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On the origins of SARS-CoV-2 main protease inhibitors

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In order to address the world-wide health challenge caused by the COVID-19 pandemic, the 3CL protease/SARS-CoV-2 main protease (SARS-CoV-2-M^{pro}) coded by its *nsp5* gene became one of the biochemical targets for the design of antiviral drugs. In less than 3 years of research, 4 inhibitors of SARS-CoV-2-M^{pro} have actually been authorized for COVID-19 treatment (nirmatrelvir, ensitrelvir, leritrelvir and simnotrelvir) and more such as EDP-235, FB-2001 and STI-1558/Olgotrelvir or five undisclosed compounds (CDI-988, ASC11, ALG-097558, QLS1128 and H-10517) are undergoing clinical trials. This review is an attempt to picture this quite unprecedented medicinal chemistry feat and provide insights on how these cysteine protease inhibitors were discovered. Since many series of covalent SARS-CoV-2-M^{pro} inhibitors owe some of their origins to previous work on other proteases, we first provided a description of various inhibitors of cysteine-bearing human caspase-1 or cathepsin K, as well as inhibitors of serine proteases such as human dipeptidyl peptidase-4 or the hepatitis C protein complex NS3/4A. This is then followed by a description of the results of the approaches adopted (repurposing, structure-based and high throughput screening) to discover coronavirus main protease inhibitors.

Introduction

The protein encoded by the *nsp5* gene of SARS-CoV-2 virus corresponds to the main protease of this coronavirus. This protein has also been named SARS-CoV-2 M^{pro}, 3C-like protease/3CLpro (CL for chymotrypsin-like) and C30 endopeptidase. Following N and O-terminal autocleavages, the mature enzyme is, at least,[1] able to hydrolyze 9 other conserved sites of the viral polyprotein produced by the host ribosome to generate the corresponding viral proteins. As well reviewed,[2–4] the protease features a characteristic cysteine/histidine catalytic dyad. It is the cysteine-145 thiol anion, depicted in Scheme 1, which acts as a nucleophile and the histidine-41 imidazole as a general base in the course of the proteolysis. The peptide **1** cleavage to release **3** and **4** takes place *via* the occurrence of transient *S*-acylcysteine (**2**) which is then hydrolyzed to regenerate the thiol function and release the protein **4**. Peptide cleavage-wise, SARS-CoV-2 M^{pro} has the same hydrolysis selectivity as SARS-CoV-1 M^{pro} or other proteases from coronaviruses.[5,6] A recent report has actually described remarkable structural insights in this sequence recognition process.[7] As depicted, the residue R_1 of any substrate has to be a glutamine, whereas, upward of the cleavage site, R_2 is usually a leucine or another hydrophobic residue, and if R_3 can vary, R_4 (which is not depicted) remains small and usually aliphatic. Downward, only the R'_1 residue appears to be governing the cleavage selectivity as it can only be a serine, an alanine or an asparagine.[7] Concerning host cell proteins, quite a few[8–11] have been reported as substrates of SARS-CoV-2 M^{pro}, thus providing further insights into the many ways[12,13] viruses play havoc in cellular biochemistry and innate immunity. A recent review on the proteins reported as substrates of this protease is also available.[14]

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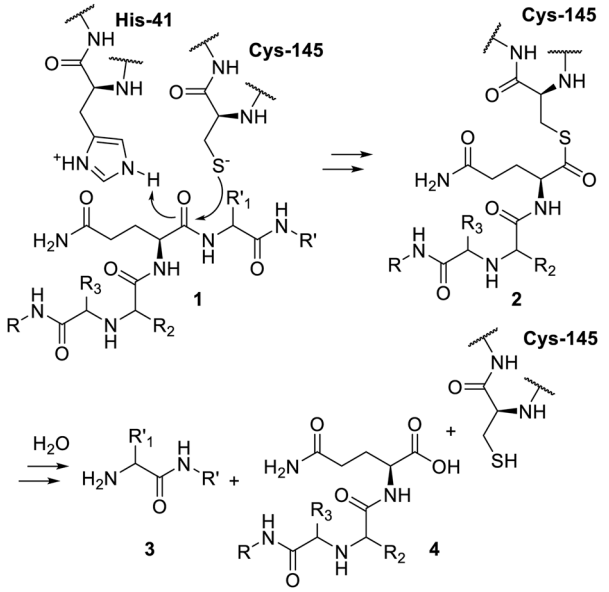


Scheme 1 Two stages of peptide **1** hydrolysis into **3** and **4** by SARS-CoV-2 M^{pro}.

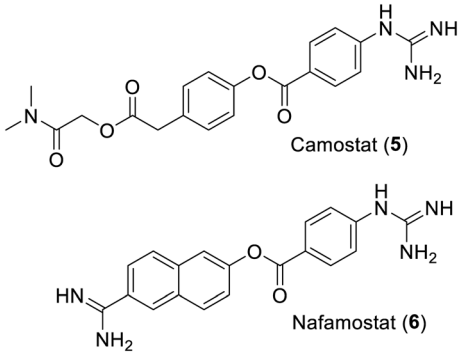


Fig. 1 Structures of camostat (**5**) and nafamostat (**6**).

Of note is that comparatively less inhibitors have been reported for the other SARS-CoV-2 protease which is a papain-like cysteine-bearing enzyme. Two papers[15,16] and a few reviews[17–20] would probably be good starting points for further information on this different viral protease. Moreover, and as far better reviewed recently,[21,22] the host cell lysosomal cysteine protease cathepsins B and L, the transmembrane protease serine 2 (TMPRSS2) and the subtilisin-like proprotein convertase furin, a calcium-dependent serine protease, are all capable of cleaving the viral spike protein coating the virus surface and this is an essential step for its cellular entry. Accordingly, in the absence of *in vitro* selectivity control, concerns have been raised on the true mechanism of observed antiviral effects for some series of unselective protease inhibitors reported,[23–25] not to mention the recurrent frequent hitters.[26–28] In fact, cathepsins B and L are actually the targets of a selective inhibitor which also displayed an antiviral effect *in cellulo*.[29] Moreover, as for past research against the MERS coronavirus (MERS-CoV),[30,31] the importance of these cellular proteases did suggest the use of camostat (**5**), an approved TMPRSS2 inhibitor, for treatment against COVID-19.[32] However, even at high dose, the clinical trials with this anticancer agent pointed out a lack of any benefit.[33] Similar reasoning, originally based on MERS-CoV research,[34] has also led to trials (NCT04352400) with the nonspecific serine protease inhibitor nafamostat (**6**). The conclusions of these 2021 human trials against COVID-19 have yet to be published although the short *in vivo* half-life of this iminoimide will remain of real concern (Fig. 1).[35]

Two general approaches to discover inhibitors of serine or cysteine-bearing proteases have been used in the past. The main one is to design compounds which can arguably be described as covalent inhibitors. Such compounds will block the enzyme *via* the occurrence of a covalent bond with their catalytically essential OH or SH residues. Of note is that depending on the chemistry involved, the formation of a covalent bond can sometimes be reversed. The probably more difficult alternative is to discover inhibitors affecting the protease function because of a high and non-covalent affinity for either its catalytic site or another essential component of the enzyme. The latter approach can of course be useful for the former one since a well-placed incorporation of a reactive moiety into a high affinity compound will lead to a possibly more selective covalent inhibitor. Many reports have already listed all the, sometimes related,[36] inhibitors reported for their effect on chymotrypsin-like proteases of human rhinovirus,[37–40] enterovirus 71,[41] SARS and MERS coronaviruses[42–46] and then SARS-CoV-2.[2–4,6,17,18,47–70] In the present text, the many publications[26] solely based on *in silico* docking approaches[71,72] and/or on traditional/ancestral medicine beliefs which only described frequent hitters/pan-assay interference compounds (PAINS)[73–77] were ignored. This choice is a bid to discourage such all too obvious pollution of the scientific literature,[78,79] not to mention the issue of lack of reproducibility of some data from the academia.[80] Aside from these, quite a few virtual-based reports describe modest inhibition of SARS-CoV-2 M^{pro} by not too obvious frequent hitters which could lead to original series of inhibitors.[81–92] However, as for the published results of high throughput or X-ray based screenings,[84,93] we chose to wait for some reports focusing on the actual hit to lead progression before including them in this text.

Designing successful covalent inhibitors, a few examples

The principle for designing a successful/selective covalent inhibitor in general is to first start with a substance with a degree of specific affinity for the active site of the targeted enzyme. Then, the inclusion of an electrophilic and thus reactive component to the structure of such compounds can lead to a far stronger and possibly more efficient *in vivo* inhibition effect. A counter example, which unfortunately keeps on attracting undue attention and funding,[94] would be the frequent hitter[74] ebselen (**7**). This compound does feature

a rather reactive nitrogen–selenium bond but very little else in its structure provides for any target selectivity. Indeed, a selective covalent inhibitor will rely on the principle that, when bound to its target, the reactive component of such a compound is oriented toward a nucleophilic and essential part of the enzyme in order to favor a reaction selectivity. This requires a fine-tuning process not only to improve the affinity of the non-reactive part of the inhibitor for its target but also to secure the best orientation of its reactive component. In other words, ebselen (7) does not comply with such criteria in contrast with, for instance, the recently authorized anticancer drug sotorasib/AMG 510 (**8**). Indeed, the latter features a Michael accepting acrylamide moiety along with other structural components providing an affinity for its biochemical target. Accordingly, this anticancer substance does preferentially lead to the occurrence of a covalent bond with the oncogenic KRAS (glycine 12 cysteine) mutant.[95,96] Of note is that more recent research, starting from BI-0474 (**9**), another covalent inhibitor of this KRAS mutant, actually led to the non-covalent pan-KRAS inhibitor BI-2865 (**10**).[97] Aside from providing a demonstration of the benefit of long-term research in medicinal chemistry, this illustrates the following facts: (i) in the course of designing inhibitors, it is indeed possible to add a reactive moiety and thus improve an inhibition effect and (ii) it is also sometimes possible to remove such a reactive moiety and, following some more structure-guided design of analogues, reach some very efficient non-covalent inhibitors (Fig. 2).

Concerning irreversible inhibitors of serine, cysteine or threonine proteases in general, a few reviews[98–101] provide an extensive description of the compounds reported. The following are only illustrations of some of the successes (and failures) of these classes of inhibitors.

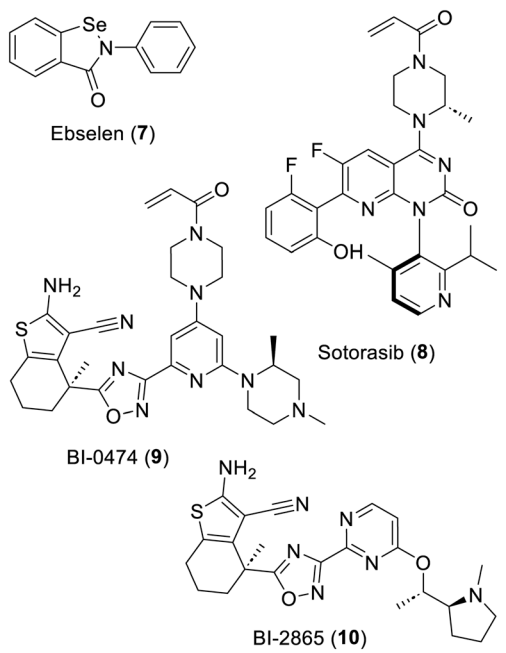


Fig. 2 Structures of compounds 7–10.

Inhibitors of caspase-1/interleukin-1 converting enzyme

The cysteine protease caspase-1/interleukin-1 converting enzyme (ICE)[102] cleaves peptides after an aspartic acid residue, preferably endowed with the sequence Tyr-Val-Ala-Asp. As reviewed,[103] research for specific inhibitors started with the aldehyde-bearing peptide Ac-Tyr-Val-Ala-Asp-H and using extensive structure-based insights, proceeded to replace/"deconstruct" most of these residues to reach more metabolically stable inhibitors. Belnacasan/VX-765 (**11**) is a hemiacetal prodrug, whose first patent application was filed by Vertex in 2000.[104] This compound will, upon a hydrolysis, leads to the aldehyde-bearing VRT-043198 (**12**), a selective covalent inhibitor of ICE. Of note is the nitrile group of analogue **13** which was introduced in 2010 as an alternative to the reactive aldehyde function of compound **11**.[105] Aside from these, a few other series were also patented by Vertex. As depicted with the structures of the randomly selected N-substituted pyridinones **14** or **15**, both "drifted" from the ICE-favored peptidic sequence mentioned above and their central heterocycle provided another type of structural lock to favor a suitable orientation of their reactive ketone.[106–108] The possible extent of such a peptide deconstruction approach is also well illustrated with the hemiacetal ICE inhibitor pralnacasan (**16**), which features a notable bicyclic piperazic component.[109] More recent work on the design of ICE inhibitors led another research group to uracil-containing derivatives such as the most advanced compound **17**.[110,111] Clinic-wise, quite a few trials were conducted with belnacasan (**11**) for treatments of conditions involving a possible disfunction of ICE, but this class of inhibitors has yet to reach an approved use in human health. Of note is the current trend in addressing the dreadful cytokine storm seen in some SARS-CoV-2 infected patients by inhibiting the many biochemical pathways involved in inflammation. In this regard, a few 2022 patents claimed ICE inhibitors such as belnacasan (**11**) or the nitrile-bearing analogue **13** for their potential benefit against coronavirus infection.[112–114] Similarly, a recent patent[115] claims the use of inhibitors of the beta secretase 1 to suppress this storm; however, both cases are quite outside the scope of this review (Fig. 3).

Inhibitors of cathepsin K

Cathepsin K, which hydrolyses a rather wide range of substrates,[116] was selected as a target to treat bone resorption. Extensive research at Merck led to the nitrile-containing inhibitor odanacatib (**18**)[117] and an X-ray based structure further proved its mechanism of inhibition *via* covalent bonding with the catalytic cysteine residue.[118] However, although this inhibitor reached a phase III clinical trial stage, its development was stopped in 2019 because of a stroke risk increase.[119] Of note is the closely related analog CZ007 (**19**) which has been under consideration as a drug against the human parasite *Trypanosoma cruzi* since it also strongly inhibits cruzipain, a key cysteine protease of this protozoan.[120,121]

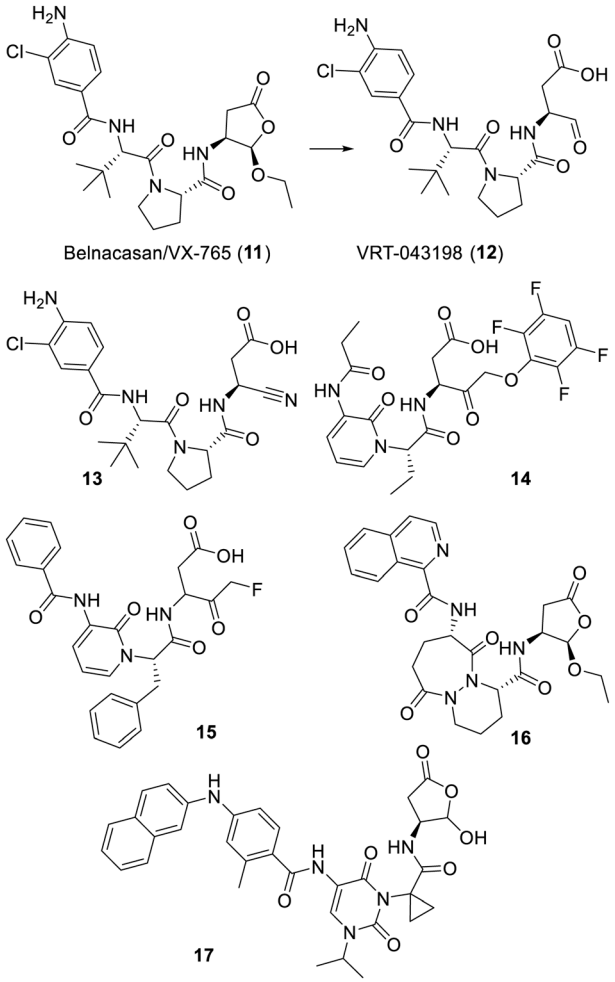


Fig. 3 Structures of interleukin-1 converting enzyme inhibitors **11**–**17**.

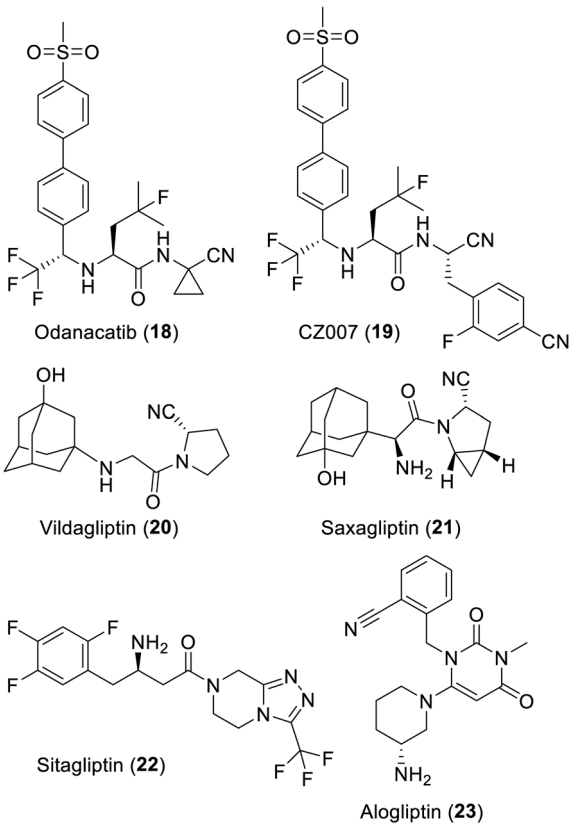


Fig. 4 Structures of compounds **18**–**23**.

Inhibitors of human dipeptidyl peptidase-4/CD26

As well reviewed,[122–127] the serine-containing dipeptidyl peptidase-4/CD26, which is a prolyl oligopeptidase, has many physiological roles. These include the proteolysis of glucagon-like peptide 1 or the glucose-dependent insulinotropic polypeptide, which are both key factors in glucose homeostasis. Since 1994, medicinal chemistry efforts have focused on cyanopyrrolidine-containing inhibitors and culminated in the discoveries of vildagliptin (**20**)[128] and saxagliptin (**21**).[129] With their nitrile function, both compounds are covalent inhibitors of this serine protease, although the serine adducts formed[130] are slowly reversible.[131,132] This class of covalent drugs have been prescribed for years to reduce hyperglycemia in patients with type 2 diabetes mellitus. Interestingly, many non-covalent inhibitors of this protease such as sitagliptin (**22**)[133] or alogliptin (**23**)[134] were also discovered. As demonstrated by X-ray based structures,[130,135] these non-covalent inhibitors also target the catalytic site of the protease and their wide structural diversity is a tribute to what can medicinal chemistry do (Fig. 4).

Inhibitors of hepatitis C serine protease NS3/4A

As described in an editorial on the 2020 Nobel Prize award to Harvey J. Alter, Michael Houghton and Charles M. Rice, the quest to first characterize and then discover treatments against hepatitis C infection has been a 30 year-long story.[136] Indeed, medicinal chemistry research on the inhibition of a number of viral proteins of hepatitis C virus has today delivered treatment efficacies nearing 95% cure![137] Since the late 90s, many laboratories have focused on the design of covalent or non-covalent inhibitors of the hepatitis C serine protease NS3/4A.[138,139] The α-ketoamide-bearing covalent inhibitors boceprevir (**24**)[140–142] and telaprevir (**25**)[143] turned out to be the first clinically approved drugs. Interestingly, a proof of concept was also achieved in patients with the remarkable macrocycle ciluprevir/BILN 2061 (**26**) which is a non-covalent inhibitor of NS3/4A.[144,145] This discovery led to many series of macrocycle-bearing analogues which reached clinical approvals such as simeprevir (**27**)[146] or grazoprevir (**28**).[147] Finally, and as well accounted,[148] research on treatment of hepatitis C also focused on discovering inhibitors of its RNA-dependent RNA polymerase NS5B. This was concluded with the prodrug sofosbuvir (**29**) which is instrumental for reaching the 95% clinical efficacy mentioned above. However, this last achievement also triggered the voluntary withdrawal, or project termination, of quite a few hepatitis C serine protease NS3/4A inhibitors (Fig. 5).

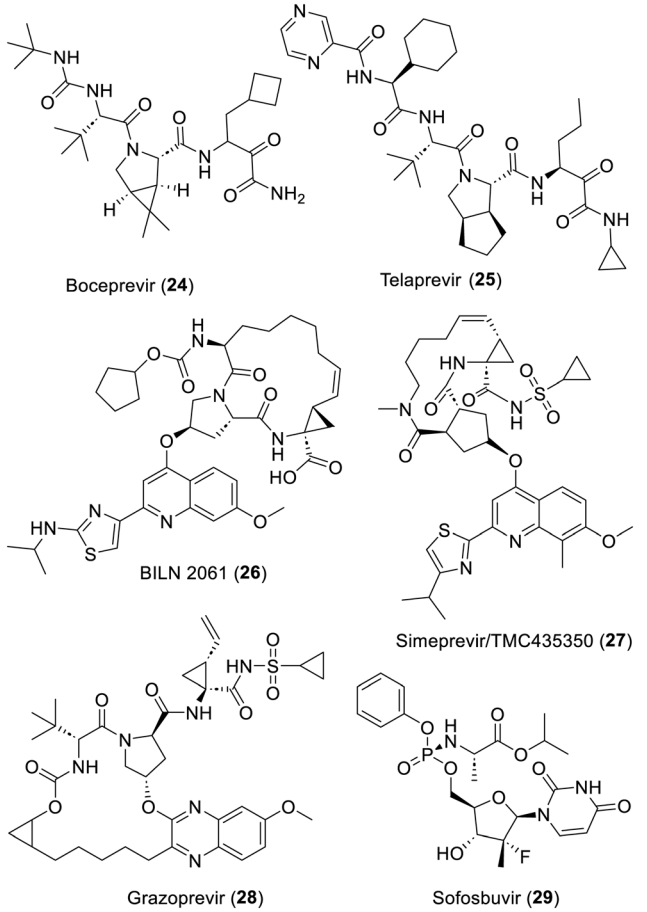


Fig. 5 Structures of compounds **24**–**29**.

Inhibitors of the SARS-CoV-2 main protease

Since the main proteases of SARS-CoV-1 and SARS-CoV-2 share a 96% amino acid sequence identity (but only 50% with the MERS-CoV main protease),[2] most if not all research on their inhibition turned out to be useful for the renewed projects focusing on improving such inhibitors. This was also the case for drugs which have been "repurposed" as inhibitors of MERS or SARS-CoV-1, and these include some potential inhibitors of their main protease.

Concerning drug repurposing

Aside from the excessive number of reports describing *in vitro* inhibition of SARS-CoV-1(or 2)-M^{pro} by well-known frequent hitters/PAINS, another approach focused on assessing libraries of drugs already or previously used or tried in humans. The SARS-CoV-2 pandemic thus saw the publication of many papers reporting *in vitro* inhibition of SARS-CoV-2-M^{pro} by such compounds. The main result of this approach is an unfortunate illustration of a lack of medicinal chemistry culture in general. Indeed, most often only micromolar level effects were observed *in vitro* for such drugs. Accordingly, it was more than unlikely that a patient would benefit from a treatment based on them, not to mention the issues of necessary dose increases which would be bound to lead to some side effects including some due to their main biological actions. In medicinal chemistry, compounds effective at the micromolar level against a given target can only be considered as hits (or early leads). Such compounds must undertake rounds of structure–activity relationship and selectivity studies to be further improved before preclinical and clinical trials can be envisaged. Attempts to cut this process short are oblivious to decades of experience in the domain and only slightly more rational than hoping for a miracle. Moreover, even in the rare event of finding a strong level of *in vitro* SARS-CoV-2-M^{pro} inhibition for a prescribed drug, it is very likely that it will lack any *in vitro* or *in vivo* selectivity. Indeed, quite a few highly reactive compounds are found in the present or past human pharmacopeia. In the following, we describe a few drugs which were reported for their effect on SARS-CoV-2-M^{pro}. Unfortunately, not all were the focus of some MedChem iterations to improve them before initiating wishful clinical trials which, predictably, led to disappointing results.[27,149–152]

From a screening which identified 14 known drugs, the antiepileptic drug perampanel (**30**) was found to be an inhibitor of the main protease of SARS-CoV-2.[153] Some MedChem helped by X-ray based structures (PDB 7L10 to 7L14) from the same research group provided 3-pyridyl-bearing analogues, such as compounds **31** and **32** (with **32** being much less cytotoxic than **31**).[154] And further work, helped by nine X-ray based structures in this case, gave improved inhibitors such as pyrimidinediones **33** and **34a**,[155] as well as the even less cytotoxic *N*-methylated derivative **34b**.[156] A more recent report has described analogues featuring a pyridone instead of the uracil moiety of compounds **33** and **34a–b**.[157] As described in more detail below, the 3-pyridyl component of these improved analogues has actually been known since 2013 for its capability to interact with the histidine-163 of the SARS-CoV-1-M^{pro} catalytic site.[158] Also of note is that this class of inhibitors do have some structural similarities with alvelestat (**35**), a serine protease (elastase) inhibitor.[159] Independent from this work and as stated by its authors, a remarkably lucky *de novo*-initiated search for inhibitors delivered the somehow related (but not computer-guided) N-substituted pyridinone derivative **36.** Further X-ray based crystallography studies are planned in order to improve its relatively modest inhibition level (Fig. 6).[160]

A repurposed curiosity would be the veterinary anticancer drug masitinib (**37**), it is a tyrosine kinase inhibitor which has also been patented for its modest effect on the replication of SARS-CoV-2.[161] Further research actually led to its co-crystallization with SARS-CoV-2-M^{pro} (PDB 7JU7).[162] A note of caution would be that this rather sticky compound, as well as imatinib (**38**), has also managed to co-crystallize with human deoxycytidine

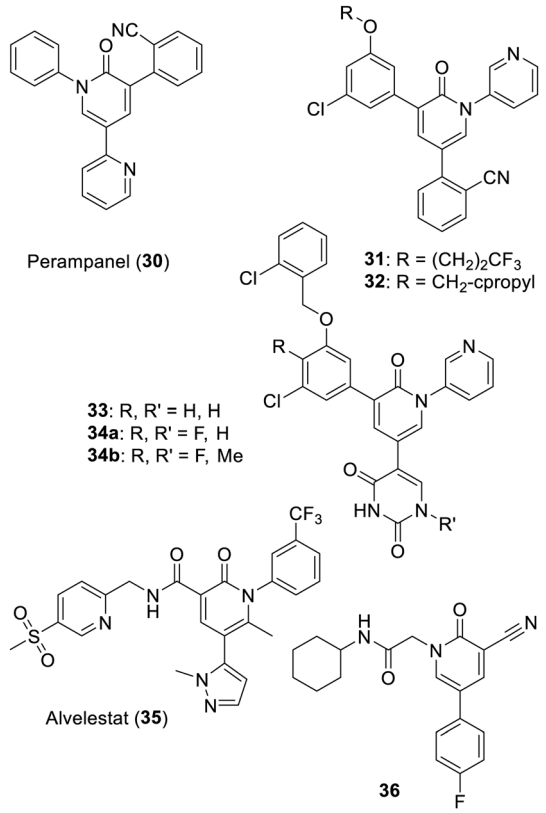


Fig. 6 Structures of compounds **30**–**36**.

kinase (PDB 5MQL).[163] In any case, undertaking clinical trials against COVID-19 (NCT05047783) with compound **37**, even in association with the polyphenolic frequent hitter isoquercetin (NCT04622865), is very likely to be disappointing. Indeed, as mentioned for the repurposing of imatinib (**38**) against COVID-19, which has also been found active *in vitro* on MERS-CoV,[164] clinically achievable doses in humans will not be high enough to be effective against the virus replication.[165] One more example of such "sticky" compounds would be dasatinib (**39**), another tyrosine kinase inhibitor, which was reported to have some effect on SARS-CoV-2-M^{pro}.[166] However, the *in cellulo* antiviral effects observed for all these amine-bearing compounds are very likely due to drug-induced phospholipidosis.[167,168] This cellular-level effect (which impacts to some degree viral replications *in cellulo*) was unfortunately the cause of a considerable waste of money (as much as 6 billion dollars) when considering all the clinical trials against COVID-19 made with many amine-bearing compounds, especially chloroquine or hydroxychloroquine.[150] Concerning other cellular kinases, a recent report has described far stronger *in cellulo* inhibition of SARS-CoV-2 replication by PI3K/mTOR inhibitors such as sapanisertib (**40**).[169] Future will tell if this translates into an *in vivo* effect although a precedent would be the inhibitors of cellular dihydroorotate dehydrogenase[170] which have yet to translate into effective RNA-based antivirals (including corona) in patients.[171–173] In 2004, niclosamide (**41**) was found to be endowed with a degree of antiviral effect on SARS-CoV-1 although it was not found to inhibit its main protease[174] and later on, this anthelminthic drug was also reported for its effect on many viruses, which has been recently reviewed.[175] Finally, inhibition of SARS CoV-2 replication was also reported[176] and, despite some ongoing structure–activity relationship studies,[177] clinical trials were undertaken (NCT04399356 and 04603924)[178] with compound **41** and have so far failed.[179] Even if mechanism of action-wise, niclosamide (**41**) should not be mentioned here,[180] and some protease inhibitors such as **42** have a puzzling degree of structural similitude to this drug. Compound **42** actually resulted from attempts to prepare protease substrates which would release a fluorescent product. However, it turned out that that these were inhibiting SARS-CoV-2-M^{pro} and the ensuing structure–activity relationship studies led to this compound.[181] More recent work on closely related analogues of compound **42** has reported very modest inhibition of SARS-CoV-2-M^{pro}.[182] Another puzzling similarity is also seen with a patent[183] claiming the effect on SARS-CoV-2-M^{pro} of closantel (**43**), a rather toxic anthelmintic drug, which shares some degree of similitude to these two amides (Fig. 7).

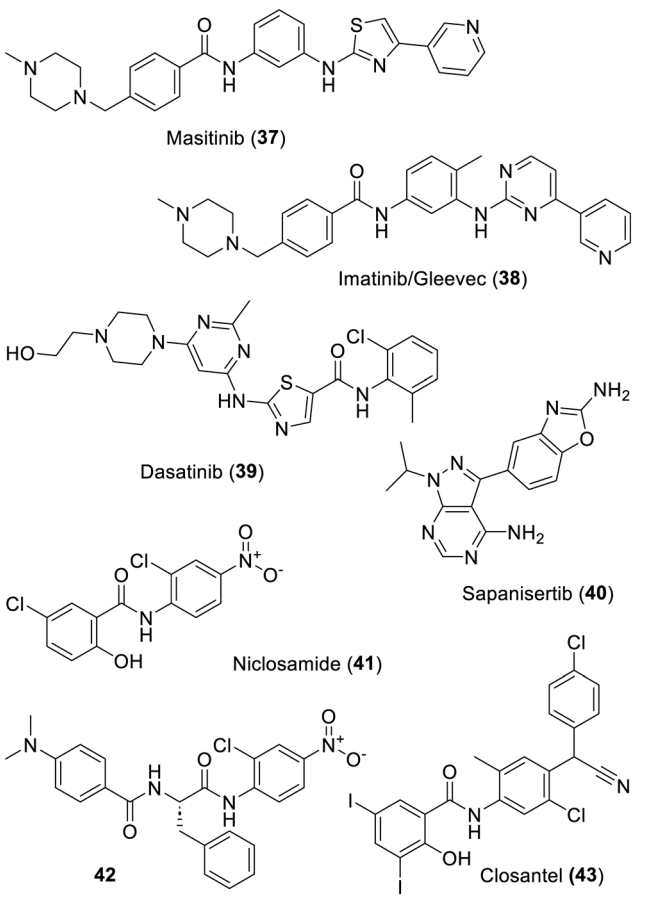


Fig. 7 Structures of compounds **37**–**43**.

Covalent or non-covalent inhibitors of SARS-CoV-2-M^{pro} from previous series

As for the series inhibiting other proteases, one of the approaches to design inhibitors started from the structure of small peptides featuring sequences recognized by the protease (*i.e.*: Ser-Ala-Val-Leu-Gln) and the addition of various types of warheads next to the cleavage site: downward the glutamine (Gln) residue in the case of SARS-CoV-2-M^{pro}. It would be beyond the scope of this review to depict all the series of peptide-derived inhibitors made, especially since 2019 an even larger array of warheads has been incorporated in such compounds.[184] Indeed, a non-exhaustive list used in the last few decades includes: aldehydes (or the corresponding bisulfite adduct),[41,185–202] ketones,[203–211] α-ketoamides,[153,185,212–214] Michael acceptors,[194,215–218] 4-iminooxazolidin-2-one,[219] reactive halogens,[220–224] β-lactam of some penicillins,[225,226] phenylsulfide,[227] thiocyanate,[228] epoxide,[24] nitriles[229–231] and, last but not least, alkynes.[232,233] Interestingly, aside from a 2005 patent[234] targeting SARS-CoV-1-M^{pro}, the design of boron-containing inhibitors, which is a fairly classic approach for protease inhibition,[235,236] has not been reported in more recent time. Along with these warheads, intensive efforts were made to modify these peptides and/or replace them with non peptidic spacers. Moreover, compounds designed to block other viral cysteine proteases were of course assayed on the coronaviruses. As an illustration of the multitude of approaches, the Michael-acceptor bearing rupintrivir/AG7088 (**44**), initially designed in 1999 as a covalent inhibitor of human rhinovirus 3C cysteine protease,[237,238] was suggested[239] in 2003 to be a starting point to target SARS-CoV-1-M^{pro}. A strong intensive to evaluate rupintrivir (**44**) was also the fact that it had previously been the subject of phase 1 and 2 clinical trials against rhinovirus.[240,241] However, rupintrivir (**44**) was "not able to significantly affect virus reduction or moderate disease severity and thus was terminated for clinical development".[242] In any case, if compound **44** was reported inactive in 2005,[243] the closely related analogue **45** turned out to modestly inhibit[243] SARS-CoV-1-M^{pro} (or MERS-M^{pro})[244] and the longer peptides N1 (**46**) and N3 (**47**) featuring the more adapted Ala-Val-Leu sequence were even better.[245] Although rupintrivir (**44**) was later found to only be a very modest inhibitor of SARS-CoV-2-M^{pro}, thanks to its reactive component, it still managed to co-crystallize with this protease (PDB 7L8I).[218] Also starting from the Ser-Ala-Val-Leu-Gln sequence, a research group reported in 2011 that the imidazole bearing aldehyde **48** was a modest inhibitor of SARS-CoV-1-M^{pro}. The ensuing structure-guided iterations of synthesis and evaluation led to the much stronger inhibitor **49** which was also co-crystallized with SARS-CoV-1-M^{pro} (PDB 3ATW).[246] More recent work actually reported related imidazole-bearing peptides.[247] Of note is that a glutamine residue is prone to cyclize at the least with ketone or aldehyde warheads.[248–250] Accordingly, effort to replace it also stemmed from the search for human rhinovirus 3C cysteine protease inhibitors and provided the bioisosteric lactams depicted in the structures of compounds **44** and **45**. As well illustrated below, this bioisosteric replacement was repeatedly used in the structures of other virus protease inhibitors.[238,248,251] A recent review has actually described in much more detail this issue of glutamine replacement.[252] As for the results reported in 2000 focusing on the inhibition of the rhinovirus 3C protease,[203] research on SARS-CoV-1-M^{pro}, dating from 2009, also explored the incorporation of large components downstream of the warhead. Similar to peptide inhibitors of the rhinovirus 3C protease,[203] if the thiazole-2-ketone-bearing peptide **50** was only a modest inhibitor of SARS-CoV-1-M^{pro},[253] the benzothiazole analogue **51** in which benzene filled a pocket of this protease provided a thousand-fold improvement.[254] Also of interest is the nitrile-containing peptide **52** which was reported in 2013 to be a weak inhibitor

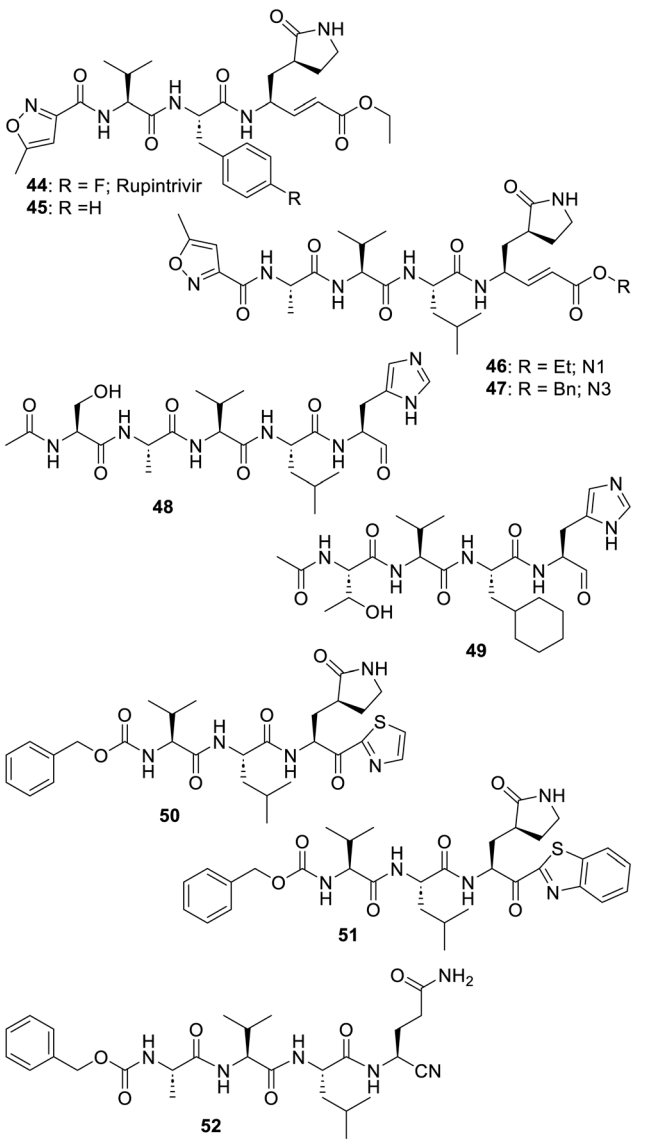


Fig. 8 Structures of compounds **44**–**52**.

of SARS-CoV-1 M^{pro}, but it was established that this function could be used to covalently inhibit this protease (Fig. 8).[255]

The shorter bisulfite prodrug GC376 (**53**) was reported in 2012 as a norovirus 3CL protease inhibitor.[256] As depicted, the bisulfite adduct **53** will release *in situ* the aldehyde function of the antiviral GC373 (**54**).[251] Interestingly, this compound has demonstrated a degree of *in vivo* effect against feline enteric coronavirus infection.[257,258] Even if it is only modestly effective *in vitro*[217] or *in vivo* against a mouse model of SARS-CoV-2 infection,[259] this pan 3CL virus protease inhibitor has often been used as a positive control in SARS-CoV-2-M^{pro} assays. Many analogues of GC376 (**53**) were reported,[185,260,261] such as compounds resulting from a "fluorine walk" on the benzyl moiety and/or its replacement by a substituted cyclohexyl, a bulkier adamentyl and even more elaborated substituents.[195,199,201,262,263] As an illustration of the "leeway" on this position, the difluorocyclohexyl-bearing analogue **57** was found to be effective against a mouse model of MERS coronavirus infection.[188] Moreover, a deuterated derivative of **50** was evaluated on a mouse model of SARS-CoV-2 infection but this analogue showed no real advantage.[198] This result may not be too surprising, since a deuteration strategy usually addresses fast metabolic issues but GC376 (**53**) was reported to be reasonably stable in human plasma ($t_{1/2}$ > 240 min) or in the presence of human liver microsomes ($t_{1/2}$ > 80 min) as well as in mice ($t_{1/2}$, plasma > 240 min, $t_{1/2}$, microsome > 80).[211] Further studies on the protease inhibition selectivity of GC376 (**53**) as well as analogues EB54 (**55**) and NK01-63/coronastat (**56**) pointed out the fact that these compounds are also very strong inhibitors of the host cell cathepsin L.[211] Another investigation reported even more analogues of GC376 (**53**) but also described solubility issues, along with suggestions to administer such bisulfite adducts at higher concentration.[264] The cyclohexyl group of compound **49** was also adopted in the design of the related compound **58** targeting the norovirus 3CL protease.[265] However, even combined with other types of warheads, this cyclohexyl feature turned out to be associated with cellular toxicity.[209,266] Compound TG-0205221 (**59**) illustrates the structure-based improvements made in 2006 when focusing on the inhibition of SARS-CoV-1-M^{pro} by this "Boc-derived" series.[267] Much later, the O-*tert*-butyl-threonine component of the tripeptide TG-0205221 (**59**) was also found to be key to improving the interactions of related analogues with the P3 site of the SARS-CoV-2-M^{pro} binding pocket and it also provided some cellular potency.[268] Interestingly, research at Glaxo, part of it dating from 2018 and focusing on the rhinovirus main protease,[269] led to tripeptides such as **60** in which an α-ketoamide warhead was used instead of an aldehyde. However, a modest antiviral activity along with a degree of cellular cytotoxicity probably prevented further development of this series.[270] The somehow larger "Boc" derivative **61** is amongst the compounds claimed in four patents by Cocrystal Pharma which has initiated a phase 1 study of the undisclosed coronavirus–norovirus protease inhibitor CDI-988 (NCT05977140) (Fig. 9).[271–274]

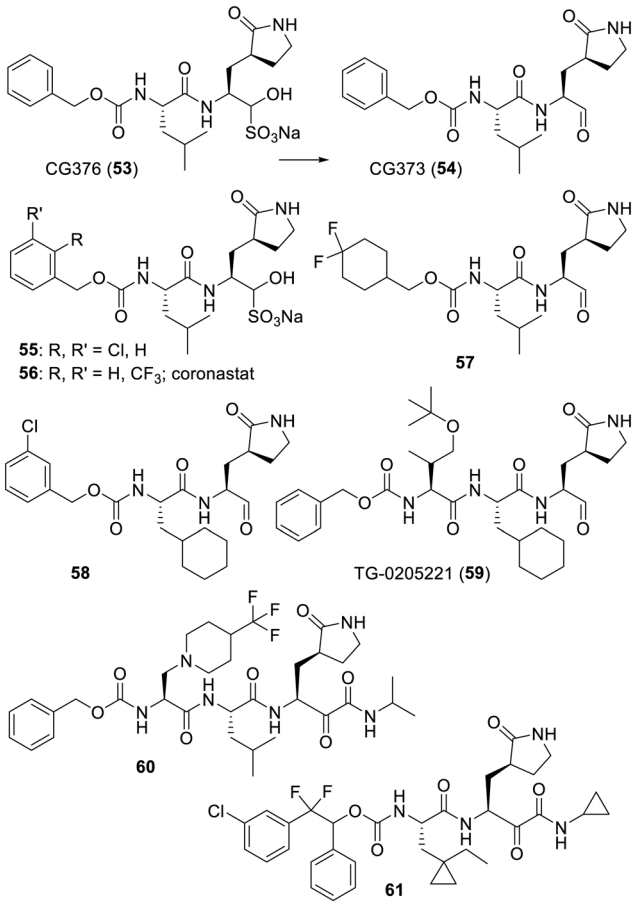


Fig. 9 Structures of compounds **53**–**61**.

Other series of short peptides were also designed when the world faced the first SARS epidemic. A 2005 patent claimed many isoleucine and lactam-containing inhibitors of SARS-CoV-1-M^{pro}, including the noteworthy indole-bearing derivative PF00835231 (**62**).[275] In 2020, the corresponding phosphate prodrug PF-07304814/lufotrelvir (**63**) was then developed by Pfizer to fight COVID-19 infection,[205,276] and this intravenous prodrug[207] underwent successful phase 1 clinical trials.[277,278] However, an additional trial (NCT05780541) was suspended by the FDA and lufotrelvir (**63**) was then withdrawn. More recent work borrowed the cyclohexane and the indole elements of **62** and led to aldehyde **64a** or to the benzyl-bearing analogues **65** and **66**.[189] Interestingly, FB-2001 (**64a**) was further evaluated[279] and has undergone some clinical trials (NCT04766931). The same research group reported two years later that the non-fluorinated analogue **66** was better suited as a broad-spectrum antiviral since, aside from being active on SARS-CoV-2, it also displayed an effect on entero and rhinoviruses.[41] Following extensive structure–activity relationship studies,[280] Pardes Biosciences undertook clinical trials (NCT05011812 and NCT05543707) with the nitrile-bearing PBI-0451/pomotrelvir (**67**) which has also been co-crystallized with SARS-CoV-2-M^{pro} (8TBE). However, a company statement reported that this compound "did not

meet the primary endpoint measured by proportion of participants below the limit of detection for infectious SARS-CoV-2 on day 3 of treatment" and further development was thus suspended.[281] The 3-methoxyindole-bearing analogue **68**, also featuring the benzothiazole seen in compound **51**, was initially designed against SARS-CoV-1-M^{pro}.[282] It was then reported to be efficient against SARS-CoV-2-M^{pro} and the virus replication.[206,210] An extensive study of various ester prodrugs such as compound **69** was reported and also demonstrated that no real difference in antiviral properties was observed between compounds featuring a 5 or a 6-membered lactam.[209] In an approach which has been used in the past against rhinovirus 3C proteases[283] and which incidentally addressed a racemization risk, the strong aza-bearing SARS-CoV-2-M^{pro} inhibitor YH-6 (**70**) featuring a chiral α,α-chlorofluoracetamide warhead was reported.[223] Two patents[224,284] also claim related α,α-chlorofluoracetamide-containing aza-peptides including the fairly elaborated compound **71** which is effective against a whole panel of coronaviruses (Fig. 10).[224]

From the end of 2019, the hepatitis C serine protease NS3/4A inhibitors boceprevir (**24**) and telaprevir (**25**) depicted above, or the related narlaprevir, were repeatedly reported to be active in SARS-CoV-2-M^{pro} screening campaigns.[153,186,187,285–287] This triggered X-ray based structural studies which pointed out that these reactive compounds did indeed bind to the catalytic site of SARS-CoV-2-M^{pro}.[212,287,288] Of course the bicyclic 3-azabicyclo[3.1.0] hexane component of boceprevir (**24**), which not only enables the removal of an NH moiety but also probably acts as a conformational lock, provided a lot inspiration for the design of many series of SARS-CoV-2-M^{pro} inhibitors. In fact, research conducted at Pfizer led, for instance, to the ketone-bearing inhibitor **72a** or the nitrile-bearing PF-07321332/nirmatrelvir (**73**).[63,231] A crucial point explaining that nirmatrelvir (**73**) turned out to be orally active on a mouse model of SARS-CoV-2 infection is the removal of this extra NH moiety with this bicycle which greatly improved its diffusion.[289] The ensuing successful clinical trials of nirmatrelvir (**73**) then provided the first approved SARS-CoV-2-M^{pro} inhibitor which must be prescribed in association with ritonavir to alter P4503A4-based metabolization and thus improve its pharmacology.[290,291] Interestingly, compound **72a** was the focus of further optimization which led to the fluorinated derivative TKB245 (**72b**).[292,293] Moreover, an extensive search for an alternative to the trifluoroacetamide moiety of nirmatrelvir (**73**) was conducted at Ascletis Bioscience.[294] The undisclosed protease inhibitor ASC11 probably resulting from this approach is currently undergoing Ascletis-sponsored phase 1 clinical trials, with the co-administration of ritonavir (NCT05718518). The 3-azabicyclo[3.1.0]hexane-bearing compounds MI-09 (**74**)[197] and UAWJ9-36-3 (**76**)[200] or the cyclopenta[*c*]pyrrole-bearing inhibitors MI-30 (**75**)[197] and UAWJ-9-36-1 (**77**)[200] also stemmed from this "structural lock" idea. Of note is that both **74** and **75** displayed *in vivo* antiviral effects as well.[197] The α-amido ketones MG-78 (**78a**) and MG-131 (**78b**) were designed according to similar lines and are very good inhibitors of SARS-CoV-2-M^{pro} as well.[295] Additional α-ketoamide-bearing derivatives featuring such component also had an improved cell permeability.[296,297] Moreover, SARS-CoV-2-M^{pro} structures bound to such compounds have been released by two distinct research groups (PDB 7U92 and 7WQK). The notable cyclopenta[*c*]pyrrole-bearing SARS-CoV-2 M^{pro} inhibitor RAY1216/leritrelvir (**79**) was developed by Raynovent[298,299] and granted conditional market approval in China. Interestingly, this strong inhibitor also displayed an improved *in vivo* half-life in comparison with nirmatrelvir (**73**) and appeared to have been evaluated on COVID-19 patients with and without ritonavir or other P4503A4 inhibitors (NCT05620160).[300,301] A structure of SARS-CoV-2 M^{pro} bound to this compound has also been released (PDB 8IGN). The design and study of a related series of aldehyde-bearing compounds featuring various conformational locks actually reported that cyclopenta[*c*]pyrrole was amongst the most efficient pan-corona protease inhibitor *in cellulo*.[302] The dithia-7-azaspiro[4.4]nonane derivative **80** is a strong SARS-CoV-2 M^{pro} inhibitor which was developed by Simcere Pharmaceutical. In association with ritonavir,[303] it has also been granted conditional market approval in China under the name Xiannuoxin/simnotrelvir[304–306] and the results of

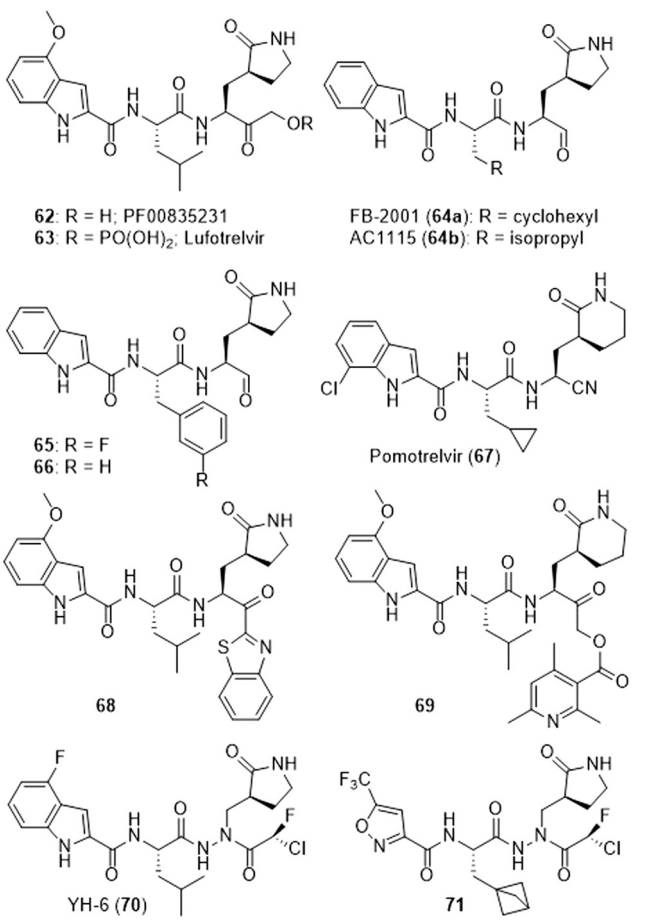


Fig. 10 Structures of compounds **62**–**71**.

phase 1 clinical trials (NCT05339646) were reported recently.[307] The undisclosed SARS-CoV-2 M^{pro} inhibitor ALG-097558 is developed by Aligos therapeutics, possibly without a co-administration of ritonavir and phase 1 clinical trials have been initiated (NCT05840952).[25] Three distinct patents,[229,308,309] from this company and the Catholic University of Leuven, describe a large number of compounds featuring a variety of conformational locks. We (randomly) choose to depict the 5-azaspiro[bicyclo[2.2.1]heptane-2,1′-cyclopropane] derivative **81**, since this strong SARS-CoV-2 M^{pro} inhibitor also illustrates what MedChem is about: innovation in chemistry leading to original and thus patentable compounds. The simpler azabicyclo[2.2.1]heptane ring system has also been introduced in the structure of such inhibitors.[310] Further insights were provided in the course of an extensive study of boceprevir analogues which reported some key elements to achieve an antiviral effect *in cellulo*.[311] Moreover, the same research group recently reported the azaspiro[4.4]nonane derivative MPI-60 (**82**), which displays promising antiviral properties[312] and a structure of SARS-CoV-2 M^{pro} bound to this compound was obtained (8STZ). Finally, CMX990 (**83**), an azaspiro[2,4]heptane-bearing derivative, is also a tribute to the creativity required in MedChem and this compound has reached the stage of phase 1 clinical trials.[313,314] This ring system and quite a few others were actually also described in a paper from another research group.[315] Moreover, many strongly effective azapeptides, including some α,α-chlorofluoracetamide-containing derivatives[284] related to **70** and **71** and featuring such conformational locks, have been claimed.[316] Finally, the bisulfite prodrug of the aldehyde derivative AC1115 (**64b**), a covalent inhibitor of SARS-CoV-2-M^{pro} and cathepsin L[317] has undergone successful clinical trials under the names STI-1558/OVYDSO/Olgotrelvir without the recourse to ritonavir. These trials were sponsored by Sorrento therapeutics/Zhejiang ACEA Pharmaceutical (NCT05716425 and NCT06044233). Interestingly, the corresponding patent is claiming a wide range of SARS-CoV-2-Mpro inhibitors featuring structural elements seen in compounds **62–83** (Fig. 11).[318]

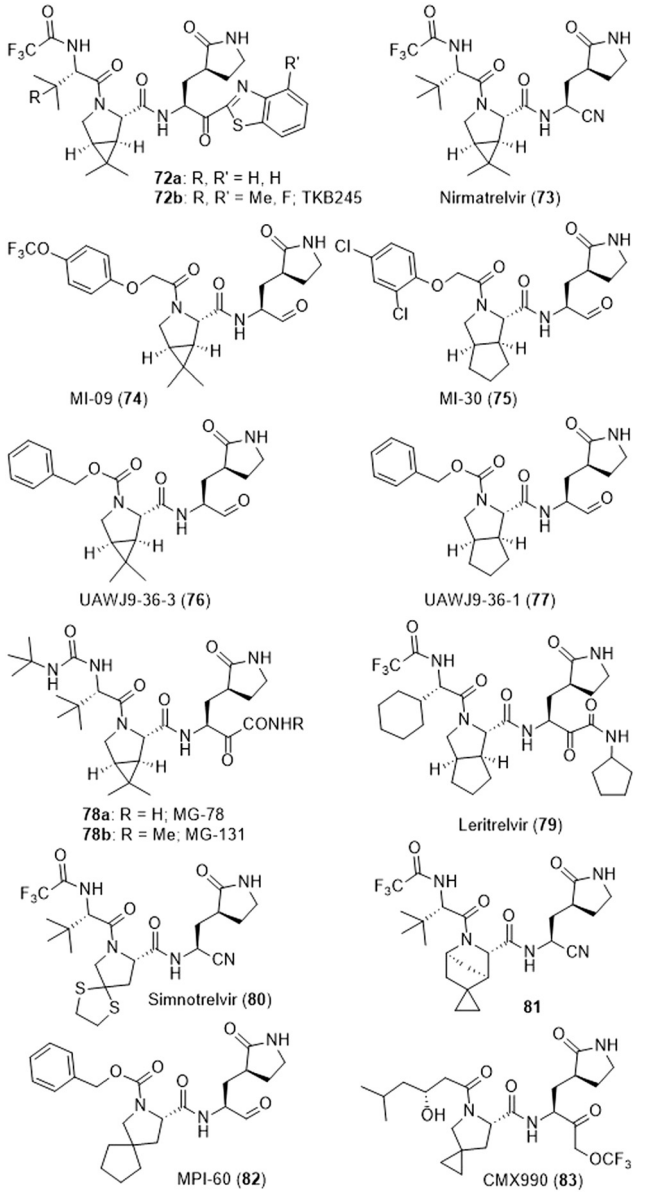


Fig. 11 Structures of compounds **72–83**.

Also of interest, the SARS-CoV-2 M^{pro} inhibitor EDP-235 (**85**) from Enanta Pharmaceuticals[319] recently met the primary end point of a phase 2 clinical trial without the coadministration of ritonavir (NCT05616728). In this case, 13 patents from this company claim a very large variety of peptides sometimes featuring conformational locks related to the one depicted above. Amongst them, compound **84** (ref. 320) not only features a cyclopenta[*c*]pyrrole in its structure but its warhead is a cyanopyrrolidine, reminiscent of vildagliptin (**20**) or saxagliptin (**21**). This cyanopyrrolidine is also rigidly connected to an indolinone which acts as the bioisoster replacement of the glutamine. Many more compounds featuring such unprecedented spiropyrrolidine along with a variety of warheads were claimed. EDP-235 (**85**),[321] which is also the subject of two process patents for its large-scale production,[322,323] or compound **86** (ref. 324) are noteworthy for their *N*-methyls. The NH homologs of these compounds were also made but their antiviral effects were apparently not deemed of sufficient interest to be mentioned in the corresponding patents.[321,324] Interestingly, the structurally very constrained macrocycle **87** (ref. 325) and the simplified compounds **88** (ref. 326) and **89** (ref. 327) were also patented as effective inhibitors of SARS-CoV-2 M^{pro} (Fig. 12).

The research on inhibitors of the rhinovirus 3C protease conducted at Agouron/Pfizer at the turn of the century, which provided rupintrivir (**44**), also led to 2-pyridone-bearing analogues of this peptide.[328–330] Amongst them, the orally available inhibitor AG7404 (**90**) underwent two phase 1 clinical trials,[331] the latter, under the drug name V7404, was sponsored by ViroDefense and focused on enterovirus infection.[332] As for rupintrivir (**44**), this alkyne-bearing

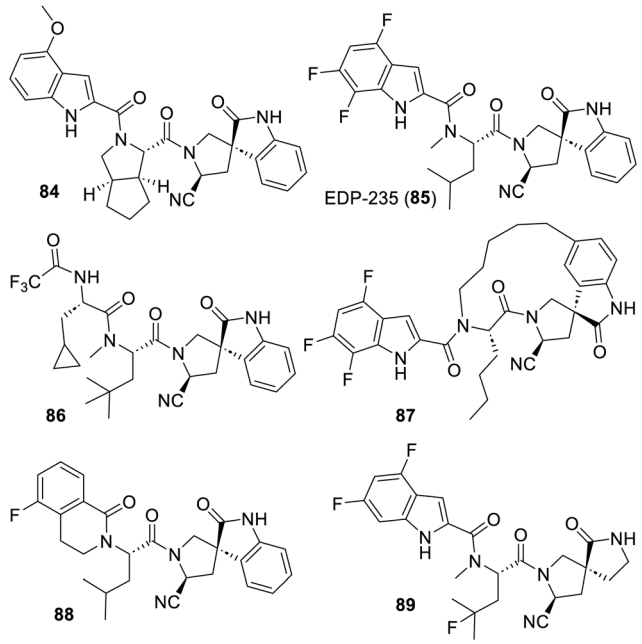


Fig. 12 Structures of compounds **84**–**89**.

compound was reported in 2022 to modestly inhibit SARS-CoV-1 and SARS-CoV-2 main proteases and it was co-crystallized with both enzymes (PDB 7ZQW and 7ZQV).[333] By following this approach, which consists of rigidifying the P2–P3 amide bond of the protease substrate, the pyridinone derivative (**91**) was designed and reported to inhibit SARS-CoV-2 M^{pro}. Moreover, this compound demonstrated an effect on cell-based virus replication assays.[212] Interestingly, it was shown that the (*S*) enantiomer depicted here was the most active although the corresponding (*R*) enantiomer also had a degree of effect. In fact, even if the (*R*) isomer was 50 times less efficient as a protease inhibitor, both isomers co-crystallized within the SARS-CoV-2 M^{pro} catalytic site (PDB 8A4T and 8A4Q) with rather drastically different binding modes.[214] This probably illustrates the non-selectivity bias induced by a reactive component in a given molecule. Indeed, if such a compound can reach the nucleophilic part of the biochemical target, it is reasonable to assume that it will react with it, in spite of having a low overall affinity for the binding site. This known bias actually led in 2011 to the following comment: "the stringent substrate specificity of the SARS-CoV M^{pro} with respect to the P1 and P2 positions can be overruled by the highly electrophilic character of the aldehyde warhead. This constitutes a deviation from the dogma that peptidic protease inhibitors should comprise an amino-acid sequence corresponding to the cleavage specificity of the target enzyme".[334] This comment is also likely valid for a number of aldehyde-bearing compounds which have been reported to be inhibitors of SARS-CoV-2 M^{pro}.[91,196,335] In any case, a patent describes further structure–activity relationship studies around such pyridone derivatives which led to the modest SARS-CoV-2 M^{pro} inhibitor **92**.[336] In a 2013 patent, an array of inhibitors, such

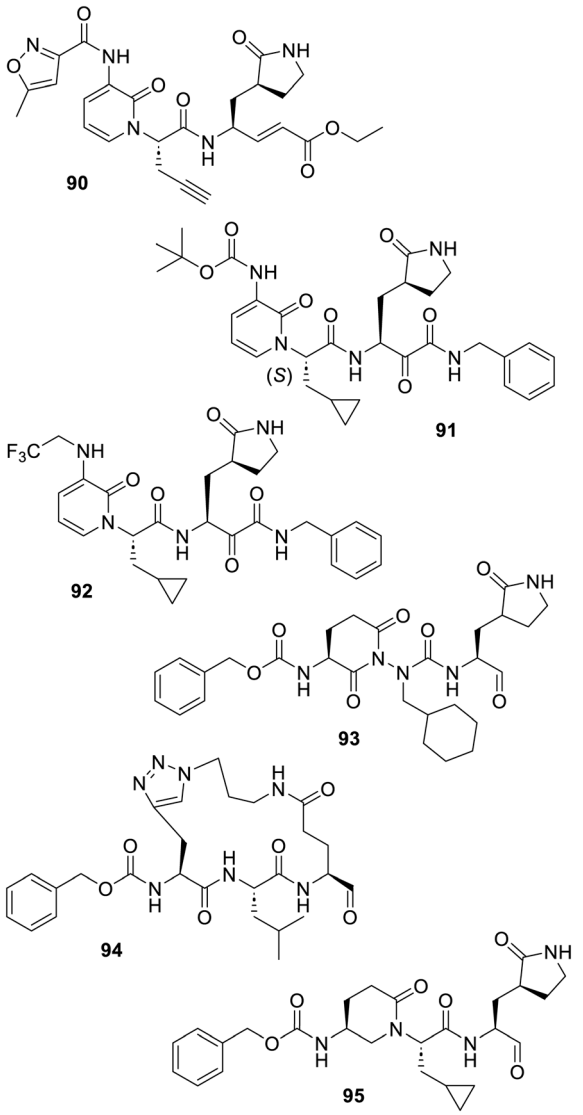


Fig. 13 Structures of compounds **90**–**95**.

as the constrained azapeptide **93** featuring a rigidifying 2,6-dioxopiperidine component,[337] or macrocyclic-bearing peptides such as **94**,[338] were claimed for their effects on 3CL proteases of picornaviruses, caliciviruses and coronaviruses. The related 3-amino-6-oxopiperidine spacer was also employed more recently and for instance, compound **95** turned out to be an effective SARS-CoV-2 M^{pro} inhibitor (Fig. 13).[339]

Amongst SARS-CoV-1 M^{pro} covalent inhibitors of less interest, many 3-pyridyl esters with the general formula **96** were reported between 2004 and 2008.[340–343] It was then demonstrated[341] by mass spectroscopy that these aryl esters (unsurprisingly) react with the cysteine of the protease. Later on, some compounds were shown to also strongly inhibit SARS-CoV-2 M^{pro} but again these had a very modest antiviral effect.[194,206,344] A more recent report provided an extensive demonstration of their chemical reactivity and further established that these compounds were probably the focus of

too much attention in view of their lack of potential in medicinal chemistry.[345] Another recent report has actually described covalent inhibitors in which the activated carboxyl was replaced by a sulfone conjugated to a reactive oxadiazole ring system,[346] and carmofur analogues also featuring an activated carboxamide side chain were reported.[347] Moreover, somehow related thioesters have been reported to similarly react with the catalytic cysteine and displayed rather strong *in cellulo* antiviral effects.[348] It remains to be seen if such compounds will retain some stability *in vivo*. To address this issue, an attempt was made in 2008 to replace the ester function of compounds **96** by a ketone, as seen in the structure of analogue **97**, but the results were disappointing.[349] More interestingly, in 2013, a high throughput screening for inhibitors of SARS-CoV-1 M^{pro}, using the 293 000 compounds of the NIH molecular library, discovered more elaborated 3-pyridyl-bearing compounds such as ML188 (**98**) or benzotriazole derivatives such as ML300 (**99**).[158,350] One of the reports also included an X-ray based structure of ML188 (**98**) bound to SARS-CoV-1 M^{pro} (PDB 3V3M),[158] and much later on, both inhibitors were co-crystallized with SARS-CoV-2 M^{pro} (PDB 7L0D[351] PDB 7LME[352]). Of note is that these inhibitors bind to the catalytic site *via* key interactions between the imidazole ring of SARS-CoV-2 M^{pro} histidine-163 and their pyridine or benzotriazole nitrogen. Moreover, for these inhibitors the protease glutamine-166 NH usually interacts with their recurrent carboxamide functions situated four "bonds away" from these nitrogens. As illustrated below, this pattern is recurrent in most of the 3-pyridyl-bearing inhibitors of SARS-CoV main proteases (Fig. 14).

By the end of 2019, these 2013 results became the starting point of research projects in many laboratories. In full collaboration with a large X-ray based facility, many structures of 3-pyridyl-bearing compounds bound to SARS-CoV-2 M^{pro} were thus made available.[93] Such structures were instrumental for the open science COVID Moonshot initiative which undertook a publicly available drug discovery project based on the iterative process required to improve 3-pyridyl-bearing compounds such as ML188 (**98**).[353–357] As described,[358,359] in one attempt, the COVID Moonshot initiative went from 3-pyridyl derivative TRY-UNI-714a760b-6 (**100**) to isoquinoline derivatives such as ADA-UCB-6c2cb422-1 (**101**), MAT-POS-b3e365b9-1 (**102**) or PET-UNK-29afea89-2 (**103**). In fact, these compounds became more and more elaborated not only to strengthen their affinity for the SARS-CoV-2 M^{pro} catalytic site but also to start addressing the myriad of problems associated with an eventual *in vivo* use. The next two inhibitors MAT-POS-4223bc15-23 (**104**) and VLA-UCB-29506327-1 (**105**) illustrate some more possibilities for further iterations which required extensive profiling before choices were made. Meanwhile, another group also reported some related inhibitors using a docking-based virtual screening along with an X-ray based structure of the derivative X77 (**112**) bound to SARS-CoV-2 M^{pro} (PDB 6W63). Interestingly, from the 3-pyridyl derivative **106** discovered with this strategy, the ensuing optimization led to the 300-fold more active inhibitor **107**.[360] Moreover, out of a virtual screening using an X-ray based structure (PDB 6Y2G) of SARS-CoV-2 M^{pro} covalently bound to the α-ketoamide inhibitor **91** depicted above, another research group also reported many (modest) hydantoin-bearing inhibitors related to compounds **105**–**107** (Fig. 15).[91]

Starting from the less deconstructed ML188 (**98**), the analogues **108** and **109**,[361] or the related MAT-POS-f2460aef-1 (**110**),[356] explored some other possibilities and the more elaborated pyrazine-bearing analogue **111** was also reported.[362] The design and synthesis of the analogue X77 (**112**) was never actually reported but this compound was co-crystallized with SARS-CoV-2 M^{pro} in 2020 and the corresponding X-ray based structure (PDB 6W63) has been repeatedly used for virtual-based approaches. Finally, a search starting with DNA-encoded chemical libraries led to the very strong SARS-CoV-2 M^{pro} inhibitor **113**. As demonstrated by X-ray studies (PDB 7UR9), the isoquinoline moiety of this compound does bind to the protease catalytic

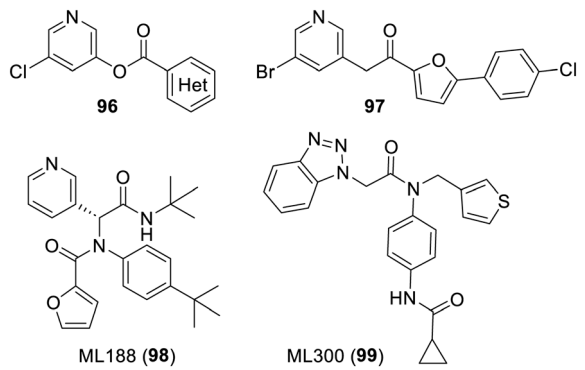


Fig. 14 Structures of compounds **96**–**99**.

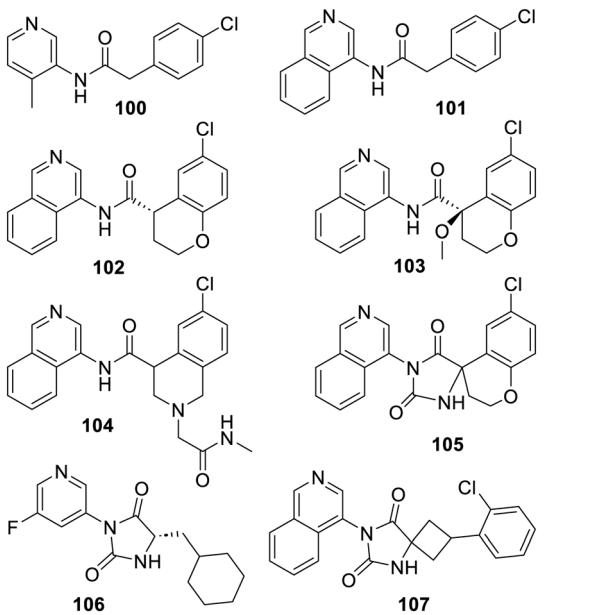


Fig. 15 Structures of compounds **100**–**107**.

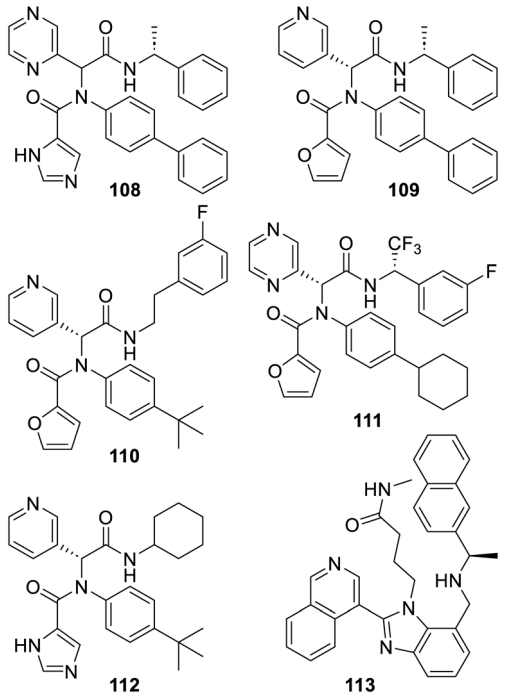


Fig. 16 Structures of compounds **108**–**113**.

site in the same way the series depicted above do (*via* a hydrogen bond with His-163). However, in one instance in these series, replacing this isoquinoline by a pyridine led to a rather unexpected complete loss of activity (Fig. 16).[363]

Finally, many research groups resorted to the incorporation of a reactive component in these series.[184] As depicted, an acrylamide was used for compound **114**,[364] and an α,α-dichloroketone for compound **115**.[221] Of note, the recourse the α,α-chlorofluoracetamide moiety seen in the structures of compounds **70** and **71** was claimed for these series as well,[365] and an X-ray based structure of SARS-CoV-2 M^{pro} covalently bound to the notable Jun10-90-3-C1 (**116**) has been released by another research group (PDB 8D4P). Out of two large patents from Pardes Biosciences, the randomly chosen α-aminonitrile **117** or even more reactive 1-aminonitriles are additional illustration of this approach.[366,367] A report describes a quite systematic introduction of an array of electrophilic moieties leading for instance to the chloroamide **118**.[368] Even more reactive analogues are described in another publication[184] and in a patent.[365] Also of interest is the rather large α-ketoamide derivative Y180 (**119**) which turned out to be an orally available inhibitor of SARS-CoV-2 M^{pro} endowed with a degree of antiviral effect *in vivo*.[369] In another original approach, two patents from Novartis claim compounds such as the very strong inhibitors **120** (ref. 370) or **121** both combining quite elegantly a reactive nitrile and structural features seen in this class. Concerning the series encompassing compound **121**, many analogues claimed in the patent[371] do not feature a reactive moiety. Finally, the incorporation of a probably less reactive and hindered nitrile

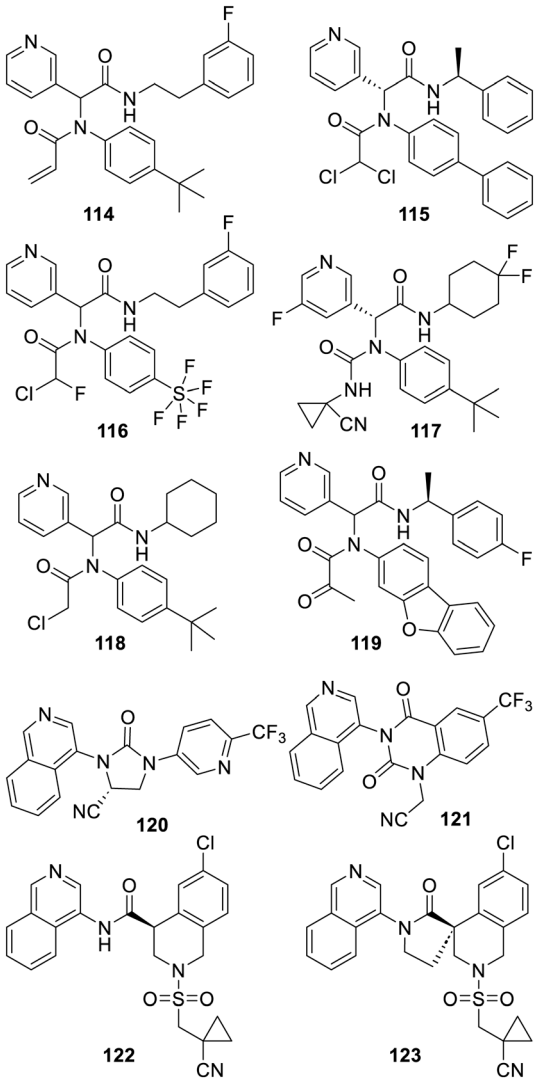


Fig. 17 Structures of compounds **114**–**123**.

as seen in the structure of MAT-POS-e194df51 (**122**),[356,358] or the more constrained MIK-ENA-5d9157e9 (**123**), provided some of the most advanced inhibitors of the remarkable COVID Moonshot initiative.[359] In fact, compound **122** does not bind covalently to SARS-CoV-2 M^{pro} as demonstrated by the X-ray based structure code P1788 accessible on the Fragalysis website (Fig. 17).[372]

Interestingly, another class of isoquinoline-bearing inhibitors of SARS-CoV-2 M^{pro} (in which this heterocycle also interacts with His-163, see PDB 7EN8) was found with the combined use of a DNA encoded chemical library and docking-based ranking. This resulted in WU-04 (**124**) which features a so far required nitro group (for its notable interaction with the backbone CO of the protease Arg188) and is effective *in vivo* on a mouse model of infection.[373] Similar series of nitro-bearing compounds were the focus of extensive structure–activity relationship studies by another research group and were, so far, only illustrated by a recent patent from Qilu Pharmaceuticals.[374] Moreover, clinical trials

of the undisclosed QLS1128 have been initiated by this company (NCT05458076). The benzotriazole-bearing inhibitor **99** reported[350] in 2013 was also the focus of some more research. The MedChem efforts of the COVID Moonshot initiative led to improved analogues such as ALP-POS-6d04362c-2 (**125**).[356] The imidazole-bearing analogue CCF981 (**126a**) was the fruit of extended SAR studies, although this work also pointed out that strong cytochrome P450 inhibition appeared to be a recurrent issue for these benzotriazole derivatives.[352] Another report describes the triazole replacement by a 3-pyridyl moiety, as seen in the structure of compound **127**, which led to a less efficient inhibitor in comparison with **126b**. But then, the same research group used an isoquinoline and this provided the powerful SARS-CoV-2 M^{pro} inhibitor **128** (ref. 375), and many more examples, patented by the Cleveland Clinic Foundation, claim a range of inhibitors featuring alternatives to this benzotriazole.[376,377] A recent report has also described additional analogues such as compound **129** which combines structural elements of compound **125** as well as 5-hydroxyisoquinoline. The X-ray structure of this inhibitor bound to SARS-CoV-2 M^{pro} was obtained (PDB 8SXR) and showed that the isoquinoline nitrogen also interacts with the histidine residue 163 of the protease.[378] Many strong inhibitors, in which the usual lactams were replaced by a whole array of other bioisosters, were patented by the Global Health Drug Discovery Institute.[379] This patent is illustrated by compound **130**, which combines peptidic elements and a 3-pyridyl moiety. Moreover, patents from Exscienta or Pardes claim related compounds featuring even more varied heterocycles acting as lactam/3-pyridyl bioisosters.[380,381] It is also very likely that an undisclosed derivative of **130** is undergoing clinical trials, sponsored by Jiangsu Hansoh Pharmaceutical, under the name H-10517 (NCT05779579). Finally, a recent patent from Merck[382] claims a whole array of inhibitors such as compound **131** which feature a remarkable difluorinated side chain instead of the recurrent lactam. A 2007 paper is actually describing analogues of Boceprivir inhibiting the HCV NS3/4A protease and featuring related difluoromethylene components on the same position.[141] In a way, these last two compounds feature most of the hard-won lessons of many structure–activity relationship studies and *la boucle est bouclée* (the circle is complete). From them, it is actually tempting to suggest to alter the non-covalent 3-pyridyl bearing series of inhibitors by replacing their 3-pyridyl with all the other groups described although it may be a real chemical challenge in some instances (Fig. 18).

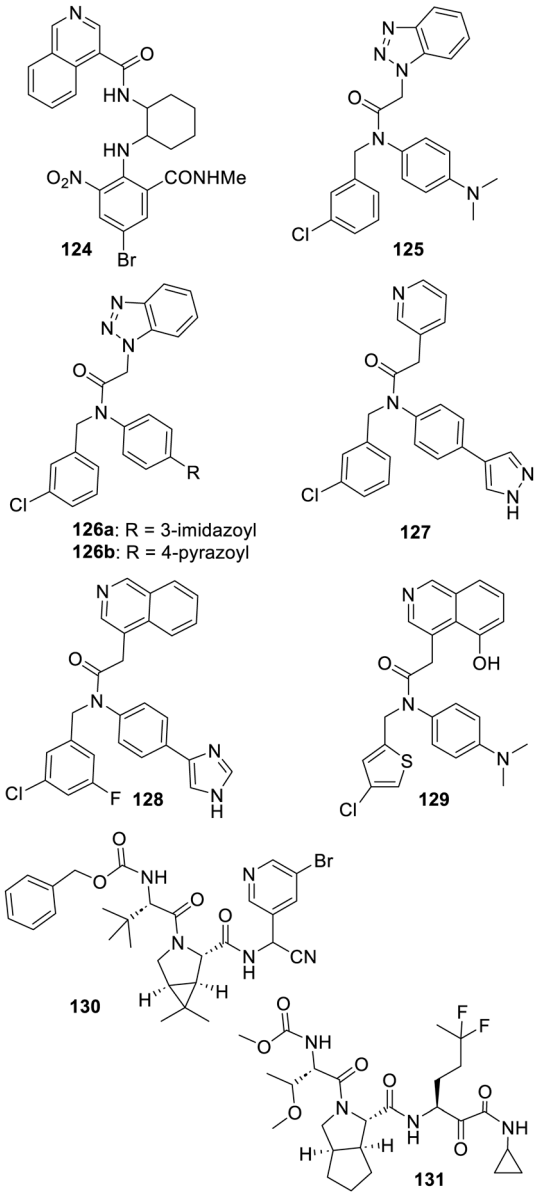


Fig. 18 Structures of compounds **124**–**131**.

Original SARS-CoV-2-M^{pro} inhibitors

Aside from all the inhibitors described above, which are arguably continuations of the research made on the inhibition of various viral proteases, including SARS-CoV-1 M^{pro}, one original approach involved the generation of a large number of random peptidic sequences which were then assayed. If a similar but more virtual-based approach failed in an early instance,[383] this also led to all D-peptides[384,385] or to macrocyclic 11–14-mer peptides featuring modified amino acids[386] endowed with affinities for the SARS-CoV-2 M^{pro} catalytic site. In the latter case, the corresponding X-ray based structure (PDB 7Z4S) may be of future use to deconstruct such rather large peptides into more drug-like compounds. Concerning smaller compounds, a docking-based approach, using half a million bioactive compounds and the structure of SARS-CoV-2 M^{pro} bound to the peptide derivative **47** (PDB 6LU7), has to be followed by more virtual-based selections, taking into account known inhibitors. This led to the very modest inhibitor **132** featuring a pyrimidinetrione component. A sulfamide derivative was also discovered by the same group but has yet to be developed.[387] The related pyrimidinedione **133** was the result of another virtual screening of 6.5 million compounds commercially

available using an array of X-ray based structures of SARS-CoV-2 M^{pro} bound to various inhibitors (compounds **47**, X77 (**112**), telaprevir (**25**) and masitinib (**37**); see PDB 7BQY, 6LU7, 6W63, 7C7P, and 7JU7).[388] Following this achievement, an X-ray based structure of pyrimidinedione **133** bound to SARS-CoV-2 M^{pro} was obtained and led to a medicinal chemistry program which has so far provided only modest results.[389] Interestingly, another hit to lead project also started with compound **133** and led to the improved GC-14 (**134**) in which the pyrimidinedione was replaced by the recurrent 3-pyridyl component which interacts with the SARS-CoV-2 M^{pro} His-163 residue (PDB 8ACL). A replacement with an isoquinoline instead led to the same level of inhibition.[390] Unexpectedly, adding instead an α-chloroketone warhead, as depicted for compound **135**, had a deleterious impact on the antiviral effect as compared with GC-14 (**134**).[391] However, only a modest antiviral effect was observed *in cellulo* for compound **134**, possibly because of a low cell membrane permeability. From the non-covalent pyridyl-bearing inhibitors listed above, a computer-based "synthesis-directed *de novo* design model" provided the non-obvious quinolone **136** which has a degree of effect on SARS-CoV-2 M^{pro} as well as on the seasonal OC43 coronavirus.[392] Interestingly, the related inhibitor JZD-07 (**137**) which gathers features found in **133** and **136** was reported later. In this case, it is the quinolone oxygen which is the bioisosteric replacement for the 3-pyridyl nitrogen (PDB 8GTV), and this inhibitor is endowed with an *in vivo* efficacy against a mouse model of SARS-CoV-2 infection.[393] A related analogue (JZD-26) has been co-crystallized with SARS-CoV-2 M^{pro} (PDB 8GTW) although a corresponding publication is still expected. The COVID Moonshot initiative also explored related quinolones such as the less rigid but rather modest inhibitor MAT-POS-3b536971-1 (**138**).[356] Another series of 3-pyridyl-bearing inhibitors of SARS-CoV-2 M^{pro} such as the rather rigid compound **139** were also patented (Fig. 19).[394]

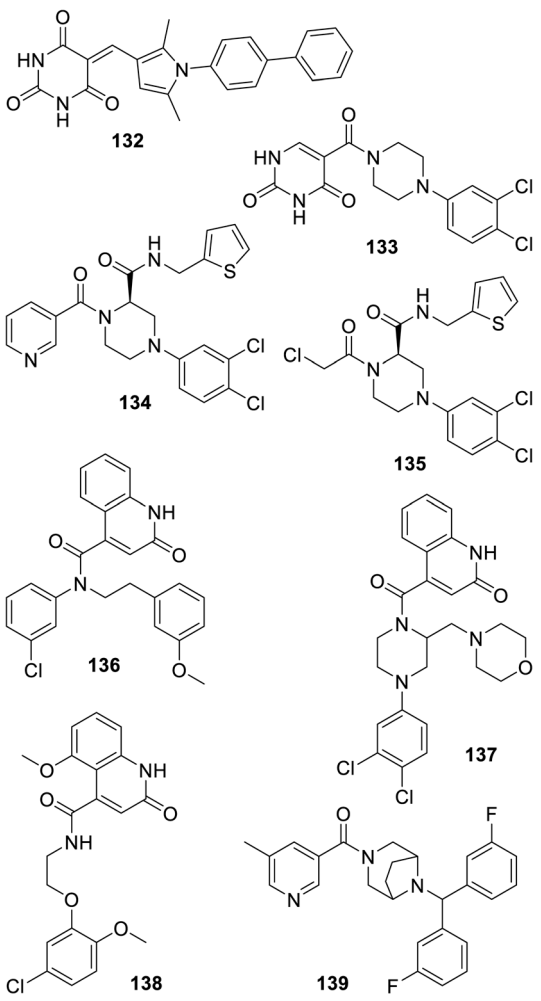


Fig. 19 Structures of compounds **132**–**139**.

Experimental screenings along with medicinal chemistry approaches were also used to search for SARS-CoV-2 M^{pro} binding inhibitors. The α-ketoamide **140**, with its 2-pyridyl actually interacting with His-163 (PDB 7AEH),[395] and compound **141** (ref. 396) were found in the course of a FRET-based screening of a chemical library of 30 000 compounds. The ensuing structure-based (PDB 8HHT) hit to lead progression led to a hundred-fold more active SARS-CoV-2 M^{pro} inhibitors such as compound SY110 (**142**).[396] A remarkable feature of this original class of peptidic and covalent inhibitors is the absence of the lactam bioisoster of the glutamine residue seen in the many series depicted above. Earlier examples have actually been reported for a modest effect on SARS-CoV-1 (ref. 397) or SARS-CoV-2 multiplication, although in the latter case, these compounds were inhibiting other proteases and had anticancer properties as well.[398] Since SY110 (**142**) displays a robust pan-coronavirus antiviral effect, an original binding mode to the catalytic site (PDB 8HHU), and good preclinical characteristics and is effective in a model animal of COVID-19 infection, further work on this class of inhibitors appears to be warranted. Another recent attempt focused on the variety of sequences found in the substrates of SARS-CoV-2 M^{pro} including downstream of the cleavage site and the determination of X-ray based structures. This led to the recognition that the peptide Ala-Ile-PheOMe, derived from VKLQ**AIF**R, a larger peptide which has been co-crystallized with SARS-CoV-2 M^{pro} (PDB 8GWS), retained a degree of affinity for the enzyme. Then, the addition of a warhead onto this peptide and some structure-based improvements led to compounds such as the α-bromoacetamide **143** which is a modest inhibitor of SARS-CoV-2 M^{pro} and viral replication.[399] It is possible that this original work along with the structure of **143** bound to the protease catalytic site reported (PDB 8JPQ) will pave the way for many research projects focusing on the discovery of non peptidic inhibitors targeting this previously unexplored pocket. The strong SARS-CoV-2 M^{pro} binding inhibitor and vinylsulfoxide-bearing PM-2-071 (**144**) was reported following a screen of 582 acrylamide or chloroacetamide-bearing compounds and some hit optimization.[400] However, the toxicity issue of vinylsulfoxide-bearing compounds should be kept in mind for further

development of this type of Michael acceptor.[184] The α-chloroamide-bearing benzodiazepine **145** was also found to be a modest inhibitor of SARS-CoV-2 M^{pro} following the screening of 5000 compounds. The ensuing hit progression has so far provided compound **146** with only a modest 10-fold improvement of activity, despite the obtention of an X-ray based structure (PDB 8JOP).[401] Finally and to conclude this part, the truly original and authorized antiviral drug ensitrelvir/S-217622 (**149**) was discovered in the course of a virtual-based selection using, again, the structure of SARS-CoV-2 M^{pro} binding X77 (**112**) (PDB 6W63).[402] This selection from hundreds of thousand compounds of an in-house chemical library led to a smaller screening and the identification of compound **147** which has been made years before in the course of a research program focusing on the design of analgesics.[403] An X-ray structure (PDB 7VTH) then revealed its binding mode and the ensuing hit to lead program proceeded, *via* compound **148**, to reach ensitrelvir (**149**). Of note is that as seen in the X-ray based structure, it is the triazole ring which interacts with the His-163 residue for this class of inhibitors (PDB 8DZ0).[404] In fact, closely related analogues featuring, amongst other heterocycles, the recurrent 3-pyridyl group instead were claimed later.[405] The clinical trials[406–408] of ensitrelvir (**149**), sponsored by Shionogi, turned out to be successful and this is so far the sole non-covalent SARS-CoV-2 M^{pro} inhibitor approved as an emergency treatment of COVID-19 in Japan. It is currently undergoing phase 3 clinical trials across the world (NCT05605093 and NCT05305547). Two more recent patents have focused on analogues of ensitrelvir (**149**), the first claims various deuterated analogs which may have improved pharmacological properties,[409] and the second has undertaken a rescaffolding of the core 1,3,5-triazine ring and claims analogs featuring a 1,2,4-triazine ring system instead (Fig. 20).[410]

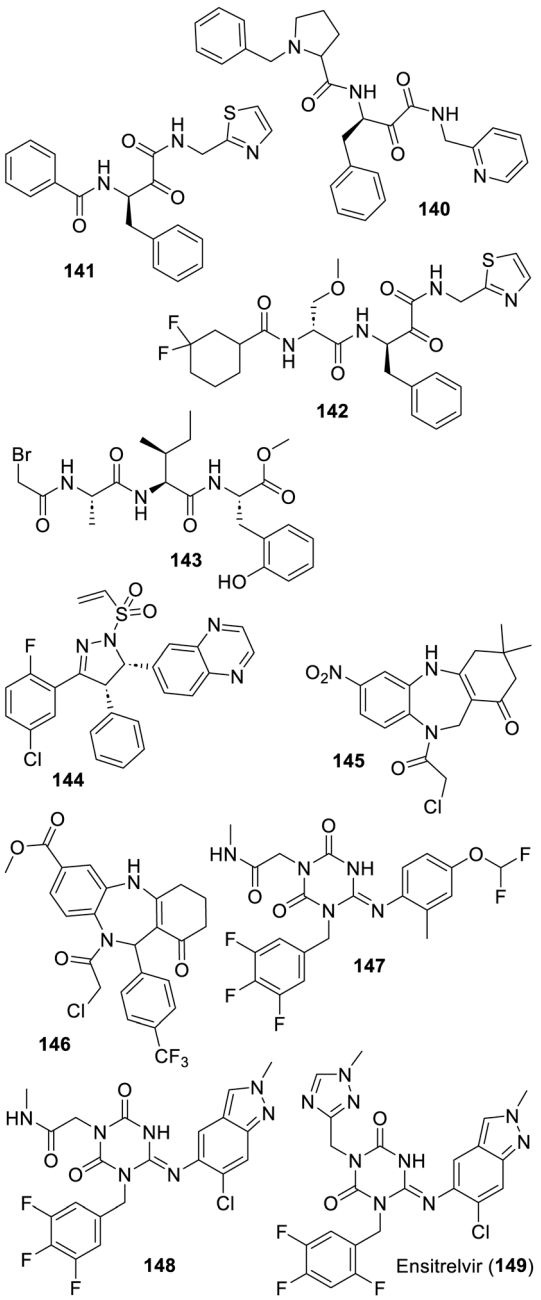
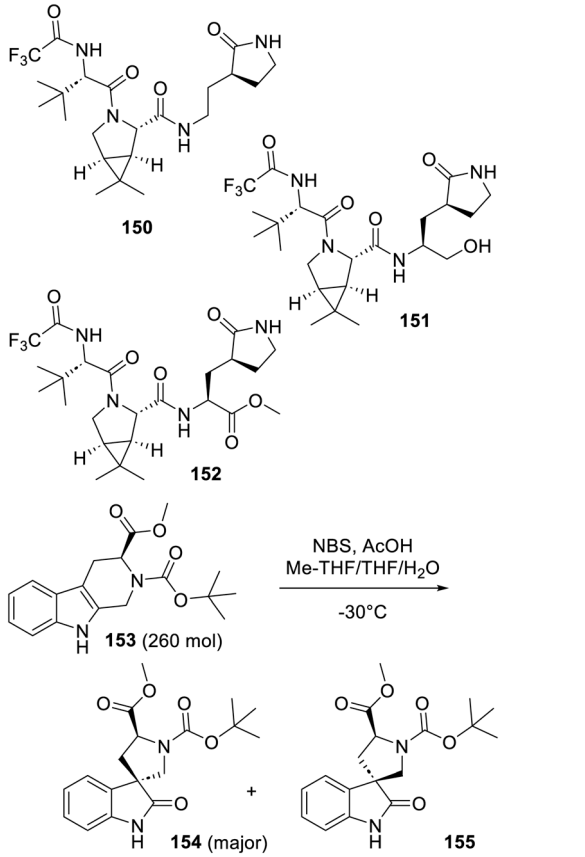


Fig. 20 Structures of compounds **140**–**149**.

Conclusions

The list of chemicals described above is only representing a portion of all the compounds which have been evaluated around the world on many types of assays targeting SARS-CoV-2 M^{pro}. In spite of belief-based treatments (using natural or human-made compounds) which unfortunately mobilized a lot of money and claimed an unacceptable number of lives[150] and in spite of far too many unexploitable[71] computer-involving reports (and patents) which also attracted much funding and raises acute questions on some authors, reviewers (if any), editors and publishers' integrity,[79] some approaches did deliver useful drugs. If drug repurposing was, as for the previous coronavirus epidemics, an unmitigated and unfortunately predictable failure,[151,152,411,412] past research results on various proteases as well as renewed screenings turned out to be successful starting points. Moreover, as probably not enough emphasized here, the staggering number of X-ray based structures solved greatly helped the resulting hit to lead progressions. A 2014 review on this subject does remain quite relevant.[42] As described above, except for ensitrelvir (**149**), all the most advanced or authorized inhibitors of SARS-CoV-2 M^{pro} owe their effect to the occurrence of a covalent bond with its catalytic cysteine. Interestingly, in a description of the invention of nirmatrelvir (**73**),[289,413] the choice of the chemically reactive component to be used (nitrile or the ketone function of analogue **72** in this case) remained a difficult one. This was the subject of some investigations,[193,414] especially in light of the metabolic and cytotoxicity concerns with aldehyde-bearing covalent inhibitors.[268] In one instance,[414] a systematic survey was made using the nirmatrelvir (**73**) structure as a template. From this work which provides precise biochemical and cell-



Scheme 2 Structures of compounds **150**–**152**; oxidative rearrangement of compound **153** into **154** and **155**.

based insights into warhead selection, another quite puzzling result emerged. In fact, if nirmatrelvir (**73**) or the corresponding ketone-bearing analogue **72b** is a really effective inhibitor of SARS-CoV-2 M^{pro}, the peptides lacking these reactive moieties, such as the decarboxylated derivative **150** or the alcohol **151**, are devoid of inhibition effect. This experimental fact is in contrast with what is observed for the KRAS inhibitors **8** and **9** depicted in Fig. 2, since the analogues lacking their acrylamide moiety are still capable of modest inhibition of this kinase. This suggests that, upon the chemical reaction between the warhead of covalent inhibitors and the cysteine of the SARS-CoV-2 M^{pro} catalytic site, a conformational shift occurs and the newly formed pocket can then bind to some more elements of these inhibitors. Even the ester function of compound **152** which, once this compound settles in the catalytic site, could react with the thiol function, does not. This suggests that **152** never binds to SARS-CoV-2 M^{pro} and this implies that before a reaction takes place with the cysteine thiol of SARS-CoV-2 M^{pro}, the catalytic site has a conformation devoid of affinity for the other components of these inhibitors. This could mean that ligands specific to this unknown site conformation have yet to be identified as such. At least one early report on the clustering of various inhibitors of SARS-CoV-2 M^{pro} according to the shape of the pocket binding to them does point out a degree of flexibility.[415] But to account for the complete lack of affinity of compounds **150**–**152** for the SARS-CoV-2 M^{pro} catalytic site, one could suspect far larger conformational changes. In fact, one way to detect and characterize such non-obvious conformations remains extensive high throughput screenings for fully original and non-covalent inhibitors, followed by X-ray based structural studies of their interactions with the protease. From the chemistry point of view, many compounds described here are tributes to the creativity of organic chemists. Of note would be the oxidative rearrangement of the tetrahydrocarboline **153** into the spiropyrrolidines **154** and **155**.[323] As depicted in Scheme 2, it is this synthetic step which paved the way to the design and synthesis of EDP-235 (**85**) and led to 14 distinct patents claiming many spiropyrrolidine series of SARS-CoV-2 M^{pro} inhibitors. Interestingly, this rearrangement[416] was previously used[417] in 1996 to prepare esters and nitrile derivatives somehow related to **154** and **155**. History will tell if it was their evaluation on SARS-CoV-2 M^{pro} which was at the source of these strong inhibitors.

Finally, in the following years some viral strains resistant to the currently available SARS-CoV-2 M^{pro} inhibitors will unfortunately emerge in the population[418–423] and these strains will likely compromise the corresponding drug efficacy. For that reason, as well as a price lowering effect, it is very important to have the widest possible range of efficient SARS-CoV-2 multiplication inhibitors so that a lack of cross-resistances between these drugs can be expected. In this regard, the possibility of a general/partial cross-resistance between all the covalent SARS-CoV-2 M^{pro} inhibitors currently used or developed today is a very relevant issue. In any case, any array of coronavirus-adapted antiviral drugs will be handy to address the next corona epidemic before specific vaccines are designed and mass-produced. Indeed, the recent major progress made with RNA-based vaccines is challenging MedChem and the much longer time usually required to provide a drug-based treatment. Past the next coronavirus pandemics, anticipating such challenges for other zoonotic diseases as well could be a good idea.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 S. Yan and G. Wu, Potential 3-chymotrypsin-like cysteine protease cleavage sites in the coronavirus polyproteins pp1a and pp1ab and their possible relevance to COVID-19 vaccine and drug development, *FASEB J.*, 2021, **35**, e21573.

2 S. Ullrich and C. Nitsche, The SARS-CoV-2 main protease as drug target, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127377.

3 M. K. Roe, N. A. Junod, A. R. Young, D. C. Beachboard and C. C. Stobart, Targeting novel structural and functional features of coronavirus protease nsp5 (3CLpro, Mpro) in the age of COVID-19, *J. Gen. Virol.*, 2021, **102**, DOI: **10.1099/jgv.0.001558**.

4 C. C. Chen, X. Yu, C. J. Kuo, J. Min, S. Chen, L. Ma, K. Liu and R. T. Guo, Overview of antiviral drug candidates targeting coronaviral 3C-like main proteases, *FEBS J.*, 2021, **288**, 5089.

5 A. Hegyi and J. Ziebuhr, Conservation of substrate specificities among coronavirus main proteases, *J. Gen. Virol.*, 2002, **83**, 595.

6 M. Xiong, H. Su, W. Zhao, H. Xie, Q. Shao and Y. Xu, What coronavirus 3C-like protease tells us: From structure, substrate selectivity, to inhibitor design, *Med. Res. Rev.*, 2021, **41**, 1965.

7 J. Lee, C. Kenward, L. J. Worrall, M. Vuckovic, F. Gentile, A. T. Ton, M. Ng, A. Cherkasov, N. C. J. Strynadka and M. Paetzel, X-ray crystallographic characterization of the SARS-CoV-2 main protease polyprotein cleavage sites essential for viral processing and maturation, *Nat. Commun.*, 2022, **13**, 5196.

8 J. Wenzel, J. Lampe, H. Müller-Fielitz, R. Schuster, M. Zille, K. Müller, M. Krohn, J. Körbelin, L. Zhang, Ü. Özorhan, V. Neve, J. U. G. Wagner, D. Bojkova, M. Shumliakivska, Y. Jiang, A. Fähnrich, F. Ott, V. Sencio, C. Robil, S. Pfefferle, F. Sauve, C. F. F. Coêlho, J. Franz, F. Spiecker, B. Lembrich, S. Binder, N. Feller, P. König, H. Busch, L. Collin, R. Villaseñor, O. Jöhren, H. C. Altmeppen, M. Pasparakis, S. Dimmeler, J. Cinatl, K. Püschel, M. Zelic, D. Ofengeim, C. Stadelmann, F. Trottein, R. Nogueiras, R. Hilgenfeld, M. Glatzel, V. Prevot and M. Schwaninger, The SARS-CoV-2 main protease Mpro causes microvascular brain pathology by cleaving NEMO in brain endothelial cells, *Nat. Neurosci.*, 2021, **24**, 1522.

9 L. Song, D. Wang, G. Abbas, M. Li, M. Cui, J. Wang, Z. Lin and X. E. Zhang, The main protease of SARS-CoV-2 cleaves histone deacetylases and DCP1A, attenuating the immune defense of the interferon-stimulated genes, *J. Biol. Chem.*, 2023, **7**(7), 102990.

10 J. L. Lu and X. L. Zhou, SARS-CoV-2 main protease Nsp5 cleaves and inactivates human tRNA methyltransferase TRMT1, *J. Mol. Cell Biol.*, 2023, **15**, mjad024.

11 K. Zhao, Y. Li, M. Guo, L. Ma and B. Dang, Identification of SARS-CoV-2 PLpro and 3CLpro human proteome substrates using substrate phage display coupled with protein network analysis, *J. Biol. Chem.*, 2023, **299**, 104831.

12 A. S. Devasthanam, Mechanisms underlying the inhibition of interferon signaling by viruses, *Virulence*, 2014, **5**, 270.

13 H. Li, X. Wang, Y. Wang, Y. Li, Y. Chen, Y. T. Wong, J. He and M. L. He, Secreted LRPAP1 binds and triggers IFNAR1 degradation to facilitate virus evasion from cellular innate immunity, *Signal Transduction Targeted Ther.*, 2023, **8**, 374.

14 I. Melano, Y. C. Lo and W. C. Su, Characterization of host substrates of SARS-CoV-2 main protease, *Front. Microbiol.*, 2023, **14**, 1251705.

15 Z. Fu, B. Huang, J. Tang, S. Liu, M. Liu, Y. Ye, Z. Liu, Y. Xiong, W. Zhu, D. Cao, J. Li, X. Niu, H. Zhou, Y. J. Zhao, G. Zhang and H. Huang, The complex structure of GRL0617 and SARS-CoV-2 PLpro reveals a hot spot for antiviral drug discovery, *Nat. Commun.*, 2021, **12**, 488.

16 C. Ma, M. D. Sacco, Z. Xia, G. Lambrinidis, J. A. Townsend, Y. Hu, X. Meng, T. Szeto, M. Ba, X. Zhang, M. Gongora, F. Zhang, M. T. Marty, Y. Xiang, A. Kolocouris, Y. Chen and J. Wang, Discovery of SARS-CoV-2 Papain-like Protease Inhibitors through a Combination of High-Throughput Screening and a FlipGFP-Based Reporter Assay, *ACS Cent. Sci.*, 2021, **7**, 1245.

17 A. K. Ghosh, M. Brindisi, D. Shahabi, M. E. Chapman and A. D. Mesecar, Drug Development and Medicinal Chemistry Efforts toward SARS-Coronavirus and Covid-19 Therapeutics, *ChemMedChem*, 2020, **15**, 907.

18 V. Anirudhan, H. Lee, H. Cheng, L. Cooper and L. Rong, Targeting SARS-CoV-2 viral proteases as a therapeutic strategy to treat COVID-19, *J. Med. Virol.*, 2021, **93**, 2722.

19 H. Tan, Y. Hu, P. Jadhav, B. Tan and J. Wang, Progress and Challenges in Targeting the SARS-CoV-2 Papain-like Protease, *J. Med. Chem.*, 2022, **65**, 7561.

20 B. C. S. Chia and P. S. Lim, A Patent Review on SARS Coronavirus Papain-Like Protease (PLpro) Inhibitors, *ChemMedChem*, 2023, e202300216.

21 M. Takeda, Proteolytic activation of SARS-CoV-2 spike protein, *Microbiol. Immunol.*, 2022, **66**, 15.

22 C. B. Jackson, M. Farzan, B. Chen and H. Choe, Mechanisms of SARS-CoV-2 entry into cells, *Nat. Rev. Mol. Cell Biol.*, 2022, **1**, 3.

23 C. Ma and J. Wang, Dipyridamole, chloroquine, montelukast sodium, candesartan, oxytetracycline, and atazanavir are not SARS-CoV-2 main protease inhibitors, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2024420118.

24 K. Steuten, H. Kim, J. Widen, B. M. Babin, O. Onguka, S. Lovell, O. Bolgi, B. Cerikan, C. J. Neufeldt, M. Cortese, R. K. Muir, J. M. Bennett, R. Geiss-Friedlander, C. Peters, R. Bartenschlager and M. Bogyo, Challenges for Targeting SARS-CoV2 Proteases as a Therapeutic Strategy for COVID-19, *ACS Infect. Dis.*, 2021, **7**, 1457.

25 K. Vandyck, R. Abdelnabi, K. Gupta, D. Jochmans, A. Jekle, J. Deval, D. Misner, D. Bardiot, C. S. Foo, C. Liu, S. Ren, L. Beigelman, L. M. Blatt, S. Boland, L. Vangeel, S. Dejonghe, P. Chaltin, A. Marchand, V. Serebryany, A. Stoycheva, S. Chanda, J. A. Symons, P. Raboisson and J. Neyts, ALG-097111, a potent and selective SARS-CoV-2 3-chymotrypsin-like cysteine protease inhibitor exhibits in vivo efficacy in a Syrian Hamster model, *Biochem. Biophys. Res. Commun.*, 2021, **555**, 134.

26 C. Ma, Y. Hu, J. A. Townsend, P. I. Lagarias, M. T. Marty, A. Kolocouris and J. Wang, Ebselen, Disulfiram, Carmofur, PX-12, Tideglusib, and Shikonin Are Nonspecific Promiscuous SARS-CoV-2 Main Protease Inhibitors, *ACS Pharmacol. Transl. Sci.*, 2020, **3**, 1265.

27 C. Ma, H. Tan, J. Choza, Y. Wang and J. Wang, Validation and invalidation of SARS-CoV-2 main protease inhibitors using the Flip-GFP and Protease-Glo luciferase assays, *Acta Pharm. Sin. B*, 2021, **12**, 1636.

28 H. Tan, C. Ma and J. Wang, Invalidation of dieckol and 1,2,3,4,6-pentagalloylglucose (PGG) as SARS-CoV-2 main

protease inhibitors and the discovery of PGG as a papain-like protease inhibitor, *Med. Chem. Res.*, 2022, **31**, 1147.

29 D. M. Mellott, C. T. Tseng, A. Drelich, P. Fajtová, B. C. Chenna, D. H. Kostomiris, J. Hsu, J. Zhu, Z. W. Taylor, K. I. Kocurek, V. Tat, A. Katzfuss, L. Li, M. A. Giardini, D. Skinner, K. Hirata, M. C. Yoon, S. Beck, A. F. Carlin, A. E. Clark, L. Beretta, D. Maneval, V. Hook, F. Frueh, B. L. Hurst, H. Wang, F. M. Raushel, A. J. O'Donoghue, J. L. de Siqueira-Neto, T. D. Meek and J. H. McKerrow, A Clinical-Stage Cysteine Protease Inhibitor blocks SARS-CoV-2 Infection of Human and Monkey Cells, *ACS Chem. Biol.*, 2021, **16**, 642.

30 S. Gierer, S. Bertram, F. Kaup, F. Wrensch, A. Heurich, A. Krämer-Kühl, K. Welsch, M. Winkler, B. Meyer, C. Drosten, U. Dittmer, H. Von, T. G. Simmons, H. Hofmann and S. Pöhlmann, The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2 and is targeted by neutralizing anti- bodies, *J. Virol.*, 2013, **87**, 5502.

31 K. Shirato, M. Kawase and S. Matsuyama, Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2, *J. Virol.*, 2013, **87**, 12552.

32 M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N. H. Wu, A. Nitsche, M. A. Müller, C. Drosten and S. Pöhlmann, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, *Cell*, 2020, **181**, 271.

33 T. Kinoshita, M. Shinoda, Y. Nishizaki, K. Shiraki, Y. Hirai, Y. Kichikawa, K. Tsushima, M. Sinkai, N. Komura, K. Yoshida, Y. Kido, H. Kakeya, N. Uemura and J. Kadota, A multicenter, double-blind, randomized, parallel-group, placebo-controlled study to evaluate the efficacy and safety of camostat mesilate in patients with COVID-19 (CANDLE study), *BMC Med.*, 2022, **20**, 342.

34 M. Yamamoto, S. Matsuyama, X. Li, M. Takeda, Y. Kawaguchi, J. I. Inoue and Z. Matsuda, Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay, *Antimicrob. Agents Chemother.*, 2016, **60**, 6532.

35 T. M. Quinn, E. E. Gaughan, A. Bruce, J. Antonelli, R. O'Connor, F. Li, S. McNamara, O. Koch, C. MacKintosh, D. Dockrell, T. Walsh, K. G. Blyth, C. Church, J. Schwarze, C. Boz, A. Valanciute, M. Burgess, P. Emanuel, B. Mills, G. Rinaldi, G. Hardisty, R. Mills, E. G. Findlay, S. Jabbal, A. Duncan, S. Plant, A. D. L. Marshall, I. Young, K. Russell, E. Scholefield, A. F. Nimmo, I. B. Nazarov, G. C. Churchill, J. S. O. McCullagh, K. H. Ebrahimi, C. Ferrett, K. Templeton, S. Rannard, A. Owen, A. Moore, K. Finlayson, M. Shankar-Hari, J. Norrie, R. A. Parker, A. R. Akram, D. C. Anthony, J. W. Dear, N. Hirani and K. Dhaliwal, Randomised controlled trial of intravenous nafamostat mesylate in COVID pneumonitis: Phase 1b/2a experimental study to investigate safety, Pharmacokinetics and Pharmacodynamics, *EBioMedicine*, 2022, **76**, 103856.

36 C. J. Kuo, H. G. Liu, Y. K. Lo, C. M. Seong, K. I. Lee, Y. S. Jung and P. H. Liang, Individual and common inhibitors of coronavirus and picornavirus main proteases, *FEBS Lett.*, 2009, **583**, 549.

37 A. A. Hernandez and W. R. Roush, Recent advances in the synthesis, design and selection of cysteine protease inhibitors, *Curr. Opin. Chem. Biol.*, 2002, **6**, 459.

38 S. R. Shih, S. J. Chen, G. H. Hakimelahi, H. J. Liu, C. T. Tseng and K. S. Shia, Selective human enterovirus and rhinovirus inhibitors: An overview of capsid-binding and protease-inhibiting molecules, *Med. Res. Rev.*, 2004, **24**, 449.

39 Q. M. Wanga and S. H. Chen, Human rhinovirus 3C protease as a potential target for the development of antiviral agents, *Curr. Protein Pept. Sci.*, 2007, **8**, 19.

40 A. M. De Palma, I. Vliegen, E. De Clercq and J. Neyts, Selective inhibitors of picornavirus replication, *Med. Res. Rev.*, 2008, **28**, 823.

41 W. Dai, D. Jochmans, H. Xie, H. Yang, J. Li, H. Su, D. Chang, J. Wang, J. Peng, L. Zhu, Y. Nian, R. Hilgenfeld, H. Jiang, K. Chen, L. Zhang, Y. Xu, J. Neyts and H. Liu, Design, Synthesis, and Biological Evaluation of Peptidomimetic Aldehydes as Broad-Spectrum Inhibitors against Enterovirus and SARS-CoV-2, *J. Med. Chem.*, 2022, **65**, 2794.

42 R. Hilgenfeld, From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design, *FEBS J.*, 2014, 4085.

43 T. Pillaiyar, M. Manickam, V. Namasivayam, Y. Hayashi and S. H. Jung, An Overview of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) 3CL Protease Inhibitors: Peptidomimetics and Small Molecule Chemotherapy, *J. Med. Chem.*, 2016, **59**, 6595.

44 P. Thanigaimalai, M. Manickam, V. Namasivayam, Y. Hayashi and S. H. Jung, An Overview of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) 3CL Protease Inhibitors: Peptidomimetics and Small Molecule Chemotherapy, *J. Med. Chem.*, 2016, **59**, 6595.

45 R. Liang, L. Wang, N. Zhang, X. Deng, M. Su, Y. Su, L. Hu, C. He, T. Ying, S. Jiang and F. Yu, Development of small-molecule MERS-CoV inhibitors, *Viruses*, 2018, **10**, 721.

46 Y. Liu, C. Liang, L. Xin, X. Ren, L. Tian, X. Ju, H. Li, Y. Wang, Q. Zhao, H. Liu, W. Cao, X. Xie, D. Zhang, Y. Wang and Y. Jian, The development of Coronavirus 3C-Like protease (3CLpro) inhibitors from 2010 to 2020, *Eur. J. Med. Chem.*, 2020, **206**, 112711.

47 K. Akaji and H. Konno, Design and Evaluation of Anti-SARS-Coronavirus Agents Based on Molecular Interactions with the Viral Protease, *Molecules*, 2020, **25**, 3920.

48 C. S. Ng, C. C. Stobart and H. Luo, Innate immune evasion mediated by picornaviral 3C protease: Possible lessons for coronaviral 3C-like protease?, *Rev. Med. Virol.*, 2021, **31**, 1.

49 R. Banerjee, L. Perera and L. M. V. Tillekeratne, Potential SARS-CoV-2 main protease inhibitors, *Drug Discovery Today*, 2021, **26**, 804.

50 K. Gao, R. Wang, J. Chen, J. J. Tepe, F. Huang and G. W. Wei, Perspectives on SARS-CoV-2 Main Protease Inhibitors, *J. Med. Chem.*, 2021, **64**, 16922.

51 A. Citarella, A. Scala, A. Piperno and N. Micale, SARS-CoV-2 M(pro): A Potential Target for Peptidomimetics and Small-Molecule Inhibitors, *Biomolecules*, 2021, **11**, 607.

52 S. A. Amin, S. Banerjee, S. Gayen and T. Jha, Protease targeted COVID-19 drug discovery: What we have learned from the past SARS-CoV inhibitors?, *Eur. J. Med. Chem.*, 2021, **215**, 113294.

53 M. Konwar and D. Sarma, Advances in developing small molecule SARS 3CLpro inhibitors as potential remedy for corona virus infection, *Tetrahedron*, 2021, **77**, 131761.

54 H. M. Mengist, T. Dilnessa and T. Jin, Structural Basis of Potential Inhibitors Targeting SARS-CoV-2 Main Protease, *Front. Chem.*, 2021, **9**, 622898.

55 H. Yang and J. Yang, A review of the latest research on Mpro targeting SARS-COV inhibitors, *RSC Med. Chem.*, 2021, **12**, 1026.

56 G. Macip, P. Garcia-Segura, J. Mestres-Truyol, B. Saldivar-Espinoza, G. Pujadas and S. Garcia-Vallvé, A Review of the Current Landscape of SARS-CoV-2 Main Protease Inhibitors: Have We Hit the Bullseye Yet?, *Int. J. Mol. Sci.*, 2022, **23**, 259.

57 T. I. Ng, I. Correia, J. Seagal, D. A. DeGoey, M. R. Schrimpf, D. J. Hardee, E. L. Noey and W. M. Kati, Antiviral Drug Discovery for the Treatment of COVID-19 Infections, *Viruses*, 2022, **14**, 961.

58 R. Cannalire, C. Cerchia, A. R. Beccari, F. S. Di Leva and V. Summa, Targeting SARS-CoV-2 Proteases and Polymerase for COVID-19 Treatment: State of the Art and Future Opportunities, *J. Med. Chem.*, 2022, **65**, 2716.

59 Q. Hu, Y. Xiong, G. H. Zhu, Y. N. Zhang, Y. W. Zhang, P. Huang and G. B. Ge, The SARS-CoV-2 main protease (Mpro): Structure, function, and emerging therapies for COVID-19, *MedComm*, 2022, **3**, e151.

60 C. S. B. Chia, W. Xu and P. Shuyi Ng, A Patent Review on SARS Coronavirus Main Protease (3CLpro) Inhibitors, *ChemMedChem*, 2022, **17**, e202100576.

61 L. Agost-Beltrán, S. de la Hoz-Rodríguez, L. Bou-Iserte, S. Rodríguez, A. Fernández-de-la-Pradilla and F. V. González, Advances in the Development of SARS-CoV-2 Mpro Inhibitors, *Molecules*, 2022, **27**, 2523.

62 G. La Monica, A. Bono, A. Lauria and A. Martorana, Targeting SARS-CoV-2 Main Protease for Treatment of COVID-19: Covalent Inhibitors Structure-Activity Relationship Insights and Evolution Perspectives, *J. Med. Chem.*, 2022, **65**, 12500.

63 R. P. Joyce, V. W. Hu and J. Wang, The history, mechanism, and perspectives of nirmatrelvir (PF-07321332): an orally bioavailable main protease inhibitor used in combination with ritonavir to reduce COVID-19-related hospitalizations, *Med. Chem. Res.*, 2022, **31**, 1637.

64 J. Zhu, H. Zhang, Q. Lin, J. Lyu, L. Lu, H. Chen, X. Zhang, Y. Zhang and K. Chen, Progress on SARS-CoV-2 3CLpro Inhibitors: Inspiration from SARS-CoV 3CLpro Peptidomimetics and Small-Molecule Anti-Inflammatory Compounds, *Drug Des., Dev. Ther.*, 2022, **16**, 1067.

65 T. Majerová and J. Konvalinka, Viral proteases as therapeutic targets, *Mol. Aspects Med.*, 2022, **88**, 101159.

66 X. Pang, W. Xu, Y. Liu, H. Li and L. Chen, The research progress of SARS-CoV-2 main protease inhibitors from 2020 to 2022, *Eur. J. Med. Chem.*, 2023, **257**, 115491.

67 T. Kronenberger, S. A. Laufer and T. Pillaiyar, COVID-19 therapeutics: Small-molecule drug development targeting SARS-CoV-2 main protease, *Drug Discovery Today*, 2023, **28**, 103579.

68 L. Yang and Z. Wang, Bench-to-bedside: Innovation of small molecule anti-SARS-CoV-2 drugs in China, *Eur. J. Med. Chem.*, 2023, **257**, 115503.

69 Y. Duan, H. Wang, Z. Yuan and H. Yang, Structural biology of SARS-CoV-2 Mpro and drug discovery, *Curr. Opin. Struct. Biol.*, 2023, **82**, 102667.

70 X. Li and Y. Song, Structure and function of SARS-CoV and SARS-CoV-2 main proteases and their inhibition: A comprehensive review, *Eur. J. Med. Chem.*, 2023, **260**, 115772.

71 E. N. Muratov, R. Amaro, C. H. Andrade, N. Brown, S. Ekins, D. Fourches, O. Isayev, D. Kozakov, J. L. Medina-Franco, K. M. Merz, T. Oprea, V. Poroikov, G. Schneider, M. Todd, A. Varnek, D. A. Winkler, A. V. Zakharov, A. Cherkasov and A. Tropsha, A critical overview of computational approaches employed for COVID-19 drug discovery, *Chem. Soc. Rev.*, 2021, **50**, 9121.

72 G. Macip, P. Garcia-Segura, J. Mestres-Truyol, B. Saldivar-Espinoza, M. J. Ojeda-Montes, A. Gimeno, A. Cereto-Massagué, S. Garcia-Vallvé and G. Pujadas, Haste makes waste: A critical review of docking-based virtual screening in drug repurposing for SARS-CoV-2 main protease (M-pro) inhibition, *Med. Res. Rev.*, 2021, **42**, 744.

73 S. L. McGovern, E. Caselli, N. Grigorieff and B. K. Shoichet, A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening, *J. Med. Chem.*, 2002, **45**, 1712.

74 J. Baell and M. A. Walters, Chemical con artists foil drug discovery, *Nature*, 2014, **513**, 481.

75 H. I. Ingolfsson, P. Thakur, K. F. Herold, E. A. Hobart, N. B. Ramsey, X. Periole, D. H. deJong, M. Zwama, D. Yilmaz, K. Hall, T. Maretzky, H. C. Hemmings, Jr., C. Blobel, S. J. Marrink, A. Kocer, J. T. Sack and O. S. Andersen, Phytochemicals perturb membranes and promiscuously alter protein function, *ACS Chem. Biol.*, 2014, **9**, 1788.

76 J. Bisson, J. B. McAlpine, J. B. Friesen, S. N. Chen, J. Graham and G. F. Pauli, Can Invalid Bioactives Undermine Natural Product-Based Drug Discovery?, *J. Med. Chem.*, 2016, **59**, 1671.

77 J. B. Baell and J. W. M. Nissink, Seven Year Itch: Pan-Assay Interference Compounds (PAINS) in 2017 - Utility and Limitations, *ACS Chem. Biol.*, 2018, **13**, 36.

78 J. B. Baell, Screening-Based Translation of Public Research Encounters Painful Problems, *ACS Med. Chem. Lett.*, 2015, **6**, 229.

79 J. B. McAlpine, D. Ferreira, N. E. Pauli, S. Gafner and G. F. Pauli, The Ethics of Publishing Biomedical and Natural Products Research, *J. Nat. Prod.*, 2023, **86**, 2228–2237.

80 M. C. Parrish, Y. J. Tan, K. V. Grimes and D. Moschly-Rosen, Surviving in the Valley of Death: Opportunities and Challenges in Translating Academic Drug Discoveries, *Annu. Rev. Pharmacol. Toxicol.*, 2019, **59**, 405.

81 L. S. Franco, R. C. Maia and E. J. Barreiro, Identification of LASSBio-1945 as an inhibitor of SARS-CoV-2 main protease (MPRO) through in silico screening supported by molecular docking and a fragment-based pharmacophore model, *RSC Med. Chem.*, 2020, **12**, 110.

82 L. Zhang, M. Howland, R. Hilgenfeld, M. O. Anderson and S. Eagon, Identification of non-covalent SARS-CoV-2 main protease inhibitors by a virtual screen of commercially available drug-like compounds, *Bioorg. Med. Chem. Lett.*, 2021, **41**, 127990.

83 F. Gentile, M. Fernandez, F. Ban, A. Ton, H. Mslati, C. Perez, E. Leblanc, J. Yaacoub, J. Gleave, A. Stern, B. Wong, F. Jean, N. Strynadka and A. Cherkasov, Automated discovery of noncovalent inhibitors of SARS-CoV-2 main protease by consensus Deep Docking of 40 billion small molecules, *Chem. Sci.*, 2021, **12**, 15960.

84 S. Günther, P. Y. A. Reinke, Y. Fernández-García, J. Lieske, T. J. Lane, H. M. Ginn, F. H. M. Koua, C. Ehrt, W. Ewert, D. Oberthuer, O. Yefanov, S. Meier, K. Lorenzen, B. Krichel, J. D. Kopicki, L. Gelisio, W. Brehm, I. Dunkel, B. Seychell, H. Gieseler, B. Norton-Baker, B. Escudero-Pérez, M. Domaracky, S. Saouane, A. Tolstikova, T. A. White, A. Hänle, M. Groessler, H. Fleckenstein, F. Trost, M. Galchenkova, Y. Gevorkov, C. Li, S. Awel, A. Peck, M. Barthelmess, F. Schluenzen, X. Lourdu, P. N. Werner, H. Andaleeb, N. Ullah, S. Falke, V. Srinivasan, B. França, M. Schwinzer, H. Brognaro, C. Rogers, D. Melo, J. J. Zaitseva-Doyle, J. Knoska, G. E. Peña-Murillo, A. R. Mashhour, V. Hennicke, P. Fischer, J. Hakanpää, J. Meyer, P. Gribbon, B. Ellinger, M. Kuzikov, M. Wolf, A. R. Beccari, G. Bourenkov, D. von Stetten, G. Pompidor, I. Bento, S. Panneerselvam, I. Karpics, T. R. Schneider, M. M. Garcia-Alai, S. Niebling, C. Günther, C. Schmidt, R. Schubert, H. Han, J. Boger, D. C. F. Monteiro, L. Zhang, X. Sun, J. Pletzer-Zelgert, J. Wollenhaupt, C. G. Feiler, M. S. Weiss, E. C. Schulz, P. Mehrabi, K. Karničar, A. Usenik, J. Loboda, H. Tidow, A. Chari, R. Hilgenfeld, C. Uetrecht, R. Cox, A. Zaliani, T. Beck, M. Rarey, S. Günther, D. Turk, W. Hinrichs, H. N. Chapman, A. R. Pearson, C. Betzel and A. Meents, X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease, *Science*, 2021, **372**, 642.

85 L. Zheng, Y. Chen, J. Bao, L. He, S. Dong, Y. Qi and J. Z. H. Zhang, Discovery of novel inhibitors of SARS-CoV-2 main protease, *J. Biomol. Struct. Dyn.*, 2022, **40**, 12526.

86 L. Wang, Z. Yu, S. Wang, Z. Guo, Q. Sun and L. Lai, Discovery of novel SARS-CoV-2 3CL protease covalent inhibitors using deep learning-based screen, *Eur. J. Med. Chem.*, 2022, **244**, 114803.

87 D. Deodato, N. Asad and T. M. Dore, Discovery of 2-thiobenzimidazoles as noncovalent inhibitors of SARS-CoV-2 main protease, *Bioorg. Med. Chem. Lett.*, 2022, **72**, 128867.

88 J. Glaser, A. Sedova, S. Galanie, D. W. Kneller, R. B. Davidson, E. Maradzike, S. Del Galdo, A. Labbé, D. J. Hsu, R. Agarwal, D. Bykov, A. Tharrington, J. M. Parks, D. M. A. Smith, I. Daidone, L. Coates, A. Kovalevsky and J. C. Smith, Hit Expansion of a Noncovalent SARS-CoV-2 Main Protease Inhibitor, *ACS Pharmacol. Transl. Sci.*, 2022, **5**, 255.

89 T. Xu, M. Xu, W. Zhu, C. Z. Chen, Q. Zhang, W. Zheng and R. Huang, Efficient Identification of Anti-SARS-CoV-2 Compounds Using Chemical Structure- and Biological Activity-Based Modeling, *J. Med. Chem.*, 2022, **65**, 4590.

90 L. El Khoury, Z. Jing, A. Cuzzolin, A. Deplano, D. Loco, B. Sattarov, F. Hédin, S. Wendeborn, C. Ho, D. El Ahbad, D. T. Jaffrelot Inizan, M. Sturlese, A. Sosic, M. Volpiana, A. Lugato, M. Barone, B. Gatto, M. L. Macchia, M. Bellanda, R. Battistutta, C. Salata, I. Kondratov, R. Iminov, A. Khairulin, Y. Mykhalonok, A. Pochepko, V. Chashka-Ratushnyi, I. Kos, S. Moro, M. Montes, P. Ren, J. W. Ponder, L. Lagardère, J. P. Piquemal and D. Sabbadin, Computationally driven discovery of SARS-CoV-2 Mpro inhibitors: from design to experimental validation, *Chem. Sci.*, 2022, **13**, 3674.

91 E. A. Fink, C. Bardine, S. Gahbauer, I. Singh, T. Detomasi, K. White, S. Gu, X. Wan, J. Chen, B. Ary, I. Glenn, J. O'Connell, H. O'Donnell, P. Fajtová, J. Lyu, S. Vigneron, N. J. Young, I. S. Kondratov, A. Alisoltani, L. M. Simons, R. Lorenzo-Redondo, E. A. Ozer, J. F. Hultquist, A. J. O'Donoghue, Y. Moroz, J. Taunton, A. R. Renslo, J. J. Irwin, A. García-Sastre, B. K. Shoichet and C. S. Craik, Large library docking for novel SARS-CoV-2 main protease non-covalent inhibitors, *Protein Sci.*, 2023, **32**, e4712.

92 N. Liu, Z. Yang, Y. Liu, X. Dang, Q. Zhang, J. Wang, X. Liu, J. Zhang and X. Pan, Identification of a Putative SARS-CoV-2 Main Protease Inhibitor through In Silico Screening of Self-Designed Molecular Library, *Int. J. Mol. Sci.*, 2023, **24**, 11390.

93 A. Douangamath, D. Fearon, P. Gehrtz, T. Krojer, P. Lukacik, C. Owen, E. Resnick, C. Strain-Damerell, A. Aimon, P. Ábrányi-Balogh, J. Brandão-Neto, A. Carbery, G. Davison, A. Dias, T. D. Downes, L. Dunnett, M. Fairhead, J. D. Firth, S. P. Jones, A. Keeley, G. M. Keserü, H. F. Klein, M. P. Martin, M. E. M. Noble, P. O'Brien, A. Powell, R. N. Reddi, R. Skyner, M. Snee, M. J. Waring, C. Wild, N. London, F. von Delft and M. A. Walsh, Crystallographic and electrophilic fragment screening of the SARS-CoV-2 main protease, *Nat. Commun.*, 2020, **11**, 5047.

94 T. M. Rana, Methods and compounds to treat SARS infections, WO2022081984, 2022.

95 B. A. Lanman, J. R. Allen, J. G. Allen, A. K. Amegadzie, K. S. Ashton, S. K. Booker, J. J. Chen, N. Chen, M. J. Frohn, G. Goodman, D. J. Kopecky, L. Liu, P. Lopez, J. D. Low, V. Ma, A. E. Minatti, T. T. Nguyen, N. Nishimura, A. Pickrell, A. B. Reed, Y. Shin, A. C. Siegmund, N. A. Tamayo, C. M. Tegley, M. C. Walton, H. L. Wang, R. P. Wurz, M. Xue, K. C. Yang,

P. Achanta, M. D. Bartberger, J. Canon, L. S. Hollis, J. D. McCarter, C. Mohr, K. Rex, A. Y. Saiki, T. San Miguel, L. P. Volak, K. H. Wang, D. A. Whittington, S. G. Zech, J. R. Lipford and V. J. Cee, Discovery of a Covalent Inhibitor of KRASG12C (AMG 510) for the Treatment of Solid Tumors, *J. Med. Chem.*, 2020, **63**, 52.

96 J. Canon, K. Rex, A. Y. Saiki, C. Mohr, K. Cooke, D. Bagal, K. Gaida, T. Holt, C. G. Knutson, N. Koppada, B. A. Lanman, J. Werner, A. S. Rapaport, T. San Miguel, R. Ortiz, T. Osgood, J. R. Sun, X. Zhu, J. D. McCarter, L. P. Volak, B. E. Houk, M. G. Fakih, B. H. O'Neil, T. J. Price, G. S. Falchook, J. Desai, J. Kuo, R. Govindan, D. S. Hong, W. Ouyang, H. Henary, T. Arvedson, V. Cee and J. R. Lipford, The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity, *Nature*, 2019, **575**, 217.

97 D. Kim, L. Herdeis, D. Rudolph, Y. Zhao, J. Böttcher, A. Vides, C. Ayala-Santos, Y. Pourfarjam, A. Cuevas-Navarro, J. Y. Xue, A. Mantoulidis, J. Bröker, T. Wunberg, O. Schaaf, J. Popow, B. Wolkerstorfer, K. G. Kropatsch, R. Qu, E. de Stanchina, B. Sang, C. Li, D. B. McConnell, N. Kraut and P. Lito, Pan-KRAS inhibitor disables oncogenic signalling and tumour growth, *Nature*, 2023, **619**, 160.

98 J. C. Powers, J. L. Asgian, O. D. Ekici and K. E. James, Irreversible inhibitors of serine, cysteine, and threonine proteases, *Chem. Rev.*, 2002, **102**, 4639.

99 B. Turk, Targeting proteases: successes, failures and future prospects, *Nat. Rev. Drug Discovery*, 2006, **5**, 785.

100 Y. Hamada and Y. Kiso, New directions for protease inhibitors directed drug discovery, *Biopolymers*, 2016, **106**, 563.

101 L. Cianni, C. W. Feldmann, E. Gilberg, M. Gütschow, L. Juliano, A. Leitão, J. Bajorath and C. A. Montanari, Can Cysteine Protease Cross-Class Inhibitors Achieve Selectivity?, *J. Med. Chem.*, 2019, **62**, 10497.

102 W. Wannamaker, R. Davies, M. Namchuk, J. Pollard, P. Ford, G. Ku, C. Decker, P. Charifson, P. Weber, U. A. Germann, K. Kuida and J. C. Randle, (S)-1-((S)-2-{[1-(4-amino-3-chloro-phenyl)-methanoyl]-amino}-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-amide (VX-765), an orally available selective interleukin (IL)-converting enzyme/caspase-1 inhibitor, exhibits potent anti-inflammatory activities by inhibiting the release of IL-1beta and IL-18, *J. Pharmacol. Exp. Ther.*, 2007, **321**, 509.

103 M. Poreba, A. Szalek, P. Kasperkiewicz, W. Rut, G. S. Salvesen and M. Drag, Small Molecule Active Site Directed Tools for Studying Human Caspases, *Chem. Rev.*, 2015, **115**, 12546.

104 M. W. Wannamaker and R. Davies, Prodrug of an ICE inhibitor, US20020013278, 2002.

105 M. B. Boxer, A. M. Quinn, M. Shen, A. Jadhav, W. Leister, A. Simeonov, D. A. Auld and C. J. Thomas, A highly potent and selective caspase 1 inhibitor that utilizes a key 3-cyanopropanoic acid moiety, *ChemMedChem*, 2010, **5**, 730.

106 M. Mortimore, A. Miller, J. Studley and J. D. Charrier, Caspase inhibitors and uses thereof, WO2002094263, 2002.

107 G. Brenchley, J. D. Charrier, S. Durrant, R. Knegtel, M. Mortimore and J. R. Studley, Caspase inhibitors and uses therof, WO2004106304, 2004.

108 J. D. Charrier, R. Knegtel, M. Mortimore and J. R. Studley, 3[2-(3-acylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-4-oxo-pentanoic acod derivatives and their use as caspase inhibitors, WO2006057961, 2006.

109 G. W. Bemis, M. C. Julian, D. J. Lauffer, M. D. Mullican, M. A. Murcko and D. J. Livingston, Inhibitors of interleukin-1-beta converting enzyme, US5716929, 1998.

110 S. Chambon, C. Millois, L. Dumais, R. Pierre, L. Tomas, C. Mathieu, A. L. Ghilini, N. Vanthuyne, K. Reverse, A. Brethon, V. Rodeschini, C. Comino, G. Mouis, G. El-Bazbouz, L. Clary, J. F. Fournier, C. Bouix-Peter, C. S. Harris and L. F. Hennequin, Synthesis and stability evaluation of novel peptidomimetic Caspase-1 inhibitors for topical application, *Tetrahedron*, 2018, **74**, 4805.

111 J. F. Fournier, L. Clary, S. Chambon, L. Dumais, C. S. Harris, C. Millois, R. Pierre, S. Talano, E. Thoreau, J. Aubert, M. Aurelly, C. Bouix-Peter, A. Brethon, L. Chantalat, O. Christin, C. Comino, G. El-Bazbouz, A. L. Ghilini, T. Isabet, C. Lardy, A. P. Luzy, C. Mathieu, K. Mebrouk, D. Orfila, J. Pascau, K. Reverse, D. Roche, V. Rodeschini and L. F. Hennequin, Rational Drug Design of Topically Administered Caspase 1 Inhibitors for the Treatment of Inflammatory Acne, *J. Med. Chem.*, 2018, **10**, 4030.

112 P. Auberger, P. Chaintreuil, O. Dufies, J. Courjon, L. Boyer and A. Jacquel, Methods and pharmaceutical composition for the treatment of infectious diseases, WO2022008597, 2022.

113 E. Jacotot, B. Bung and N. Howard, Treatments of coronavirus infections, cytokine release syndrome, cytokine storm syndrome, or diseases associated with excessive activation of inflammasomes by the use of inhibitors of inflammatory caspases, WO2022074134, 2022.

114 O. Alpan, Treatment for diseases caused by RNA viruses, WO2022271877, 2022.

115 S. Bao, K. Zhai and Z. Huang, BACE1 inhibitor treatment for suppressing cytokine storm, US20230302009, 2023.

116 F. Lecaille, D. Brömme and G. Lalamanach, Biochemical properties and regulation of cathepsin K activity, *Biochimie*, 2008, **90**, 208.

117 J. Gauthier, N. Chauret, W. Cromlish, S. Desmarais, L. T. Duong, J. P. Falgueyret, D. B. Kimmel, S. Lamontagne, S. Léger, T. LeRiche, C. S. Li, F. Massé, D. J. McKay, D. A. Nicoll-Griffith, R. M. Oballa, J. T. Palmer, M. D. Percival, D. Riendeau, J. Robichaud, G. A. Rodan, S. B. Rodan, C. Seto, M. Thérien, V. Truong, M. C. Venuti, G. Wesolowski, R. N. Young, R. Zamboni and W. C. Black, The discovery of Odanacatib (MK-0822), a selective inhibitor of cathepsin K, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 923.

118 S. Law, P. M. Andrault, A. H. Aguda, N. T. Nguyen, N. Kruglyak, G. D. Brayer and D. Brömme, Identification of mouse cathepsin K structural elements that regulate the potency of odanacatib, *Biochem. J.*, 2017, **474**, 851.

119 M. R. McClung, M. L. O'Donoghue, S. E. Papapoulos, H. Bone, B. Langdahl, K. G. Saag, I. R. Reid, D. P. Kiel, I. Cavallari, M. P. Bonaca, S. D. Wiviott, T. de Villiers, X. Ling, K. Lippuner, T. Nakamura, J. Y. Reginster, J. A. Rodriguez-Portales, C. Roux, J. Zanchetta, C. A. F. Zerbini, J. G. Park, K. Im, A. Cange, L. T. Grip, N. Heyden, C. DaSilva, D. Cohn, R. Massaad, B. B. Scott, N. Verbruggen, D. Gurner, D. L. Miller, M. L. Blair, A. B. Polis, S. A. Stoch, A. Santora, A. Lombardi, A. T. Leung, K. D. Kaufman and M. S. Sabatine, Odanacatib for the treatment of postmenopausal osteoporosis: results of the LOFT multicentre, randomised, double-blind, placebo-controlled trial and LOFT Extension study, *Lancet Diabetes Endocrinol.*, 2019, **7**, 899.

120 C. Beaulieu, E. Isabel, A. Fortier, F. Massé, C. Mellon, N. Méthot, M. Ndao, D. Nicoll-Griffith, D. Lee, H. Park and W. C. Black, Identification of potent and reversible cruzipain inhibitors for the treatment of Chagas disease, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7444.

121 M. Ndao, C. Beaulieu, W. C. Black, E. Isabel, F. Vasquez-Camargo, M. Nath-Chowdhury, F. Massé, C. Mellon, N. Methot and D. A. Nicoll-Griffith, Reversible cysteine protease inhibitors show promise for a Chagas disease cure, *Antimicrob. Agents Chemother.*, 2014, **58**, 1167.

122 A. E. Weber, Dipeptidyl peptidase IV inhibitors for the treatment of diabetes, *J. Med. Chem.*, 2004, **47**, 4135.

123 S. L. Gwaltney and J. A. Stafford, Inhibitors of dipeptidyl peptidase, *Annu. Rep. Med. Chem.*, 2005, **40**, 149.

124 J. U. Peters, 11 Years of cyanopyrrolidines as DPP-IV inhibitors, *Curr. Top. Med. Chem.*, 2007, **7**, 579.

125 S. H. Havale and M. Pal, Medicinal chemistry approaches to the inhibition of dipeptidyl peptidase-4 for the treatment of type 2 diabetes, *Bioorg. Med. Chem.*, 2009, **17**, 1783.

126 Y. Liu, Y. Hu and T. Liu, Recent Advances in Non-Peptidomimetic Dipeptidyl Peptidase 4 Inhibitors: Medicinal Chemistry and Preclinical Aspects, *Curr. Med. Chem.*, 2012, **19**, 3982.

127 S. Kumar, A. Mittal and A. Mittal, A review upon medicinal perspective and designing rationale of DPP-4 inhibitors, *Bioorg. Med. Chem.*, 2021, **46**, 116354.

128 E. B. Villhauer, J. A. Brinkman, G. B. Naderi, B. F. Burkey, B. E. Dunning, K. Prasad, B. L. Mangold, M. E. Russell and T. E. Hughes, 1-[[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties, *J. Med. Chem.*, 2003, **46**, 2774.

129 D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins, P. Taunk, Q. Huang, S.-P. Han, B. Abboa-Offei, M. Cap, L. Xin, L. Tao, E. Tozzo, G. E. Welzel, D. M. Egan, J. Marcinkeviciene, S. Y. Chang, S. A. Biller, M. S. Kirby, R. A. Parker and L. G. Hamann, Discovery and Preclinical Profile of Saxagliptin (BMS-477118): A Highly Potent, Long-Acting, Orally Active Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes, *J. Med. Chem.*, 2005, **48**, 5025.

130 M. Nabeno, F. Akahoshi, H. Kishida, I. Miyaguchi, Y. Tanaka, S. Ishii and T. Kadowaki, A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site, *Biochem. Biophys. Res. Commun.*, 2013, **434**, 191.

131 T. E. Hughes, M. D. Mone, M. E. Russell, S. C. Weldon and E. B. Villhauer, NVP-DPP728 (1-[[[2-[(5-Cyanopyridin-2-yl) amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine), a Slow-Binding Inhibitor of Dipeptidyl Peptidase IV, *Biochemistry*, 1999, **38**, 11597.

132 M. Engel, T. Hoffmann, L. Wagner, M. Wermann, U. Heiser, R. Kiefersauer, R. Huber, W. Bode, H.-U. Demuth and H. Brandstetter, The crystal structure of dipeptidyl peptidase IV (CD26) reveals its functional regulation and enzymatic mechanism, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 5063.

133 D. Kim, L. Wang, M. Beconi, G. J. Eiermann, M. H. Fisher, H. He, G. J. Hickey, J. E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M. E. McCann, R. A. Patel, A. Petrov, G. Scapin, S. B. Patel, R. S. Roy, J. K. Wu, M. J. Wyvratt, B. B. Zhang, L. Zhu, N. A. Thornberry and A. E. Weber, (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes, *J. Med. Chem.*, 2005, **48**, 141.

134 J. Feng, Z. Zhang, M. B. Wallace, J. A. Stafford, S. W. Kaldor, D. B. Kassel, M. Navre, L. Shi, R. J. Skene, T. Asakawa, K. Takeuchi, R. Xu, D. R. Webb and S. L. N. Gwaltney, Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV, *J. Med. Chem.*, 2007, **50**, 2297.

135 Z. Zhang, M. B. Wallace, J. Feng, J. A. Stafford, R. J. Skene, L. Shi, B. Lee, K. Aertgeerts, A. Jennings, R. Xu, D. B. Kassel, S. W. Kaldor, M. Navre, D. R. Webb and S. L. Gwaltney, Design and synthesis of pyrimidinone and pyrimidinedione inhibitors of dipeptidyl peptidase IV, *J. Med. Chem.*, 2011, **54**, 510.

136 N. A. Meanwell, G. I. Georg and S. Wang, The 2020 Nobel Prize in Physiology or Medicine, *J. Med. Chem.*, 2020, **63**, 13197.

137 R. D'Ambrosio, E. Degasperi, M. Colombo and A. Aghemo, Direct-acting antivirals: the endgame for hepatitis C?, *Curr. Opin. Virol.*, 2017, **24**, 31.

138 J. A. McCauley and M. T. Rudd, Hepatitis C virus NS3/4a protease inhibitors, *Curr. Opin. Pharmacol.*, 2016, **30**, 84.

139 T. Pillaiyar, V. Namasivayam and M. Manickam, Macrocyclic Hepatitis C Virus NS3/4A Protease Inhibitors: An Overview of Medicinal Chemistry, *Curr. Med. Chem.*, 2016, **29**, 3404.

140 S. Venkatraman, S. L. Bogen, A. Arasappan, F. Bennett, K. Chen, E. Jao, Y. T. Liu, R. Lovey, S. Hendrata, Y. Huang, W. Pan, T. Parekh, P. Pinto, V. Popov, R. Pike, S. Ruan, B. Santhanam, B. Vibulbhan, W. Wu, W. Yang, J. Kong, X. Liang, J. Wong, R. Liu, N. Butkiewicz, R. Chase, A. Hart, S. Agrawal, P. Ingravallo, J. Pichardo, R. Kong, B. Baroudy, B. Malcolm, Z. Guo, A. Prongay, V. Madison, L. Broske, X. Cui,

K. C. Cheng, Y. Hsieh, J. M. Brisson, D. Prelusky, W. Korfmacher, R. White, S. Bogdanowich-Knipp, A. Pavlovsky, P. Bradley, A. K. Saksena, A. Ganguly, J. Piwinski, V. Girijavallabhan and F. G. Njoroge, Discovery of (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]- 3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]- 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide (SCH 503034), a selective, potent, orally bioavailable hepatitis C virus NS3 protease inhibitor: a potential therapeutic agent for the treatment of hepatitis C infection, *J. Med. Chem.*, 2006, **49**, 6074.

141 A. J. Prongay, Z. Guo, N. Yao, J. Pichardo, T. Fischmann, C. Strickland, J. J. Myers, P. C. Weber, B. M. Beyer, R. Ingram, Z. Hong, W. W. Prosise, L. Ramanathan, S. S. Taremi, T. Yarosh-Tomaine, R. Zhang, M. Senior, R. S. Yang, B. Malcolm, A. Arasappan, F. Bennett, S. L. Bogen, K. Chen, E. Jao, Y. T. Liu, R. G. Lovey, A. K. Saksena, S. Venkatraman, V. Girijavallabhan, F. G. Njoroge and V. Madison, Discovery of the HCV NS3/4A protease inhibitor (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3- [2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]- 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide (Sch 503034) II. Key steps in structure-based optimization, *J. Med. Chem.*, 2007, **50**, 2310.

142 A. Y. Howe and S. Venkatraman, The Discovery and Development of Boceprevir: A Novel, First-generation Inhibitor of the Hepatitis C Virus NS3/4A Serine Protease, *J. Clin. Transl. Hepatol.*, 2013, **1**, 22.

143 A. D. Kwong, R. S. Kauffman, P. Hurter and P. Mueller, Discovery and development of telaprevir: an NS3-4A protease inhibitor for treating genotype 1 chronic hepatitis C virus, *Nat. Biotechnol.*, 2011, **29**, 993.

144 M. Llinàs-Brunet, M. D. Bailey, G. Bolger, C. Brochu, A. M. Faucher, J. M. Ferland, M. Garneau, E. Ghiro, V. Gorys, C. Grand-Maître, T. Halmos, N. Lapeyre-Paquette, F. Liard, M. Poirier, M. Rhéaume, Y. S. Tsantrizos and D. Lamarre, Structure-activity study on a novel series of macrocyclic inhibitors of the hepatitis C virus NS3 protease leading to the discovery of BILN 2061, *J. Med. Chem.*, 2004, **47**, 1605.

145 D. Lamarre, P. C. Anderson, M. Bailey, P. Beaulieu, G. Bolger, P. Bonneau, M. Bös, D. R. Cameron, M. Cartier, M. G. Cordingley, A. M. Faucher, N. Goudreau, S. H. Kawai, G. Kukolj, L. Lagacé, S. R. LaPlante, H. Narjes, M. A. Poupart, J. Rancourt, R. E. Sentjens, R St George, R. B. Simoneau, G. Steinmann, D. Thibeault, Y. S. Tsantrizos, S. M. Weldon, C. L. Yong and M. Llinàs-Brunet, An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus, *Nature*, 2003, **426**, 186.

146 Å. Rosenquist, B. Samuelsson, P. O. Johansson, M. D. Cummings, O. Lenz, P. Raboisson, K. Simmen, S. Vendeville, H. de Kock, M. Nilsson, A. Horvath, R. Kalmeijer, G. de la Rosa and M. Beumont-Mauviel, Discovery and development of simeprevir (TMC435), a HCV NS3/4A protease inhibitor, *J. Med. Chem.*, 2014, **57**, 1673.

147 S. Harper, J. A. McCauley, M. T. Rudd, M. Ferrara, M. DiFilippo, B. Crescenzi, U. Koch, A. Petrocchi, M. K. Holloway, J. W. Butcher, J. J. Romano, K. J. Bush, K. F. Gilbert, C. J. McIntyre, K. T. Nguyen, E. Nizi, S. S. Carroll, S. W. Ludmerer, C. Burlein, J. M. DiMuzio, D. J. Graham, C. M. McHale, M. W. Stahlhut, D. B. Olsen, E. Monteagudo, S. Cianetti, C. Giuliano, V. Pucci, N. Trainor, C. M. Fandozzi, M. Rowley, P. J. Coleman, J. P. Vacca, V. Summa and N. J. Liverton, Discovery of MK-5172, a Macrocyclic Hepatitis C Virus NS3/4a Protease Inhibitor, *ACS Med. Chem. Lett.*, 2012, **3**, 332.

148 S. Coats, E. C. Garnier-Amblard, F. Amblard, M. Ehteshami, S. Amiralaei, H. Zhang, L. Zhou, S. R. Boucle, X. Lu, L. Bondada, J. R. Shelton, H. Li, P. Liu, C. Li, J. H. Cho, S. N. Chavre, S. Zhou, J. Mathew and R. F. Schinazi, Chutes and ladders in hepatitis C nucleoside drug development, *Antiviral Res.*, 2014, **102**, 119.

149 P. P. Glasziou, S. Sanders and T. Hoffmann, Waste in covid-19 research, *BMJ*, 2020, (369), m1847.

150 L. K. Boerner, The antivirals that weren't: drug repurposing for COVID-19 produced misleading results, *C&En*, 2021, vol. 99, (25), p. 7.

151 C. L. Bellera, M. Llanos, M. E. Gantner, S. Rodriguez, L. Gavernet, M. Comini and A. Talevi, Can drug repurposing strategies be the solution to the COVID-19 crisis?, *Expert Opin. Drug Discovery*, 2021, **16**, 605.

152 C. G. Begley, M. Ashton, J. Baell, M. Bettess, M. P. Brown, B. Carter, W. N. Charman, C. Davis, S. Fisher, I. Frazer, A. Gautam, M. P. Jennings, P. Kearney, E. Keeffe, D. Kelly, A. F. Lopez, M. McGuckin, M. W. Parker, C. Rayner, B. Roberts, J. S. Rush and M. Sullivan, Drug repurposing: Misconceptions, challenges, and opportunities for academic researchers, *Sci. Transl. Med.*, 2021, **61**, eabd5524.

153 M. M. Ghahremanpour, J. Tirado-Rives, M. Deshmukh, J. A. Ippolito, C. H. Zhang, I. Cabeza de Vaca, M. E. Liosi, K. S. Anderson and W. L. Jorgensen, Identification of 14 Known Drugs as Inhibitors of the Main Protease of SARS-CoV-2, *ACS Med. Chem. Lett.*, 2020, **11**, 2526.

154 C. H. Zhang, E. A. Stone, M. Deshmukh, J. A. Ippolito, M. M. Ghahremanpour, J. Tirado-Rives, K. A. Spasov, S. Zhang, Y. Takeo, S. N. Kudalkar, Z. Liang, F. Isaacs, B. Lindenbach, S. Miller, K. S. Anderson and W. L. Jorgensen, Potent Noncovalent Inhibitors of the Main Protease of SARS-CoV-2 from Molecular Sculpting of the Drug Perampanel Guided by Free Energy Perturbation Calculations, *ACS Cent. Sci.*, 2021, **7**, 467.

155 M. G. Deshmukh, J. A. Ippolito, C. H. Zhang, E. A. Stone, R. A. Reilly, S. J. Miller, W. L. Jorgensen and K. S. Anderson, Structure-guided design of a perampanel-derived pharmacophore targeting the SARS-CoV-2 main protease, *Structure*, 2021, **29**, 823.

156 C. H. Zhang, K. A. Spasov, R. A. Reilly, K. Hollander, E. A. Stone, J. A. Ippolito, M. E. Liosi, M. G. Deshmukh, J. Tirado-Rives, S. Zhang, Z. Liang, S. Miller, F. Isaacs, B. D. Lindenbach, K. S. Anderson and W. L. Jorgensen, Optimization of Triarylpyridinone Inhibitors of the Main Protease of SARS-CoV-2 to Low-Nanomolar Antiviral Potency, *ACS Med. Chem. Lett.*, 2021, **12**, 1325.

157 L. Jacobs, A. van der Westhuyzen, N. Pribut, D. Cui, M. P. D'Erasmo, P. W. Bartsch, K. Liu, M. C. Cox, S. J. Greenlund, R. K. Plemper, D. Mitchell, J. Marlow, M. K. Andrews, R. E. Krueger, Z. M. Sticher, A. A. Kolykhalov, M. G. Natchus, B. Zhou, S. C. Pelly and D. C. Liotta, Design and Optimization of Novel Competitive, Non-peptidic, SARS-CoV-2 Mpro Inhibitors, *ACS Med. Chem. Lett.*, 2023, **14**, 1434.

158 J. Jacobs, V. Grum-Tokars, Y. Zhou, M. Turlington, S. A. Saldanha, P. Chase, A. Eggler, E. S. Dawson, Y. M. Baez-Santos, S. Tomar, A. M. Mielech, S. C. Baker, C. W. Lindsley, P. Hodder, A. Mesecar and S. R. Stauffer, Discovery, synthesis, and structure-based optimization of a series of N-(tert-butyl)-2-(N-arylamido)-2-(pyridin-3-yl) acetamides (ML188) as potent noncovalent small molecule inhibitors of the severe acute respiratory syndrome coronavirus (SARS-CoV) 3CL protease, *J. Med. Chem.*, 2013, **56**, 534.

159 F. von Nussbaum and V. M. Li, Neutrophil elastase inhibitors for the treatment of (cardio)pulmonary diseases: Into clinical testing with pre-adaptive pharmacophores, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4370.

160 C. Fischer, N. A. Vepřek, Z. Peitsinis, K. P. Rühmann, C. Yang, J. N. Spradlin, D. Dovala, D. K. Nomura, Y. Zhang and D. Trauner, De novo Design of SARS-CoV-2 Main Protease Inhibitors, *Synlett*, 2021, **33**, 458.

161 A. Moussy, S. Tay, N. Drayman, G. Randal and S. Chen, The use of masitinib for the treatment of coronavirus disease 2019 (COVID-19), WO2021205029, 2021.

162 N. Drayman, J. K. DeMarco, K. A. Jones, S. A. Azizi, H. M. Froggatt, K. Tan, N. I. Maltseva, S. Chen, V. Nicolaescu, S. Dvorkin, K. Furlong, R. S. Kathayat, M. R. Firpo, V. Mastrodomenico, E. Bruce, M. M. Schmidt, R. Jedrzejczak, M. Á. Muñoz-Alía, B. Schuster, V. Nair, K. Y. Han, A. O'Brien, A. Tomatsidou, B. Meyer, M. Vignuzzi, D. Missiakas, J. W. Botten, C. B. Brooke, H. Lee, S. C. Baker, B. C. Mounce, N. S. Heaton, W. E. Severson, K. E. Palmer, B. C. Dickinson, A. Joachimiak, G. Randall and S. Tay, Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2, *Science*, 2021, **373**, 931.

163 K. Hammam, M. Saez-Ayala, E. Rebuffet, L. Gros, S. Lopez, B. Hajem, M. Humbert, E. Baudelet, S. Audebert, S. Betzi, A. Lugari, S. Combes, S. Letard, N. Casteran, C. Mansfield, A. Moussy, S. De Sepulveda, P. X. Morelli and P. Dubreuil, Dual protein kinase and nucleoside kinase modulators for rationally designed polypharmacology, *Nat. Commun.*, 2017, **8**, 1420.

164 J. Dyall, C. M. Coleman, B. J. Hart, T. Venkataraman, M. R. Holbrook, J. Kindrachuk, R. F. Johnson, G. G. J. Olinger, P. B. Jahrling, M. Laidlaw, L. M. Johansen, C. M. Lear-Rooney, P. J. Glass, L. E. Hensley and M. B. Frieman, Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection, *Antimicrob. Agents Chemother.*, 2014, **58**, 4885.

165 H. Zhao, M. Mendenhall and M. W. Deininger, Imatinib is not a potent anti-SARS-CoV-2 drug, *Leukemia*, 2020, **34**, 3085.

166 J. Loschwitz, A. Jäckering, M. Keutmann, M. Olagunju, R. J. Eberle, M. A. Coronado, O. O. Olubiyi and B. Strodel, Novel inhibitors of the main protease enzyme of SARS-CoV-2 identified via molecular dynamics simulation-guided in vitro assay, *Bioorg. Chem.*, 2021, **111**, 104862.

167 A. Sauvat, F. Ciccosanti, F. Colavita, R. Di Rienzo, M. C. Castilletti, M. R. Capobianchi, O. Kepp, L. Zitvogel, G. M. Fimia, M. Piacentini and G. Kroemer, On-target versus off-target effects of drugs inhibiting the replication of SARS-CoV-2, *Cell Death Dis.*, 2020, **11**, 656.

168 T. A. Tummino, V. V. Rezelj, B. Fischer, A. Fischer, M. J. O'Meara, B. Monel, T. Vallet, K. M. White, Z. Zhang, A. Alon, H. Schadt, H. R. O'Donnell, J. Lyu, R. Rosales, B. L. McGovern, R. Rathnasinghe, S. Jangra, M. Schotsaert, J. R. Galarneau, N. J. Krogan, L. Urban, K. M. Shokat, A. Kruse, A. García-Sastre, O. Schwartz, F. Moretti, M. Vignuzzi, F. Pognan and B. K. Shoichet, Drug-induced phospholipidosis confounds drug repurposing for SARS-CoV-2, *Science*, 2021, **373**, 541.

169 E. J. Fritch, A. L. Mordant, T. S. K. Gilbert, C. I. Wells, X. Yang, N. K. Barker, E. A. Madden, K. H. R. Dinnon, Y. J. Hou, L. V. Tse, I. N. Castillo, A. C. Sims, N. J. Moorman, P. Lakshmanane, T. M. Willson, L. E. Herring, L. M. Graves and R. S. Baric, Investigation of the Host Kinome Response to Coronavirus Infection Reveals PI3K/mTOR Inhibitors as Betacoronavirus Antivirals, *J. Proteome Res.*, 2023, **22**, 3159.

170 H. Munier-Lehmann, P.-O. Vidalain, F. Tangy and Y. L. Janin, On dihydroorotate dehydrogenases, their inhibitors and uses, *J. Med. Chem.*, 2013, **56**, 3148.

171 M. Wang, Y. Zhao, W. Hu, D. Zhao, Y. Zhang, T. Wang, Z. Zheng, X. Li, S. Zeng, Z. Liu, L. Lu, Z. Wan and K. Hu, Treatment of Coronavirus Disease 2019 Patients With Prolonged Postsymptomatic Viral Shedding With Leflunomide: A Single-center Randomized Controlled Clinical Trial, *Clin. Infect. Dis.*, 2021, **73**, e4012.

172 M. J. G. T. Vehreschild, P. Atanasov, K. Yurko, C. Oancea, G. Popov, V. Smesnoi, G. Placinta, H. Kohlhof, D. Vitt, E. Peelen, J. Mihajlović and A. R. Muehler, Safety and Efficacy of Vidofludimus Calcium in Patients Hospitalized with COVID-19: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Trial, *Infect. Dis. Ther.*, 2022, **6**, 2159.

173 I. Kralj-Hans, K. Li, A. Wesek, A. Lamorgese, F. Omar, K. Ranasinghe, M. McGee, K. Brack, S. Li, R. Aggarwal, A. Bulle, A. Kodre, S. Sharma, D. Fluck, I. John, P. Sharma, J. D. Belsey, L. Li, S. R. K. Seshasai, H. L. Li, N. Marczin, Z. Chen and DEFEAT-COVID Investigators, Leflunomide treatment for patients hospitalised with COVID-19: DEFEAT-COVID randomised controlled trial, *BMJ Open*, 2023, **13**, e068179.

174 C. J. Wu, J. T. Jan, C. M. Chen, H. P. Hsieh, D. R. Hwang, H. W. Liu, C. Y. Liu, H. W. Huang, S. C. Chen, C. F. Hong, R. K. Lin, Y. S. Chao and J. T. A. Hsu, Inhibition of Severe Acute Respiratory Syndrome Coronavirus Replication by Niclosamide, *Antimicrob. Agents Chemother.*, 2004, **48**, 2693.

175 J. Xu, P. Y. Shi, H. Li and J. Zhou, Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential, *ACS Infect. Dis.*, 2020, **8**, 909.

176 S. Jeon, M. Ko, J. Lee, I. Choi, S. Y. Byun, S. Park, D. Shum and S. Kim, Identification of Antiviral Drug Candidates against SARS-CoV-2 from FDA-Approved Drugs, *Antimicrob. Agents Chemother.*, 2020, **64**, e00819.

177 K. Shamim, M. Xu, X. Hu, E. M. Lee, X. Lu, R. Huang, P. Shah, X. Xu, C. Z. Chen, M. Shen, H. Guo, L. Chen, Z. Itkin, R. T. Eastman, P. Shinn, C. Klumpp-Thomas, S. Michael, A. Simeonov, D. C. Lo, G. L. Ming, H. Song, H. Tang, W. Zheng and W. Huang, Application of niclosamide and analogs as small molecule inhibitors of Zika virus and SARS-CoV-2 infection, *Bioorg. Med. Chem. Lett.*, 2021, **40**, 127906.

178 V. Backer, U. Sjöbring, J. Sonne, A. Weiss, M. Hostrup, H. K. Johansen, V. Becker, D. P. Sonne, T. Balchen, M. Jellingsø and M. O. A. Sommer, A randomized, double-blind, placebo-controlled phase 1 trial of inhaled and intranasal niclosamide: A broad spectrum antiviral candidate for treatment of COVID-19, *Lancet Reg. Health Eur.*, 2021, 100084.

179 D. M. Cairns, D. Dulko, J. K. Griffiths, Y. Golan, T. Cohen, L. Trinquart, L. L. Price, K. R. Beaulac and H. P. Selker, Efficacy of Niclosamide vs Placebo in SARS-CoV-2 Respiratory Viral Clearance, Viral Shedding, and Duration of Symptoms Among Patients With Mild to Moderate COVID-19: A Phase 2 Randomized Clinical Trial, *JAMA Netw. Open*, 2022, **5**(2), e2144942.

180 L. Braga, H. Ali, I. Secco, E. Chiavacci, G. Neves, D. Goldhill, R. Penn, J. M. Jimenez-Guardeño, A. M. Ortega-Prieto, R. Bussani, A. Cannatà, G. Rizzari, C. Collesi, E. Schneider, D. Arosio, A. M. Shah, W. S. Barclay, M. H. Malim, J. Burrone and M. Giacca, Drugs that inhibit TMEM16 proteins block SARS-CoV-2 Spike-induced syncytia, *Nature*, 2021, **594**, 88.

181 J. J. Shie, J. M. Fang, C. J. Kuo, T. H. Kuo, P. H. Liang, H. J. Huang, W. B. Yang, C. H. Lin, J. L. Chen, Y. T. Wu and C. H. Wong, Discovery of potent anilide inhibitors against the severe acute respiratory syndrome 3CL protease, *J. Med. Chem.*, 2005, **48**, 4469.

182 S. K. Samrat, J. Xu, X. Xie, E. Gianti, H. Chen, J. Zou, J. G. Pattis, K. Elokely, H. Lee, Z. Li, M. L. Klein, P. Y. Shi, J. Zhou and H. Li, Allosteric inhibitors of the main protease of SARS-CoV-2, *Antiviral Res.*, 2022, 105381.

183 C. Yanyan, Y. Jimbo, W. Zhuoya, Z. Chenyang, Y. Rilei, L. Li and Y. Menglin, Application of closantel or its pharmaceutically acceptable salt in preparation of medicine for preventing and/or treating coronavirus infection, CN112294793, 2020.

184 B. Tan, M. Sacco, H. Tan, K. Li, R. Joyce, X. Zhang, Y. Chen and J. Wang, Exploring diverse reactive warheads for the design of SARS-CoV-2 main protease inhibitors, *Eur. J. Med. Chem.*, 2023, **259**, 115667.

185 M. D. Sacco, C. Ma, P. Lagarias, A. Gao, J. A. Townsend, X. Meng, P. Dube, X. Zhang, Y. Hu, N. Kitamura, B. Hurst, B. Tarbet, M. T. Marty, A. Kolocouris, Y. Xiang, Y. Chen and J. Wang, Structure and inhibition of the SARS-CoV-2 main protease reveal strategy for developing dual inhibitors against Mpro and cathepsin L, *Sci. Adv.*, 2020, **6**, eabe0751.

186 L. Fu, F. Ye, Y. Feng, F. Yu, Q. Wang, Y. Wu, C. Zhao, H. Sun, B. Huang, P. Niu, H. Song, Y. Shi, X. Li, W. Tan, J. Qi and G. F. Gao, Both Boceprevir and GC376 efficaciously inhibit SARS-CoV-2 by targeting its main protease, *Nat. Commun.*, 2020, **11**, 4417.

187 C. Ma, M. D. Sacco, B. Hurst, J. A. Townsend, Y. Hu, T. Szeto, X. Zhang, B. Tarbet, M. T. Marty, Y. Chen and J. Wang, Boceprevir, GC-376, and calpain inhibitors II, XII inhibit SARS-CoV-2 viral replication by targeting the viral main protease, *Cell Res.*, 2020, **30**, 678.

188 A. D. Rathnayake, J. Zheng, Y. Kim, K. D. Perera, S. Mackin, D. K. Meyerholz, M. M. Kashipathy, K. P. Battaile, S. Lovell, S. Perlman, W. C. Groutas and K. O. Chang, 3C-like protease inhibitors block coronavirus replication in vitro and improve survival in MERS-CoV-infected mice, *Sci. Transl. Med.*, 2020, **12**, eabc5332.

189 W. Dai, B. Zhang, X. M. Jiang, H. Su, J. Li, Y. Zhao, X. Xie, Z. Jin, J. Peng, F. Liu, C. Li, Y. Li, F. Bai, H. Wang, X. Cheng, X. Cen, S. Hu, X. Yang, J. Wang, X. Liu, G. Xiao, H. Jiang, Z. Rao, L. K. Zhang, Y. Xu, H. Yang and H. Liu, Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease, *Science*, 2020, **368**, 1331.

190 H. C. Hung, Y. Y. Ke, S. Y. Huang, P. N. Huang, Y. A. Kung, T. Y. Chang, K. J. Yen, T. T. Peng, S. E. Chang, C. T. Huang, Y. R. Tsai, S. H. Wu, S. J. Lee, J. H. Lin, B. S. Liu, W. C. Sung, S. R. Shih, C. T. Chen and J. T. Hsu, Discovery of M Protease Inhibitors Encoded by SARS-CoV-2, *Antimicrob. Agents Chemother.*, 2020, **64**, e00872.

191 Y. C. Wang, W. H. Yang, C. S. Yang, M. H. Hou, C. L. Tsai, Y. Z. Chou, M. C. Hung and Y. Chen, Structural basis of SARS-CoV-2 main protease inhibition by a broad-spectrum anti-coronaviral drug, *Am. J. Cancer Res.*, 2020, **10**, 2535.

192 W. Vuong, M. B. Khan, C. Fischer, E. Arutyunova, T. Lamer, J. Shields, H. A. Saffran, R. T. McKay, M. J. van Belkum, M. A. Joyce, H. S. Young, D. L. Tyrrell, J. C. Vederas and M. J. Lemieux, Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication, *Nat. Commun.*, 2020, **27**, 4282.

193 S. Vankadara, Y. X. Wong, B. Liu, Y. Y. See, L. H. Tan, Q. W. Tan, G. Wang, R. Karuna, X. Guo, S. T. Tan, J. Y. Fong, J. Joy and C. S. B. Chia, A head-to-head comparison of the inhibitory activities of 15 peptidomimetic SARS-CoV-2 3CLpro inhibitors, *Bioorg. Med. Chem. Lett.*, 2021, **48**, 128263.

194 S. Iketani, F. Forouhar, H. Liu, S. J. Hong, F. Y. Lin, M. S. Nair, A. Zask, Y. Huang, L. Xing, B. R. Stockwell, A. Chavez and D. D. Ho, Lead compounds for the development of SARS-CoV-2 3CL protease inhibitors, *Nat. Commun.*, 2021, **12**, 2016.

195 C. S. Dampalla, A. D. Rathnayake, K. D. Perera, A. M. Jesri, H. N. Nguyen, M. J. Miller, H. A. Thurman, J. Zheng, M. M.

Kashipathy, K. P. Battaile, S. Lovell, S. Perlman, Y. Kim, W. C. Groutas and K. O. Chang, Structure-Guided Design of Potent Inhibitors of SARS-CoV-2 3CL Protease: Structural, Biochemical, and Cell-Based Studies, *J. Med. Chem.*, 2021, **64**, 17846.

196 S. Chamakuri, S. Lu, M. N. Ucisik, K. M. Bohren, Y. C. Chen, H. C. Du, J. C. Faver, R. Jimmidi, F. Li, J. Y. Li, P. Nyshadham, S. S. Palmer, J. Pollet, X. Qin, S. E. Ronca, B. Sankaran, K. L. Sharma, Z. Tan, L. Versteeg, Z. Yu, M. M. Matzuk, T. Palzkill and D. W. Young, DNA-encoded chemistry technology yields expedient access to SARS-CoV-2 Mpro inhibitors, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2111172118.

197 J. Qiao, Y. S. Li, R. Zeng, F. L. Liu, R. H. Luo, C. Huang, Y. F. Wang, J. Zhang, B. Quan, C. Shen, X. Mao, X. Liu, W. Sun, W. Yang, X. Ni, K. Wang, L. Xu, Z. L. Duan, Q. C. Zou, H. L. Zhang, W. Qu, Y. H. Long, M. H. Li, R. C. Yang, X. Liu, J. You, Y. Zhou, R. Yao, W. P. Li, J. M. Liu, P. Chen, Y. Liu, G. F. Lin, X. Yang, J. Zou, L. Li, Y. Hu, G. W. Lu, W. M. Li, Y. Q. Wei, Y. T. Zheng, J. Lei and S. Yang, SARS-CoV-2 Mpro inhibitors with antiviral activity in a transgenic mouse model, *Science*, 2021, **371**, 1374.

198 C. S. Dampalla, J. Zheng, K. D. Perera, L. R. Wong, D. K. Meyerholz, H. N. Nguyen, M. M. Kashipathy, K. P. Battaile, S. Lovell, Y. Kim, S. Perlman, W. C. Groutas and K. O. Chang, Postinfection treatment with a protease inhibitor increases survival of mice with a fatal SARS-CoV-2 infection, *Proc. Natl. Acad. Sci. U. S. A.*, 2021, **118**, e2101555118.

199 C. S. Dampalla, Y. Kim, N. Bickmeier, A. D. Rathnayake, H. N. Nguyen, J. Zheng, M. M. Kashipathy, M. A. Baird, K. P. Battaile, S. Lovell, S. Perlman, K. O. Chang and W. C. Groutas, Structure-Guided Design of Conformationally Constrained Cyclohexane Inhibitors of Severe Acute Respiratory Syndrome Coronavirus-2 3CL Protease, *J. Med. Chem.*, 2021, **64**, 10047.

200 Z. Xia, M. Sacco, Y. Hu, C. Ma, X. Meng, F. Zhang, T. Szeto, Y. Xiang, Y. Chen and J. Wang, Rational Design of Hybrid SARS-CoV-2 Main Protease Inhibitors Guided by the Superimposed Cocrystal Structures with the Peptidomimetic Inhibitors GC-376, Telaprevir, and Boceprevir, *ACS Pharmacol. Transl. Sci.*, 2021, **4**, 1048.

201 C. S. Dampalla, A. D. Rathnayake, A. C. Galasiti Kankanamalage, Y. Kim, K. D. Perera, H. N. Nguyen, M. J. Miller, T. K. Madden, H. R. Picard, H. A. Thurman, M. M. Kashipathy, L. Liu, K. P. Battaile, S. Lovell, K. O. Chang and W. C. Groutas, Structure-Guided Design of Potent Spirocyclic Inhibitors of Severe Acute Respiratory Syndrome Coronavirus-2 3C-like Protease, *J. Med. Chem.*, 2022, **65**, 7818.

202 H. Wang, R. Pei, X. Li, W. Deng, S. Xing, Y. Zhang, C. Zhang, S. He, H. Sun, S. Xiao, J. Xiong, Y. Zhang, X. Chen, Y. Wang, Y. Guo, B. Zhang and L. Shang, The structure-based design of peptidomimetic inhibitors against SARS-CoV-2 3C like protease as Potent anti-viral drug candidate, *Eur. J. Med. Chem.*, 2022, **238**, 114458.

203 P. S. Dragovich, R. Zhou, S. E. Webber, T. J. Prins, A. K. Kwok, K. Okano, S. A. Fuhrman, L. S. Zalman, F. C. Maldonado, E. L. Brown, J. W. R. Meador, A. K. Patick, C. E. Ford, M. A. Brothers, S. L. Binford, D. A. Matthews, R. A. Ferre and S. T. Worland, Structure-based design of ketone-containing, tripeptidyl human rhinovirus 3C protease inhibitors, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 45.

204 M. A. T. van de Plassche, M. Barniol-Xicota and S. H. L. Verhelst, Peptidyl Acyloxymethyl Ketones as Activity-Based Probes for the Main Protease of SARS-CoV-2, *ChemBioChem*, 2020, **21**, 3383.

205 R. L. Hoffman, R. S. Kania, M. A. Brothers, J. F. Davies, R. A. Ferre, K. S. Gajiwala, M. He, R. J. Hogan, K. Kozminski, L. Y. Li, J. W. Lockner, J. Lou, M. T. Marra, L. J. J. Mitchell, B. W. Murray, J. A. Nieman, S. Noell, S. P. Planken, T. Rowe, K. Ryan, G. J. R. Smith, J. E. Solowiej, C. M. Steppan and B. Taggart, Discovery of Ketone-Based Covalent Inhibitors of Coronavirus 3CL Proteases for the Potential Therapeutic Treatment of COVID-19, *J. Med. Chem.*, 2020, **63**, 12725.

206 S. I. Hattori, N. Higashi-Kuwata, H. Hayashi, S. R. Allu, J. Raghavaiah, H. Bulut, D. Das, B. J. Anson, E. K. Lendy, Y. Takamatsu, N. Takamune, N. Kishimoto, K. Murayama, K. Hasegawa, M. Li, D. A. Davis, E. N. Kodama, R. Yarchoan, A. Wlodawer, S. Misumi, A. D. Mesecar, A. K. Ghosh and H. Mitsuya, A small molecule compound with an indole moiety inhibits the main protease of SARS-CoV-2 and blocks virus replication, *Nat. Commun.*, 2021, **12**, 668.

207 B. Boras, R. M. Jones, B. J. Anson, D. Arenson, L. Aschenbrenner, M. A. Bakowski, N. Beutler, J. Binder, E. Chen, H. Eng, H. Hammond, J. Hammond, R. E. Haupt, R. Hoffman, E. P. Kadar, R. Kania, E. Kimoto, M. G. Kirkpatrick, L. Lanyon, E. K. Lendy, J. R. Lillis, J. Logue, S. A. Luthra, C. Ma, S. W. Mason, M. E. McGrath, S. Noell, R. S. Obach, M. N. O'Brien, R. O'Connor, K. Ogilvie, D. Owen, M. Pettersson, M. R. Reese, T. F. Rogers, R. Rosales, M. I. Rossulek, J. G. Sathish, N. Shirai, C. Steppan, M. Ticehurst, L. W. Updyke, S. Weston, Y. Zhu, K. M. White, A. García-Sastre, J. Wang, A. K. Chatterjee, A. D. Mesecar, M. B. Frieman, A. S. Anderson, C. Allerton and C. Allerton, Preclinical characterization of an intravenous coronavirus 3CL protease inhibitor for the potential treatment of COVID19, *Nat. Commun.*, 2021, **12**, 6055.

208 M. A. Redhead, C. D. Owen, L. Brewitz, A. H. Collette, P. Lukacik, C. Strain-Damerell, S. W. Robinson, P. M. Collins, P. Schäfer, M. Swindells, C. J. Radoux, I. N. Hopkins, D. Fearon, A. Douangamath, F. von Delft, T. R. Malla, L. Vangeel, T. Vercruysse, J. Thibaut, P. Leyssen, T. T. Nguyen, M. Hull, A. Tumber, D. J. Hallett, C. J. Schofield, D. I. Stuart, A. L. Hopkins and M. A. Walsh, Bispecific repurposed medicines targeting the viral and immunological arms of COVID-19, *Sci. Rep.*, 2021, **11**, 13208.

209 B. Bai, A. Belovodskiy, M. Hena, A. S. Kandadai, M. A. Joyce, H. A. Saffran, J. Shields, M. Khan, E. Arutyunova, J. Lu, S. K. Bajwa, D. Hockman, C. Fischer, T. Lamer, W. Vuong, M. J. van Belkum, Z. Gu, F. Lin, Y. Du, J. Xu, M. Rahim, H. S. Young, J. Vederas, D. L. Tyrrell, M. J. Lemieux

and J. A. Nieman, Peptidomimetic α-Acyloxymethylketone Warheads with Six-Membered Lactam P1 Glutamine Mimic: SARS-CoV-2 3CL Protease Inhibition, Coronavirus Antiviral Activity, and in Vitro Biological Stability, *J. Med. Chem.*, 2022, **65**, 2905.

210 S. Konno, K. Kobayashi, M. Senda, Y. Funai, Y. Seki, I. Tamai, L. Schäkel, K. Sakata, T. Pillaiyar, A. Taguchi, A. Taniguchi, M. Gütschow, C. E. Müller, K. Takeuchi, M. Hirohama, A. Kawaguchi, M. Kojima, T. Senda, Y. Shirasaka, W. Kamitani and Y. Hayashi, 3CL Protease Inhibitors with an Electrophilic Arylketone Moiety as Anti-SARS-CoV-2 Agents, *J. Med. Chem.*, 2022, **65**, 2926.

211 H. Liu, S. Iketani, A. Zask, N. Khanizeman, E. Bednarova, F. Forouhar, B. Fowler, S. J. Hong, H. Mohri, M. S. Nair, Y. Huang, N. E. S. Tay, S. Lee, C. Karan, S. J. Resnick, C. Quinn, W. Li, H. Shion, X. Xia, J. D. Daniels, M. Bartolo-Cruz, M. Farina, P. Rajbhandari, C. Jurtschenko, M. A. Lauber, T. McDonald, M. E. Stokes, B. L. Hurst, T. Rovis, A. Chavez, D. D. Ho and B. R. Stockwell, Development of optimized drug-like small molecule inhibitors of the SARS-CoV-2 3CL protease for treatment of COVID-19, *Nat. Commun.*, 2022, **13**, 1891.

212 L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox and R. Hilgenfeld, Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors, *Science*, 2020, **368**, 409.

213 L. Zhang, D. Lin, Y. Kusov, Y. Nian, Q. Ma, J. Wang, A. von Brunn, P. Leyssen, K. Lanko, J. Neyts, A. de Wilde, E. J. Snijder, H. Liu and R. Hilgenfeld, α-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment, *J. Med. Chem.*, 2020, **63**, 4562.

214 M. S. Cooper, L. Zhang, M. Ibrahim, K. Zhang, X. Sun, J. Röske, M. Göhl, M. Brönstrup, J. K. Cowell, L. Sauerhering, S. Becker, L. Vangeel, D. Jochmans, J. Neyts, K. Rox, G. P. Marsh, H. J. Maple and R. Hilgenfeld, Diastereomeric Resolution Yields Highly Potent Inhibitor of SARS-CoV-2 Main Protease, *J. Med. Chem.*, 2022, **65**, 13328.

215 P. S. Dragovich, S. E. Webber, R. E. Babine, S. A. Fuhrman, A. K. Patick, D. A. Matthews, C. A. Lee, S. H. Reich, T. J. Prins, J. T. Marakovits, E. S. Littlefield, R. Zhou, J. Tikhe, C. E. Ford, M. B. Wallace, J. W. R. Meador, R. A. Ferre, E. L. Brown, S. L. Binford, J. E. Harr, D. M. DeLisle and S. T. Worland, Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 1. Michael acceptor structure-activity studies, *J. Med. Chem.*, 1998, **41**, 2806.

216 P. Li, B. Yang, F. Hao, P. Wang, H. He, L. Huang, X. Zhang, S. Zhang, X. Peng, K. Yin, J. Hu, X. Chen, Z. Gu, L. Wang, L. Shen, G. Hu, N. Li, J. Li, S. Chen, W. Xiao, Z. Wang, Q. Guo, X. Chang, L. Zhang, Q. Cai and T. Lin, Design, synthesis, and biological evaluation of anti-EV71 agents, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3346.

217 Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L. W. Guddat, W. Xu, G. Xiao, C. Qin, Z. Shi, H. Jiang, Z. Rao and H. Yang, Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors, *Nature*, 2020, **582**, 289.

218 G. J. Lockbaum, M. Henes, J. M. Lee, J. Timm, E. A. Nalivaika, P. R. Thompson, N. Kurt Yilmaz and C. A. Schiffer, Pan-3C Protease Inhibitor Rupintrivir Binds SARS-CoV-2 Main Protease in a Unique Binding Mode, *Biochemistry*, 2021, **60**, 2925.

219 Y. Ma, C. Shang, P. Yang, L. Li, Y. Zhai, Z. Yin, B. Wang and L. Shang, 4-Iminooxazolidin-2-one as a Bioisostere of the Cyanohydrin Moiety: Inhibitors of Enterovirus 71 3C Protease, *J. Med. Chem.*, 2018, **61**, 10333.

220 W. Zhu, M. Xu, C. Z. Chen, H. Guo, M. Shen, X. Hu, P. Shinn, C. Klumpp-Thomas, S. G. Michael and W. Zheng, Identification of SARS-CoV-2 3CL Protease Inhibitors by a Quantitative High-Throughput Screening, *ACS Pharmacol. Transl. Sci.*, 2020, **3**, 1008.

221 C. Ma, Z. Xia, M. D. Sacco, Y. Hu, J. A. Townsend, X. Meng, J. Choza, H. Tan, J. Jang, M. V. Gongora, X. Zhang, F. Zhang, Y. Xiang, M. T. Marty, Y. Chen and J. Wang, Discovery of Di- and Trihaloacetamides as Covalent SARS-CoV-2 Main Protease Inhibitors with High Target Specificity, *J. Am. Chem. Soc.*, 2021, **143**, 20697.

222 J. C. Milligan, T. U. Zeisner, G. Papageorgiou, D. Joshi, C. Soudy, R. Ulferts, M. Wu, C. T. Lim, K. W. Tan, F. Weissmann, B. Canal, R. Fulisawa, T. Deegan, H. Nagara, G. Bineva-Todd, C. Basier, J. F. Curran, M. H. Howell, R. Beale, K. Labib, N. O'Reilly and J. F. X. Diffley, Identifying SARS-CoV-2 Antiviral Compounds by Screening for Small Molecule Inhibitors of nsp5 Main Protease, *Biochem. J.*, 2021, **478**, 2499.

223 Y. Hirose, N. Shindo, M. Mori, S. Onitsuka, H. Isogai, R. Hamada, T. Hiramoto, J. Ochi, D. Takahashi, T. Ueda, J. M. M. Caaveiro, Y. Yoshida, S. Ohdo, N. Matsunaga, S. Toba, M. Sasaki, Y. Orba, H. Sawa, A. Sato, E. Kawanishi and A. Ojida, Discovery of Chlorofluoroacetamide-Based Covalent Inhibitors for Severe Acute Respiratory Syndrome Coronavirus 2 3CL Protease, *J. Med. Chem.*, 2022, **65**, 13852.

224 J. Chen, C. Liang, K. Miao, Y. Wu, H. Yun and W. Zhang, Aminocarbamoyl compounds for the treatment of viral infections, WO2022043374, 2022.

225 T. R. Malla, A. Tumber, T. John, L. Brewitz, C. Strain-Damerell, C. D. Owen, P. Lukacik, H. T. H. Chan, P. Maheswaran, E. Salah, F. Duarte, H. Yang, Z. Rao, M. A. Walsh and C. J. Schofield, Mass spectrometry reveals potential of β-lactams as SARS-CoV-2 Mpro inhibitors, *Chem. Commun.*, 2021, **57**, 1430.

226 T. R. Malla, L. Brewitz, D. G. Muntean, H. Aslam, C. D. Owen, E. Salah, A. Tumber, P. Lukacik, C. Strain-Damerell, H. Mikolajek, M. A. Walsh and C. J. Schofield, Penicillin Derivatives Inhibit the SARS-CoV-2 Main Protease by Reaction with Its Nucleophilic Cysteine, *J. Med. Chem.*, 2022, **65**, 7682.

227 E. J. Niesor, G. Boivin, E. Rhéaume, R. Shi, V. Lavoie, N. Goyette, M. E. Picard, A. Perez, F. Laghrissi-Thode and J. C. Tardif, Inhibition of the 3CL Protease and SARS-CoV-2 Replication by Dalcetrapib, *ACS Omega*, 2021, **6**, 16584.

228 P. Ren, H. Li, T. Nie, X. Jian, C. Yu, J. Li, H. Su, X. Zhang, S. Li, X. Yang, C. Peng, Y. Yin, L. Zhang, Y. Xu, H. Liu and F. Bai, Discovery and Mechanism Study of SARS-CoV-2 3C-like Protease Inhibitors with a New Reactive Group, *J. Med. Chem.*, 2023, **66**, 12266.

229 K. Vandyck, P. J. M. B. Raboisson, L. Beigelman, V. Serebryany, A. D. Stoycheva, D. A. M.-E. Bardiot, S. Boland and A. D. M. Marchand, Anti-viral compounds for treating coronavirus, picornavirus, and norovirus infections, WO2021252491, 2021.

230 B. Bai, E. Arutyunova, M. Khan, J. Lu, M. A. Joyce, H. A. Saffran, J. A. Shields, A. S. Kandadai, A. Belovodskiy, M. Hena, W. Vuong, T. Lamer, H. S. Young, J. C. Vederas, D. L. Tyrrell, M. J. Lemieux and J. A. Nieman, Peptidomimetic nitrile warheads as SARS-CoV-2 3CL protease inhibitors, *RSC Med. Chem.*, 2021, **12**, 1722.

231 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. Kalgutkar, 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, L. Wei, Q. Yang and Y. Zhu, An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19, *Science*, 2021, **374**, 1586.

232 L. Brewitz, L. Dumjahn, Y. Zhao, C. D. Owen, S. M. Laidlaw, T. R. Malla, D. Nguyen, P. Lukacik, E. Salah, A. D. Crawshaw, A. J. Warren, J. Trincao, C. Strain-Damerell, M. W. Carroll, M. A. Walsh and C. J. Schofield, Alkyne Derivatives of SARS-CoV-2 Main Protease Inhibitors Including Nirmatrelvir Inhibit by Reacting Covalently with the Nucleophilic Cysteine, *J. Med. Chem.*, 2023, **66**, 2663.

233 C. Ngo, W. Fried, S. Aliyari, J. Feng, C. Qin, S. Zhang, H. Yang, J. Shanaa, P. Feng, G. Cheng, X. S. Chen and C. Zhang, Alkyne as a Latent Warhead to Covalently Target SARS-CoV-2 Main Protease, *J. Med. Chem.*, 2023, **66**, 12237.

234 E. Freire, R. Ottenbrite, Y. Xiao, A. Velazquez-Campoy, S. Leavitt, U. Bacha and J. Barrila, Inhibitors of coronavirus protease and methods of use thereof, WO2005041904, 2005.

235 R. Smoum, A. Rubinstein, V. M. Dembitsky and M. Srebnik, Boron containing compounds as protease inhibitors, *Chem. Rev.*, 2012, **112**, 4156.

236 S. Song, P. Gao, L. Sun, D. Kang, J. Kongsted, V. Poongavanam, P. Zhan and X. Liu, Recent developments in the medicinal chemistry of single boron atom-containing compounds, *Acta Pharm. Sin. B*, 2021, **11**, 3035.

237 A. K. Patick, S. L. Binford, M. A. Brothers, R. L. Jackson, C. E. Ford, M. D. Diem, F. Maldonado, P. S. Dragovich, R. Zhou, T. J. Prins, S. A. Fuhrman, J. W. Meador, L. Zalman, D. A. Matthews and S. T. Worland, In vitro antiviral activity of AG7088, a potent inhibitor of human rhinovirus 3C protease, *Antimicrob. Agents Chemother.*, 1999, **43**, 2444.

238 P. S. Dragovich, T. J. Prins, R. Zhou, S. E. Webber, J. T. Marakovits, S. A. Fuhrman, A. K. Patick, D. A. Matthews, C. A. Lee, C. E. Ford, B. J. Burke, P. A. Rejto, T. F. Hendrickson, T. Tuntland, E. L. Brown, J. W. R. Meador, R. A. Ferre, J. E. Harr, M. B. Kosa and S. T. Worland, Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 4. Incorporation of P1 lactam moieties as L-glutamine replacements, *J. Med. Chem.*, 1999, **42**, 1213.

239 K. Anand, J. Ziebuhr, P. Wadhwani, J. R. Mesters and R. Hilgenfeld, Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs, *Science*, 2003, **300**, 1763.

240 P. H. Hsyu, Y. K. Pithavala, M. Gersten, C. A. Penning and B. M. Kerr, Pharmacokinetics and safety of an antirhinoviral agent, ruprintrivir, in healthy volunteers, *Antimicrob. Agents Chemother.*, 2002, **46**, 392.

241 F. G. Hayden, R. B. Turner, J. M. Gwaltney, K. Chi-Burris, M. Gersten, P. Hsyu, A. K. Patick, G. J. R. Smith and L. S. Zalman, Phase II, randomized, double-blind, placebo-controlled studies of ruprintrivir nasal spray 2-percent suspension for prevention and treatment of experimentally induced rhinovirus colds in healthy volunteers, *Antimicrob. Agents Chemother.*, 2003, **47**, 3907.

242 A. K. Patick, Rhinovirus chemotherapy, *Antiviral Res.*, 2006, **71**, 391.

243 J. J. Shie, J. M. Fang, T. H. Kuo, C. J. Kuo, P. H. Liang, H. J. Huang, Y. T. Wu, J. T. Jan, Y. S. Cheng and C. H. Wong, Inhibition of the severe acute respiratory syndrome 3CL protease by peptidomimetic alpha,beta-unsaturated esters, *Bioorg. Med. Chem.*, 2005, **13**, 5240.

244 S. Tomar, M. L. Johnston, S. E. St John, H. L. Osswald, P. R. Nyalapatla, L. N. Paul, A. K. Ghosh, M. R. Denison and A. D. Mesecar, Ligand-induced Dimerization of Middle East Respiratory Syndrome (MERS) Coronavirus nsp5 Protease (3CLpro), *J. Biol. Chem.*, 2015, **290**, 19403.

245 H. Yang, W. Xie, X. Xue, K. Yang, J. Ma, W. Liang, Q. Zhao, Z. Zhou, D. Pei, J. Ziebuhr, R. Hilgenfeld, K. Y. Yuen, L. Wong, G. Gao, S. Chen, Z. Chen, D. Ma, M. Bartlam and Z. Rao, Design of wide-spectrum inhibitors targeting coronavirus main proteases, *PLoS Biol.*, 2005, **3**, e324.

246 K. Akaji, H. Konno, H. Mitsui, K. Teruya, Y. Shimamoto, Y. Hattori, T. Ozaki, M. Kusunoki and A. Sanjoh, Structure-Based Design, Synthesis, and Evaluation of Peptide-Mimetic SARS 3CL Protease Inhibitors, *J. Med. Chem.*, 2011, **54**, 7962.

247 S. Di Micco, R. Rahimova, M. Sala, M. C. Scala, G. Vivenzio, S. Musella, G. Andrei, K. Remans, L. Mammri, R. Snoeck, G. Bifulco, F. Di Matteo, V. Vestuto, P. Campiglia, J. A. Márquez and A. Fasano, Rational design of the zonulin inhibitor AT1001 derivatives as potential anti SARS-CoV-2, *Eur. J. Med. Chem.*, 2022, **244**, 114857.

248 S. E. Webber, K. Okano, T. L. Little, S. H. Reich, Y. Xin, S. A. Fuhrman, D. A. Matthews, R. A. Love, T. F. Hendrickson, A. K. Patick, J. W. Meador, R. A. Ferre, E. L. Brown, C. E. Ford, S. L. Binford and S. T. Worland, Tripeptide aldehyde inhibitors of human rhinovirus 3C protease: design, synthesis, biological evaluation, and cocrystal structure solution of P1 glutamine isosteric replacements, *J. Med. Chem.*, 1998, **41**, 2786.

249 H.-Z. Zhang, H. Zhang, W. Kemnitzer, B. Tseng, J. Cinatl, M. Michaelis, H. W. Doerr and S. X. Cai, Design and Synthesis of Dipeptidyl Glutaminyl Fluoromethyl Ketones as Potent Severe Acute Respiratory Syndrome Coronovirus (SARS-CoV) Inhibitors, *J. Med. Chem.*, 2006, **49**, 1198.

250 S. I. Al-Gharabli, S. T. Shah, S. Weik, M. F. Schmidt, J. R. Mesters, D. Kuhn, G. Klebe, R. Hilgenfeld and J. Rademann, An efficient method for the synthesis of peptide aldehyde libraries employed in the discovery of reversible SARS coronavirus main protease (SARS-CoV Mpro) inhibitors, *ChemBioChem*, 2006, **7**, 1048.

251 K. C. Tiew, G. He, S. Aravapalli, S. R. Mandadapu, M. R. Gunnam, K. R. Alliston, G. H. Lushington, Y. Kim, K. O. Chang and W. C. Groutas, Design, synthesis, and evaluation of inhibitors of Norwalk virus 3C protease, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5315.

252 L. A. Stubbing, J. G. Hubert, J. Bell-Tyrer, Y. O. Hermant, S. H. Yang, A. M. McSweeney, G. M. McKenzie-Goldsmith, V. K. Ward, D. P. Furkert and M. A. Brimble, P1 Glutamine isosteres in the design of inhibitors of 3C/3CL protease of human viruses of the Pisoniviricetes class, *RSC Chem. Biol.*, 2023, **4**, 533.

253 T. Regnier, D. Sarma, K. Hidaka, U. Bacha, E. Freire, Y. Hayashi and Y. Kiso, New developments for the design, synthesis and biological evaluation of potent SARS-CoV 3CLpro inhibitors, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2722.

254 S. Konno, P. Thanigaimalai, T. Yamamoto, K. Nakada, R. Kakiuchi, K. Takayama, Y. Yamazaki, F. Yakushiji, K. Akaji, Y. Kiso, Y. Kawasaki, S. Chen, E. Freire and Y. Hayashi, Design and synthesis of new tripeptide-type SARS-CoV 3CL protease inhibitors containing an electrophilic arylketone moiety, *Bioorg. Med. Chem.*, 2013, **21**, 412.

255 C. P. Chuck, C. Chen, Z. Ke, D. C. Wan, H. F. Chow and K. B. Wong, Design, synthesis and crystallographic analysis of nitrile-based broad-spectrum peptidomimetic inhibitors for coronavirus 3C-like proteases, *Eur. J. Med. Chem.*, 2013, **59**, 1.

256 Y. Kim, S. Lovell, K. C. Tiew, S. R. Mandadapu, K. R. Alliston, K. P. Battaile, W. C. Groutas and K. O. Chang, Broad-spectrum antivirals against 3C or 3C-like proteases of picornaviruses, noroviruses, and coronaviruses, *J. Virol.*, 2012, **86**, 11754.

257 Y. Kim, H. Liu, A. C. Galasiti Kankanamalage, S. Weerasekara, D. Hua, W. C. Groutas, K. O. Chang and N. C. Pedersen, Reversal of the Progression of Fatal Coronavirus Infection in Cats by a Broad-Spectrum Coronavirus Protease Inhibitor, *PLoS Pathog.*, 2016, **12**, e1005531.

258 N. C. Pedersen, Y. Kim, H. Liu, A. C. Galasiti Kankanamalage, C. Eckstrand, W. C. Groutas, M. Bannasch, J. M. Meadows and K. O. Chang, Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis, *J. Feline Med. Surg.*, 2018, **20**, 378.

259 C. J. Cáceres, S. Cardenas-Garcia, S. Carnaccini, B. Seibert, D. S. Rajao, J. Wang and D. R. Perez, Efficacy of GC-376 against SARS-CoV-2 virus infection in the K18 hACE2 transgenic mouse model, *Sci. Rep.*, 2021, **11**, 9609.

260 S. R. Mandadapu, P. M. Weerawarna, M. R. Gunnam, K. R. Alliston, G. H. Lushington, Y. Kim, K. O. Chang and W. C. Groutas, Potent inhibition of norovirus 3CL protease by peptidyl α-ketoamides and α-ketoheterocycles, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4820.

261 K. S. Yang, X. R. Ma, Y. Ma, Y. R. Alugubelli, D. A. Scott, E. C. Vatansever, A. K. Drelich, B. Sankaran, Z. Z. Geng, L. R. Blankenship, H. E. Ward, Y. J. Sheng, J. C. Hsu, K. C. Kratch, B. Zhao, H. S. Hayatshahi, J. Liu, P. Li, C. A. Fierke, C. K. Tseng, S. Xu and W. R. Liu, A Quick Route to Multiple Highly Potent SARS-CoV-2 Main Protease Inhibitors, *ChemMedChem*, 2021, **16**, 942.

262 C. S. Dampalla, H. N. Nguyen, A. D. Rathnayake, Y. Kim, K. D. Perera, T. K. Madden, H. A. Thurman, A. J. Machen, M. M. Kashipathy, L. Liu, K. P. Battaile, S. Lovell, K. O. Chang and W. C. Groutas, Broad-Spectrum Cyclopropane-Based Inhibitors of Coronavirus 3C-like Proteases: Biochemical, Structural, and Virological Studies, *ACS Pharmacol. Transl. Sci.*, 2023, **6**, 181.

263 C. S. Dampalla, M. J. Miller, Y. Kim, A. Zabiegala, H. N. Nguyen, T. K. Madden, H. A. Thurman, A. J. Machen, A. Cooper, L. Liu, K. P. Battaile, S. Lovell, K. O. Chang and W. C. Groutas, Structure-guided design of direct-acting antivirals that exploit the gem-dimethyl effect and potently inhibit 3CL proteases of severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) and middle east respiratory syndrome coronavirus (MERS-CoV), *Eur. J. Med. Chem.*, 2023, **254**, 115376.

264 W. Vuong, C. Fischer, M. B. Khan, M. J. van Belkum, T. Lamer, K. D. Willoughby, J. Lu, E. Arutyunova, M. A. Joyce, H. A. Saffran, J. A. Shields, H. S. Young, J. A. Nieman, D. L. Tyrrell, M. J. Lemieux and J. C. Vederas, Improved SARS-CoV-2 Mpro inhibitors based on feline antiviral drug GC376: Structural enhancements, increased solubility, and micellar studies, *Eur. J. Med. Chem.*, 2021, **222**, 113584.

265 A. C. Galasiti Kankanamalage, Y. Kim, P. M. Weerawarna, R. A. Z. Uy, V. C. Damalanka, S. R. Mandadapu, K. R. Alliston, N. Mehzabeen, K. P. Battaile, S. Lovell, K.-O. Chang and W. C. Groutas, Structure-Guided Design and Optimization of Dipeptidyl Inhibitors of Norovirus 3CL Protease. Structure–Activity Relationships and Biochemical, X-ray Crystallographic, Cell-Based, and In Vivo Studies, *J. Med. Chem.*, 2015, **58**, 3144.

266 A. D. Rathnayake, Y. Kim, C. S. Dampalla, H. N. Nguyen, A.-R. M. Jesri, M. M. Kashipathy, G. H. Lushington, K. P. Battaile, S. Lovell, K.-O. Chang and W. C. Groutas,

Structure-Guided Optimization of Dipeptidyl Inhibitors of Norovirus 3CL Protease, *J. Med. Chem.*, 2020, **63**, 11945.

267 S. Yang, S. J. Chen, M. F. Hsu, J. D. Wu, C. T. Tseng, Y. F. Liu, H. C. Chen, C. W. Kuo, C. S. Wu, L. W. Chang, W. C. Chen, S. Y. Liao, T. Y. Chang, H. H. Hung, H. L. Shr, C. Y. Liu, Y. A. Huang, L. Y. Chang, J. C. Hsu, C. J. Peters, A. H. Wang and M. C. Hsu, Synthesis, crystal structure, structure-activity relationships, and antiviral activity of a potent SARS coronavirus 3CL protease inhibitor, *J. Med. Chem.*, 2006, **49**, 4971.

268 Y. Ma, K. S. Yang, Z. Z. Geng, Y. R. Alugubelli, N. Shaabani, E. C. Vatansever, X. R. Ma, C. C. Cho, K. Khatua, J. Xiao, L. R. Blankenship, G. Yu, B. Sankaran, P. Li, R. Allen, H. Ji, S. Xu and W. R. Liu, A multi-pronged evaluation of aldehyde-based tripeptidyl main protease inhibitors as SARS-CoV-2 antivirals, *Eur. J. Med. Chem.*, 2022, **240**, 114570.

269 J. Botyanszki, J. G. Catalano, P. Y. Chong, H. Dickson, Q. Jin, A. Leivers, A. Maynard, X. Liao, J. Miller, J. B. Shotwell, V. W. F. Tai and R. K. Thalji, Compounds that inhibit 3C and 3CL proteases and methods of use therof, WO2018042343, 2018.

270 J. Botyanszki, Q. Jin, N. D. Pearson and R. K. Thalji, Tripeptides derivatives for treating sars-cov-2 infections, WO2021191827, 2021.

271 I. C. Jacobson, S. S. K. Lee and J. C. Pizarro Novoa, Peptidomimetic N5-methyl-N2-(nonanoyl-L-leucyl)-L-glutaminate derivatives, triazaspiro[4.14]nonadecane derivatives and similar compounds as inhibitors of norovirus and coronavirus replication, WO2021188620, 2021.

272 I. C. Jacobson, Inhibitors of norovirus and coronavirus replication, WO2021206877, 2021.

273 I. C. Jacobson ,Inhibitors of norovirus and coronavirus replication, WO2021206876, 2021.

274 I. C. Jacobson, Inhibitors for coronavirus, WO2023014758, 2023.

275 R. L. Hoffman, R. S. Kania, J. A. Nieman, S. P. Planken and G. J. Smith, Anticoronaviral Compounds and Compositions, Their Pharmaceutical Uses And Materials For Their Synthesis, WO2005113580, 2005.

276 C. Allais, D. Bernhardson, A. R. Brown, G. M. Chinigo, J.-N. Desrosiers, K. J. DiRico, I. Hotham, B. P. Jones, S. A. Kulkarni, C. A. Lewis, R. Lira, R. P. Loach, P. D. Morse, J. J. Mousseau, M. A. Perry, Z. Peng, D. W. Place, A. M. Rane, L. Samp, R. A. Singer, Z. Wang, G. A. Weisenburger, H. G. Yayla and J. M. Zanghi, Early Clinical Development of Lufotrelvir as a Potential Therapy for COVID-19, *Org. Process Res. Dev.*, 2023, DOI: **10.1021/acs.oprd.2c00375**.

277 N. Cheruvu, E. van Duijn, P. A. Spigt, I. M. Barbu, S. S. Toussi, K. Schildknegt, R. M. Jones and R. S. Obach, The metabolism of lufotrelvir, a prodrug investigated for the treatment of sars-cov-2, in humans following intravenous administration, *Drug Metab. Dispos.*, 2023, **51**, 1419.

278 P. Robinson, S. S. Toussi, S. Aggarwal, A. Bergman, T. Zhu, F. Hackman, J. G. Sathish, L. Updyke, P. Loudon, G. Krishna, P. Clevenbergh, M. G. Hernandez-Mora, J. M. Cisneros Herreros, T. E. Albertson, M. Dougan, A. Thacker, M. L. Baniecki, H. Soares, M. Whitlock, G. Nucci, S. Menon, A. S. Anderson and M. Binks, Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Intravenous Infusions of PF-07304814 (Lufotrelvir) in Hospitalized Participants With COVID-19, *Open Forum Infect. Dis.*, 2023, **10**, ofad355.

279 W. Shang, W. Dai, C. Yao, L. Xu, X. Tao, H. Su, J. Li, X. Xie, Y. Xu, M. Hu, D. Xie, H. Jiang, L. Zhang and H. Liu, In vitro and in vivo evaluation of the main protease inhibitor FB2001 against SARS-CoV-2, *Antiviral Res.*, 2022, **208**, 105450.

280 L. D. Arnold, A. Jennings and W. Keung, Inhibitors of cysteine proteases and methods of use thereof, WO2021252644, 2021.

281 Pardes Biosciences, **https://ir.pardesbio.com/news**, (accessed July, 26, 2023).

282 P. Thanigaimalai, S. Konno, T. Yamamoto, Y. Koiwai, A. Taguchi, K. Takayama, F. Yakushiji, K. Akaji, S. E. Chen, A. Naser-Tavakolian, A. Schön, E. Freire and Y. Hayashi, Development of potent dipeptide-type SARS-CoV 3CL protease inhibitors with novel P3 scaffolds: design, synthesis, biological evaluation, and docking studies, *Eur. J. Med. Chem.*, 2013, **68**, 372.

283 W. M. Kati, H. L. Sham, J. O. McCall, D. A. Montgomery, G. T. Wang, W. Rosenbrook, L. Miesbauer, A. Buko and D. W. Norbeck, Inhibition of 3C protease from human rhinovirus strain 1B by peptidyl bromomethylketonehydrazides, *Arch. Biochem. Biophys.*, 1999, **362**, 363.

284 D. Edmonds, C. Liang, H. Yun, B. Zhang and X. Zheng, Antiviral compounds, WO2023104882, 2023.

285 J. D. Baker, R. L. Uhrich, G. C. Kraemer, J. E. Love and B. C. Kraemer, A drug repurposing screen identifies hepatitis C antivirals as inhibitors of the SARS-CoV2 main protease, *PLoS One*, 2021, **16**, e0245962.

286 C. Liu, S. Boland, M. D. Scholle, D. Bardiot, A. Marchand, P. Chaltin, L. M. Blatt, L. Beigelman, J. A. Symons, P. Raboisson, Z. A. Gurard-Levin, K. Vandyck and J. Deval, Dual inhibition of SARS-CoV-2 and human rhinovirus with protease inhibitors in clinical development, *Antiviral Res.*, 2021, **187**, 105020.

287 Y. Bai, F. Ye, Y. Feng, H. Liao, H. Song, J. Qi, G. F. Gao, W. Tan, L. Fu and Y. Shi, Structural basis for the inhibition of the SARS-CoV-2 main protease by the anti-HCV drug narlaprevir, *Signal Transduction Targeted Ther.*, 2021, **6**, 51.

288 D. W. Kneller, S. Galanie, G. Phillips, H. M. O'Neill, L. Coates and A. Kovalevsky, Malleability of the SARS-CoV-2 3CL Mpro Active-Site Cavity Facilitates Binding of Clinical Antivirals, *Structure*, 2020, **28**, 1313.

289 B. Halford, The path to Paxlovid, *C&En*, 2022, vol. 100, p. 16.

290 B. Halford, Pfizer unveils its oral SARS-CoV-2 inhibitor, *C&En*, 2021, vol. 99, p. 7.

291 J. Hammond, H. Leister-Tebbe, A. Gardner, P. Abreu, W. Bao, W. Wisemandle, M. Baniecki, V. M. Hendrick, B. Damle, A. Simón-Campos, R. Pypstra and J. M. Rusnak, Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19, *N. Engl. J. Med.*, 2022, **386**, 1397.

292 N. Higashi-Kuwata, K. Tsuji, H. Hayashi, H. Bulut, M. Kiso, M. Imai, H. Ogata-Aoki, T. Ishii, T. Kobayakawa, K. Nakano, N. Takamune, N. Kishimoto, S. Hattori, D. Das, Y. Uemura, Y. Shimizu, M. Aoki, K. Hasegawa, S. Suzuki, A. Nishiyama, J. Saruwatari, Y. Shimizu, Y. Sukenaga, Y. Takamatsu, K. Tsuchiya, K. Maeda, K. Yoshimura, S. Iida, S. Ozono, T. Suzuki, T. Okamura, S. Misumi, Y. Kawaoka, H. Tamamura and H. Mitsuya, Identification of SARS-CoV-2 Mpro inhibitors containing P1' 4-fluorobenzothiazole moiety highly active against SARS-CoV-2, *Nat. Commun.*, 2023, **14**, 1076.

293 K. Tsuji, T. Ishii, T. Kobayakawa, N. Higashi-Kuwata, K. Shinohara, C. Azuma, Y. Miura, H. Nakano, N. Wada, S. Hattori, H. Bulut, H. Mitsuya and H. Tamamura, Structure-Activity Relationship Studies of SARS-CoV-2 Main Protease Inhibitors Containing 4-Fluorobenzothiazole-2-carbonyl Moieties, *J. Med. Chem.*, 2023, **66**, 13516.

294 B. Yang, B. Liang, Y. Lai and J. J. Wu, Inhibitors of cysteine proteases and method of use thereof, WO2023139402, 2023.

295 M. Göhl, L. Zhang, H. El Kilani, X. Sun, K. Zhang, M. Brönstrup and R. Hilgenfeld, From Repurposing to Redesign: Optimization of Boceprevir to Highly Potent Inhibitors of the SARS-CoV-2 Main Protease, *Molecules*, 2022, **27**, 4292.

296 M. Z. Lin and M. W. Soerensen, Cell-permeant inhibitors of viral cysteine protease, WO2023114516, 2023.

297 M. Westberg, Y. Su, X. Zou, P. Huang, A. Rustagi, J. Garhyan, P. B. Patel, D. Fernandez, Y. Wu, L. Ning, A. Beck, M. Karim, C. Hao, P. Saenkham-Huntsinger, V. Tat, A. Drelich, B. H. Peng, S. Einav, C. T. K. Tseng, C. Blish and M. Z. Lin, Design of SARS-CoV-2 protease inhibitors with improved affinity and reduced sensitivity to mutations, *BioRxiv*, 2023, preprint, DOI: **10.1101/2023.07.19.549739**.

298 X. Chen, P. Li, J. Huang, Y. Yang, H. Zhang, Z. Wang, Z. Zhu, J. Wang, J. Zhang, K. Chen, H. He, C. Long and S. Chen, Discovery of novel bicyclic[3.3.0] proline peptidyl α-ketoamides as potent 3CL-protease inhibitors for SARS-CoV-2, *Bioorg. Med. Chem. Lett.*, 2023, **90**, 129324.

299 X. Chen, X. Huang, Q. Ma, P. Kuzmic, B. Zhou, J. Xu, B. Liu, H. Jiang, W. Zhang, C. Yang, S. Wu, J. Huang, H. Li, C. Long, X. Zhao, H. Xu, Y. J. Sheng, Y. Guo, C. Niu, L. Xue, Y. Xu, J. Liu, T. Zhang, J. Spencer, W. Deng, S.-H. Chen, X. Xiong, Z. Yang and N. Zhong, Inhibition mechanism and antiviral activity of an α-ketoamide based SARS-CoV-2 main protease inhibitor, *BioRxiv*, 2023, preprint, DOI: **10.1101/2023.03.09.53186**.

300 X. Chen, J. Wang, J. Huang, Z. Liu, C. Long, S. Chen and K. X. Chen, Ketoamide derivatives and application thereof, WO2023036093, 2023.

301 B. Wang, H. J. Li, M. M. Cai, Z. X. Lin, X. F. Ou, S. H. Wu, R. H. Cai, Y. N. Wei, F. Yang, Y. M. Zhu, Z. F. Yang, N. S. Zhong and L. Lin, Antiviral efficacy of RAY1216 monotherapy and combination therapy with ritonavir in patients with COVID-19: a phase 2, single centre, randomised, double-blind, placebo-controlled trial, *EClinicalMedicine*, 2023, **63**, 102189.

302 I. Stefanelli, A. Corona, C. Cerchia, E. Cassese, S. Improta, E. Costanzi, S. Pelliccia, S. Morasso, F. Esposito, A. Paulis, S. Scognamiglio, F. Di Leva, P. Storici, M. Brindisi, E. Tramontano, R. Cannalire and V. Summa, Broad-spectrum coronavirus 3C-like protease peptidomimetic inhibitors effectively block SARS-CoV-2 replication in cells: Design, synthesis, biological evaluation, and X-ray structure determination, *Eur. J. Med. Chem.*, 2023, **253**, 115311.

303 F. Wang, W. Xiao, Y. Tang, M. Cao, D. Shu, T. Asakawa, Y. Xu, X. Jiang, L. Zhang, W. Wang, J. Tang, Y. Huang, Y. Yang, Y. Yang, R. Tang, J. Shen and H. Lu, Efficacy and safety of SIM0417 (SSD8432) plus ritonavir for COVID-19 treatment: a randomised, double-blind, placebo-controlled, phase 1b trial, *Lancet Reg. Health West. Pac.*, 2023, **38**, 100835.

304 X. Jiang, Y. Xu, L. Zhang, H. Su, Q. Zhang, W. Zhao, W. Shang, J. Shen, G. Xiao and H. Jiang, Cyano compound, and preparation method therefor and use thereof, WO2023051657, 2023.

305 K. W. Zhu, Deuremidevir and Simnotrelvir–Ritonavir for the Treatment of COVID-19, *ACS Pharmacol. Transl. Sci.*, 2023, **6**, 1306.

306 X. Jiang, H. Su, W. Shang, F. Zhou, W. Zhang, W. Zhao, Q. Zhang, H. Xie, L. Jiang, T. Nie, F. Yang, M. Xiong, X. Huang, M. Li, P. Chen, S. Peng, G. Xiao, H. Jiang, R. Tang, L. Zhang, J. Shen and Y. Xu, Structure-based development and preclinical evaluation of the SARS-CoV-2 3C-like protease inhibitor simnotrelvir, *Nat. Commun.*, 2023, **14**, 6463.

307 X. M. Yang, Y. Yang, B. F. Yao, P. P. Ye, Y. Xu, S. P. Peng, Y. M. Yang, P. Shu, P. J. Li, S. Li, H. L. Hu, Q. Li, L. L. Song, K. G. Chen, H. Y. Zhou, Y. H. Zhang, F. R. Zhao, B. H. Tang, W. Zhang, X. F. Zhang, S. M. Fu, G. X. Hao, Y. Zheng, J. S. Shen, Y. C. Xu, X. R. Jiang, L. K. Zhang, R. H. Tang and W. Zhao, A First-In-Human Phase 1 Study of Simnotrelvir, a 3CL-like Protease Inhibitor for Treatment of COVID-19, in Healthy Adult Subjects, *Eur. J. Pharm. Sci.*, 2023, **30**, 106598.

308 D. A. M.-E. Bardiot, K. Vandyck, S. Boland, A. D. Stoycheva, A. D. M. Marchand, P. J. M. B. Raboisson and L. Beigelman, Anti-viral compounds for treating coronavirus, picornavirus, and norovirus infections, WO2023043816, 2023.

309 K. Vandyck, D. A. M.-E. Bardiot, P. J. M. B. Raboisson, L. Beigelman, A. D. Stoycheva, S. Boland and A. D. M. Marchand, Anti-viral compounds, WO2023283256, 2023.

310 H. Yang, M. You, X. Shu, J. Zhen, M. Zhu, T. Fu, Y. Zhang, X. Jiang, L. Zhang, Y. Xu, Y. Zhang, H. Su, Q. Zhang and J. Shen, Design, synthesis and biological evaluation of peptidomimetic benzothiazolyl ketones as 3CLpro inhibitors against SARS-CoV-2, *Eur. J. Med. Chem.*, 2023, **257**, 115512.

311 Y. R. Alugubelli, Z. Z. Geng, K. Yang, N. Shaabani, K. Khatua, X. R. Ma, E. C. Vatansever, C. C. Cho, Y. Ma, J. Xiao, L. R. Blankenship, G. Yu, B. Sankaran, P. Li, R. Allen, H. Ji, S. Xu and W. R. Liu, A systematic exploration of boceprevir-based main protease inhibitors as SARS-CoV-2 antivirals, *Eur. J. Med. Chem.*, 2022, **240**, 114596.

312 Z. Z. Geng, S. Atla, N. Shaabani, V. R. Vulupala, K. S. Yang, Y. R. Alugubelli, K. Khatua, P. C. Chen, J. Xiao, L. R. Blankenship, X. R. Ma, E. C. Vatansever, C. C. Cho, Y. Ma, R. Allen, H. Ji, S. Xu and W. R. Liu, A Systematic Survey of Reversibly Covalent Dipeptidyl Inhibitors of the SARS-CoV-2 Main Protease, *J. Med. Chem.*, 2023, **66**, 11040.

313 A. K. Chatterjee, J. J. Chen, E. Nakath, A. Rahimi, A. K. Gupta, G. Grabovyi, K. Wilson, S. Ghorai, A. Nazarian, J. Pedroarena, W. Mazumdar, F. Weiss, L. Song, M. A. Bakowski, L. Riva, K. Wolff, C. W. McNamara, T. F. Rogers, J. Malvin, S. Li, S. Joseph, A. Woods, Y. L. Liu and N. Okwor, Protease inhibitors for the treatment of coronavirus infections, WO2022261473, 2022.

314 N. G. R. D. Elshan, K. C. Wolff, L. Riva, A. K. Woods, G. Grabovyi, K. Wilson, A. Rahimi, J. Pedroarena, S. Ghorai, A. K. Gupta, A. Nazarian, F. Weiss, Y. Liu, W. Mazumdar, L. Song, N. Okwor, J. Malvin, M. A. Bakowski, N. Beutler, M. G. Kirkpatrick, A. Gebara-Lamb, E. Huang, V. Nguyen-Tran, V. Chi, S. Li, T. F. Rogers, C. W. McNamara, J. J. Chen, S. B. Joseph, P. G. Schultz and A. K. Chatterjee, Discovery of CMX990: A Potent SARS-CoV-2 3CL Protease Inhibitor Bearing a Novel Covalent Warhead, *BioRxiv*, 2023, preprint, DOI: **10.1101/2023.10.24.563688**.

315 M. Zhu, T. Fu, M. You, J. Cao, H. Yang, X. Chen, Q. Zhang, Y. Xu, X. Jiang, L. Zhang, H. Su, Y. Zhang and J. Shen, Design, synthesis and biological evaluation of covalent peptidomimetic 3CL protease inhibitors containing nitrile moiety, *Bioorg. Med. Chem.*, 2023, **87**, 117316.

316 W. Liu, C. A. Fierke, S. Xu, K. Yang, X. Ma, Y. Ma, Y. R. Alugubelli, E. C. Vatansever, C. C. Cho, Z. Geng and K. Khatua, SARS-COV-2 main protease inhibitors, WO2022020711, 2022.

317 Sorrento Therapeutics, **https://sorrentotherapeutics.com/research/covid**, (accessed July, 26, 2023).

318 L. Mao, X. Xu, N. Shaabani and C. Jin, Protease inhibitors as antiviral, WO2022256434, 2022.

319 A. Balakrishnan, A. Reyes, R. Shen, N. Bisht, J. Sweeney, R. Levene, N. McAllister, T. Cressey, N. Manalo, M. H. Rhodin, M. Vaine, G. Wang, Y. S. Or and B. Goodwin, Molecular Basis for Antiviral Action of EDP-235: A Potent and Selective SARS-CoV-2 3CLpro Inhibitor for the Treatment of Covid 19, *FASEB J.*, 2022, **36**, DOI: **10.1096/fasebj.2022.36.S1.0R514**.

320 G. Wang, R. Shen, J. Ma, Y. He, X. Xing, H. Cao, X. Gao, X. Peng, J. D. Panarese and Y. S. Or, Novel spiropyrolidine derived antiviral agents, WO2022109360, 2022.

321 G. Wang, R. Shen, J. Ma, X. Xing, H. Cao, X. Gao, X. Peng, J. Long, W. Li, J. Zhang, J. D. Panarese, N. T. Kenton, S. Bartlett and Y. S. Or, Novel spiropyrolidine derived antiviral agents, WO2022109363, 2022.

322 K. Zhu, G. Wang, J. Zhang, H. Cao, R. Shen, Q. Wang, G. Wu and Y. S. Or, Process for the preparation of 4,6,7-trifluoro-1H-indole-2-carboxylic acid, WO2023177854, 2023.

323 K. Zhu, G. Wang, X. Zhang, X. Peng, R. Shen, J. Zhang, W. Li, H. Cao, X. Gao, Q. Wang, G. Wu and Y. S. Or, Process for the preparation of substituted spirooxindole derivatives, WO2023177854, 2023.

324 R. Shen, Y. He, X. Xing, M. Rhodes, J. D. Panarese, S. Bartlett, W. Li, H. Cao, J. Zhang, X. Peng, G. Wang and Y. S. Or, Novel macrocyclic spiropyrolidine derived antiviral agents, WO2023009187, 2023.

325 J. Zhang, X. Peng, B.-C. Suh, J. Kass, X. Gao, H. Cao, W. Li, J. D. Panarese, G. Wang and Y. S. Or, Novel macrocyclic spiropyrolidine derived antiviral agents, WO2022240541, 2022.

326 J. D. Panarese, S. Rafferty, J. Thielman, N. T. Kenton, S. Bartlett and Y. S. Or, Heterocyclic antiviral agents, WO2023107417, 2023.

327 J. D. Panarese, S. Bartlett and Y. S. Or, Saturated spirocyclics as antiviral agents, WO2023107419, 2023.

328 P. S. Dragovich, T. J. Prins, R. Zhou, E. L. Brown, F. C. Maldonado, S. A. Fuhrman, L. S. Zalman, T. Tuntland, C. Lee, A. K. Patick, D. A. Matthews, T. F. Hendrickson, M. B. Kosa, B. Liu, M. R. Batugo, J. P. Gleeson, S. K. Sakata, L. Chen, M. C. Guzman, J. W. R. Meador, R. A. Ferre and S. T. Worland, Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 6. Structure-activity studies of orally bioavailable, 2-pyridone-containing peptidomimetics, *J. Med. Chem.*, 2002, **45**, 1607.

329 P. S. Dragovich, T. J. Prins, R. Zhou, T. O. Johnson, E. L. Brown, F. C. Maldonado, S. A. Fuhrman, L. S. Zalman, A. K. Patick, D. A. Matthews, X. Hou, J. W. Meador, R. A. Ferre and S. T. Worland, Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. Part 7: structure-activity studies of bicyclic 2-pyridone-containing peptidomimetics, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 733.

330 P. S. Dragovich, T. J. Prins, R. Zhou, T. O. Johnson, Y. Hua, H. T. Luu, S. K. Sakata, E. L. Brown, F. C. Maldonado, T. Tuntland, C. A. Lee, S. A. Fuhrman, L. S. Zalman, A. K. Patick, D. A. Matthews, E. Y. Wu, M. Guo, B. C. Borer, N. K. Nayyar, T. Moran, L. Chen, P. A. Rejto, P. W. Rose, M. C. Guzman, E. Z. Dovalsantos, S. Lee, K. McGee, M. Mohajeri, A. Liese, J. Tao, M. B. Kosa, B. Liu, M. R. Batugo, J. P. Gleeson, Z. P. Wu, J. Liu, J. W. R. Meador and R. A. Ferre, Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 8. Pharmacological optimization of orally bioavailable 2-pyridone-containing peptidomimetics, *J. Med. Chem.*, 2003, **46**, 4572.

331 A. K. Patick, M. A. Brothers, F. Maldonado, S. Binford, O. Maldonado, S. Fuhrman, A. Petersen, G. J. R. Smith, L. S. Zalman, L. A. Burns-Naas and J. Q. Tran, In vitro antiviral activity and single-dose pharmacokinetics in humans of a

novel, orally bioavailable inhibitor of human rhinovirus 3C protease, *Antimicrob. Agents Chemother.*, 2005, **49**, 2267.

332 M. K. Kankam, J. M. Burns, M. S. Collett, M. L. Corrado and J. R. Hincks, A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Oral Doses of V-7404 in Healthy Adult Volunteers, *Antimicrob. Agents Chemother.*, 2021, **65**, e0102921.

333 M. Fàbrega-Ferrer, A. Herrera-Morandé, S. Muriel-Goñi, J. Pérez-Saavedra, P. Bueno, V. Castro, U. Garaigorta, P. Gastaminza and M. Coll, Structure and inhibition of SARS-CoV-1 and SARS-CoV-2 main proteases by oral antiviral compound AG7404, *Antiviral Res.*, 2022, **208**, 105458.

334 L. Zhu, S. George, M. F. Schmidt, S. Al-Gharabli, J. Rademann and R. Hilgenfeld, Peptide aldehyde inhibitors challenge the substrate specificity of the SARS-coronavirus main protease, *Antiviral Res.*, 2011, **92**, 204.

335 Z. Shen, Y. Li, J. Zhu, Q. Huang, J. Yin, Y. Xu, A. M. Wu, W. Su and L. Kuai, Virus main protease inhibitor, preparation method therefor, and use, WO2023283831, 2023.

336 L. D. Arnold, A. Jennings and W. Keung, Inhibitors of cysteine proteases and methods of use thereof, US11174231, 2021.

337 K. O. Chang, Y. Kim and W. C. Groutas, Macrocyclic and peptidomimetic compounds as broad-spectrum antivirals against 3C or 3C-like proteases of picornaviruses, caliciviruses and coronaviruses, WO2013166319, 2013.

338 S. R. Mandadapu, P. M. Weerawarna, A. M. Prior, R. A. Uy, S. Aravapalli, K. R. Alliston, G. H. Lushington, Y. Kim, D. H. Hua, K. O. Chang and W. C. Groutas, Macrocyclic inhibitors of 3C and 3C-like proteases of picornavirus, norovirus, and coronavirus, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3709.

339 L. Wang, C. Ma, M. D. Sacco, S. Xue, M. Mahmoud, L. Calcul, Y. Chen, J. Wang and J. Cai, Development of the Safe and Broad-Spectrum Aldehyde and Ketoamide Mpro inhibitors Derived from the Constrained α, γ-AA Peptide Scaffold, *Chemistry*, 2023, **29**, e202300476.

340 J. E. Blanchard, N. H. Elowe, C. Huitema, P. D. Fortin, J. D. Cechetto, L. D. Eltis and E. D. Brown, High-throughput screening identifies inhibitors of the SARS coronavirus main proteinase, *Chem. Biol.*, 2004, **11**, 1445.

341 J. Zhang, H. I. Pettersson, C. Huitema, C. Niu, J. Yin, M. N. James, L. D. Eltis and J. C. Vederas, Design, synthesis, and evaluation of inhibitors for severe acute respiratory syndrome 3C-like protease based on phthalhydrazide ketones or heteroaromatic esters, *J. Med. Chem.*, 2007, **50**, 1850.

342 C. Niu, J. Yin, J. Zhang, J. C. Vederas and M. N. James, Molecular docking identifies the binding of 3-chloropyridine moieties specifically to the S1 pocket of SARS-CoV Mpro, *Bioorg. Med. Chem.*, 2008, **16**, 293.

343 A. K. Ghosh, G. Gong, V. Grum-Tokars, D. C. Mulhearn, S. C. Baker, M. Coughlin, B. S. Prabhakar, K. Sleeman, M. E. Johnson and A. D. Mesecar, Design, synthesis and antiviral efficacy of a series of potent chloropyridyl ester-derived SARS-CoV 3CLpro inhibitors, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5684.

344 J. Breidenbach, C. Lemke, T. Pillaiyar, L. Schäkel, G. Al Hamwi, M. Diett, R. Gedschold, N. Geiger, V. Lopez, S. Mirza, V. Namasivayam, A. Schiedel, K. Sylvester, D. Thimm, C. Vielmuth, L. Phuong Vu, M. Zyulina, J. Bodem, M. Gütschow and C. E. Müller, Targeting the Main Protease of SARS-CoV-2: From the Establishment of High Throughput Screening to the Design of Tailored Inhibitors, *Angew. Chem., Int. Ed.*, 2021, **60**, 10423.

345 R. Wamser, S. Pach, C. Arkona, M. Baumgardt, U. B. A. Aziz, A. C. Hocke, G. Wolber and J. Rademann, A Critical Study on Acylating and Covalent Reversible Fragment Inhibitors of SARS-CoV-2 Main Protease Targeting the S1-Site with Pyridine, *ChemMedChem*, 2023, **18**, e202200635.

346 F. M. Zhang, T. Huang, F. Wang, G. S. Zhang, D. Liu, J. Dai, J. W. Zhang, Q. H. Li, G. Q. Lin, D. Gao, J. Zhao and P. Tian, Discovery of highly potent covalent SARS-CoV-2 3CLpro inhibitors bearing 2-sulfoxyl-1,3,4-oxadiazole scaffold for combating COVID-19, *Eur. J. Med. Chem.*, 2023, **260**, 115721.

347 K. M. Kang, Y. Jang, S. S. Lee, M. S. Jin, C. D. Jun, M. Kim and Y. C. Kim, Discovery of antiviral SARS-CoV-2 main protease inhibitors by structure-guided hit-to-lead optimization of carmofur, *Eur. J. Med. Chem.*, 2023, **260**, 115720.

348 T. Pillaiyar, P. Flury, N. Krüger, H. Su, L. Schäkel, E. Barbosa Da Silva, O. Eppler, T. Kronenberger, T. Nie, S. Luedtke, C. Rocha, K. Sylvester, M. R. I. Petry, J. H. McKerrow, A. Poso, S. Pöhlmann, M. Gütschow, A. J. O'Donoghue, Y. Xu, C. E. Müller and S. A. Laufer, Small-Molecule Thioesters as SARS-CoV-2 Main Protease Inhibitors: Enzyme Inhibition, Structure-Activity Relationships, Antiviral Activity, and X-ray Structure Determination, *J. Med. Chem.*, 2022, **65**, 9376.

349 J. Zhang, C. Huitema, C. Niu, J. Yin, M. N. G. James, L. D. Eltis and J. C. Vederas, Aryl methylene ketones and fluorinated methylene ketones as reversible inhibitors for severe acute respiratory syndrome (SARS) 3C-like proteinase, *Bioorg. Chem.*, 2008, **26**, 229.

350 M. Turlington, A. Chun, S. Tomar, A. Eggler, V. Grum-Tokars, J. Jacobs, J. S. Daniels, E. Dawson, A. Saldanha, P. Chase, Y. M. Baez-Santos, C. W. Lindsley, P. Hodder, A. D. Mesecar and S. R. Stauffer, Discovery of N-(benzo[1,2,3]triazol-1-yl)-N-(benzyl)acetamidophenyl carboxamides as severe acute respiratory syndrome coronavirus (SARS-CoV) 3CLpro inhibitors: identification of ML300 and noncovalent nanomolar inhibitors with an induced-fit binding, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6172.

351 G. J. Lockbaum, A. C. Reyes, J. M. Lee, R. Tilvawala, E. A. Nalivaika, A. Ali, N. Kurt Yilmaz, P. R. Thompson and C. A. Schiffer, Crystal Structure of SARS-CoV-2 Main Protease in Complex with the Non-Covalent Inhibitor ML188, *Viruses*, 2021, **13**, 174.

352 S. H. Han, C. M. Goins, T. Arya, W. J. Shin, J. Maw, A. Hooper, D. P. Sonawane, M. R. Porter, B. E. Bannister, R. D. Crouch,

A. A. Lindsey, G. Lakatos, S. R. Martinez, J. Alvarado, W. S. Akers, N. S. Wang, J. U. Jung, J. D. Macdonald and S. R. Stauffer, Structure-Based Optimization of ML300-Derived, Noncovalent Inhibitors Targeting the Severe Acute Respiratory Syndrome Coronavirus 3CL Protease (SARS-CoV-2 3CL(pro)), *J. Med. Chem.*, 2022, **65**, 2880.

353 J. Chodera, A. A. Lee, N. London and F. von Delft, Crowdsourcing drug discovery for pandemics, *Nat. Chem.*, 2020, **12**, 581.

354 F. von Delft, M. Calmiano, J. Chodera, E. Griffen, A. Lee, N. London, T. Matviuk, B. Perry, M. Robinson and A. von Delft, A white-knuckle ride of open COVID drug discovery, *Nature*, 2021, **594**, 330.

355 The COVID Moonshot Consortium, J. Chodera, A. Lee, N. London and F. von Delft, Open Science Discovery of Oral Non-Covalent SARS-CoV-2 Main Protease Inhibitors, *ChemRxiv*, 2021, preprint, DOI: **10.33774/chemrxiv**.

356 H. Achdout, A. Aimon, E. Bar-David, H. Barr, A. Ben-Shmuel, J. Bennett, V. A. Bilenko, M. L. Boby, B. Borden, G. R. Bowman, J. Brun, B. V. N. B. S. Sarma, M. Calmiano, A. Carbery, D. Carney, E. Cattermole, E. Chang, E. Chernyshenko, J. D. Chodera, A. Clyde, J. E. Coffland, G. Cohen, J. Cole, A. Contini, L. Cox, M. Cvitkovic, A. Dias, K. Donckers, D. L. Dotson, A. Douangamath, S. Duberstein, T. Dudgeon, L. Dunnett, P. K. Eastman, N. Erez, C. J. Eyermann, M. Fairhead, G. Fate, D. Fearon, O. Fedorov, M. Ferla, R. S. Fernandes, L. Ferrins, R. Foster, H. Foster, R. Gabizon, A. Garcia-Sastre, V. O. Gawriljuk, P. Gehrtz, C. Gileadi, C. Giroud, W. G. Glass, R. Glen, I. Glinert, A. S. Godoy, M. Gorichko, T. Gorrie-Stone, E. J. Griffen, S. Hassell Hart, J. Heer, M. Henry, M. Hill, S. Horrell, V. D. Huliak, M. F. D. Hurley, T. Israely, A. Jajack, J. Jansen, E. Jnoff, D. Jochmans, T. John, S. De Jonghe, A. L. Kantsadi, P. W. Kenny, J. L. Kiappes, S. O. Kinakh, L. Koekemoer, B. Kovar, T. Krojer, A. Lee, B. A. Lefker, H. Levy, I. G. Logvinenko, N. London, P. Lukacik, H. B. Macdonald, B. MacLean, T. R. Malla, T. Matviiuk, W. McCorkindale, B. L. McGovern, S. Melamed, K. P. Melnykov, O. Michurin, H. Mikolajek, B. F. Milne, A. Morris, G. M. Morris, M. J. Morwitzer, D. Moustakas, A. M. Nakamura, J. Brandao Neto, J. Neyts, L. Nguyen, G. D. Noske, V. Oleinikovas, G. Oliva, G. J. Overheul, D. Owen, R. Pai, J. Pan, N. Paran, B. Perry, M. Pingle, J. Pinjari, B. Politi, A. Powell, V. Psenak, R. Puni, V. L. Rangel, R. N. Reddi, S. P. Reid, E. Resnick, E. G. Ripka, M. C. Robinson, R. P. Robinson, J. Rodriguez-Guerra, R. Rosales, D. Rufa, K. Saar, K. Singh Saikatendu, C. Schofield, M. Shafeev, A. Shaikh, J. Shi, K. Shurrush, S. Singh, A. Sittner, R. Skyner, A. Smalley, B. Smeets, M. D. Smilova, L. J. Solmesky, J. Spencer, C. Strain-Damerell, V. Swamy, H. Tamir, R. Tennant, W. Thompson, A. Thompson, S. Tomasio, I. S. Tsurupa, A. Tumber, I. Vakonakis, R. P. van Rij, L. Vangeel, F. S. Varghese, M. Vaschetto, E. B. Vitner, V. Voelz, A. Volkamer, F. von Delft, A. von Delft, M. Walsh, W. Ward, C. Weatherall, S. Weiss, K. M. White, C. F. Wild, M. Wittmann, N. Wright, Y. Yahalom-Ronen, D. Zaidmann, H. Zidane and N. Zitzmann, Open Science Discovery of Oral Non-Covalent SARS-CoV-2 Main Protease Inhibitor Therapeutics, *BioRxiv*, 2022, preprint, DOI: **10.1101/2020.10.29.339317**.

357 K. L. Saar, W. McCorkindale, D. Fearon, M. Boby, H. Barr, A. Ben-Shmuel, COVID Moonshot Consortium, N. London, F. Von Delft, J. D. Chodera and A. A. Lee, Turning high-throughput structural biology into predictive inhibitor design, *Proc. Natl. Acad. Sci. U. S. A.*, 2023, **120**, e2214168120.

358 E. Griffen, **https://dndi.org/wp-content/uploads/2021/09/COVID_Moonshot_RSC_Cambridge_MedChem_Sept_2021.pdf**, (accessed 6th of January 2022).

359 M. L. Boby, D. Fearon, M. Ferla, M. Filep, L. Koekemoer, M. C. Robinson, The COVID Moonshot Consortium, J. D. Chodera, A. A. Lee, N. London, A. von Delft and F. von Delft, Open Science Discovery of Potent Non-Covalent SARS-CoV-2 Main Protease Inhibitors, *BioRxiv*, 2023, preprint, DOI: **10.1101/2020.10.29.339317**.

360 A. Luttens, H. Gullberg, E. Abdurakhmanov, D. D. Vo, D. Akaberi, V. O. Talibov, N. Nekhotiaeva, L. Vangeel, S. De Jonghe, D. Jochmans, J. Krambrich, A. Tas, B. Lundgren, Y. Gravenfors, A. J. Craig, Y. Atilaw, A. Sandström, L. W. K. Moodie, Å. Lundkvist, M. J. van Hemert, J. Neyts, J. Lennerstrand, J. Kihlberg, K. Sandberg, U. H. Danielson and J. Carlsson, Ultralarge Virtual Screening Identifies SARS-CoV-2 Main Protease Inhibitors with Broad-Spectrum Activity against Coronaviruses, *J. Am. Chem. Soc.*, 2022, **144**, 2905.

361 N. Kitamura, M. D. Sacco, C. Ma, Y. Hu, J. A. Townsend, X. Meng, F. Zhang, X. Zhang, M. Ba, T. Szeto, A. Kukuljac, M. T. Marty, D. Schultz, S. Cherry, Y. Xiang, Y. Chen and J. Wang, Expedited Approach toward the Rational Design of Noncovalent SARS-CoV-2 Main Protease Inhibitors, *J. Med. Chem.*, 2022, **65**, 2848.

362 H. Wang, J. Wen, Y. Yang, H. Liu, S. Wang, X. Ding, C. Zhou and X. Zhang, Identification of highly effective inhibitors against SARS-CoV-2 main protease: From virtual screening to in vitro study, *Front. Pharmacol.*, 2022, **13**, 1036208.

363 R. Jimmidi, S. Chamakuri, S. Lu, M. N. Ucisik, P. J. Chen, K. M. Bohren, S. A. Moghadasi, L. Versteeg, C. Nnabuife, J. Y. Li, X. Qin, Y. C. Chen, J. C. Faver, P. Nyshadham, K. L. Sharma, B. Sankaran, A. Judge, Z. Yu, F. Li, J. Pollet, R. S. Harris, M. M. Matzuk, T. Palzkill and D. W. Young, DNA-encoded chemical libraries yield non-covalent and non-peptidic SARS-CoV-2 main protease inhibitors, *Commun. Chem.*, 2023, **6**, 164.

364 D. Zaidman, P. Gehrtz, M. Filep, D. Fearon, R. Gabizon, A. Douangamath, J. Prilusky, S. Duberstein, G. Cohen, C. D. Owen, E. Resnick, C. Strain-Damerell, P. Lukacik, C.-M. Consortium, H. Barr, M. A. Walsh, F. von Delft and N. London, An automatic pipeline for the design of irreversible derivatives identifies a potent SARS-CoV-2 Mpro inhibitor, *Cell Chem. Biol.*, 2021, **28**, 1.

365 A. Zavoronkovs, Y. A. Ivanenkov and B. Zagribelnyy, SARS-CoV-2 inhibitors having covalent modifications for treating coronavirus infections, WO2021219089, 2021.

366 L. D. Arnold, U. Lopatin and W. Keung, Inhibitors of cysteine proteases and methods of use thereof, WO2021212039, 2021.
367 L. D. Arnold and W. Keung, Inhibitors of cysteine proteases and methods of use thereof, WO2022221686, 2022.
368 J. K. Stille, J. Tjutrins, G. Wang, F. A. Venegas, C. Hennecker, A. M. Rueda, I. Sharon, N. Blaine, C. E. Miron, S. Pinus, A. Labarre, J. Plescia, M. Burai Patrascu, X. Zhang, A. S. Wahba, D. Vlaho, M. J. Huot, T. M. Schmeing, A. K. Mittermaier and N. Moitessier, Design, synthesis and in vitro evaluation of novel SARS-CoV-2 3CLpro covalent inhibitors, *Eur. J. Med. Chem.*, 2022, **229**, 114046.
369 B. X. Quan, H. Shuai, A. J. Xia, Y. Hou, R. Zeng, X. L. Liu, G. F. Lin, J. X. Qiao, W. P. Li, F. L. Wang, K. Wang, R. J. Zhou, T. T. Yuen, M. X. Chen, C. Yoon, M. Wu, S. Y. Zhang, C. Huang, Y. F. Wang, W. Yang, C. Tian, W. M. Li, Y. Q. Wei, K. Y. Yuen, J. F. Chan, J. Lei, H. Chu and S. Yang, An orally available Mpro inhibitor is effective against wild-type SARS-CoV-2 and variants including Omicron, *Nat. Microbiol.*, 2022, **7**, 716.
370 M. J. Hesse, V. Hornak, S. Joseph, H. E. Moser, J. Papillon, T. Patel, G. Robinson, D. C. Tully and J. Yuan, Compounds and compositions for the treatment of coronaviral related diseases, WO2022224223, 2022.
371 D. Bao, F. Guo, M. J. Hesse, V. Hornak, S. Joseph, T. M. Kirrane, B. Liu, H. Lin, Y. Miao, H. E. Moser, J. Papillon, Y. Qu, L. Shi, J. Yuan and T. Zhang, Compounds and compositions for the treatment of coronaviral related diseases, WO2023002409, 2023.
372 **https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro**, (accessed 18th of August 2023).
373 N. Hou, L. Shuai, L. Zhang, X. Xie, K. Tang, Y. Zhu, Y. Yu, W. Zhang, Q. Tan, G. Zhong, Z. Wen, C. Wang, X. He, H. Huo, H. Gao, Y. Xu, J. Xue, C. Peng, J. Zou, C. Schindewolf, V. Menachery, W. Su, Y. Yuan, Z. Shen, R. Zhang, S. Yuan, H. Yu, P. Shi, Z. Bu, J. Huang and Q. Hu, Development of Highly Potent Noncovalent Inhibitors of SARS-CoV-2 3CLpro, *ACS Cent. Sci.*, 2023, **9**, 217.
374 J. Wang, C. Cheng, B. Chi and D. Sun, 3CL PRO protease inhibitors, WO2023036140, 2023.
375 A. Hooper, J. D. Macdonald, B. Reilly, J. Maw, A. P. Wirrick, S. H. Han, A. A. Lindsey, E. G. Rico, T. Romigh, C. M. Goins, N. S. Wang and S. Stauffer, SARS-CoV-2 3CL-protease inhibitors derived from ML300: investigation of P1 and replacements of the 1,2,3-benzotriazole, *Res. Sq.*, 2023, DOI: **10.21203/rs.3.rs**.
376 S. R. Stauffer, S. H. Han, A. Hooper, J. Maw, D. P. Sonawane, M. R. Porter, S. Martinez, J. Alvarado and J. D. Macdonald, Protease inhibitor and method of use, WO2022266203, 2022.
377 S. R. Stauffer, J. D. Macdonald, A. Hooper, S. H. Han, D. P. Sonawane, M. R. Porter, J. Maw, S. Martinez and J. Alvarado, Protease inhibitors and method of use, WO2022266368, 2022.
378 J. Pérez-Vargas, L. J. Worrall, A. D. Olmstead, A. T. Ton, J. Lee, I. Villanueva, C. A. H. Thompson, S. Dudek, S. Ennis, J. R. Smith, T. Shapira, J. Guzman, S. Gang, F. Ban, M. Vuckovic, M. Bielecki, S. Kovacic, C. Kenward, C. Y. Hong, D. G. Gordon, P. N. Levett, M. Krajden, R. Leduc, P. L. Boudreault, M. Niikura, M. Paetzel, R. N. Young, A. Cherkasov, N. C. J. Strynadka and F. Jean, A novel class of broad-spectrum active-site-directed 3C-like protease inhibitors with nanomolar antiviral activity against highly immune-evasive SARS-CoV-2 Omicron subvariants, *Emerging Microbes Infect.*, 2023, 2246594.
379 R. Liu, Y. Xu, L. Hua, J. Zhou, H. Deng, X. Chu and S. Ding, 3CL protease small-molecule inhibitor for treating or preventing coronavirus infection, and use thereof, WO2023011443, 2023.
380 S. Richards, M. Derudas, N. Ahlsten and K. Papachristos, MPro targeting antiviral compounds, WO2023180189, 2023.
381 L. D. Arnold, W. Keung and D. V. Kumar, Inhibitors of cysteine proteases and methods of use thereof, WO2023044171, 2023.
382 B. T. Campbell, W. Chang, T. J. Hartingh, D. M. Hurzy, M. J. Kelly III, F. M. Klinger, M. E. Layton, J. A. Mccauley, C. C. Nawrat, C. A. Parish, J. J. Perkins, A. J. Roecker, M. De Lera Ruiz, J. D. Schreier, V. W. Shurtleff, J. Su and Q. T. Truong, Protease Inhibitors for Treating or Preventing Coronavirus Infection, WO2023133174, 2023.
383 S. Ullrich, V. M. Sasi, M. C. Mahawaththa, K. B. Ekanayake, R. Morewood, J. George, L. Shuttleworth, X. Zhang, C. Whitefield, G. Otting, C. Jackson and C. Nitsche, Challenges of short substrate analogues as SARS-CoV-2 main protease inhibitors, *Bioorg. Med. Chem. Lett.*, 2021, **50**, 128333.
384 J. E. Hernández González, R. J. Eberle, D. Willbold and M. A. Coronado, A Computer-Aided Approach for the Discovery of D-Peptides as Inhibitors of SARS-CoV-2 Main Protease, *Front. Mol. Biosci.*, 2022, **8**, 816166.
385 R. Eberle, M. Sevenich, I. Gering, L. Scharbert, B. Strodel, N. A. Lakomek, K. Santur, J. Mohrlüder, M. A. Coronado and D. Willbold, Discovery of All-d-Peptide Inhibitors of SARS-CoV-2 3C-like Protease, *ACS Chem. Biol.*, 2023, **18**, 315.
386 T. Miura, T. R. Malla, C. D. Owen, A. Tumber, L. Brewitz, M. McDonough, E. Salah, N. Terasaka, T. Katoh, P. Lukacik, C. Strain-Damerell, H. Mikolajek, M. A. Walsh, A. Kawamura, C. J. Schofield and H. Suga, In vitro selection of macrocyclic peptide inhibitors containing cyclic γ2,4-amino acids targeting the SARS-CoV-2 main protease, *Nat. Chem.*, 2023, **15**, 998.
387 T. Zhai, F. Zhang, S. Haider, D. Kraut and Z. Huang, An Integrated Computational and Experimental Approach to Identifying Inhibitors for SARS-CoV-2 3CL Protease, *Front. Mol. Biosci.*, 2021, **8**, 661424.
388 A. Clyde, S. Galanie, D. W. Kneller, H. Ma, Y. Babuji, B. Blaiszik, A. Brace, T. Brettin, K. Chard, R. Chard, L. Coates, I. Foster, D. Hauner, V. Kertesz, N. Kumar, H. Lee, Z. Li, A. Merzky, J. Schmidt, L. Tan, M. Titov, A. Trifan, M. Turilli, H. Van Dam, S. C. Chennubhotla, S. Jha, A. Kovalevsky, A. Ramanathan, M. S. Head and R. Stevens, High-Throughput

Virtual Screening and Validation of a SARS-CoV-2 Main Protease Noncovalent Inhibitor, *J. Chem. Inf. Model.*, 2022, **62**, 116.

389 D. W. Kneller, H. Li, S. Galanie, G. Phillips, A. Labbé, K. L. Weiss, Q. Zhang, M. A. Arnould, A. Clyde, H. Ma, A. Ramanathan, C. B. Jonsson, M. S. Head, L. Coates, J. M. Louis, P. V. Bonnesen and A. Kovalevsky, Structural, Electronic, and Electrostatic Determinants for Inhibitor Binding to Subsites S1 and S2 in SARS-CoV-2 Main Protease, *J. Med. Chem.*, 2021, **64**, 17366.

390 S. Gao, K. Sylvester, L. Song, T. Claff, L. Jing, M. Woodson, R. H. Weiße, Y. Cheng, L. Schäkel, M. Petry, M. Gütschow, A. C. Schiedel, N. Sträter, D. Kang, S. Xu, K. Toth, J. Tavis, A. E. Tollefson, C. E. Müller, X. Liu and P. Zhan, Discovery and Crystallographic Studies of Trisubstituted Piperazine Derivatives as Non-Covalent SARS-CoV-2 Main Protease Inhibitors with High Target Specificity and Low Toxicity, *J. Med. Chem.*, 2022, **65**, 13343.

391 S. Gao, L. Song, T. Claff, M. Woodson, K. Sylvester, L. Jing, R. H. Weiße, Y. Cheng, N. Sträter, L. Schäkel, M. Gütschow, B. Ye, M. Yang, T. Zhang, D. Kang, K. Toth, J. Tavis, A. E. Tollefson, C. E. Müller, P. Zhan and X. Liu, Discovery and Crystallographic Studies of Nonpeptidic Piperazine Derivatives as Covalent SARS-CoV-2 Main Protease Inhibitors, *J. Med. Chem.*, 2022, **65**, 16902.

392 A. Morris, W. McCorkindale, T. C. M. Consortium, N. Drayman, J. D. Chodera, S. Tay, N. London and A. A. Lee, Discovery of SARS-CoV-2 main protease inhibitors using a synthesis-directed de novo design model, *Chem. Commun.*, 2021, **57**, 5909.

393 Z. Jiang, B. Feng, Y. Zhang, T. Nie, H. Liu, J. Li, H. Su, L. Zhang, Y. Zang and Y. Zhou, Discovery of novel non-peptidic and non-covalent small-molecule 3CLpro inhibitors as potential candidate for COVID-19 treatment, *Signal Transduction Targeted Ther.*, 2023, **8**, 209.

394 J. Sacchettini, N. E. Zhou, M. K. Parai, J. C. Shin, J. L. Wood, I. Krieger, A. C. F. Flores, A. Archarya, Z. Shi, X. Bian, S. Tang, R. Bam and P. K. Jaiswal, Inhibitors of SARS-COV-2, WO2022235813, 2022.

395 C. Huang, R. Zeng, J. Qiao, B. Quan, R. Luo, Q. Huang, N. Guo, Y. Li, X. Long, R. Ma, A. Xia, Z. Fang, Y. Wang, Y. Li, Y. Zheng, L. Li, J. Lei and S. Yang, Discovery and structure-activity relationship studies of novel α-ketoamide derivatives targeting the SARS-CoV-2 main protease, *Eur. J. Med. Chem.*, 2023, **259**, 115657.

396 C. Huang, H. Shuai, J. Qiao, Y. Hou, R. Zeng, A. Xia, L. Xie, Z. Fang, Y. Li, C. Yoon, Q. Huang, B. Hu, J. You, B. Quan, X. Zhao, N. Guo, S. Zhang, R. Ma, J. Zhang, Y. Wang, R. Yang, S. Zhang, J. Nan, H. Xu, F. Wang, J. Lei, H. Chu and S. Yang, A new generation Mpro inhibitor with potent activity against SARS-CoV-2 Omicron variants, *Signal Transduction Targeted Ther.*, 2023, **8**, 128.

397 Y. M. Shao, W. B. Yang, T. H. Kuo, K. C. Tsai, C. H. Lin, A. S. Yang, P. H. Liang and C. H. Wong, Design, synthesis, and evaluation of trifluoromethyl ketones as inhibitors of SARS-CoV 3CL protease, *Bioorg. Med. Chem.*, 2008, **16**, 4652.

398 J. Wang, B. Liang, Y. Chen, J. Fuk-Woo Chan, S. Yuan, H. Ye, L. Nie, J. Zhou, Y. Wu, M. Wu, L. S. Huang, J. An, A. Warshel, K. Y. Yuen, A. Ciechanover, Z. Huang and Y. Xu, A new class of α-ketoamide derivatives with potent anticancer and anti-SARS-CoV-2 activities, *Eur. J. Med. Chem.*, 2021, **215**, 113267.

399 M. Liu, J. Li, W. Liu, Y. Yang, M. Zhang, Y. Ye, W. Zhu, C. Zhou, H. Zhai, Z. Xu, G. Zhang and H. Huang, The S1'-S3' Pocket of the SARS-CoV-2 Main Protease Is Critical for Substrate Selectivity and Can Be Targeted with Covalent Inhibitors, *Angew. Chem., Int. Ed.*, 2023, e202309657.

400 P. Moon, C. M. Zammit, Q. Shao, D. Dovala, L. Boike, N. J. Henning, M. Knapp, J. N. Spradlin, C. C. Ward, H. Wolleb, D. Fuller, G. Blake, J. P. Murphy, F. Wang, Y. Lu, S. A. Moquin, L. Tandeske, M. J. Hesse, J. M. McKenna, J. A. Tallarico, M. Schirle, F. D. Toste and D. K. Nomura, Discovery of Potent Pyrazoline-Based Covalent SARS-CoV-2 Main Protease Inhibitors, *ChemBioChem*, 2023, **24**, e202300116.

401 F. Wang, R. Zeng, J. Qiao, A. Xia, Y. Li, F. Li, Y. Wu, Y. Liu, X. Zhao, J. Lei and S. Yang, Discovery of benzodiazepine derivatives as a new class of covalent inhibitors of SARS-CoV-2 main protease, *Bioorg. Med. Chem. Lett.*, 2023, **92**, 129407.

402 Y. Unoh, S. Uehara, K. Nakahara, H. Nobori, Y. Yamatsu, S. Yamamoto, Y. Maruyama, Y. Taoda, K. Kasamatsu, T. Suto, K. Kouki, A. Nakahashi, S. Kawashima, T. Sanaki, S. Toba, K. Uemura, T. Mizutare, S. Ando, M. Sasaki, Y. Orba, H. Sawa, A. Sato, T. Sato, T. Kato and Y. Tachibana, Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19, *J. Med. Chem.*, 2022, **65**, 6499.

403 H. Kai, T. Kameyama, T. Horiguchi, K. Asahi, T. Endoh, Y. Fujii, T. Shintani, K. Nakamura, S. Matsumoto, T. Hasegawa, M. Oohara, Y. Tada, T. Maki and A. Iida, Preparation of triazine derivatives and pharmaceutical compound that contains same and exhibits analgesic activity, WO2012020749, 2012.

404 G. D. Noske, E. de Souza Silva, M. O. de Godoy, I. Dolci, R. S. Fernandes, R. V. C. Guido, P. Sjö, G. Oliva and A. S. Godoy, Structural basis of nirmatrelvir and ensitrelvir activity against naturally occurring polymorphisms of the SARS-CoV-2 main protease, *J. Biol. Chem.*, 2023, **299**, 103004.

405 J. J. Wu, Triazine derivatives and methods of use thereof, US11702406, 2023.

406 H. Mukae, H. Yotsuyanagi, N. Ohmagari, Y. Doi, T. Imamura, T. Sonoyama, T. Fukuhara, G. Ichihashi, T. Sanaki, K. Baba, Y. Takeda, Y. Tsuge and T. Uehara, A Randomized Phase 2/3 Study of Ensitrelvir, a Novel Oral SARS-CoV-2 3C-Like Protease Inhibitor, in Japanese Patients with Mild-to-Moderate COVID-19 or Asymptomatic SARS-CoV-2 Infection: Results of the Phase 2a Part, *Antimicrob. Agents Chemother.*, 2022, **66**, e0069722.

407 R. Shimizu, T. Sonoyama, T. Fukuhara, A. Kuwata, Y. Matsuo and R. Kubota, Safety, Tolerability, and

Pharmacokinetics of the Novel Antiviral Agent Ensitrelvir Fumaric Acid, a SARS-CoV-2 3CL Protease Inhibitor, in Healthy Adults, *Antimicrob. Agents Chemother.*, 2022, **66**, e0063222.

408 H. Yotsuyanagi, N. Ohmagari, Y. Doi, T. Imamura, T. Sonoyama, G. Ichihashi, T. Sanaki, Y. Tsuge, T. Uehara and H. Mukae, A phase 2/3 study of S-217622 in participants with SARS-CoV-2 infection (Phase 3 part), *Medicine*, 2023, **102**, e33024.

409 S. Jiang, Y. Xiao, B. Guo, K. Zhang and C. Liu, Triazine compounds or pharamceutically acceptable salt or isomer therof, pharmaceutical composition, and use of thereof, WO2023173708, 2023.

410 C. He, H. Xu, Q. Liu, B. Liu, Y. Qi, Z. Zhou, R. Tan, Z. Huang, H. Tan, Z. Chen, Z. Li, Y. Wang, L. Chen, X. Wang, L. Yang, W. Dong, S. J. Lin, X. Zhao and W. Wang, Compounds as SARS-CoV-2 inhibitors, WO2023165459, 2023.

411 G. Li, R. Hilgenfeld, R. Whitley and E. De Clercq, Therapeutic strategies for COVID-19: progress and lessons learned, *Nat. Rev. Drug Discovery*, 2023, **22**, 449.

412 U.S. Department of Health & Human Services, **https://www.nih.gov/research**, (accessed 22/08/2023).

413 B. Halford, The Path to Paxlovid, *ACS Cent. Sci.*, 2022, **8**, 405.

414 S. Vankadara, M. D. Dawson, J. Y. Fong, Q. Y. Oh, Q. A. Ang, B. Liu, H. Y. Chang, J. Koh, X. Koh, Q. W. Tan, J. Joy and C. S. B. Chia, A Warhead Substitution Study on the Coronavirus Main Protease Inhibitor Nirmatrelvir, *ACS Med. Chem. Lett.*, 2022, **13**, 1345.

415 N. Pathak, Y. T. Chen, Y. C. Hsu, N. Y. Hsu, C. J. Kuo, H. P. Tsai, J. J. Kang, C. H. Huang, S. Y. Chang, Y. H. Chang, P. H. Liang and J. M. Yang, Uncovering Flexible Active Site Conformations of SARS-CoV-2 3CL Proteases through Protease Pharmacophore Clusters and COVID-19 Drug Repurposing, *ACS Nano*, 2021, **15**, 857.

416 N. Finch, C. W. Gemenden, I. H. S. Hsu, A. Kerr, G. A. Sim and W. I. Taylor, Oxidative Transformations of Indole Alkaloids. III. Pseudoindoxyls from Yohimbinoid Alkaloids and Their Conversion to "Invert" Alkaloids, *J. Am. Chem. Soc.*, 1965, **87**, 2229.

417 C. Pelligrini, M. Weber and H. J. Borschberg, Total synthesis of (+)-Elacomine and (−)-Isoelacomine, the two hiterto unamed oxindole alkaloids fro Elaeagnus commutata, *Helv. Chim. Acta*, 1996, **79**, 151.

418 S. Iketani, H. Mohri, B. Culbertson, S. Hong, Y. Duan, M. I. Luck, M. K. Annavajhala, Y. Guo, Z. Sheng, A. C. Uhlemann, S. P. Goff, Y. Sabo, H. Yang, A. Chavez and D. D. Ho, Multiple pathways for SARS-CoV-2 resistance to nirmatrelvir, *Nature*, 2023, **613**, 558.

419 M. Kiso, Y. Furusawa, R. Uraki, M. Imai, S. Yamayoshi and Y. Kawaoka, In vitro and in vivo characterization of SARS-CoV-2 strains resistant to nirmatrelvir, *Nat. Commun.*, 2023, **14**, 3952.

420 E. Takashita, S. Fujisaki, H. Morita, S. Nagata, H. Miura, M. Nagashima, S. Watanabe, M. Takeda, Y. Kawaoka and H. Hasegawa, Assessment of the frequency of SARS-CoV-2 Omicron variant escape from RNA-dependent RNA polymerase inhibitors and 3C-like protease inhibitors, *Antiviral Res.*, 2023, **216**, 105671.

421 M. Kiso, S. Yamayoshi, S. Iida, Y. Furusawa, Y. Hirata, R. Uraki, M. Imai, T. Suzuki and Y. Kawaoka, In vitro and in vivo characterization of SARS-CoV-2 resistance to ensitrelvir, *Nat. Commun.*, 2023, **14**, 4231.

422 Y. Hu, E. M. Lewandowski, H. Tan, X. Zhang, R. T. Morgan, X. Zhang, L. M. C. Jacobs, S. G. Butler, M. V. Gongora, J. Choy, X. Deng, Y. Chen and J. Wang, Naturally Occurring Mutations of SARS-CoV-2 Main Protease Confer Drug Resistance to Nirmatrelvir, *ACS Cent. Sci.*, 2023, **9**, 1658.

423 B. Tan, R. Joyce, H. Tan, Y. Hu and J. Wang, SARS-CoV-2 Main Protease Drug Design, Assay Development, and Drug Resistance Studies, *Acc. Chem. Res.*, 2023, **56**, 157.

