain several biological and pharmaceutical phenomena[1]. Nucleosides exhibit anticancer, antiviral activities such as anti HIV (AIDS)[2-4], anti HBV, anti HCV (Hepatitis B and C viral infections)[5-10], and more recently anti SARS-CoV-2.[11-23]

Vorbruggen coupling is one of the methods of nucleoside synthesis[24-26], this method can be considered as a modification of the Hilbert-Johnson method. The coupling takes place this time in the presence of Lewis acid, between a base in the form of silylated iminol ethers and a methyl or acetyl ribofuranoside. 1,2-dichoroethane and acetonitrile are the solvents generally used, on other hand the use of the required Lewis acids and trimethylsilyltrifluoromethanesulfonate ($Me_3SiOSO_2CF_3$), leads to suitable yields with better stereoselectivity during the synthesis of purine and pyrimidine ribonucleosides (**Scheme 1**).

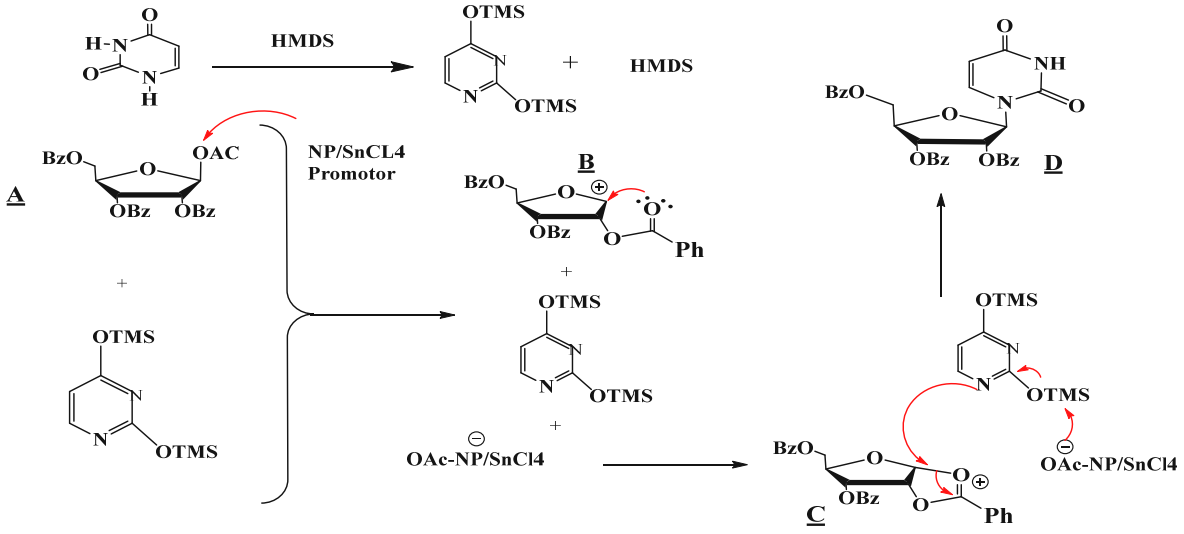


Scheme 1. Synthesis of 2', 3',5'-tri-O-benzoyl-β-D- Uridine

* Corresponding author.
E-mail address m.elidrissi2018@gmail.com (M. E. Idrissi)

doi: 10.5267/j.ccl.2023.10.001

The general mechanism of this coupling can be described in two steps. Lewis acid makes it possible to initiate the nucleofuge departure of the activating group introduced beforehand on the anomeric position of the carbohydrate; this thus results in the formation of an electrophilic intermediate of the resonance-stabilized oxonium type[27]. The next step concerns the nucleophilic addition of the silylated nucleic base to the anomeric carbon of the aforementioned intermediate. During this glycosylation, the two faces of the oxonium remain available for the addition of the nucleic base. This step is therefore not stereoselective and logically leads to the formation of mixtures of α and β anomers. The free nucleoside is then obtained by hydrolysis of the protective groups (**Scheme 2**).



Scheme 2. The general mechanism to prepare ribonucleoside

Many methodological approaches have been developed in recent years, such as heterogeneous catalysis or supported catalysis. The catalytic agents are supported on species such as alumina Al_2O_3[28], silica SiO_2[29], montmorillonite K- 10 (MK-10)[30] and recently naturel phosphate[31].

Herein, and within the framework of green chemistry, we will carry out the synthesis of ribonucleoside products, using stannic tetrachloride ($SnCl_4$) supported on natural phosphate, in addition we will test the products obtained against the variant corona virus omicron using molecular docking and compared with molnupiravir drug (**Fig. 1**).

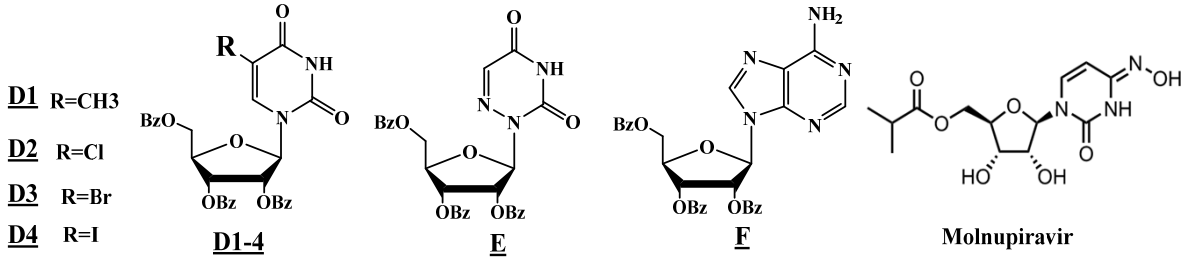


Figure 1. Products tested against the corona variant virus Omicron

2. Results and discussion

2.1 General method for preparation of N-glycosylation

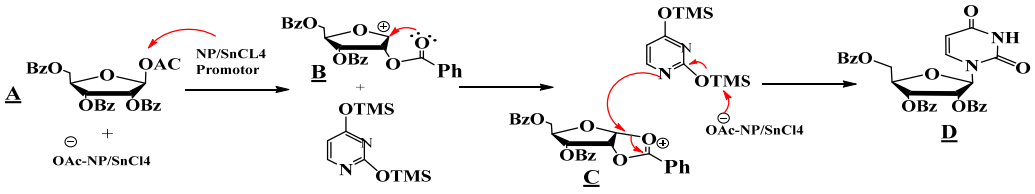
The results grouped in Table 1 of the first experiment when only natural phosphate has been employed, the condensation of 1-O-acetyl-2, 3, 5-tri-O-benzoyl-β-D-ribofuranoside with uracil silylated gave the ribonucleoside in 8% yield, when using $SnCl_4$ the ribonucleoside is obtained with a yield of 30% and when $SnCl_4$ mixed with naturel phosphate (catalyst A) the desired ribonucleoside was obtained in 64% yield. Other catalysts (entries 4 to 14) were used for the N-glycosylation reaction which gives yields of approximately 64%, this reaction is regioselective and stereoselective.

To understand how the N-glycosilation reaction takes place, we propose a reaction mechanism that explains the formation of the nucleosiode. In this context, the C-N glycosidic bond formed can be α or β (respectively axial or equatorial on a pyrano ring in the gluco, manno or galacto series). The stereoselectivity of this bond is largely controlled by the nature of the protective group in position 2. In this case the group is involved (for example an ester), it intervenes in the selective

formation of a glycosidic bond β. In this case, as described in scheme 3, the intermediate cation B will be trapped intramolecularly, resulting in the formation of the acyloxonium intermediate C. This is called "anchimeric assistance". The face of the acyloxonium leading to α product is not accessible, hence the observed β selectivity. For natural nucleosides, the bond between the base and the sugar is always equatorial (β). It is therefore judicious to insert a participating group in position 2 of the donor.

Table 1. Synthesis of 2,3,5-tri-O-benzoyl-β-D-Uridine

Entry	Catalysts	Yield %
1	Natural Phosphate (NP) 325 mg	8
2	$SnCl_4$ (1eq : 0.1ml)	30
3	$SnCl_4$ (0.5eq :0.05ml)	20
4	$SnCl_4$ (0.2eq :0.02 ml)	No Reaction
5	NP/$SnCl_4$ (**A**) (1eq : 470mg)	**64**
6	NP/$SnCl_4$ (**A**) (1eq : 470mg)+0.2eq of $SnCl_4$ (0.02 ml)	32
7	NP/$SnCl_4$ (**A**) (0.5eq :235mg)	55
8	NP/$SnCl_4$ (**A**) (0.2eq : 94mg)	35
9	NP/$SnCl_4$ (**B**) (1eq : 470mg)	46
10	NP$SnCl_4$ (**B**) (0.5eq :235mg)	36
11	NP/$SnCl_4$ (**B**) (0.2eq : 94mg)	30
12	NP/$SnCl_4$ (**C**) (1eq : 470mg)	37
13	NP$SnCl_4$ (**C**) (0.5eq :235mg)	32
14	NP/$SnCl_4$ (**C**) (0.2eq : 94mg)	20



Scheme 3. N-glycosylation mechanism

2.2 Molecular Docking

Omicron mutated variant (B.1.1.529) of SARS-CoV-2 is a recently emerged, reported for high infectivity[32]. Although various antiviral drugs have been developed against Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we still do not have an effective therapeutic strategy to control this viral infection. Molnupiravir is the first oral antiviral for COVID-19 approved by Medicines and Healthcare products Regulatory Agency (MHRA)[33]. The investigated (**D1**, **D2**, **D3**, **D4**, **E**, **F**) compounds were tested for their antiviral activity against omicron S protein (PDB ID: 7T9J) by comparing to the standard drug molnupiravir, which was found to be more efficient in comparison to other drugs against COVID-19[34,35]. In the present study, the molecular docking study between **D1**, **D2**, **D3**, **D4**, **E**, **F** compounds, and omicron S protein (PDB ID: 7T9J)[36] performed to find the best orientational of ligands with protein by using the Autodock 4.2 software tool interfaced with the AutoDock Tools (ADT) version 1.5.6[37]. Protein preparation was performed by the removal of water, addition of polar hydrogen and Kollman charges. Discovery Studio Visualizer software was applied to visually verify 2D diagrams of the docked compounds and its H-bond interactions[38]. PyMol was used to analyze and visualize the protein-ligand complex molecules[39]. The active site has been determined using the Discovery Studio Visualizer software and it corresponds to the coordinates: x= 177.335, y = 146.474 and z= 258.535. The grid size was set at 60×60×60 xyz points with grid spacing of 0.375 Å. The results (inhibition constant μM, intermolecular energy kcal/mol, binding energy kcal/mol) of molecular docking for the compounds (**D1**, **D2**, **D3**, **D4**, **E**, **F**, and molnupiravir) are listed in Table 1. In comparison, we can conclude that compound **E** has the lowest binding energy (stronger interactions between ligand and the receptor) -8.13 kcal/mol, while compound **D2** has the highest binding energy -5.49 kcal/mol from the data of Table 1. As shown in Table 1, **D1** and **D2** compounds (binding affinities -5.92 and -5.49 kcal/mol) showed comparatively higher binding affinities compared to the parent molnupiravir drug. From **Fig. 1** it can be observed that hydrogen and oxygen atoms in the **D1**, **D2**, **D3**, **D4**, **E**, **F** compounds are responsible for forming conventional hydrogen bonds with omicron S protein residues. It was also observed in Fig. 1 that all **D1**, **D2**, **D3**, **D4**, **E**, **F** ligands that interacted with this omicron 7T9J protein had conventional hydrogen bond with the amino acid GLN134 with bond lengths of 2.1, 2.1, 2.4, 2.4, 2.0, and 2.1 Å, respectively, in the active site of the omicron S protein. Hence, all these results of **D3**, **D4**, **E**, **F** compounds will be useful for the development of anti-viral drugs.

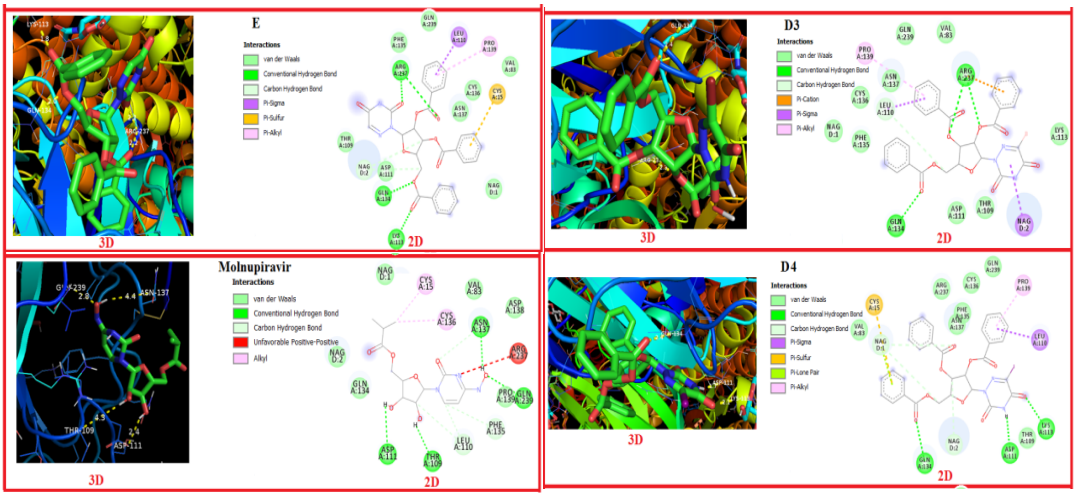


Fig. 2. Interactions of **D3**, **D4**, **E** and molnupiravir with residues of variant omicron of COVID-19 main protease

2.3 Experimental part

a. Preparation of catalysts

Method 1. Preparation of NP/$SnCl_4$ catalyst (A)

In a flask, put 1g of $SnCl_4$ (0.45 ml) and 5 ml of water, stir for 3 minutes then add 1g of natural phosphate and stir for 15 minutes. The mixture is evaporated to dryness and finally the precipitate is obtained.

Method 2. Preparation of NP/$SnCl_4$ catalyst (B), we take the NP/$SnCl_4$ (A) and wash it with water, the residue is evaporated to dryness, after which we obtain a new precipitate, it is the NP/$SnCl_4$ (B).

Method 3. Preparation of NP/$SnCl_4$ catalyst (C) 1 g of $SnCl_4$ (0.45 ml) and 5 ml of acetonitrile are put in a flask and stirred for 3 minutes, then 1 g of natural phosphate is added, the mixture is stirred for 15 minutes then evaporated to dryness, the precipitate obtained is NP/$SnCl_4$(C).

b. Procedure experimental: N-Glycosylation

1 mmol of uracil, 4 ml of HMDS and 10 mg of ammonium sulfate are added, and then the mixture is heated under reflux for two hours. The 1-O-acetyl-2,3,5-tri-O -benzoyl-β-D- ribofuranose (0.9eq, 453mg), NP /$SnCl_4$ (**A**) (526mg, 1eq of $SnCl_4$) and 5 ml of acetonitrile are added. Overnight at reflux, the mixture is filtered, and the solvent is evaporated .The residue was purified by column chromatography (CH_2Cl_2/MeOH (98/2 v/v) to give the desired nucleoside with 64% yield

^{1}H NMR and ^{13}C NMR spectra of 2', 3', 5'-Tri-O-benzoyl- β -D-uridine

^{1}H NMR ($CDCl_3$) (300MHz) δ(ppm) 4.40 (m,2H,H'5) 4.90 (m,1H,H'4) 5.55 (d,1H,H5,J=6Hz) 5.65 (t,1H,H'3) 5.80 (t,1H,H'2) 6.38 (d,1H,H'1βJ=5.4Hz) 7.44 (d,1H,H6,J=6Hz) 7.40-8.10 (m,15H,HaromBz) 8.10 (m,6H) 10.40 (s,1H,N-H).

^{13}C NMR ($CDCl_3$) δ(ppm) 64.01 (C5') 71.38 (C4') 75.01 (C3') 79.99 (C2') 88(C1'β) 100.59 (C5) 128.43-133.70 (Ph) 145.09 (C6) 150.33 (C4) 163 (C2) 165.05-168.77 (PhCO).

3. Conclusion

In this work we have described a simple and less expensive reaction for the synthesis of D-ribonucleosides using $SnCl_4$ supported on rock phosphate as the solid phase. This method is kind to the environment and more ecological; in addition, we have done molecular docking for derivatives similar to the molnupiravir drug which has been used against Covid-19. Our results show that D3, D4, E and F products have the potential for conventional hydrogen bonding, which is very important for the stability of the protein-ligand complex, with higher binding affinity than molnupiravir. We speculated that these products might be drugs for the SARS-CoV-2 omicron variant.

Table 2. The obtained docking parameters of the (**D1**, **D2**, **D3**, **D4**, **E**, **F**) compounds by comparing to the standard drug molnupiravir.

Protein [PDB ID]	Bonded residues	Bond distances (Å)	Inhibition constant (μM)	Intermolecular energy (kcal/mol)	Binding energy (kcal/mol)
D1	ASN17	2.3	45.87	-9.20	-5.92
	ASN17	2.2			
	GLN134	2.6			
	GLN134	2.1			
D2	GLN14	2.6	95.17	-8.77	-5.49
	GLN134	2.1			
D3	ARG237	2.3	27.98	-9.49	-6.21
	GLN134	2.4			
D4	ASP111	1.7	4.52	-10.57	-7.29
	LYS113	2.1			
	GLN134	2.4			
E	ARG237	2.2	1.1	-11.41	-8.13
	ARG237	2.2			
	GLN134	2.0			
	LYS113	1.8			
F	GLN134	2.1	18.79	-10.03	-6.45
	GLN134	3.2			
	ARG237	1.9			
	GLN239	2.3			
Molnupiravir	ASN137	4.4	31.84	-8.52	-6.14
	GLN239	2.8			
	ASP111	2.4			
	THR109	4.3			

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Conflicts of interest: The authors declare no conflict of interest.

Availability of data and material: All data generated or analyzed during this study are included in this published article.

References

1. Andreeva OV., Garifullin BF., Zarubaev V.V., Slita AV., Yesaulkova IL., Saifina LF., Shulaeva MM., Belenok MG., Semenov VE., Kataev VE. **(2021)** Synthesis of 1,2,3-triazolyl nucleoside analogues and their antiviral Activity. Molecular Diversity, 25, 473–490. DOI:10.1007/s11030-020-10141-y.
2. Blanco JL., Ambrosioni J., Garcia F., Martinez E., Soriano A., Mallolas J., et al. **(2020)** Investigators, COVID-19 in Patients With HIV: Clinical Case Series. Lancet HIV, 7:e314–6. DOI: 10.1016/S2352-3018(20)30111-9.
3. Del Amo J., Polo R., Moreno S., Díaz A., Martínez E., Arribas JR., et al. **(2020)** Antiretrovirals and Risk of COVID-19 Diagnosis and Hospitalization in HIV-Positive Persons. Epidemiology, 31:e49–51. DOI:10.1097/ EDE.0000000000001235.
4. Dallocchio RN., Dessi A., De Vito A., Delogu G., Serra PA., Madeddu G. **(2021)** Early Combination Treatment With Existing HIV Antivirals: An Effective Treatment for COVID-19. Eur Rev Med Pharmacol Sci, 25:2435–48. DOI: 10.21203/rs.3.rs-35791/v1.
5. Saxena RK., Samad AA., Khan UR., Vinay V., Wankhede SV., et al. **(2021)** Assessment Prevalence of SARS-CoV-2 Infection in Patients on Anti-HBV (Lamivudine) Treatment: A Questionnaire Based Survey. IP Int J Med Microbiol Trop Dis, 7:7. DOI: 10.18231/j.ijmmtd.2021.005.
6. Yamauchi N., Maruyama D., Choi I., Atsuta Y., Sakai R., Miyashita K., et al. **(2021)** Prophylactic Antiviral Therapy for Hepatitis B Virus Surface Antigen-Positive Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab- Containing Chemotherapy. Cancer Sci, 112:1943–54. DOI: 10.1111/cas.14846.
7. Zhang S., Li N., Sheng Y., Chen W., Ma Q., Yu X., et al. **(2021)** Hepatitis B Virus Induces Sorafenib Resistance in Liver Cancer via Upregulation of cIAP2 Expression. Infect Agent Cancer, 16:20. DOI: 10.1186/s13027-021-00359-2.
8. Hui VW., Chan SL., Wong VW., Liang LY., Yip TC., Lai JC., et al. **(2020)** Increasing Antiviral Treatment Uptake Improves Survival in Patients With HBV-Related HCC. JHEP Rep, 2:100152. DOI: 10.1016/j.jhepr.2020.100152.
9. Wang X., Liu X., Dang Z., Yu L., Jiang Y., Wang X., et al. **(2020)** Nucleos(t)ide Analogues for Reducing Hepatocellular Carcinoma in Chronic Hepatitis B Patients: A Systematic Review and Meta-Analysis. Gut Liver, 14:16. DOI: 10.5009/gnl18546.
10. Madeddu G., Fiore V., Melis M., Ortu S., Mannu F., Muredda AA., et al. **(2020)** Mitochondrial Toxicity and Body Shape Changes During Nucleos(T)Ide Analogues Administration in Patients With Chronic Hepatitis B. Sci Rep, 10:2014. DOI: 10.1038/s41598-020-58837-3.
11. Arun KG., Sharanya CS., Abhithaj J., Francis D., Sadasivan C. **(2020)** Drug Repurposing Against SARS-CoV-2 Using E-Pharmacophore Based Virtual Screening, Molecular Docking and Molecular Dynamics With Main Protease as the Target. J Biomol Struct Dyn, 1–12. DOI: 10.1080/07391102. 2020.1779819.
12. Prajapat M., Shekhar N., Sarma P., Avti P., Singh S., Kaur H., et al. (2020) Virtual Screening and Molecular Dynamics Study of Approved Drugs as Inhibitors of Spike Protein S1 Domain and ACE2 Interaction in SARS-CoV-2. J Mol Graph Model, 101:107716. DOI: 10.1016/j.jmgm.2020.107716.

13. Fadaka AO., Aruleba RT., Sibuyi NRS., Klein A., Madiehe AM., Meyer M. (2020) Inhibitory Potential of Repurposed Drugs Against the SARS-CoV-2 Main Protease: A Computational-Aided Approach. J Biomol Struct Dyn, 1–13. DOI: 10.1080/07391102.2020.1847197.
14. Jacome R., Campillo-Balderas JA., Ponce de Leon S., Becerra A., Lazcano A. **(2020)** Sofosbuvir as a Potential Alternative to Treat the SARS-CoV-2 Epidemic. Sci Rep, 10:9294. DOI: 10.1038/s41598-020-66440-9.
15. Chien M., Anderson TK., Jockusch S., Tao C., Li X., Kumar S., et al. **(2022)** Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. J Proteome Res, 19:4690–7.
16. El idrissi M., El ghozlani M., Eşme A., Ríos-Gutiérrez M., Ouled Aitouna A., Salah M., El Alaoui El Abdallaoui H., Zeroual A., Mazoir N., Domingo L.R. **(2021)** Mpro-SARS-CoV-2 Inhibitors and Various Chemical Reactivity of 1-Bromo- and 1-Chloro-4-vinylbenzene in [3 + 2] Cycloaddition Reactions. Organics, 2 1-16. DOI: 10.3390/org2010001.
17. Raji H., Ouled Aitouna A., Barhoumi A., Chekroun A., Zeroual A., Syed A., Elgorban A. M., Verma M., Benharref A., Varma R. S. (2023) Antiviral docking analysis, semisynthesis and mechanistic studies on the origin of stereo- and chemoselectivity in epoxidation reaction of α′-trans-Himachalene, Journal of Molecular Liquids, 385: 122204, https://doi.org/10.1016/j.
18. Del Amo J., Polo R., Moreno S., Díaz A., Martínez E., Arribas JR., et al. **(2020)** Antiretrovirals and Risk of COVID-19 Diagnosis and Hospitalization in HIV-Positive Persons. Epidemiology 31:e49–51. DOI: 10.1097/EDE.0000000000001235.
19. Grein J., Ohmagari N., Shin D., Diaz G., Asperges E., Castagna A., et al. **(2020)** Compassionate Use of Remdesivir for Patients With Severe COVID-19. N Engl J Med, 382:2327–36. DOI: 10.1056/NEJMoa2007016.
20. Chien M., Anderson TK., Jockusch S., Tao C., Kumar S., Li X., et al. **(2020)** Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target forCOVID-19. J Proteome Res, 19:4690–7. DOI: 10.1021/acs.jproteome.0c00392.
21. Ju J., Li X., Kumar S., Jockusch S., Chien M., Tao C., et al. **(2020)** Nucleotide Analogues as Inhibitors of SARS-CoV Polymerase. Pharmacol Res Perspect, 8:e00674. DOI: 10.1002/prp2.674.
22. Koulgi S., Jani V., NMU V., Sonavane U., Joshi R. **(2021)** Structural Insight Into theBinding Interactions of NTPs and Nucleotide Analogues to RNA Dependent RNA Polymerase of SARS-CoV-2. J Biomol Struct Dyn, 1–15. DOI: 10.1080/07391102.2021.1894985.
23. Khan S., Attar F., Bloukh SH., Sharifi M., Nabi F., Bai Q., et al. **(2021)** A Review on the nInteraction of Nucleoside Analogues With SARS-CoV-2 RNA Dependent RNA Polymerase. Int J Biol Macromol, 181:605–11. DOI: 10.1016/ j.ijbiomac.2021.03.112.
24. Abou-Elkhair R.A.I., Wasfy A.A., Mao S., Du J., Eladl S., Metwally K., Sheng, J. **(2020)** 2-Hydroxyimino-6-aza-pyrimidine nucleosides: Synthesis, DFT calculations, and antiviral evaluations. New Journal of Chemistry, 44, 19650-19662. DOI: 10.1039/DONJ04154H.
25. Umesh P., Aher ORCID Logo., Dhananjai Srivastava., Girij P., Singh and Jayashree B.S. **(2021)** Synthetic strategies toward 1,3-oxathiolane nucleoside analogues. J. Org. Chem, 17, 2680–2715. DOI: 10.3762/bjoc.17.182.
26. Gregory L.B., Michael S.B., Benjamin M.C., Junying F., Jonathan M., Chris Sfouggataki**. (2019)** Follow the Silyl Cation: Insights into the Vorbrüggen Reaction, Org. Process Res. Dev, 23, 9, 2050–2056. DOI:10.1021/acs.oprd.9b00304.
27. Lenka T., Jakub S. **(2021)** Study of the N^7 Regioselective Glycosylation of 6-Chloropurine and 2,6-Dichloropurine with Tin and Titanium Tetrachloride,. J. Org. Chem, 86, 19, 13265–13275. DOI: 10.1021/acs.joc.1c01186.
28. Miller J.M., Goodchild M., Lakshmi L. J., Wails D., Hartman, J. S. **(2000)** Friedel–Crafts catalysis using supported reagents. Synthesis, characterization, and catalytic application of ZnCl2 supported on sol–gel-derived alumina. Mat. Lett, 44, 164-169. DOI:10.1016/j.apcata.2014.04.016.
29. Pillai, S. K., Abidli, A., Belkacemi, K. **(2014)** Triacylglycerol self-metathesis over highly chemoselective methyltrioxorhenium supported on ZnCl2-promoted mesoporous alumina. Appl. Catal. A, 479, 121-133. DOI:10.1016/j.apcata.2014.04.016.
30. Jacob R.G., Radatz C.S., Rodrigues M.B., Alves D., Perin G., Lenardão E.J., Savegnago L. **(2011)** Synthesis of 1-H-1,5-benzodiazepines derivatives using SiO2/ZnCl2. Heteroatom Chem, 22, 180-185. DOI:10.1002/hc.20674.
31. Baddi L., Ouzebla D., El Mansouri A., Smietana M., Vasseur J-J., Lazrek H.B. **(2020)** Efficient one-pot, three-component procedure to prepare new α-aminophosphonate and phosphonic acid acyclic nucleosides, Nucleosides, Nucleotides & Nucleic Acids, 40:1, 43-67. DOI: 10.1080/15257770.2020.1826516.
32. Collie, S., Champion, J., Moultrie, H., Bekker, L.G., and Gray, G. **(2021)** Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. The New England Journal of Medicine, 3:386(5):494-496. DOI: 10.1056/NEJMc2119270.
33. Salah M., El Alaoui El Abdallaoui O., Zeroual A., Acharjee N., El idrissi M. **(2023)** Insight into a new discovery of SARS-CoV-2 inhibitor activated through Chloroquine derivatives. Current Chemistry Letters, 12, 477–488. DOI:10.5267/j.ccl.2023.8.010.
34. Salah M., Belghiti M.E., Aitouna A.O., Zeroual A., Jorio S., El Alaoui Abdellaoui H., El Hadki H., Marakchi K., Komiha N. **(2021)** MEDT Study of the 1,3-DC Reaction of Diazomethane with Psilostachyin and investigation about the interactions of some pyrazoline derivatives with Protease (Mpro) of nCoV-2, Journal of Molecular Graphics and Modelling, 102, 107763. DOI: 10.1016/j.jmgm.2020.107763.
35. Schooley RT,. Carlin AF,. Beadle JR. **(2021)** Rethinking remdesivir: synthesis, antiviral activity and pharmacokinetics of oral lipid prodrugs. Antimicrobial Agents and Chemotherapy DOI: 10.1101/2020.08.26.269159.
36. Sanner M.F. **(1999)** Python: a programming language for software integration and development, J. Mol. Graphics Mod. 17, 57-61.
37. https://www.rcsb.org/
38. Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K., Olson A.J.. **(1998)** Automated docking using a lamarckian genetic algorithm and empirical binding free energy function, J. Comput. Chem. 19, 1639-1662.
39. The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrodinger LLC. (2010).