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Ashish Kumar
Research Scholar, Department of Chemistry, North Campus B.N.M.U, Madhepura, Bihar, India

Dr. Mohit Gupta
Sr. Assistant Professor, Department of chemistry L.N.M.S College, Birpur, Supaul, Bihar, India

Corresponding Author:
Dr. Mohit Gupta
Sr. Assistant Professor, Department of chemistry L.N.M.S College, Birpur, Supaul, Bihar, India

Targeting the sars-cov-2 main protease: A mini-review of warheads, p-site design, and lead optimization

Ashish Kumar and Mohit Gupta

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Abstract
SARS-CoV-2 main protease (Mpro / 3CLpro) is an essential viral enzyme responsible for polyprotein processing and maturation of the replication complex. Its strict preference for a Leu-Gln↓(Ser/Ala/Gly) motif and lack of close human homologs make it a high-selectivity antiviral target. Following early release of high-resolution crystal structures, global discovery programs rapidly applied structure-based design, converging on three non-negotiable interaction principles: (i) a P1 glutamine surrogate anchoring the S1 pocket, (ii) hydrophobic P2 bulk occupying S2, and (iii) tunable P3/P4 groups to balance solubility and pharmacokinetics. This mini-review summarizes the major chemotype classes advanced in 2020-2022: peptidomimetic aldehydes (11a/11b), ketoamides (13b), repurposed covalent inhibitors (N3, GC-376, boceprevir), nitrile-based reversible covalent inhibitors culminating in nirmatrelvir (Paxlovid), and emerging non-peptidyl scaffolds and metal complexes. We highlight design rules that consistently produced potent leads and caution against scaffolds that showed biochemical activity but failed under reducing or orthogonal validation assays. Collectively, these efforts illustrate how structural biology and computer-aided drug design accelerated the transition from concept to a clinically approved oral antiviral.

Keywords: Sars-cov-2, main protease (Mpro/3clpro), covalent warheads, p-site design, structure-based drug design

Introduction
"The COVID-19 pandemic exposed the limitations of relying solely on vaccines and immune-based therapeutics. SARS-CoV-2 continues to evolve, generating variants with altered transmissibility and partial immune escape, reducing the sustained effectiveness of antibody-based therapies and first-generation vaccines. In contrast, small-molecule antivirals that target conserved viral mechanisms remain resilient to viral evolution and are essential for outpatient treatment, early intervention, and protection of immunocompromised patients.
Among the viral proteins required for replication, two cysteine proteases such as the papain-like protease (PLpro) and the main protease (Mpro / 3CLpro) cleave the viral polyprotein into functional non-structural proteins (nsps). Mpro performs more than 11 out of 14 proteolytic cleavages, making it indispensable for viral maturation. Unlike host proteases, Mpro requires a unique Leu-Gln↓(Ser/Ala/Gly) motif, which does not occur in human proteases.

This gives Mpro two critical properties from a drug-discovery standpoint
1. High target selectivity: low risk of off-target protease toxicity
2. Conserved substrate recognition: low likelihood of resistance development

With the first Mpro crystal structures released just weeks into the pandemic (PDB 6LU7), global research rapidly converged on structure-guided inhibitor design. Early medicinal chemistry campaigns discovered three non-negotiable interaction principles:
- A P1 glutamine surrogate (e.g., (S)-γ-lactam or hydantoin) to anchor the S1 pocket via His163/Glu166,
- A hydrophobic P2 group to occupy the deep S2 subsite,
- A modifiable P3/P4 cap, affecting solubility and pharmacokinetics more than potency.

Warhead choice defined the direction of each scaffold like aldehydes and ketoamides (covalent), Michael acceptors (irreversible), and nitriles (reversible covalent). The earliest leads (11a/11b and 13b) validated the design logic, while repurposing efforts identified N3, boceprevir, and GC-376. Optimization of polarity, metabolic stability, and warhead reactivity ultimately produced nirmatrelvir (Paxlovid), the first FDA-approved oral Mpro inhibitor and a clinical proof that rational covalent design works.

This mini-review summarizes the evolution of Mpro inhibitor design across four chemotype classes peptidomimetic aldehydes/ketoamides, repurposed covalent inhibitors, non-peptidyl small molecules, and metal-based complexes and extracts practical design rules: which decisions led to clinical success, and which scaffolds looked promising but collapsed under biochemical scrutiny (redox sensitivity, PAINS behavior).

Target and Pocket Primer

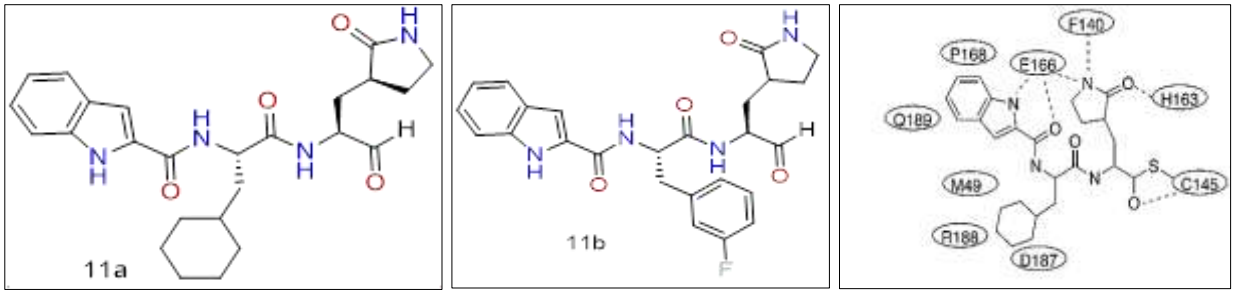
The SARS-CoV-2 main protease (Mpro) contains a catalytic dyad Cys145-His41, responsible for peptide bond cleavage during viral polyprotein processing. The active site is organized into well-defined subsites: S1, S2, S3, and S4, each accommodating corresponding positions on the inhibitor (P1, P2, P3, P4) according to Schechter-Berger notation. The S1 pocket forms a highly conserved hydrogen-bonding network (His163, Glu166, Phe140/oxyanion hole), which requires a glutamine-mimicking group at P1 typically an (S)-γ-lactam or hydantoin making it the most critical determinant of potency and selectivity. The S2 pocket is deep and hydrophobic, favoring bulky aliphatic or bicyclic residues at P2, while S3/S4 are more solvent exposed and allow chemical variation to tune solubility and pharmacokinetics rather than intrinsic binding energy. Together, these structural features define the "anchor points" that guide rational inhibitor design.

Peptidomimetic aldehydes were the first chemotype to validate covalent inhibition of Mpro through rational structure-guided design. They exploit the anchoring interactions in the S1 (P1 glutamine mimic) and S2 (hydrophobic P2) pockets while presenting an electrophilic aldehyde warhead that forms a covalent adduct with Cys145. Early optimization focused on identifying the optimal P2 bulky group and a solubility-improving P3 cap. Dai *et al.* reported the first low-nanomolar leads (11a/11b), establishing aldehydes as credible antiviral candidates and setting the SAR template for subsequent scaffolds.

Peptidomimetic Aldehyde Inhibitors (11a and 11b, Dai *et al.*, 2020)

One of the earliest studies applying structure-based drug design to SARS-CoV-2 Mpro was carried out by Dai and colleagues. Building on knowledge of SARS-CoV inhibitors, particularly those containing an (S)-γ-lactam ring for the S1 pocket, the group designed two new compounds, 11a and 11b. Substituents at P2 (cyclohexyl or 3-fluorophenyl) and an indole group at P3 were introduced to enhance interactions. Both inhibitors covalently bound to Cys145 in the protease active site.

Crystallographic analysis revealed hydrogen bonding of the lactam oxygen with His163 and Phe140, as hydrophobic stabilization by the P2 group. Additionally, there were contacts from the P3 indole with Glu166 and Pro168. Compound 11a exhibited a half-life of 7.6 hours in rats and 5.5 hours in dogs, with low clearance, making it a stronger candidate than 11b. Both compounds exhibited nanomolar inhibitory activity (IC_{50} = 0.053 μM for 11a; 0.040 μM for 11b) and sub micromolar EC_{50} values in infected cells, with no observed toxicity (CC_{50} > 100 μM). These findings established aldehyde-based peptidomimetics as promising leads for COVID-19 therapy [1].

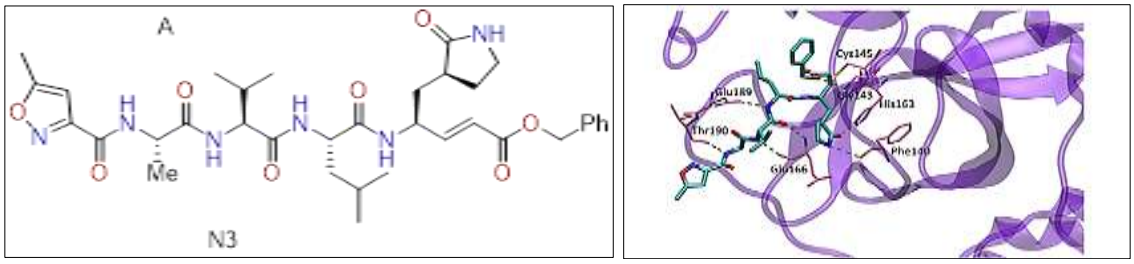


A B

Fig 1: (A) Inhibitors 11a and 11b. (B) Scheme of the interactions in the X-ray structure of inhibitor **11a** with SARS-CoV-2 Mpro.

Repurposed Covalent Inhibitor N3 (Jin *et al.*, 2020)

In parallel, Jin and colleagues identified **N3**, a Michael acceptor compound known to inhibit SARS-CoV and MERS-CoV proteases, as a time-dependent inhibitor of SARS-CoV-2 Mpro. The enzyme-inhibitor complex (PDB 6LU7) was resolved at 2.1 Å, showing covalent bond formation between the vinyl group and Cys145, with additional stabilization by water molecules and residues in the S1 and S2 pockets. N3 displayed antiviral activity in Vero cells (EC_{50} = 16.77 μM). Its lactam ring occupied the S1 site, while isobutyl and isopropyl side chains engaged S2 and S3. This study provided the first structural framework for SARS-CoV-2 protease inhibition, guiding subsequent design efforts [2].



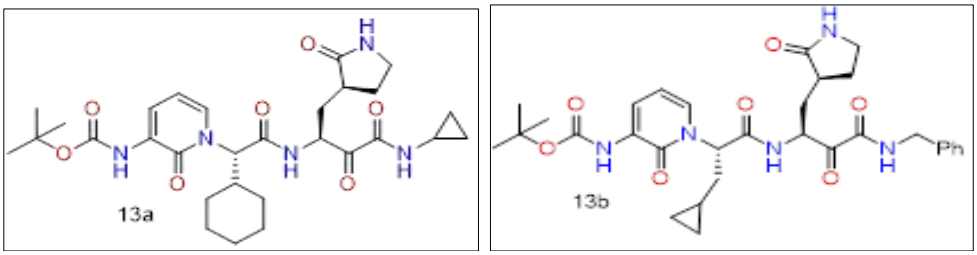
A B

Fig 2: (A) Chemical structure of N3 inhibitor. (B) X-ray structure of the complex between N3 and SARS-CoV-2 Mpro.

Ketoamide Derivatives 13a and 13b (Hilgenfeld *et al.*, 2020)

Hilgenfeld's group advanced ketoamide-based inhibitors originally developed for MERS-CoV. By introducing a pyridone at the P2-P3 position to prevent cleavage and enhance plasma stability, they created 13a and 13b. The more potent 13b inhibited Mpro with an IC_{50} of 0.67 µM and blocked viral replication in Calu-3 cells (EC_{50} = 4-5 µM) [3].

The crystal structure (PDB 6Y2F) revealed the formation of a thiohemiketal at Cys145, stabilized by hydrogen bonds within the oxyanion hole. A γ-lactam occupied the S1 pocket, while cyclopropyl at P2 gave better fit than cyclohexyl. These results confirmed ketoamides as viable protease inhibitors [2].



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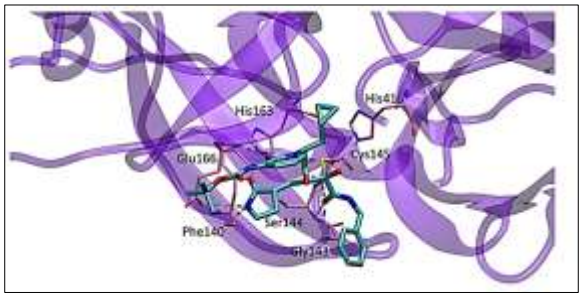
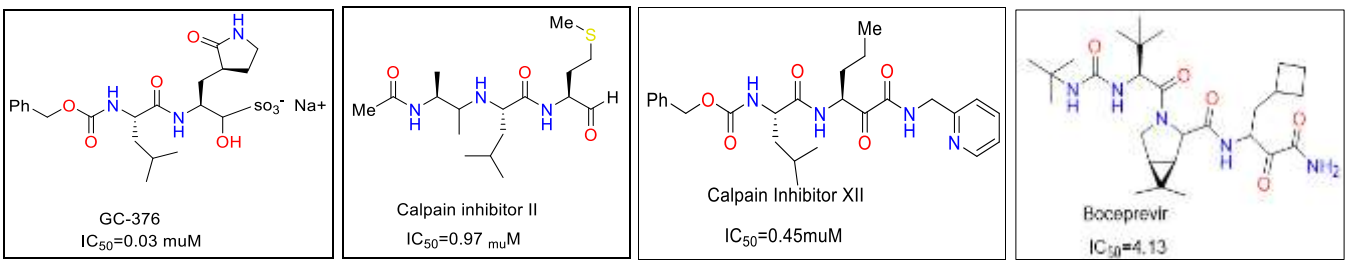


B

Fig 3: (A) Inhibitors **13a** and **13b**. (B) X- ray structure of SARS-CoV-2 Mpro in complex with inhibitor 13b.

Broad screening of known protease inhibitors (Dai *et al.*, 2020) Another study screened 55 protease inhibitors against Mpro using a FRET assay. Four compounds emerged with strong inhibitory activity: boceprevir (an HCV drug), GC-376, and calpain inhibitors II and XII. Their IC_{50} values were in the low micromolar to submicromolar range, with antiviral activity in cell culture and low toxicity (CC_{50} > 50-100 µM) [4].

The crystal structure of GC-376 bound to Mpro (PDB 6WTT) showed hemithioketal formation with Cys145, a γ-lactam interacting with His163 and Glu166, and benzyl groups filling the S4 pocket. These findings highlighted the potential of repurposing existing protease-targeting drugs [2, 5].



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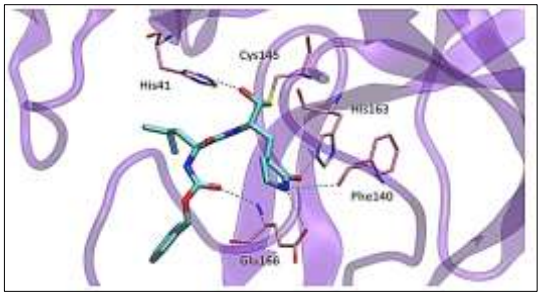


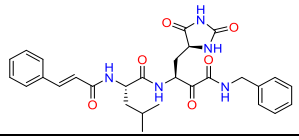
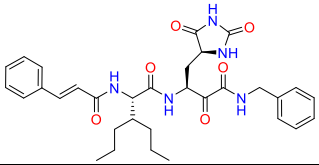
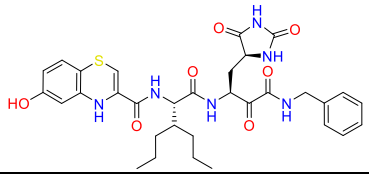
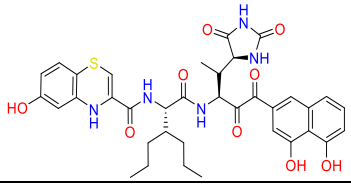
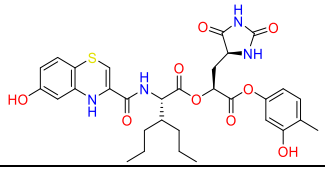
B

Fig 4: (A) Inhibitors of SARS-CoV-2 Mpro Enzyme. (B) X-ray structure of the complex between GC-376 and SARS-CoV-2 Mpro.

In 2020, Frecer and colleagues reported a rational design campaign targeting the SARS-CoV-2 main protease (Mpro) using peptidomimetic ketoamide scaffolds closely related to earlier SARS-CoV inhibitors. Beginning with the parent compound 11a, the team performed systematic fragment optimization at the P1, P2, P3, and P1′ positions. Each stage of modification was guided by in silico interaction energy calculations (MM-OPLS3e in solution) and validated through binding affinity estimations.

The optimization sequence revealed that C4, bearing a hydantoin ring at P1, enhanced binding by ~5 kcal·mol^{-1} relative to the starting scaffold. Further substitution at P2 with aliphatic/alicyclic residues yielded C9 as the best variant in this set. At P3, replacement of the aromatic moiety afforded improved activity, culminating in analogs with binding free energies as low as -3.6 kcal·mol^{-1}. Exploration of the P1′ site indicated that phenolic substitutions achieved the strongest stabilization, with binding energies reaching -14.7 kcal·mol^{-1}. Integrating these optimized fragments cooperatively led to higher-order candidates, where C34 emerged as the most potent inhibitor (-16.8 kcal/mol^{-1}), although C31 and C33 also displayed competitive activity. Collectively, this study demonstrated the power of fragment-wise tailoring in advancing lead ketoamides against SARS-CoV-2 Mpro

Table 1: Stepwise optimization of peptidomimetic ketoamide inhibitors of SARS-CoV-2 Mpro as reported by Frecer *et al*., highlighting fragment modifications and their impact on binding affinity

Optimization Step	Representative Compound	Structural Change	Observed Effect on Binding	Best Outcome
P1 site	C4 	Hydantoin ring introduced	Improved stabilization by ~5 kcal·mol^{-1}	C4 selected as template for next step
P2 site	C9 	Iso-butyl replaced with aliphatic/alicyclic residues	Highest gain ~0.7 kcal·mol^{-1}	C9 chosen for P3 design
P3 site	C17(best aromatic analog) 	Parent aromatic ring substituted with diverse aromatics	Binding energy down to -3.6 kcal·mol^{-1}	Optimized P3 fragment integrated
P1′ site	C20 (phenol derivative) 	Phenolic group introduced	Strongest interaction (-14.7 kcal·mol^{-1})	Phenolic group prioritized
Combined scaffold	C34 (also C31, C33) 	Integration of optimized P1, P2, P3, and P1′ fragments	Cooperative effect enhanced binding	C34 best candidate (-16.8 kcal·mol^{-1})

Aldehyde-Based Series (Qiao *et al*., 2021)

Qiao and coworkers synthesized 32 aldehyde inhibitors, incorporating a glutamine surrogate at P1, bicycloproline at P2, and variable P3 groups. Most compounds were highly active, with IC_{50} values ranging from 7.6 to 748.5 nM. One standout, MI-23, achieved a potency of 7.6 nM potency [6].

The crystal structure showed covalent bonding to Cys145 and multiple stabilizing hydrogen bonds within the oxyanion hole and S1 pocket. Many compounds exhibited favorable pharmacokinetics and oral bioavailability of greater than 10%, supporting their development as candidates [2].

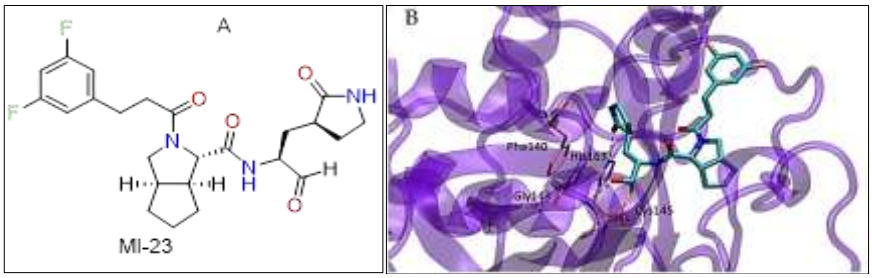


Fig 5: Chemical structure of Inhibitor MI-23. (B) Detail of x-ray structure

Pfizer Series: PF-00835231 and PF-07321332 (nirmatrelvir)

Pfizer's initial candidate, PF-00835231, was originally developed for SARS-CoV and repurposed for SARS-CoV-2. A phosphate prodrug (PF-07304814) improved solubility for IV administration. Both compounds showed strong *in vitro* activity and good safety [7, 8].

Later, oral bioavailability issues with PF-00835231 prompted the design of PF-07321332, a nitrile-based reversible inhibitor. Substitutions at P2 and P3 improved solubility and potency. This compound, now known as nirmatrelvir (marketed as Paxlovid with ritonavir), became the first FDA-approved oral antiviral targeting SARS-CoV-2 Mpro [9].

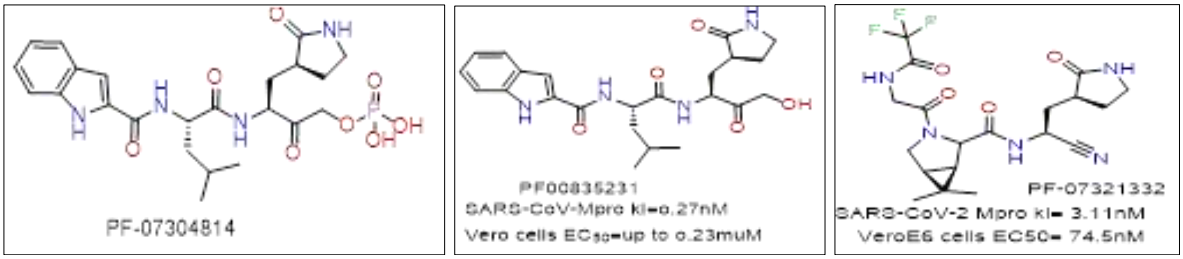


Fig 6: Pfizer inhibitors of SARS-CoV-2 Mpro enzyme

Organoselenium compounds: Ebselen and derivatives

Screening identified ebselen, a seleno-organic drug with antioxidant and anti-inflammatory activity, as a SARS-CoV-2 Mpro inhibitor (IC_{50} = 0.67 µM). It also inhibited PLpro (IC_{50} = 2.26 µM). Crystal structures revealed binding via selenium-sulfur interaction with Cys145 and a secondary domain interface site important for dimerization [10-16].

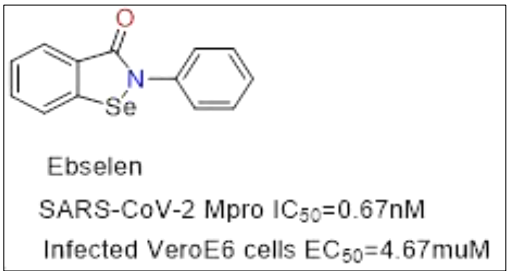


Fig 7: Chemical structure and inhibitory data of ebselen

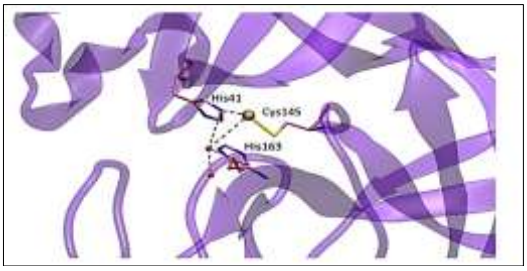


Fig 8: Crystal structure of selenium-Mpro complex

Further analogues such as ebsulfur derivatives (compounds 1i, 2k) and hydantoin-based analogs improved potency (IC_{50} = 0.077 µM). However, activity was diminished in reducing conditions (e.g., DTT), raising concerns of non-specific inhibition [17-19].

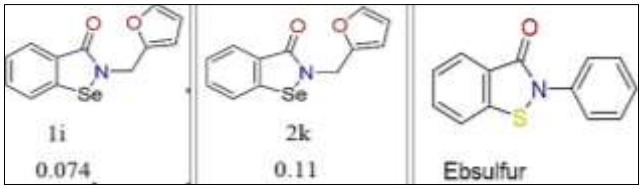


Fig 9: Ebselen derivatives and Ebsulfur

Non-peptidyl small molecules

Several non-peptidyl scaffolds emerged to address limitations of peptidomimetics (large size, polarity, limited oral exposure), multiple groups explored non-peptidyl chemotypes indole esters, dihydroquinolinones, natural products, and organoselenium compounds. These scaffolds engage Mpro through π-stacking, hydrophobic interactions, or alternative covalent chemistries. However, several hits showed redox sensitivity or promiscuous inhibition, highlighting the need for stringent validation beyond enzymatic IC_{50}.

- Dihydroquinolinone derivative Z222979552, from large library screening, showed antiviral activity in cells and favorable binding (PDB 7P2G) [20].

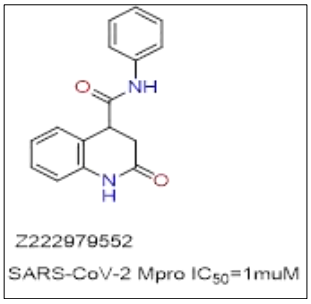


Fig 10: Chemical structure of compound Z222979552

- Indole chloropyridinyl esters such as GRL-1720 and optimized analog 7d acted as covalent inhibitors, acylating Cys145. Crystal structures confirmed indole-mediated π-π interactions (PDB 7RC0) [21, 22, 2].

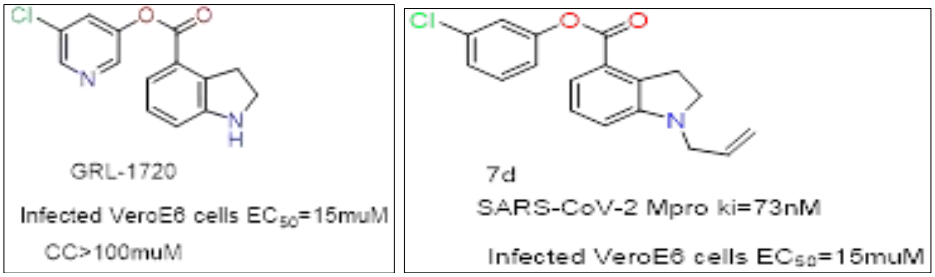


Fig 11: Indole chloropyridinyl esters as SARS-CoV-2 Mpro inhibitors

- Natural products neoechinulin A and echinulin A inhibited Mpro with IC_{50} values of 0.47 and 3.90 μM, stabilized by hydrogen bonds with active-site residues [23].

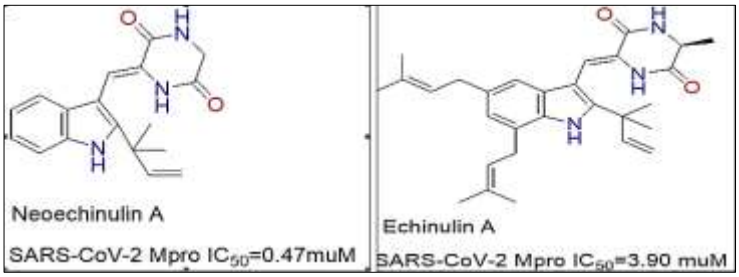


Fig 12: Marine natural products neoechinulin A and echinulin A inhibitors of SARS-CoV-2 Mpro enzyme.

- Polyphenols **PGG** and **EGCG** showed micromolar inhibition of Mpro through hydrogen bonding and hydrophobic contacts [24].

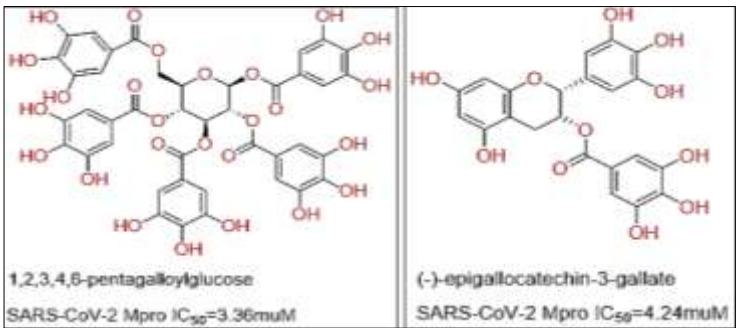


Fig 13: Natural products pentagalloyl glucose (PGG) and (-)-epigallocatechin-3-gallate (EGCG) as SARS-CoV-2 Mpro inhibitors

- **Shikonin**, a naphthoquinone, induced conformational changes at the catalytic dyad but lost activity in reducing conditions [2, 25].

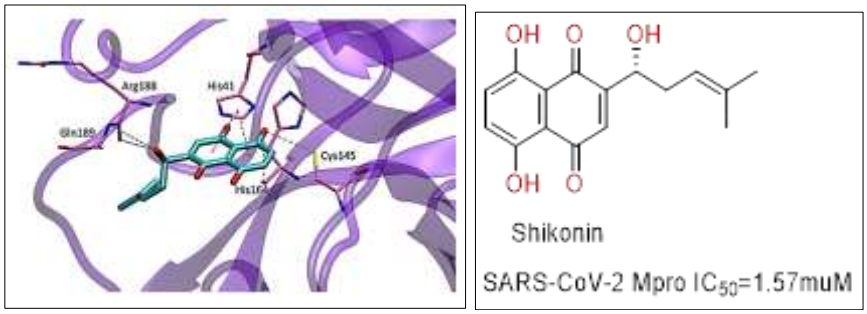


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Fig 14: (A) Crystal structure of the complex formed between shikonin and SARS.CoV-2 Mpro Chemical structure of shikonin.

- **9, 10-Dihydrophenanthrene derivatives** also inhibited Mpro by binding near the dimer interface [26].

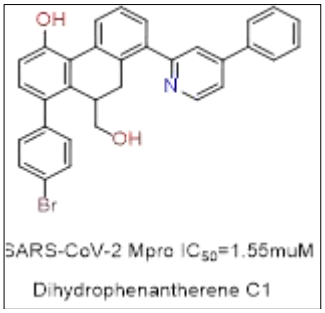

Fig 15. Dihydrophenantherene

- Novel covalent inhibitors derived from X77 were synthesized using Ugi chemistry; vinyl sulfone (14a) and chloroketone (16a) were 10-fold more potent than the parent compound [27].

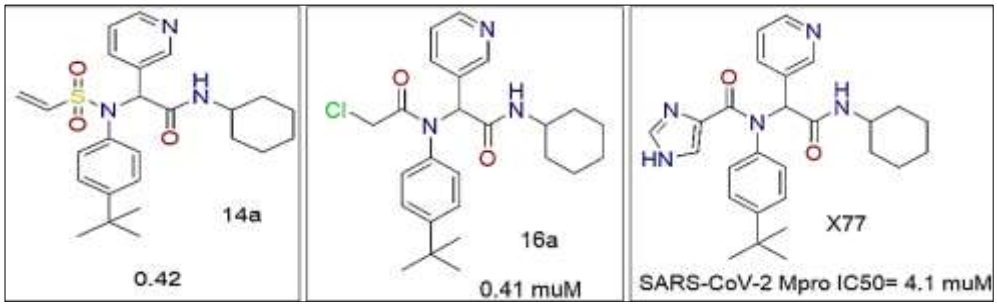

Fig 16: Inhibitors 14a and 16a derived from X77

Metal-based inhibitors

Metal complexes also demonstrated inhibitory activity. Rhenium tricarbonyl complex 34 inhibited Mpro [28], while zinc [29] and zinc-thiotropilone complexes showed nanomolar potency [30]. Bismuth drugs such as colloidal bismuth subcitrate (CBS), alone or combined with N-acetyl-L-cysteine, also reduced protease activity [31].

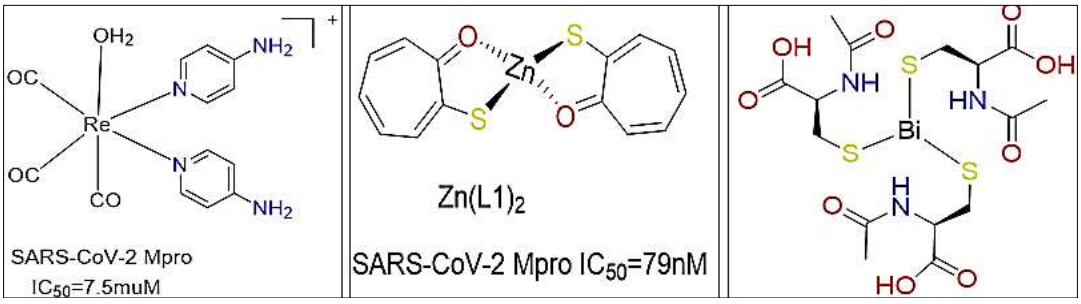

Fig 2.21. Metal complexes as inhibitors of SARS-CoV-2 main protease.

Conclusion

The rapid discovery of SARS-CoV-2 Mpro inhibitors demonstrated how structural biology and rational design can compress the antiviral discovery timeline. Early peptidomimetic aldehydes and ketoamides established the essential binding rules a P1 glutamine mimic, hydrophobic P2 bulk, and a warhead positioned toward Cys145. Repurposed inhibitors validated covalent engagement, and systematic optimization ultimately produced nirmatrelvir, the first oral clinical Mpro inhibitor. Although many non-peptidyl and metal-based molecules displayed biochemical activity, only those guided by structure-activity logic and pharmacokinetic feasibility translated into drug-like candidates. Future antiviral development against emerging variants must continue to integrate CADD, crystallography, and fragment-wise optimization to rapidly identify leads with genuine translational potential.

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