

**Two short approaches to the COVID-19 drug  $\beta$ -D- $N^4$ -hydroxycytidine and its prodrug molnupiravir**

Journal:	<i>Organic &amp; Biomolecular Chemistry</i>
Manuscript ID	OB-COM-12-2023-002039
Article Type:	Communication
Date Submitted by the Author:	14-Dec-2023
Complete List of Authors:	Persaud, Kevin; The City College of New York, Department of Chemistry Sahu, Rajesh; Institute of Chemical Technology Department of Chemistry, Chemistry Neary, Michelle; Hunter College, Chemistry Kapdi, Anant; Institute of Chemical Technology Department of Chemistry, Chemistry Lakshman, Mahesh; The City College of New York, Department of Chemistry and Biochemistry

## COMMUNICATION

Two short approaches to the COVID-19 drug  $\beta$ -D- $N^4$ -hydroxycytidine and its prodrug molnupiravir

Received 00th January 20xx,  
Accepted 00th January 20xx

Kevin E. Persaud,<sup>a</sup> Rajesh Sahu,<sup>b</sup> Michelle C. Neary,<sup>c</sup> Anant R. Kapdi\*<sup>b</sup>  
and Mahesh K. Lakshman\*<sup>a</sup>

DOI: 10.1039/x0xx00000x

**Molnupiravir, the prodrug for  $\beta$ -D- $N^4$ -hydroxycytidine (NHC), is marketed by Merck as Lagevrio™ against mild-moderate COVID-19, under FDA emergency use authorization. It was the first oral drug against the disease. This work describes two synthetic approaches to NHC and molnupiravir by amide activation in uridine with a peptide-coupling agent and with a 4-chloropyrimidinone nucleoside intermediate.**

## Introduction

The COVID-19 pandemic highlighted the need for rapid development and deployment of therapeutics against the rapid emergence of an infective agent. This led to developments in vaccines, monoclonal antibodies, immunoglobulins, and mRNA therapeutics.<sup>1</sup> Among small molecule candidates (Figure 1), remdesivir, a nucleoside analogue, received FDA approval for use against COVID-19, but its administration requires IV infusion. Another nucleoside analogue that received emergency use authorization from the FDA is molnupiravir, marketed by Merck as Lagevrio™. This orally administered compound (also called MK-4482 or EIDD-2801) is a prodrug that undergoes hydrolysis to  $\beta$ -D- $N^4$ -hydroxycytidine (NHC).<sup>2</sup> Triphosphorylated NHC is then a substrate for RNA-dependent RNA polymerase (RdRp) in place of either cytidine or uridine triphosphate, and use of the ensuing RNA template by RdRp results in mutated viral RNA products through misincorporation of either A or G.<sup>3</sup> By contrast, the FDA approved Pfizer drug, Paxlovid™, is an orally administered combination of a viral main protease M<sup>Pro</sup>

inhibitor<sup>4,5</sup> (nirmatrelvir) boosted by a protease inhibitor (ritonavir, used in treatment of HIV/AIDS) to inactivate nirmatrelvir metabolizing CYP3A4.<sup>4</sup>

According to the NIH guidelines, nirmatrelvir is preferred over molnupiravir for treating patients at high risk for disease progression,<sup>6</sup> but a recent study demonstrates that both molnupiravir and nirmatrelvir are associated with mortality reduction.<sup>7</sup> Neither drug is problem free. Paxlovid has significant drug-drug interactions,<sup>6,7</sup> and triphosphorylated NHC has been shown to be a substrate for mitochondrial DNA-dependent RNA-polymerase.<sup>8</sup> The FDA determined that molnupiravir does not have drug-drug interactions and, on the basis of genotoxicity data, that it posed a low risk for the 5 days of treatment.<sup>7,9</sup> Although there has been a recent claim that transmission of mutated virus could occur from molnupiravir-treated patients who have not completely cleared the virus,<sup>10</sup> the US has a plan to purchase 1.7 million doses of molnupiravir.<sup>11</sup> Recently, both  $N^4$ -hydroxycytidine and molnupiravir have been found to show broad-spectrum activity against enterovirus *in vitro* and *in vivo*.<sup>12</sup>

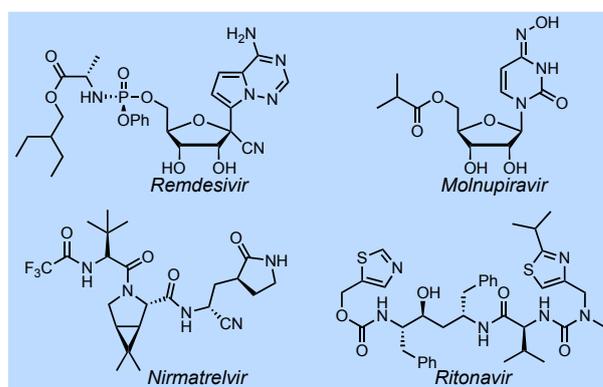


Fig. 1 Currently utilized COVID-19 therapeutics.

The original patented 5-step approach to molnupiravir from uridine appeared prior to the pandemic.<sup>13</sup> Subsequently, other approaches have been reported starting from uridine and

<sup>a</sup> Department of Chemistry and Biochemistry, The City College of New York, 160 Convent Avenue, New York, NY 10031, USA. E-mail: mlakshman@ccny.cuny.edu

<sup>b</sup> Department of Chemistry, Institute of Chemical Technology, Nathalal Parekh Road, Matunga, Mumbai 400019, India.

<sup>c</sup> Department of Chemistry, Hunter College, 695 Park Avenue, New York, NY 10065, USA.

† Electronic Supplementary Information (ESI) available: Experimental procedures, structural characterizations and copies of NMR spectra. See

DOI: 10.1039/x0xx00000x

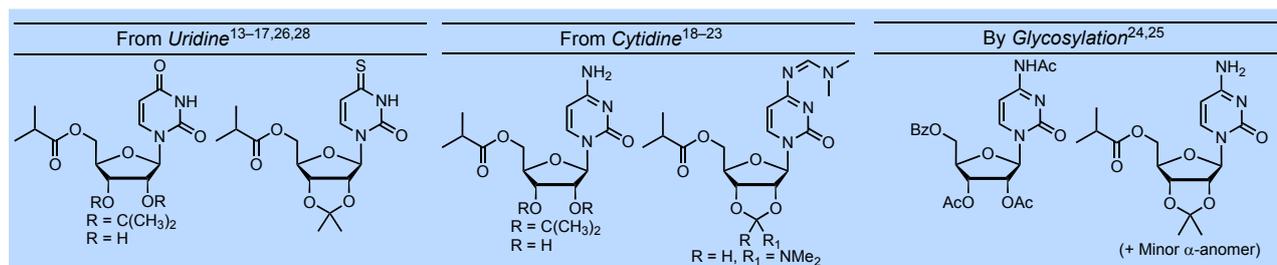


Fig. 2 Intermediates in the various syntheses of molnupiravir.

proceeding *via* its 2',3'-acetonide-protected 5'-isobutyrate ester (as in the original patent). These involve (a) reordering the synthetic steps,<sup>14</sup> (b) use of HMDS/imidazole instead of triazolization for C4 carbonyl group activation, followed by reaction with hydroxylammonium sulfate,<sup>15</sup> and (c) conversion of the uridine derivative to a 4-thio derivative followed by reaction with  $\text{NH}_2\text{OH}$ .<sup>16</sup> A manufacture method for molnupiravir retains the original steps.<sup>17</sup> Cytidine has been used as an alternate precursor, and both 2',3'-acetonide-protected nucleoside<sup>18,19</sup> as well as unprotected cytidine have been evaluated.<sup>20,21</sup> In these cases, the final step is a transamination with  $\text{NH}_2\text{OH}$ . A large-scale synthesis also utilized the unprotected nucleoside.<sup>22</sup> In some cases, the impurity profile at the various steps has been assessed.<sup>19,21</sup> Notably, in the methods proceeding without 2',3'-protection, Novozyme 435 ( $\approx$ £18–132/g) and the isobutyrate ester of acetone oxime are required for installation of the 5'-ester.<sup>20–22</sup> In another approach, DMF-dimethylacetal has been used to protect the 2',3'-hydroxyls as well as the C4 amino group but relies on the transamination.<sup>23</sup> Finally, a glycosylation approach has been used to assemble suitable cytidine precursors that are then

carried forth.<sup>24,25</sup> Beyond these, enzymatic approaches have also been reported. In one, uridine 5'-isobutyrate ester was assembled by a combination of six enzymes, followed by chemical conversion to the C4 oxime.<sup>26</sup> An engineered cytidine deaminase has been developed to access NHC directly from cytidine<sup>27</sup> and NHC has also been prepared using four enzymes and an electrochemical recycling of ATP.<sup>28</sup> Although not reported, in both cases the 5'-hydroxyl group of NHC can potentially be esterified with the isobutyrate ester of acetone oxime, but this reaction may need to be stopped short of completion<sup>20</sup> or require an oxime diacylation step.<sup>21</sup> Table 1 summarizes elements of the previous methods.

## Results and Discussion

Castro's reagent, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), is a carboxylic acid activator used for amide bond formation in peptide synthesis. This reagent has gained importance for substitution reactions on nucleoside substrates,

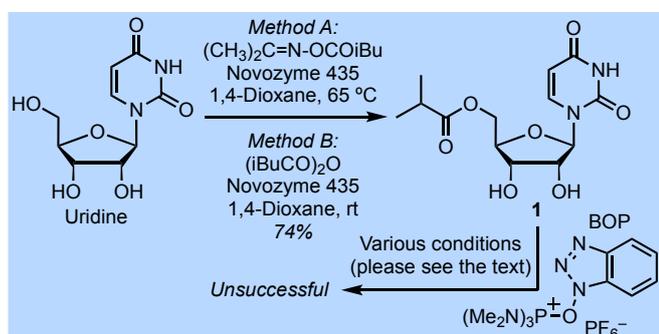
Table 1 A summary of previous approaches to molnupiravir (references 27 and 28 describe intermediates and do not proceed to molnupiravir and therefore, are not included)

Ref.	Number of steps and key features	Precursor (scale)	Overall yield
13	Original patent: <i>five</i> discrete steps.	Uridine (5 g)	17%
14	Modification of original patent: <i>six</i> steps with an <i>in situ</i> TMS protection of sugar prior to a one-pot triazolization and esterification, and acetonide deprotection by continuous flow due for ester deprotection.	Uridine (5 g)	61%
15	<i>Four</i> steps, with a two-step, one-pot acetonide formation and esterification, followed by a two-step one-pot oxime introduction and deprotection.	Uridine (5 g) Uridine (10 g)	68% 64%
16	<i>Five</i> steps, three discrete steps followed by a two-step, one-pot introduction of the oxime unit and acetonide hydrolysis.	Uridine (5 g)	62%
17	Manufacturing route: <i>five</i> discrete steps	Uridine (55.18 g)	57%
18	<i>Four</i> steps, the transamination and deprotection steps could be telescoped by prolonging the reaction time. However, that led to some cleavage of the ester.	Cytidine (18.8 g)	44%
19	Multigram synthesis, <i>four</i> discrete steps.	Cytidine (100 g)	36%
20	<i>Two</i> discrete steps involving an enzymatic esterification and transamination.	Cytidine (5 g)	75%
21	Towards a manufacturing route, <i>two</i> discrete steps involving a transamination and an enzymatic esterification. The oxime ester by-product is cleaved in a separate step with 50% aq. $\text{NH}_2\text{OH}$ .	Cytidine (500 g)	60%
22	Supply-centred route, <i>two</i> discrete steps, enzymatic acylation followed by transamination.	Cytidine (200 g)	41%
23	<i>Three</i> steps accomplished as a one-pot procedure.	Cytidine (100 g)	63%
24	<i>Nine</i> steps, three discrete steps for preparation of the ribose unit, followed by the silyl Hilbert Johnson glycosylation, and a subsequent five discrete steps.	D-Ribose (5 g)	39%
25	<i>Four</i> discrete steps, two steps for preparation of the ribose unit, followed by glycosylation, and then introduction of the oxime unit and deprotection as a one-pot reaction	D-Ribose (20 g)	30%
26	<i>Three</i> discrete steps, one of which is the mono esterification of ribose and glycosylation by a biocatalytic cascade, followed by introduction of the oxime unit.	D-Ribose (50 g)	69%

## COMMUNICATION

Notably, amide activation in pyrimidines and substitution with nucleophiles has been achieved in a two-step, one-pot manner by activation of the amide linkages in purine and pyrimidine nucleosides.<sup>29–34</sup> Therefore, we wanted to assess whether this methodology could provide an *alternate discovery approach* to molnupiravir. Our initial proposal was a Novozyme 435-catalyzed acylation of the 5'-hydroxyl group in uridine, an *in situ* activation of the amide linkage of uridine, and reaction with  $\text{NH}_2\text{OH}$ .

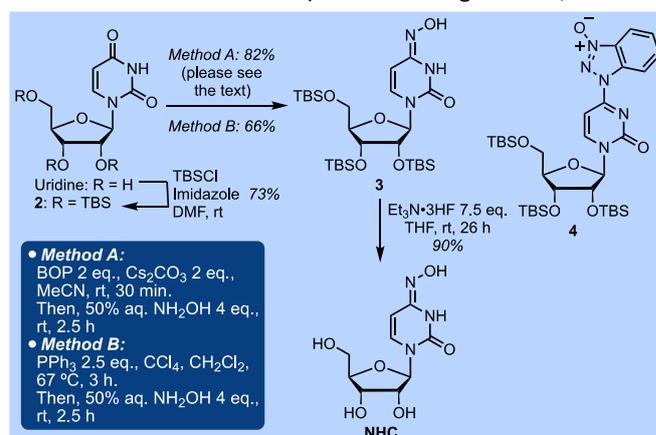
Esterification of the 5'-hydroxyl group was attempted using the isobutyrate ester of acetone oxime ( $(\text{CH}_3)_2\text{C}=\text{N}-\text{OCO}i\text{Bu}$ , Scheme 1, *Method A*). However, in our hands this reaction was capricious, and use of the crude oxime ester (deep orange colour) did not yield product **1**. We reasoned that enzyme inactivation occurred by some contaminant(s) not detectable in the  $^1\text{H}$  NMR spectrum of the oxime ester. Chromatography of the oxime ester over silica gel gave a pale-yellow sample that was successfully applied to obtaining the 5'-ester (56% yield on a 0.2 mmol scale). A nearly ten-fold scale-up led to multiple unidentified by-products that rendered product purification difficult.



Scheme 1. The first approach to molnupiravir.

Because of these issues,  $(i\text{BuCO})_2\text{O}$  was applied under slightly modified conditions (Scheme 1, *Method B*).<sup>35</sup> Product **1** was successfully obtained in a 74% yield on a 2.06 mmol scale (77% on a 0.20 mmol scale). However, surprisingly, subjecting this acyl derivative to reaction with BOP (2 equiv.) and  $\text{Cs}_2\text{CO}_3$  (2 equiv.) in MeCN, at room temperature, did not show formation of the uridine  $O^4$ -(benzotriazol-1-yl) intermediate. Adding more BOP (1 equiv.) and  $\text{Cs}_2\text{CO}_3$  (2 equiv.) to the reaction did not change the outcome. It was noticed that  $\text{Cs}_2\text{CO}_3$  turned to a spherical ball during the reaction course. DBU, successfully used for the activation of pyrimidine nucleosides,<sup>33,34</sup> was evaluated next, but without success here. Assuming that the free hydroxyl groups could be a problem,  $i\text{Pr}_2\text{NEt}$  ( $\text{p}K_a$  8.5 in DMSO) was used in place of DBU ( $\text{p}K_a$  13.9 in DMSO). But this was also unsuccessful.

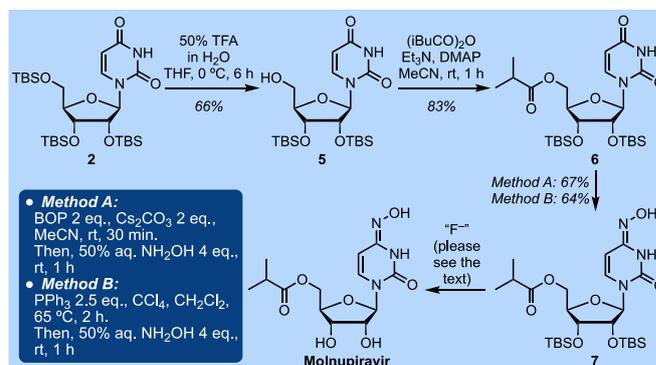
Fully silylated pyrimidine nucleosides have been successfully activated by BOP and subjected to substitution reactions.<sup>33,34</sup> Thus, we considered use of 2',3',5'-tri-*O*-TBS-protected uridine (**2**, Scheme 2, *Method A*). Exposure of this precursor to BOP/ $\text{Cs}_2\text{CO}_3$  gave the uridine  $O^4$ -(benzotriazol-1-yl) intermediate within 30 min. Subsequent addition of aqueous  $\text{NH}_2\text{OH}$  then gave the oxime **3** (83% yield on a 0.09 mmol scale, 82% on a 0.5 mmol scale). On the larger scale, a minor



contaminant **4** (4.4% by  $^1\text{H}$  NMR) was observed to form. While this by-product, not observed on the smaller scale reaction, can in theory also undergo conversion to **3**, this was not pursued. Formation of such a by-product has been noted previously.<sup>33</sup> Desilylation of compound **3** (and the by-product) with  $\text{Et}_3\text{N}\cdot 3\text{HF}$ , followed by washing  $\text{CH}_2\text{Cl}_2$ , gave NHC without the presence of a by-product.

Scheme 2. Approaches to  $\beta$ -D- $N^4$ -hydroxycytidine (NHC) by pyrimidine amide group activation with BOP and *via* C4 chlorination.

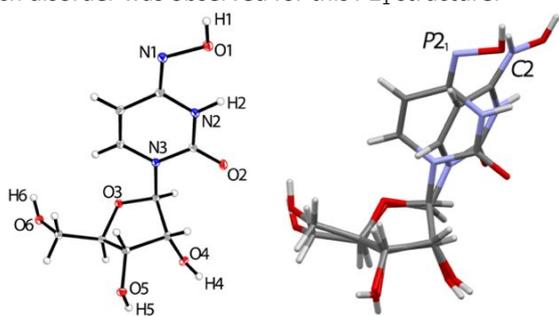
In a second approach (*Method B*), silylated uridine was chlorinated at the C4 position with  $\text{PPh}_3/\text{CCl}_4$  in  $\text{CH}_2\text{Cl}_2$ .<sup>36–38</sup> Evaporation of the volatiles, followed by exposure of the crude 4-chloropyrimidinone nucleoside to aqueous  $\text{NH}_2\text{OH}$  in MeCN also gave product **3** (90% yield on a 0.09 mmol scale, 66% on a 0.5 mmol scale).



**Scheme 3.** Approaches to molnupiravir by pyrimidine amide group activation and via C4 chlorination.

Having developed these two approaches to NHC, we modified these to access molnupiravir. The approach relied on a selective, hydrolytic release of the 5'-hydroxyl group from persilylated nucleosides (Scheme 3).<sup>39–41</sup> Exposure of precursor **2** to 50% aqueous TFA at 0 °C gave intermediate **5** (66% yield on an 8.6 mmol scale) and esterification of the 5'-hydroxyl group gave orthogonally protected intermediate **6** (83% yield on a 5.0 mmol scale). Application of the two-step, amide activation protocol with BOP/Cs<sub>2</sub>CO<sub>3</sub>, followed by reaction with aqueous NH<sub>2</sub>OH, as a one-pot procedure, gave protected oxime **7** (67% yield on a 2 mmol scale, *Method A*). Application of the *in situ* formed C4 chloropyrimidinone nucleoside also proceeded well (64% on a 0.5 mmol scale, *Method B*). Two fluoride sources were investigated for desilylation. *n*-Bu<sub>4</sub>NF (2.5 eq. in THF at rt) was inferior, returning only a 42% yield of molnupiravir (0.2 mmol scale). On the other hand, Et<sub>3</sub>N•3HF gave a much better 62% yield (on a 0.5 mmol scale).

With the synthetic campaign completed, we attempted to crystallize NHC and molnupiravir. Unfortunately, we were unable to crystallize the latter under a variety of conditions. However, crystals of NHC obtained from MeCN with a trace of MeOH were used for X-ray crystallographic analysis (Figure 3, CCDC 2307658). The structure revealed an NHC monohydrate in the monoclinic space group *P*2<sub>1</sub>. This is in contrast to a previously reported NHC•OH<sub>2</sub> polymorph that crystallized in a different monoclinic space group, *C*2, from both H<sub>2</sub>O and anhydrous DMF.<sup>21</sup> NHC takes on slightly different conformations in each polymorph, likely driven by the difference in hydrogen bonding networks. Most notably, the oxime is responsible for the hydrogen bond to the water oxygen in the *C*2 polymorph, while the 5'-hydroxymethyl is the comparable H-bond donor in the *P*2<sub>1</sub> polymorph reported here. Additionally, the *C*2 polymorph displayed disorder between amino and imino tautomers of the oxime moiety, whereas no such disorder was observed for this *P*2<sub>1</sub> structure.



**Fig. 3** X-ray crystal structure of NHC (atomic displacement parameters are displayed at the 30% probability level) and an overlay of the *P*2<sub>1</sub> and *C*2 polymorphs showing the differing conformations.

Whereas this work describes bench-scale discovery chemistry, there is a question on scalability. In such a context, BOP and PyBOP (another peptide-coupling agent) have been used at scale<sup>42</sup> (for example in the synthesis of MN447<sup>43</sup> and an amphotericin B derivative<sup>44</sup>). In relation to the use of PPh<sub>3</sub>/CCl<sub>4</sub>, sustainable Appel reactions utilizing catalytic Ph<sub>3</sub>PO are

known,<sup>45,46</sup> and a recent study reported an environmentally benign Appel reaction and attempted to utilize a continuous flow synthesis.<sup>47</sup> However, current equipment limitations at introducing slurries precluded success. Beyond these, removal of Ph<sub>3</sub>PO, and that too at scale is known.<sup>48–50</sup> Nevertheless, process development is likely to lead to new approaches.

## Conclusions

Our initial proposal of esterification of the 5'-hydroxyl group, followed by a two-step, one pot amide-group activation and substitution were not successful. However, in this aspect we determined that enzymatic esterification of uridine is easily performed with (iBuCO)<sub>2</sub>O, and this will find use in other chemistry. Because molnupiravir could not be obtained *via* this approach, 2',3',5'-*O*-silyl uridine (**2**) was considered as a substrate. This led to an evaluation of two approaches to NHC and molnupiravir. Protected uridine **2** underwent activation by BOP and it could also be converted to a C4 chloropyrimidinone nucleoside derivative. Reaction of each with NH<sub>2</sub>OH gave NHC (**5**) after complete desilylation. In both cases, the two steps can be telescoped into one-pot procedures. Protected uridine derivative **2** also provided a segue to molnupiravir. Selective cleavage of the 5'-silyl ether and esterification gave an intermediate that also underwent smooth amide group activation or conversion to a 4-chloropyrimidinone nucleoside intermediate. Again, as in the synthesis of NHC reaction of the electrophilic nucleoside intermediates with NH<sub>2</sub>OH and a final desilylation then led to molnupiravir. Here as well, the amide activation or conversion to the chloro nucleoside, and subsequent displacement could be telescoped into one-pot reactions. The overall approaches are unique from those reported and add to the arsenal of methods to these nucleoside oximes, as well as methodology for such nucleobase modification.

## Acknowledgments

Support of this work by the Fulbright-Nehru Academic and Professional Excellence Award to MKL is gratefully acknowledged. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Fulbright Program, the Government of the United States, or the United States-India Educational Foundation. The X-ray diffractometer used by MCN was supported by the Air Force Office of Scientific Research (award number FA9550-20-1-0158). We thank Nihar R. Panigrahi and Prof. Paramjit Arora (New York University) for their help with some HRMS data.

## Author Contributions

The research strategy was conceived by MKL, who also wrote the manuscript. The work was executed by KEP and RS, the latter supported grant awards to ARK. KEP assisted RS with critical trouble shooting and generated a draft MS. KEP and RS

produced a draft of the ESI. MCN performed the X-ray crystallographic analysis.

### Conflicts of interest

There are no conflicts to declare.

### Notes and references

‡ A working version of this article was deposited to ChemRxiv (<https://chemrxiv.org/engage/chemrxiv/article-details/65766a2429a13c4d472501b7>)

- 1 A. Philippidis, *Genet. Eng. Biotechnol. News*, 2020, **40**, 10–13.
- 2 Y. Shen, W. Eades, W. Liu and B. Yan, *Drug Metab. Dispos.*, 2022, **50**, 1151–1160.
- 3 F. Kabinger, C. Stiller, J. Schmitzová, C. Dienemann, G. Kocik, H. S. Hillen, C. Höbartner and P. Cramer, *Nat. Struct. Mol. Biol.*, 2021, **28**, 740–746.
- 4 D. R. Owen, C. M. N. Allerton, A. S. Anderson, L. Aschenbrenner, M. Avery, S. Berritt, B. Boras, R. D. Cardin, A. Carlo, K. J. Coffman, A. Dantonio, L. Di, H. Eng, R. Ferre, K. S. Gajiwala, S. A. Gibson, S. E. Greasley, B. L. Hurst, E. P. Kadar, A. S. Kalgutar, J. C. Lee, J. Lee, W. Liu, S. W. Mason, S. Noell, J. J. Novak, R. S. Obach, K. Ogilvie, N. C. Patel, M. Pettersson, D. K. Rai, M. R. Reese, M. F. Sammons, J. G. Sathish, R. S. P. Singh, C. M. Steppan, A. E. Stewart, J. B. Tuttle, L. Updyke, P. R. Verhoest, Li. Wei, Q. Yang and Y. Zhu, *Science*, 2021, **374**, 1586–1593.
- 5 Y. Zhao, C. Fang, Q. Zhang, R. Zhang, X. Zhao, Y. Duan, H. Wang, Y. Zhu, L. Feng, J. Zhao, M. Shao, X. Yang, L. Zhang, C. Peng, K. Yang, D. Ma, Z. Rao and H. Yang, *Protein Cell*, 2022, **13**, 689–693.
- 6 National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. February 27, 2023. Accessed September 26, 2023. <https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf>
- 7 D.-Y. Lin, F. A. Fadel, S. Huang, A. T. Milinovic, G. L. Sacha, P. Bartley, A. Duggal and X. Wang, *JAMA Netw. Open*, 2023, **6**, e2335077.
- 8 Z. M. Sticher, G. Lu, D. G. Mitchell, J. Marlow, L. Moellering, G. R. Bluemling, D. B. Guthrie, M. G. Natchus, G. R. Painter and A. A. Kolykhalov, *Antimicrob. Agents Chemother.*, 2020, **64**, e01719-19.
- 9 Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for Lagevrio (molnupiravir) capsules. 2023. Available at: <https://www.fda.gov/media/155054/download>
- 10 T. Sanderson, R. Hisner, I. Donovan-Banfield, H. Hartman, A. Løchen, T. P. Peacock and C. Ruis, *Nature*, 2023, doi: 10.1038/s41586-023-06649-6
- 11 C. Willyard, *Nature*, 2021, doi: 10.1038/d41586-021-02783-1.
- 12 Y. Li, M. Liu, Y. Yan, Z. Wang, Q. Dai, X. Yang, X. Guo, W. Li, X. Chen, R. Cao and W. Zhong, *Viruses*, 2022, **14**, 1142.
- 13 (a) G. R. Painter, G. R. Bluemling, M. G. Natchus and D. Guthrie, WO2019113462, 2018; (b) G. R. Painter, D. Perryman and G. R. Bluemling, WO2019173602, 2019.
- 14 A. Steiner, D. Snidar, S. B. Ötvös, D. R. Snead, D. Dallinger and C. O. Kappe, *Eur. J. Org. Chem.*, 2020, 6736–6739.
- 15 V. R. D. Pereira, M. A. M. Bezerra, M. R. B. P. Gomez, G. M. Martins, A. D. da Silva, K. T. de Oliveira, R. O. M. A. de Souza and G. W. Amarante, *RSC Adv.*, 2022, **12**, 30120–30124.
- 16 R. Dey, S. Nayak, P. Das and S. Yadav, *ACS Omega*, 2021, **6**, 28366–28372.
- 17 P. S. Fier, Y. Xu, M. Poirier, G. Brito, M. Zheng, R. Bade, E. Sirota, K. Stone, L. Tan, G. R. Humphrey, D. Chang, J. Bothe, Y. Zhang, F. Bernardoni, S. Castro, M. A. Zompa, J. Taylor, K. M. Sirk, A. Diaz-Santana, I. Diribe, K. M. Emerson, B. Krishnamurthi, R. Zhao, M. Ward, C. Xiao, H. Ouyand, J. Zhan and W. J. Morris, *Org. Process Res. Dev.*, 2021, **25**, 2806–2815.
- 18 V. Gopalsamuthiram, C. Williams, J. Noble, T. F. Jamison, B. F. Gupton, D. R. Snead, *Synlett*, 2021, **32**, 326–328.
- 19 V. Gopalsamuthiram, A. L. Kadam, J. K. Noble, D. R. Snead, C. Williams, T. F. Jamison, C. Shenanayake, A. K. Yadaw, S. Roy, G. Sirasani, B. F. Gupton, J. Burns, D. W. Cook, R. W. Stringham, S. Ahmad and R. Krak, *Org. Process Res. Dev.*, 2021, **25**, 2679–2685.
- 20 N. Vasudevan, G. P. Ahlqvist, C. P. McGeough, D. J. Paymode, F. S. P. Cardoso, T. Lucas, J.-P. Dietz, T. Optaz, T. F. Jamison, F. B. Gupton and D. R. Snead, *Chem. Commun.*, 2020, **56**, 13363–13364.
- 21 D. J. Paymode, N. Vasudevan, S. Ahmad, A. L. Kadam, F. S. P. Cardoso, J. M. Burns, D. W. Cook, R. W. Stringham and D. R. Snead, *Org. Process Res. Dev.*, 2021, **25**, 1822–1830.
- 22 G. P. Ahlqvist, C. P. McGeough, C. Senanayake, J. D. Armstrong, A. Yadaw, S. Roy, S. Ahmad, D. R. Snead and T. F. Jamison, *ACS Omega*, 2021, **6**, 10396–10402.
- 23 T. Hu, Y. Xie, F. Zhu, X. Gong, Y. Liu, H. Xue and H. A. Aisa, *Org. Process Res. Dev.*, 2022, **26**, 358–364.
- 24 A. Ahmed, Q. N. Ahmed and D. Mukherjee, *RSC Adv.*, 2021, **11**, 36143–36147.
- 25 T. Sahoo and B. V. S. Reddy, *Tetrahedron Lett.*, 2022, **97**, 153783.
- 26 J. A. McIntosh, T. Benkovic, S. M. Silverman, M. A. Huffman, J. Kong, P. E. Maligres, T. Itoh, H. Yang, D. Verma, W. Pan, H.-I. Ho, J. Vroom, A. M. Knight, J. A. Hurtak, A. Klapars, A. Fryszkowska, W. J. Morris, N. A. Strotman, G. S. Murphy, K. A. Maloney and P. S. Fier, *ACS Cent. Sci.*, 2021, **7**, 1980–1985.
- 27 A. J. Burke, W. R. Birmingham, Y. Zhuo, T. W. Thorpe, B. Z. da Costa, R. Crenshaw, I. Rowles, J. D. Finnigan, C. Young, G. M. Holgate, M. P. Muldowney, S. J. Charnock, S. L. Lovelock, N. J. Turner and A. P. Green, *J. Am. Chem. Soc.*, 2022, **144**, 3761–3765.
- 28 S. Ruccolo, G. Brito, M. Christensen, T. Itoh, K. Mattern, K. Stone, N. A. Strothman and A. C. Sun, *J. Am. Chem. Soc.*, 2022, **144**, 22582–22588.
- 29 Z.-K. Wan, E. Binnun, D. P. Wilson and J. Lee, *Org. Lett.*, 2005, **7**, 5877–5880.
- 30 S. Bae and M. K. Lakshman, *J. Am. Chem. Soc.*, 2007, **129**, 782–789.
- 31 S. Bae and M. K. Lakshman, *J. Org. Chem.*, 2008, **73**, 3707–3713.
- 32 M. K. Lakshman, *Chem. Rec.*, 2023, **23**, e202200182.
- 33 H. K. Akula, H. Kokatla, G. Andrei, R. Snoeck, D. Schols, J. Balzarini, L. Yang and M. K. Lakshman, *Org. Biomol. Chem.*, 2017, **15**, 1130–1139.
- 34 H. K. Akula and M. K. Lakshman, *Curr. Protoc. Nucleic Acid Chem.*, 2019, **76**, e73.
- 35 A. Maina, B. A. Blackburn, C. J. Parronchi, E. Morozko, M. E. Bender, A. D. Blake and D. Sabatino, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 5270–5274.
- 36 N. Barhate, P. Cekan, A. P. Massey and S. T. Sigurdsson, *Angew. Chem. Int. Ed.*, 2007, **46**, 2655–2658.
- 37 C. Hôbartner, G. Sicoli, F. Wachowius, D. B. Gophane and S. T. Sigurdsson, *J. Org. Chem.*, 2012, **77**, 7749–7754.
- 38 A.-L. J. Segler and S. T. Sigurdsson, *J. Org. Chem.*, 2021, **86**, 11647–11659.
- 39 X.-F. Zhu, H. J. Williams and A. I. Scott, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2305–2306.
- 40 C. Amiable, S. Pochet, *Tetrahedron*, 2015, **71**, 2525–2529.
- 41 D. Sebastian, S. Satishkumar, P. Pradhan, L. Yang and M. K. Lakshman, *J. Org. Chem.*, 2022, **87**, 18–39.

- 42 J. Magano, *Org. Process Res. Dev.*, 2022, **26**, 1562–1689.
- 43 M. Ishikawa, M. Tsushima, D. Kubota, Y. Yanagisawa, Y. Hiraiwa, Y. Kojima, K. Ajito and N. Anzai, *Org. Process Res. Dev.*, 2008, **12**, 596–602.
- 44 J. D. Flores-Romero, J. R.-Lozada, M. López-Ortiz, R. Magaña, I. Ortega-Blake, I. Regla and M. Fernández-Zertuche, *Org. Process Res. Dev.*, 2016, **20**, 1529–1532.
- 45 R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis and A. M. Poulton, *J. Org. Chem.*, 2011, **76**, 6749–6767.
- 46 A. Jordan, R. M. Denton and H. F. Sneddon, *ACS Sustainable Chem. Eng.*, 2020, **8**, 2300–2309.
- 47 N. M. Del Rio Fuenzalida, E. Alme, F. J. Lundevall and H-R. Bjørsvik, *React. Chem. Eng.*, 2022, **7**, 1650–1659.
- 48 D. C. Batesky, M. J. Goldfogel and D. J. Weix, *J. Org. Chem.*, 2017, **82**, 9931–9936.
- 49 Y. Tamboli, B. B. Kashid, R. P. Yadav, M. Rafeeq, R. Yeole and A. Y. Merwade, *ACS Omega*, 2021, **6**, 13940–13945.
- 50 A. R. Hergueta, *Org. Process Res. Dev.*, 2022, **26**, 1845–1853.