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Advances in developing small molecule SARS 3CL^{pro} inhibitors as potential remedy for corona virus infection

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ABSTRACT

Originated in China, coronavirus disease 2019 (COVID-19)- the highly contagious and fatal respiratory disease caused by SARS-CoV-2 has already infected more than 29 million people worldwide with a mortality rate of 3.15% (according to World Health Organization's (WHO's) report, September 2020) and the number is exponentially increasing with no remedy whatsoever discovered till date. But it is not the first time this infectious viral disease has appeared, in 2002 SARS-CoV infected more than 8000 individuals of which 9.6% patients died and in 2012 approximately 35% of MERS-CoV infected patients have died. Literature reports indicate that a chymotripsin-like cystein protease (3CL^{pro}) is responsible for the replication of the virus inside the host cell. Therefore, design and synthesis of 3CL^{pro} inhibitor molecules play a great impact in drug development against this COVID-19 pandemic. In this review, we are discussing the anti-SARS effect of some small molecule 3CL^{pro} inhibitors with their various binding modes of interactions to the target protein.

Contents

1. Introduction

After the official declaration of the public health emergency of international concern by World Health Organization (WHO) on 30 January 2020; there has been a proliferation of research activities on COVID-19 disease in search for an immediate remedy [1,2]. This

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novel coronavirus SARS-CoV-2, emerged in the Wuhan city of China in December 2019, is rapidly spreading into various countries/regions of the world within few days [3,4]. The virus was provisionally named as the 2019 novel coronavirus (2019-nCoV) which was later renamed by the International Committee on Taxonomy of Viruses as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) on 11 February 2020 [5,6]. On the same day WHO also announced the name of the contagion disease caused by this novel coronavirus as Corona Virus Disease (COVID-19) [7]. It was the sixth public health emergency of international concern as declared by WHO after novel influenza A or H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in Congo (2019) [8].

1.1. Why SARS-CoV-2?

The emergence of SARS-CoV-2 is not totally new to the world as Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) already hit the various parts of the world in 2002 and 2012 respectively [9,10]. Moreover replication mechanism and pathogenesis of various coronaviruses were studied in early 1970s, but it gained much more attention after the SARS outbreak in 2002 [11]. In the history of 21st century, SARS-CoV-2 has been recognized as the most infectious, fatal and pathogenic coronavirus after SARS-CoV and MERS-CoV as until now more than 0.9 million people died out of more than 29 million infected people [the infected fatality rate (IFR) around 3.15% as compared to the SARS-CoV (800 deaths) and MERS-CoV (858 deaths)] [12,13]. From the above data it is clear that SARS-CoV-2 is much more dangerous and virulent as compared to SARS-CoV and MERS-CoV and the number of infected people/deaths are increasing at a very high rate day by day. The similar name of SARS-CoV and SARS-CoV-2 was introduced by scientific community due to the 86% genome sequence similarity of SARS-CoV-2 with SARS-CoV while MERS-CoV has almost 50% similarity to that of the SARS-CoV-2.[14a] In addition, bats are the primary origin of these viruses as genome sequence of SARS-CoV-2 has significant homology (96.2%) to that of the bat coronavirus (Scheme 1) [14b].

1.2. What is coronavirus?

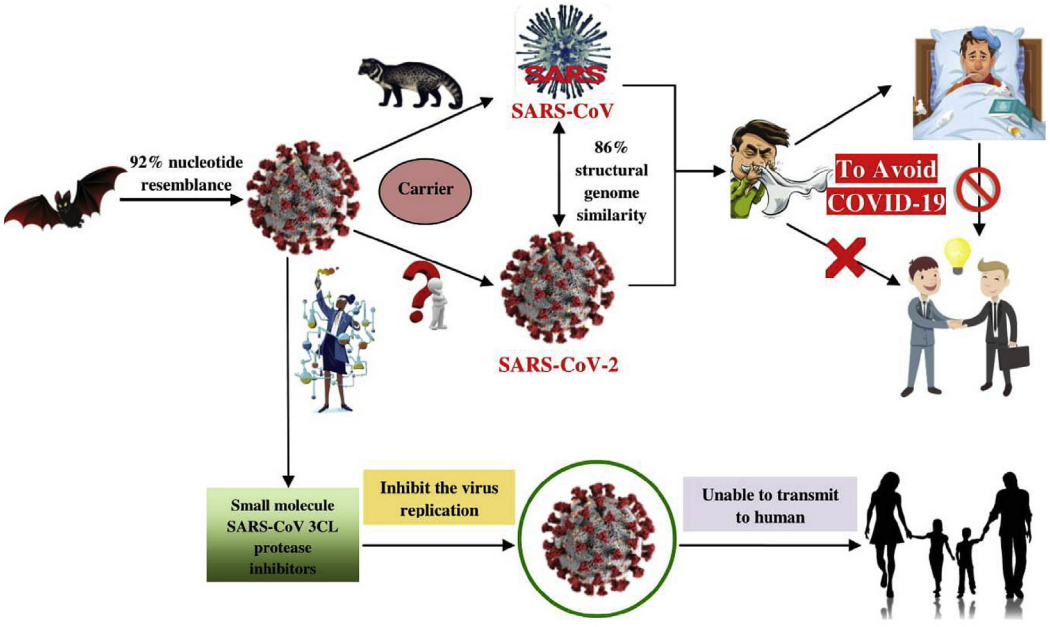
Structurally, SARS-CoV-2 is encircled with positive-sense, mono-stranded RNA virus with basic reproductive number around 2–4 [15]. Coronavirus is an enveloped RNA virus which belongs to the family of coronaviridae with the classification of four genera including α, β, γ, δ-CoV [13]. As reported, α- and β-CoV are responsible for the infection in mammals while γ- and δ-CoV are responsible for the infection in birds. But out of α- and β-coronaviruses, α-CoVs have less fatal effects causing only common cold with mild respiratory problems while β-CoVs are mainly conscientious for the harsh and potentially incurable SARS-CoV and MERS-CoV [16–18]. As mentioned earlier, SARS-CoV-2 has 86% genome sequence similarity with that of SARS-CoV, it is clear that SARS-CoV-2 also belongs to the β-coronavirus. The primary symptoms of the SARS are the fever above 38 °C with the pneumonia and breathe related problems [19].

2. Way of transmission and outbreak of SARS-CoV-2

Literature report suggested that the advancement of SARS-CoV and SARS-CoV-2 was emerged from the non-human sources (bat) while there is probably an unidentified intermediary reservoir for SARS-CoV-2 (intermediary reservoir for SARS-CoV was Civet cat while camel was the intermediary reservoir for MERS-CoV) [20]. The key feature for the human-to-human transmission involves the transfer of respiratory droplets, direct contact, fecal-oral route, suspected mother to the new born baby, through aerosols etc. [21] Moreover, reports also suggested that SARS-CoV-2 was also independently introduced from the animals to human with or without the involvement of carrier. As reported, bat coronavirus and SARS-CoV-2 might assign the identical precursor as bats are recognized to be host reservoir for more than 30 coronaviruses with more than 92% nucleotide resemblance [22].

3. Structure and key features of SARS-CoV-2

SARS-CoV-2 is a mono-stranded RNA virus surrounded with positive-sense containing club-shaped spikes pointing upwards



Scheme 1. Pictorial representation showing the difference of SARS-CoV from SARS-CoV-2.

Similarity between SARS-CoV and SARS-CoV-2
1. Both of them have 86% structural genome similarity.
2. Bat is the primary reservoir of the both of them.
3. Pneumonia is the most common symptoms in both of them with the fever above 38 °C.
4. Both of them have the structurally similar to the bat coronavirus.
5. Both of them are β−coronavirus.
6. Pandemic potential is very high in both the cases.
7. Highly efficient human-to-human transmission.
8. Incubation period is 1−14 days in both the cases while the initial 3−8 days are most potent to infection.
9. Fatality rate is more than 3% in both the cases (as per WHO report).*

* For SARS-CoV-2 it is increasing day by day.

from its surface. These spikes are actually a type of glycoprotein and named as spikes proteins (S) [23]. Along with spikes proteins, the membrane of coronavirus is composed of other two proteins *viz*. membrane proteins (M) and a highly hydrophobic small structured envelope protein (E). Membrane protein is responsible for the extension of virus membrane while envelope protein mainly wraps the integral part of the virus [24]. Integral part of the virus mainly contains nucleocapsid protein, replicase polyproteins and other accessory proteins which hamper the host's intrinsic resistant system. Nucleocapsid proteins are mainly responsible for the formation of helical capsids when they come in contact with genomic RNA inside the cell membranes. Replicase polyproteins are of two types' *viz*. pp1a and pp1ab which are found in open reading frames of the virus and from these polyproteins, the replication of the virus is proceeded by prevalent proteolytic process [25].

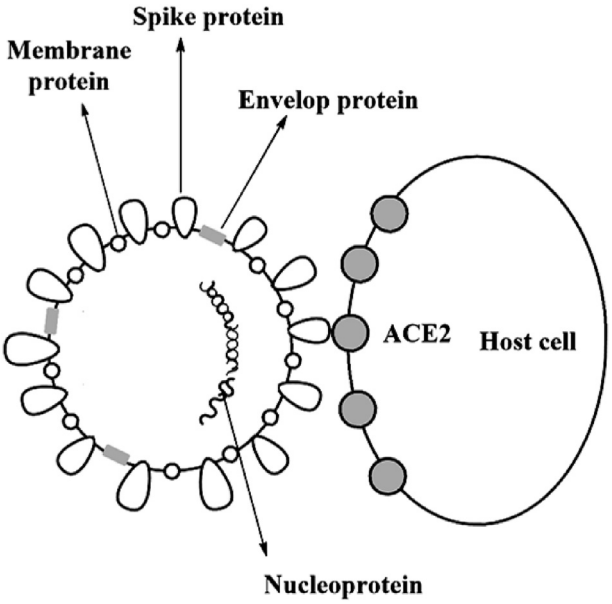
4. Replication and its pathogenicity

The angiotensin-converting enzyme 2 (ACE2) is the key receptor for the cell access for both SARS-CoV and SARS-CoV-2 which infect humans while dipeptidyl peptidase 4 was the receptor for the MERS-CoV [26]. Reports have also established that SARS-CoV-2 has an analogous binding receptor (S protein of coronavirus) to SARS-CoV, which attaches the receptor protein of the infected cell, enabling the virus to raid and infect the host cells [27,28]. ACE2 which is known as cell receptor for both SARS-CoV-2 and SARS-CoV is found in the lower respiratory area of human body in which S-glycoprotein of coronavirus attaches to replicate the virus and regulates human-to-human transmission [29]. The two subunits, S1 and S2 of S-glycoprotein of coronavirus are mainly responsible for the various activities of the SARS-CoV-2. The S1 subunit is mainly responsible for the determination of range of the virus-host ability and cellular tropism whereas S2 subunit intercedes the fusion ability of the virus-cell membrane by two simultaneous domains, heptad repeats 1 and 2 (HR 1 and 2) [30,31]. Following the virus-cell membrane fusion, the viral RNA is liberated into the cytoplasm and the two replicase polyproteins, pp1a and pp1ab which convert the non-structural virus proteins to form replication complex (RTC) to infect the host cell and thus the replication goes on [32]. For proteolytic and replication processing of SARS-CoV and SARS-CoV-2, they have to encode a protease, known as chymotripsin-like cystein protease ($3CL^{pro}$) or more commonly known as Main protease (M^{pro}) [33]. $3CL^{pro}$ is a part of the replicase polyproteins (similar to the 3C protease of main picoronavirus) which plays the major role in the viral imitation through proteolysis releasing replicative proteins from their polyproteins precursor to the infected host cell at 11 different cleavage sites [34]. Therefore, for viral replication and infection process of the coronavirus inside the host cell, $3CL^{pro}$ is very much requisite [35]. The practical congregation of $3CL^{pro}$ is believed to be in the form of dimer where each monomer contains one independent active site making $3CL^{pro}$ dimer more active than the monomer [36]. Moreover, in the active site of the enzyme $3CL^{pro}$, cysteine acts as a nucleophile and histidine residue acts as a base [37]. The key steps during the viral entry of the SARS-CoV-2 include the binding interaction of the host cells receptor, ACE2 with the spike protein of virus S protein, subsequent changes in the conformation of the S protein followed by proteolysis for the activation of the COVID-19 in the human cells [38]. In addition to that, the two replicase polyproteins, pp1a and pp1ab which are also known as the promoters for viral replication are arranged perpendicularly to one another and both of them contain three domains I, II and III. Domains I and II have similar structural β−patterns as present in picoronavirus 3C proteinases [39]. These domains are mainly responsible for the substrate binding and the autocatalytic ability containing Cys145 and His41 residues. In addition, domain III attaches to the domain II via five different α-helices with an exterior circle which primarily preserves the accurate conformation of the dimer after proteolytic activity of SARS-CoV $3CL^{pro}$.

5. Symptoms and clinical approaches

As mentioned earlier, SARS is mainly characterized by high fever above 38 °C or higher accompanied with breathing problems due to infection in lower respiratory tract, fatigue, dry cough, runny nose, atypical pneumonia and sore throat which are very common in nature [40]. Moreover, several other patients are found to have different gastrointestinal symptoms such as diarrhea, vomiting, nausea, abdominal discomfort etc. [41] The incubation period of SARS-CoV-2 infection is 1−14 days, but generally 3−7 days are the most significant to show the above mentioned symptoms. These clinical symptoms are further analyzed and classified in four different stages: a) Asymptomatic or recessive infection which occur in the initial 3−5 days of the infection; b) Respiratory tract infection which involves mild fever, sore throat, fatigue, headache and abdominal discomfort; c) Mild pneumonia which involves dry cough accompanied with or without serene fever; d) Severe pneumonia involving severe respiratory problems with high respiratory rate (more than 72 times per min), lower saturated oxygen percentage in blood (below 92%), unconsciousness etc. [42] By analysing various data related to the COVID-19, it was well reported that around 50% of the adult patients suffering from SARS-CoV-2 have diverse abnormal liver functions which may be due to dysfunction of bile duct caused by the viral infection.

Various chemical and analytical techniques such as next-generation sequencing, cell-culture, real time PCR, electron microscopy etc. have been used to detect SARS-CoV-2 [43,44]. From medicinal chemistry perspectives, an imperative and promising advance to fight with COVID-19 is to develop molecules that can inhibit the essential major polyprotein processing, $3CL^{pro}$. As $3CL^{pro}$ is very much crucial for the viral replication, it is widely regarded as a major drug target for the development of SARS treatment [45]. Several synthetic inhibitors for the $3CL^{pro}$ have been reported but they are relatively weak in nature [46]. The inhibitors initially bind with the $3CL^{pro}$ through covalent bonding with the active site of the cysteine 145 residue leading to the deactivation of $3CL^{pro}$'s enzymatic activity [47]. The binding of S-glycoprotein of the virus and ACE2 receptor is a decisive step for virus entry and the virus-receptor binding affinity is under intensive study through different approaches. Additionally this approach also suggests that the S pockets of $3CL^{pro}$ have been the principal targeting sites for anti-SARS molecules which can block the cysteine site and do not make them free to attach with the ACE2 receptor molecule. The reasons behind the choice of $3CL^{pro}$ inhibition as the target are a)



Scheme 2. Schematic representation showing viral binding of SARS-CoV with the receptor, ACE2.

$3CL^{pro}$ has the predetermined crystal structure which makes them more approachable in the study, b) $3CL^{pro}$ is the most studied enzyme of coronavirus which is also common in various bacterial systems and its functional examination such as proteolytic activity is very much easy in presence of inhibitor molecules, c) practical importance of $3CL^{pro}$ in the life cycle of coronavirus make them more practically superlative as a target for antiviral drug design [48,49].

In this review, we are trying to analyse the various small molecules/drugs developed as cysteine protease inhibitors or anti-SARS therapy. As COVID-19 is virus infected disease and till now there is not a single commercially available protective drug/vaccine present in the market, therapies currently undergoing include the application of existing drugs used to treat malaria and autoimmune diseases [50]. Antiviral drugs developed for other viral diseases and antibodies from recovered COVID-19 patients have also been used as potential remedy for the disease. The SARS infected person is kept in isolation for 14 days in a low pressure zone with mechanical ventilation [51]. Moreover in case of severe breathing problems of patient a high dose of steroid is also needed. In addition to that patients with SARS may also have severe damage of their immune systems due to which various other diseases may also occur. Therefore, people are advised to keep away from the SARS infected patients or the probable SARS infected people to diminish the infection of SARS.

Most of the human diseases are directly or indirectly linked to the cysteine protease; the nucleophilic sulphur atom of Cys145 forms covalent bond with the receptor of the human body causing the disease [52]. Now if we block this nucleophilic centre with some other small molecule drugs or inhibitors, this will lead to the deactivation of the enzymatic activity of $3CL^{pro}$. After this covalent binding with the small molecule inhibitors, $3CL^{pro}$ is not free to bind with the ACE2 receptor of the human body causing no infection of SARS CoV (Scheme 2). Literature reports clearly state that the principal targeting site for the anti-SARS molecules/drugs is the S pockets of the SARS-CoV $3CL^{pro}$ [53,54].

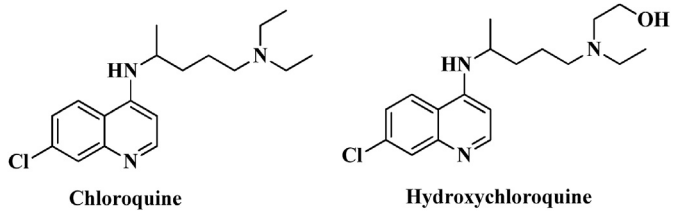


Fig. 1. Structure of chloroquine and hydroxychloroquine.

6. Treatment

6.1. Repurpose drugs and their stage of study for SARS $3CL^{pro}$ inhibitors

The conventional method of finding the biologically pronounced small molecule inhibitors is primarily based on the rigorous screening of the chemical libraries which is actually very time consuming as well as involves laborious work. In this lengthy process the success of finding the drug molecules also greatly relies on the superiority of the existing libraries. Consequently, at the initial stage most of the researchers tried different protease inhibitors which were previously used to cure and prevent various infectious diseases to inhibit the COVID-19 infection. Out of all well-known drugs, chloroquine (antimalarial drug) is the foremost drug that comes into the mind which has the ability to hold back the SARS-CoV replication through various pH-dependent steps [55]. Moreover, chloroquine has the ability to modify the various functions related to the immune system such as antibody formation and hence it is known as immunomodulatory drug (Fig. 1). Various literature reports reveal that functioning cellular receptors of SARS-CoV-2 was impeded by chloroquine (through glycosylation) for the entrance of the virus into the Vero E6 cells of human to keep away the COVID-19 infection from human body [56]. Similarly, teicoplanin [57], an antibiotic used for prophylaxis had also proven efficacy (less than that of the chloroquine) through in vitro manner to hold back the SARS-CoV replication [58]. But the results obtained are not so much effective towards the inhibition of the SARS-CoV, only lowers the fever of the patient as a secondary treatment.

Several other drug molecules which have the ability to inhibit/reduce the SARS-CoV are cinanserin [59], ribavirin [60], corticosteroids [61], lopinavir/ritonavir [62], neuraminidase inhibitors, umifenovir [63] etc. (Fig. 2)

Use of cinanserin significantly reduces the replication of SARS-CoV in cell culture with the evidence of negligibly lower cytotoxicity at the inhibitory concentrations. Cinanserin is also available in the form of water soluble hydrochloride salt form but its hydrochloride salt form is less active than the neutral molecule. This is due to the fact that cinanserin has less hydrophilic nature making it more efficient to penetrate the cell membrane and inhibit the viral replication [59].

Furthermore, the inhibition of SARS-CoV in tissue culture can also be shown by individual use of ribavirin (a nucleoside analogue), corticosteroids, lopinavir and type I interferon (INF α) [64,65] which were proved by the clinical trial methods and in vitro studies but their applications in human body is still not beneficial [66–68]. But the combined use of ribavirin and corticosteroids proved to be a beneficial antiviral agent against SARS [69].

A well known naturally occurring alkaloid reserpine which was originally used as sedative and antihypertensive drug also has a potential ability against SARS-CoV [70]. (Fig. 3).

A significant inhibitory efficiency against the replication of SARS-CoV was analyzed by He et al. [71] by the use of

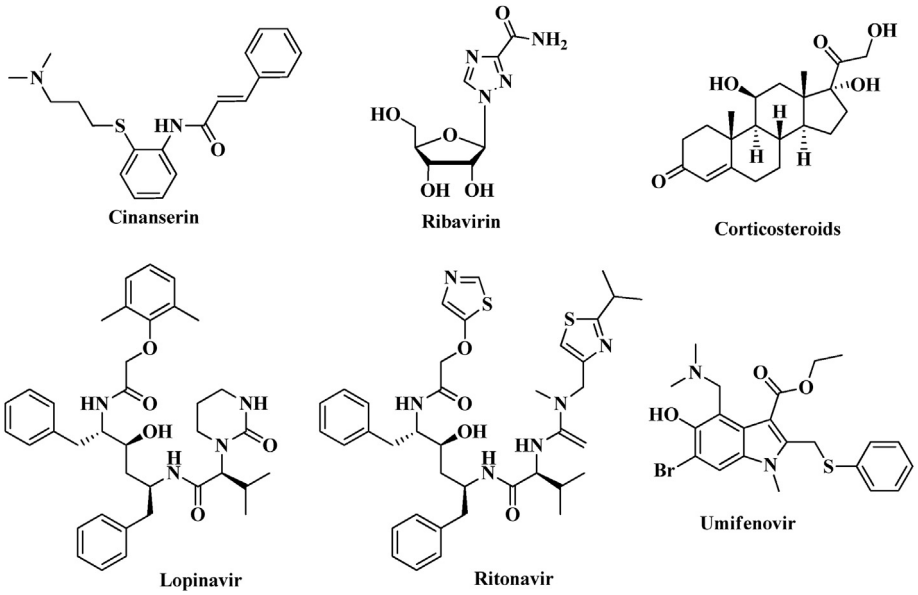


Fig. 2. Structure of various commercially available antiviral drugs.

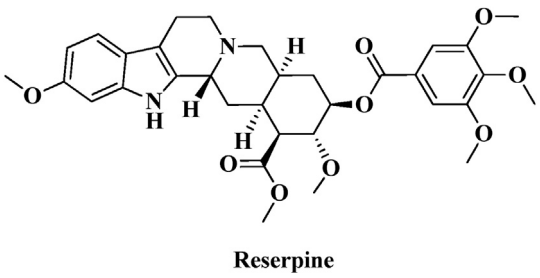


Fig. 3. Structure of reserpine.

aurintricarboxylic acid (ATA) in cell culture. The drastic efficiency of the ATA compound as anti-SARS-CoV agent was attributed due to its polymerization ability in aqueous solution forming a stable free radical which prevents the binding of the protease enzyme to the human cell. In their study, they found that aurintricarboxylic acid has the EC_{50} value of 0.2 mg/ml which implies that the use of 0.2 mg per ml (concentration) of ATA gave 50% of its maximal effect (Fig. 4). While comparing aurintricarboxylic acid with the Interferon α and β (INF α and β), it was observed that aurintricarboxylic acid is 10 and 100 times more effective than IFN α and interferon β respectively against SARS-CoV replication.

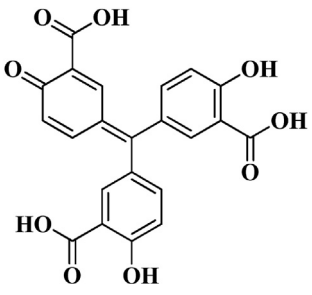


Fig. 4. Structure of aurintricarboxylic acid.

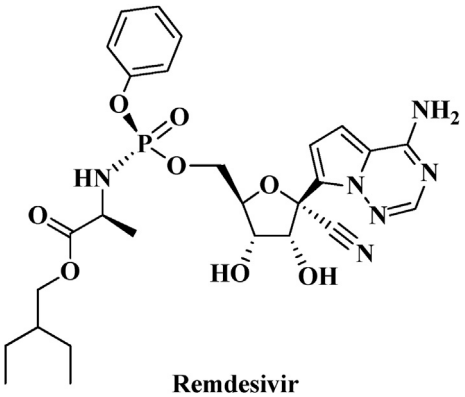


Fig. 5. Structure of remdesivir.

Most recently, SARS-CoV-2 has been found to inhibit by the use of two well known drugs *viz*. remdesivir and chloroquine with high efficacy [7,72]. (Fig. 5).

6.2. Small organic compounds as SARS 3CL^{pro} inhibitors

Because of the less effectiveness of the commercially available drugs against SARS-CoV-2, the current interest of research in the various fields is to develop more effectual and potent anti-SARS-CoV-2 inhibitors. Various techniques such as structure based discovery, virtual and experimental screening have been utilized by the researchers in the search for small molecules cysteine protease inhibitors and their implication in the mammalian cells [73].

In search of the cysteine protease inhibitors, we reported a research article describing the inhibitory effect of peptidic compounds bearing a several heteroatom ketone groups such as benzothaizoyl or thaizolyl and trifluoromethyl ketone groups as SARS-CoV 3CL protease inhibitors [74]. In our study, we found that in the series of trifluoromethyl ketone containing peptidic compounds, the compound with N-morpholine groups as substituent, **1** was found to be most potent with the inhibition constant (K_i) value of 21.0 μM. In the second series of compounds bearing benzothaizoyl

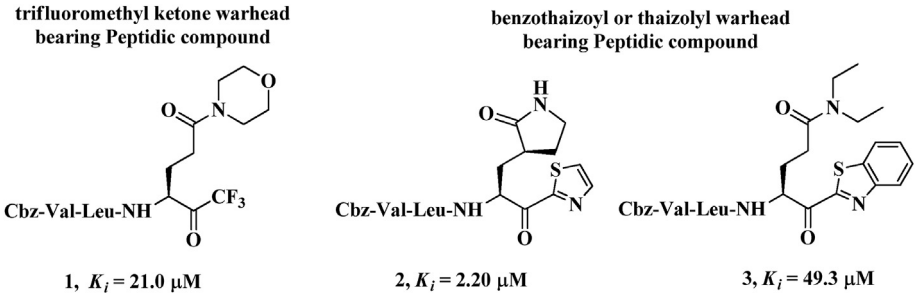


Fig. 6. Structure of trifluoromethyl ketone and benzothaizoyl or thaizolyl warhed containing peptidic compounds.

or thaizolyl ketone group, the compound with P1-pyrrolidone and thaizolyl warhead, **2** was found to be the most potent against 3CL protease with the inhibition constant (K_i) value of 2.20 μM while the compound containing benzothaizoyl warhead, **3** was observed to be little less effective with 49.3 μM. From this report we can assure that the presence/introduction of such groups (fluorine atom, heterocyclic aromatic ring with two or more than two heteroatoms, naturally occurring compounds with such type of rings etc.) in different small molecules may be effective as anti-SARS-CoV agent or cysteine protease inhibitors [53]. (Fig. 6) As peptide chemistry is very complex and broad in nature, researchers usually utilized various techniques such as structure based discovery, virtual and experimental screening in the search for small molecules cysteine protease inhibitors bearing such kind of warhead groups, effectiveness and its implication in the mammalian cells.

Ikejiri et al. [75] developed and evaluated the biological activity against SARS-CoV using nucleoside analogues based on 6-chloropurine derivatives. This kind of nucleoside based purine derivatives have already been reported as antiviral compounds and also show potent as anti-SARS-CoV activity [76]. Out of several synthesized nucleoside analogues, two compounds (**4** and **5**) exhibited major significant activity as anti-SARS-CoV agent with the IC_{50} values 48.7 and 14.5 μM respectively (Fig. 7). The structure-activity relationship of these compounds revealed that the presence of 6-chloropurine motif in both the compounds, unprotected 5′-hydroxyl group in **4** and protected (benzoylated) 5′-hydroxyl group in **5** mainly enhanced the antiviral activities in these compounds.

Blanchard et al. [77] synthesized novel drug-like small molecule, **6** (named as MAC-5576) which acts as one of the potent inhibitors of the SARS coronavirus main proteinase through vigorous screening (Fig. 8). Actually, MAC-5576 is 2-(5-chloropyridin-3-yl)-1-(thiophen-2-yl)ethanone which showed IC_{50} value of 0.5 ± 0.3 μM, makes it a better one than the previous compounds.

Similarly, Niu et al. [39] also synthesized non-peptidic 3-chloropyridine derivatives which are structurally similar to that

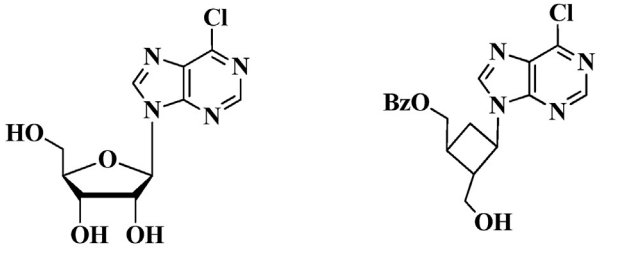


Fig. 7. Structure of nucleoside analogues bearing 6-chloropurine derivatives.

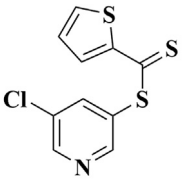


Fig. 8. Structure of drug-like small molecule MAC-5576.

of MAC-5576 and evaluated the biological activity of these compounds as chymotripsin-like proteinase inhibitors to diminish the SARS infection.

The molecular docking study of these compounds proved that the chloropyridine moieties of these inhibitors initially bind inside the S1 pocket of the inhibitor to the enzyme through in vitro manner whereas ester part specially binds to the S1 substrate binding site of $3CL^{pro}$. In their report they summarized all the molecules in the different groups of chloropyridine molecules. Group I compounds contained chloropyridine ester moiety as well as heterocyclic furan moiety (**7** and **8**) which is found to be more potent for $3CL^{pro}$ inhibitor than the group II compounds containing simply chloropyridine ester moieties (**9**) along with fused rings such as naphthalene and coumarin (**10** and **11** respectively). The best potent compounds of both the groups are shown in the figure with the IC_{50} value (Fig. 9).

To evaluate the potent biological activity of 3-chloropyridine ring containing compounds as SARS-CoV $3CL^{pro}$ inhibitor, Ghosh et al. [78] designed and synthesize a series of chloropyridyl ester-derived compounds which have prominent activity as $3CL^{pro}$ inhibitors. The synthetic methodology involves the treatment of 5-chloro-3-pyridinol with various carboxylic acids through esterification using carbodiimide based coupling agents and racemization suppressor (mainly DMAP, *N,N*-dimethylaminopyridine). Out of the synthesized compounds, indole-4-carboxylic acid containing 3-chloropyridyl ester **12** shows most potent activity against SARS-CoV $3CL^{pro}$ with the IC_{50} value of 0.03 μM (30 nM). (Fig. 10).

Docking study also reveals the molecular binding of the above mentioned most potent compound, **12** where the sulphur atom of Cys-145 is in close proximity to the carbonyl carbon atom of the compound, the imidazole nitrogen of His-163 residue to the 3-chloropyridinyl group and indole group to the His-41 residue.

Zhang et al. [79] synthesized a series of two or three aromatic rings containing aryl methylene ketones and their mono and difluoro derivatives. Out of various compounds synthesized; two compounds *viz.* 2-(5-bromopyridin-3-yl)-1-(5-(4-chlorophenyl) furan-2-yl)ethanone, **13** and its monofluorinated derivative, **14** were found to be most potent SARS $3CL^{pro}$ inhibitors with the IC_{50}

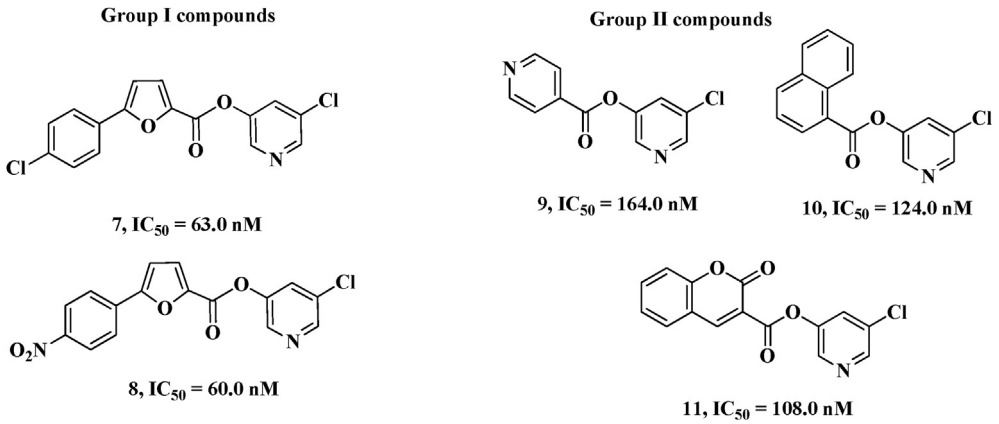


Fig. 9. Structure of 3-chloropyridine ester derivatives.

values of 13 μM and 28 μM, respectively (Fig. 11). They found that introduction of fluorine substituent to the aryl methylene ketones containing 4-chlorophenyl ring (most potent compound) lowers the inhibitor activity while the inhibitors with the three aromatic rings are considered to have more potent inhibitor efficiency than the inhibitors with the two aromatic rings. Herein, in **13**, the oxygen atom of the furan ring binds with the -NH of Glu166 residue through hydrogen bonding interaction. Similarly, the pyridinyl moiety also binds with the Cys145 reside inside the S1 pocket and in case of the fluoro substituent, **14** the oxygen atom of carbonyl group binds with the His164 residue.

Similar to the previous report, Zhang et al. [80] also reported different heteroaromatic ester compounds as inhibitors (**15**–**18**) for 3CL protease. In their study they found four most potent inhibitors bearing 3-chloropyridine ring and other heteroatoms with the ester linkage with IC_{50} value ranging from 50 to 65 nM (Fig. 12).

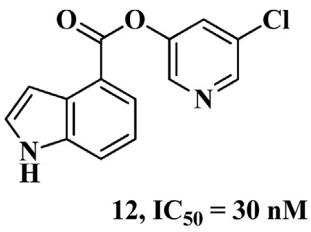


Fig. 10. The structure of indole moiety bearing chloropyridyl ester analogue.

Development of new pyrazole and pyrimidine derivatives was carried out by Mohamed et al. [81] starting from 3-indolaldehyde moiety with 3-aminoacetophenone giving a chalcone. This chalcone then reacts with hydrazine hydrate or phenylhydrazine to give pyrazole derivaties, **19** while pyrimidine derivatives were obtained by the reaction of chalcone with hydroxylamine hydrochloride, thiosemicarbazide (**20**–**23**). Both pyrazole and pyrimidine moieties are well known to exhibit various biological activities [82] and this newly developed series of compounds have the activity as SARS-CoV $3CL^{pro}$ protease inhibitors (Fig. 13). Out of these two different series of compounds the five compounds are found to be the best SARS-CoV $3CL^{pro}$ protease inhibitors having prominent IC_{50} values ranging from 0.12 to 0.38 μM.

Chen et al. [83] initially synthesized *N*-Substituted isatin derivatives by the simple reaction of isatin molecule (2,3-dioxindole) and various bromide sources. The SARS-CoV $3CL^{pro}$ inhibition assays were conducted via fluorescence resonance energy transfer (FRET) followed by HPLC analysis of the fragment peaks cleaved by $3CL^{pro}$. The two thiophene containing isatin derivatives such as thiophenecarboxylic 7-bromo-3-pyridinol ester, **24** and thiophenecarboxylic 5-iodo-3-pyridinol ester, **25** are reported as the most potent SARS-CoV $3CL^{pro}$ inhibitors with the IC_{50} values 0.98 and 0.95 μM respectively (Fig. 14). Molecular docking of these molecules showed that the isatin scaffold was located in the S1 site whereas S2 site was blocked by the N-substituted side chain.

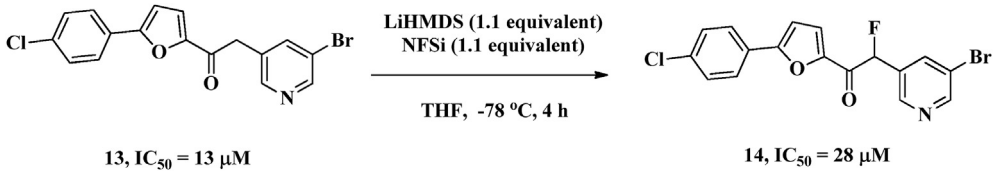


Fig. 11. Structure of aryl methylene ketone and fluorinated methylene ketone with pyridinyl ring moiety.

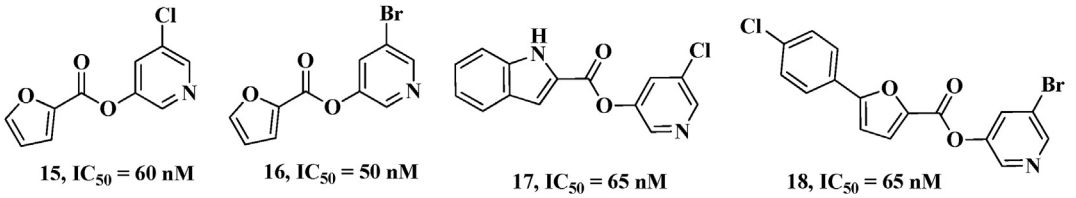


Fig. 12. Structure of heteroaromatic esters with 3-halopyridinyl ring motif.

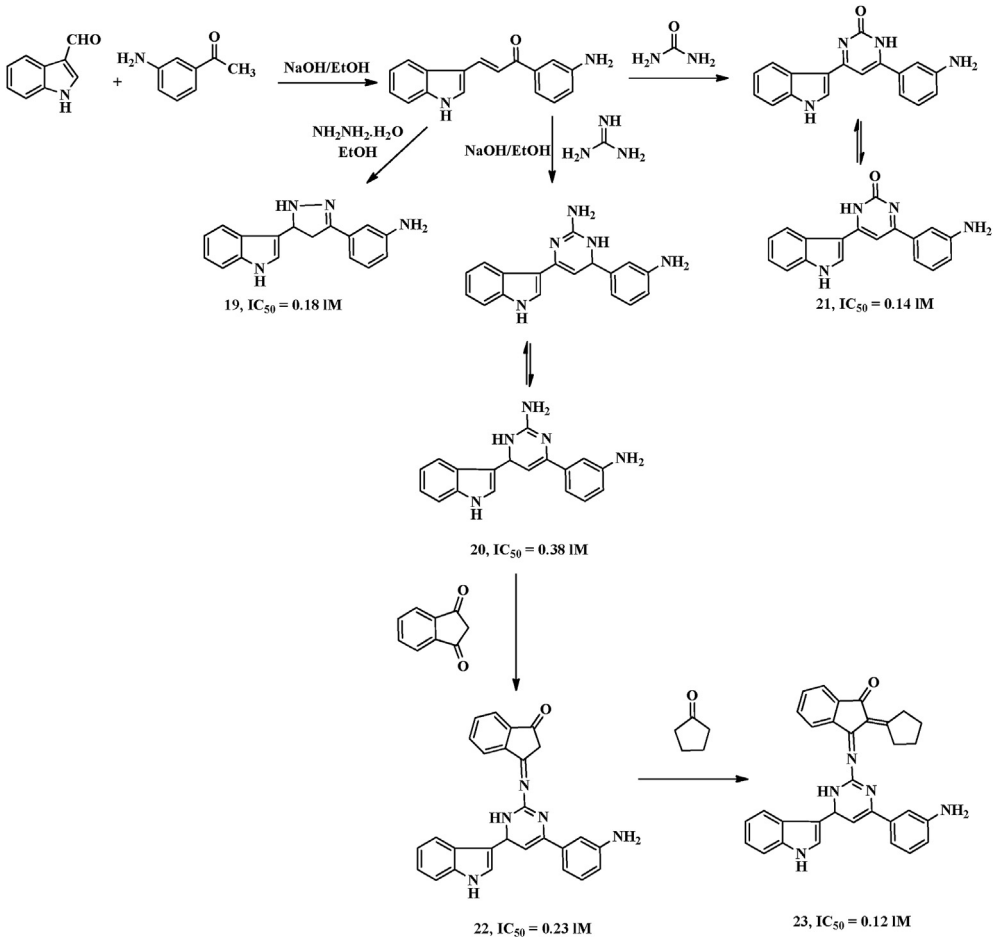


Fig. 13. Preparation scheme and the structure of substituted pyrazoles and substituted pyrimidines derivatives.

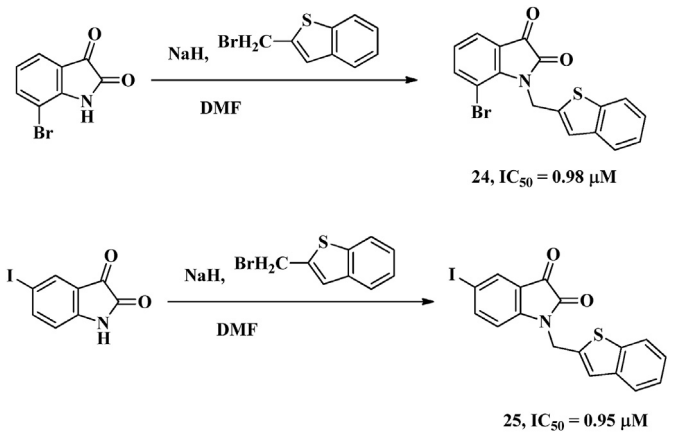


Fig. 14. Preparation scheme and the structure of *N*-Substituted isatin derivatives with thiophenecarboxylic ester analogues.

Moreover it also showed that both the oxygen atoms of the carbonyl group of the synthesized isatin derivative was bonded through hydrogen bond to the- NH groups of the different protein chain residues such as Cys145, His41, Ser144, and Gly143.

Similarly, isatin derivatives as SARS-CoV 3C-like protease were also designed by Liu et al. [84] Out of their synthesized isatin derivatives, three compound *viz*. 5-[(4-methylpiperidin-1-yl)sulfonyl]-1H-indole-2,3-dione, **26** 1-methyl-5-[(4-methylpiperidin-1-yl)sulfonyl]-1H-indole-2,3-dione, **27** and 1-benzyl-5-[(4-methylpiperidin-1-yl)sulfonyl]-1H-indole-2,3-dione, **28** showed the most potent activity as SARS-CoV 3C-like protease inhibitors with the IC_{50} values ranging from 1.04 to 1.68 μM (Fig. 15).

The potent inhibitory activity of the compound 5-[(4-methylpiperidin-1-yl)sulfonyl]-1*H*-indole-2,3-dione, **26** was enhanced by the presence of sulfonyl group with the simple six-membered ring in the 5-position of the isatin molecule which was well fixed at the S2 site of SARS CoV $3CL^{pro}$. Furthermore, two different *N*-substituted derivatives of the previous compound, 1-methyl-5-[(4-methylpiperidin-1-yl)sulfonyl]-1H-indole-2,3-dione, **27** was bonded through hydrogen bonding with Gly143 and Cys145 of protease and the carbonyl group of 2-position and the nitrogen atom at the 1-postion of isatin molecule respectively. Similarly, in 1-benzyl-5-[(4-methylpiperidin-1-yl)sulfonyl]-1H-indole-2,3-dione, **28** the carbonyl group of C2-position also formed hydrogen bonds with Gly143 and Ser144 residue of the protease while Asn142 residue binds with the nitrogen atom at the 1-postion of isatin molecule. Moreover, molecular docking revealed that the S1/site of SARS CoV $3CL^{pro}$ was blocked by the isatin scaffold while the S2 and S1 sites are booked by the side chain of R^2 and R^3 of the newly synthesized 5-sulfonyl isatin derivatives respectively.

Zhou et al. [85] reported various isatin derivatives substituted at the N-1 positions with different alkyl/aryl groups and C-5 positions with the iodo and amide groups. They examined these derivatives to elucidate the various binding sites of the $3CL^{pro}$. In their analyses, they got the best potent isatin derivative with the *N*-substituted 2-

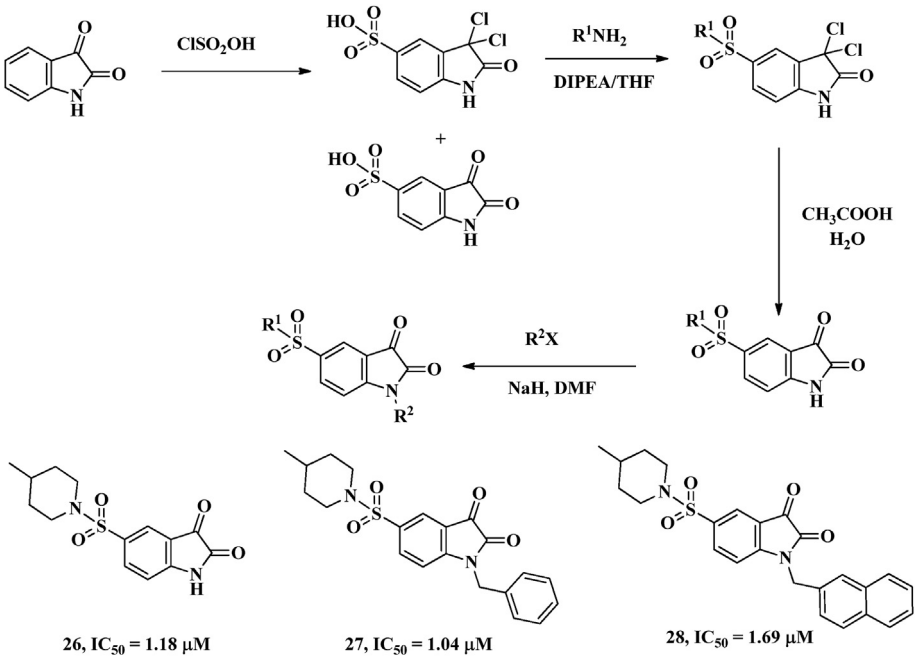


Fig. 15. Preparation scheme and the structure of 5-sulfonyl isatin derivatives.

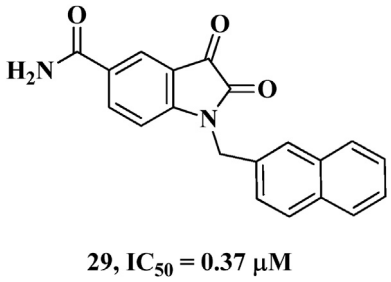


Fig. 16. Structure of *N*-substituted isatin derivatives with C-5 substituted carboxyamide group.

methylnaphthalene group and C-5 substituted carboxyamide group, **29** with an IC_{50} value of 0.37 μM against SARS CoV 3C-like protease (Fig. 16). The active site residues His41 and Cys145 were attached to the C-2 and C-3 position carbonyl oxygen atoms through hydrogen bonding respectively. Similarly, the carboxamide at C-5 also formed the H-bonds with the backbone carbonyl of Phe140 and the imidazole ring of His163 residue. Moreover, the hydrophobic S2 site originally generated by the Met49 and Met165 residues of the protease was well occupied by the alkyl groups of N-1 position.

Lee et al. [86] reported benzimidazole based SARS-CoV 3-Chymotrypsin-like protease inhibitors with IC_{50} value 13.9–18.2 μM (**30** and **31**) (Fig. 17). These inhibitors bind the S1 site of the His163 and Glu166 residues through hydrogen bonding interactions while hydrophobic S2 site was booked with Met, Asp, His, Pro and Tyr residues. Moreover two additional aromatic/hydrophobic interactions were also found in the S1 and S2 sites close to the catalytic cysteine residue where a donor site interacts with residues His163 and His164 in the S1 site.

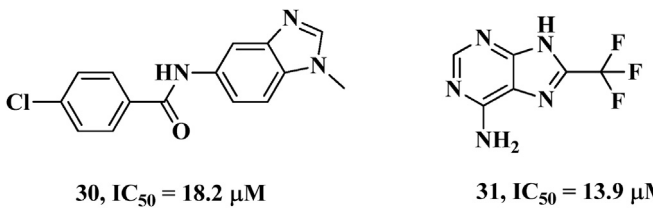


Fig. 17. Structure of benzimidazole based $3CL^{pro}$ inhibitors.

Kao et al. [87] developed a 3-quinolinecarboxylic acid derivative that has the potent inhibitor efficacy against the SARS-CoV M^{pro}. They named the compound as MP576, **32** which has the IC_{50} value 2.5 μM and EC_{50} value 7 μM (Fig. 18).

The ether linked oxygen atom and the oxygen atom of nitro group of the synthesized derivative **32** is proved to bind with the nitrogen of His41 and Cys145 residue respectively through hydrogen bonding interaction.

Shimamoto et al. [88] designed and developed novel decahydroisoquinoline motif as an inhibitor for SARS. In their study, they found three most potent derivatives, **33**–**35** for the inhibition of the SARS $3CL^{pro}$ protease with the IC_{50} values 57–68 μM (Fig. 19).

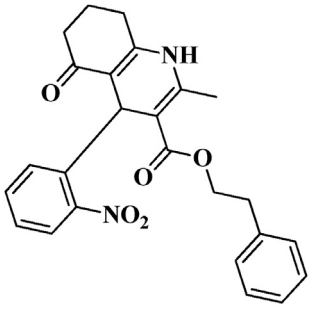


Fig. 18. Structure of 3-quinolinecarboxylic acid derivatives.

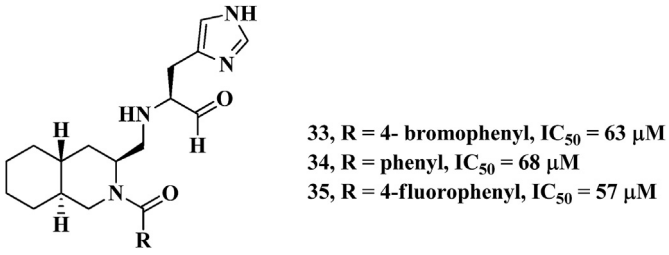


Fig. 19. Structure of decahydroisoquinoline motif containing 3CL^{pro} inhibitors.

Herein, the S2 pocket originated by the residues such as His41, Met49, Met165 and Asp187 side chains of the protease was occupied by the novel decahydroisoquinoline scaffold of **33**. Similarly, the S1 site which was originated by the residues Phe-140, Leu-141 and Glu-166 was occupied by the P1 site nitrogen atom of the imidazole of **33** and it forms hydrogen bonding interaction with the His-163 residue of the protease.

Ramajayam et al. [89] developed a series of 1,6-dihydropyrimidine derivatives as SARS-CoV 3CL protease inhibitors and their effectiveness was appraised by in vitro protease inhibitor analyses. These 1,6-dihydropyrimidine derivatives were synthesized by the two step reaction of substituted benzaldehyde, ethyl cyanoacetate and thiourea followed by the slow addition of different halide derivatives in DMF as solvent and K_2CO_3 as base at 0–5 °C. In this study, they found two compounds, **36** and **37** showing most potent activity against SARS-CoV 3CL protease with the IC_{50} values of 6.1 and 10.6 μM respectively (Fig. 20).

In the most potent molecule, **36** the -NH group of the pyrimidine ring was constrained in the distance of 2.0 Å with the oxygen atom of Glu-166 residue. Herein, the nitro group is the main functional group for showing the potent inhibitor efficacy and its one of the oxygen atoms is in secure vicinity to the Gly-143 residue while the other oxygen atom binds with the Cys-145 residue of the protease through hydrogen bond interaction. Furthermore, the S2 pocket was blocked by the chlorophenyl ring with Met-49 and Gln-189 through hydrophobic interactions.

Ramajayam et al. [90] designed and synthesized a series of pyrazolone derivatives and evaluated the in vitro SARS-coronavirus 3C-like protease inhibitor activity. These compounds were synthesized by the two step reaction of different aromatic hydrazine hydrate derivatives with the ethyl benzoylacetate in presence of triethylamine as base and acetic acid as solvent to give pyrazolone product followed by the reaction with aromatic aldehydes in presence of piperidine affording substituted pyrazolone compounds. From their study, three pyrazolone compounds **38**, **39** and **40** were found to be most potent against SARS 3CL^{pro} with the IC_{50} values 5.5, 6.8 and 8.4 μM respectively (Fig. 21). In **40**, S1′pocket of the 3CL^{pro} is blocked by the N1-phenyl group while one of the oxygen atoms of the nitro group forms H-bonding interaction with the Gly-143 residue of 3CL^{pro}. Similarly, the carbonyl group of the pyrazolone ring also forms H-bonding interaction with the Glu-166 residue. Moreover, the C-3 phenyl ring is situated in the S2 pocket and forms hydrophobic interactions with Met-49, Arg-188, and Gln-189 residue meanwhile the carboxyl benzylidene group fits into the S3 pocket of the 3CL^{pro} and forms H-bonding interaction with the Gln-192 residue.

Jacobs et al. [91] designed a series of furyl amide derivatives with 3-pyridyl ring and applied for the inhibition of 3CL^{pro}. These compounds are derivatives of N-(tert-butyl)-2-(N-arylamido)-2-(pyridin-3-yl) acetamides. The pyridyl ring of the best inhibitor compound interacts with the His163 residue through hydrogen bond while furan ring oxygen and the amide carbonyl oxygen have a diverse interaction with Gly143 residue. After that, the enantiomers of the compound was separated and isolated through supercritical fluid chromatography and they found that only R-stereoisomer of the compound, **41** (named as MT188) was inherently active for the inhibition of 3CL^{pro} with IC_{50} value of 1.5 μM

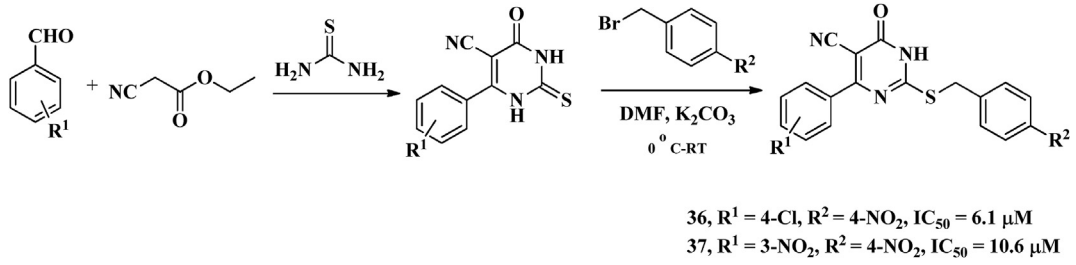


Fig. 20. Preparation scheme and the structure of 1,6-dihydropyrimidine derivatives.

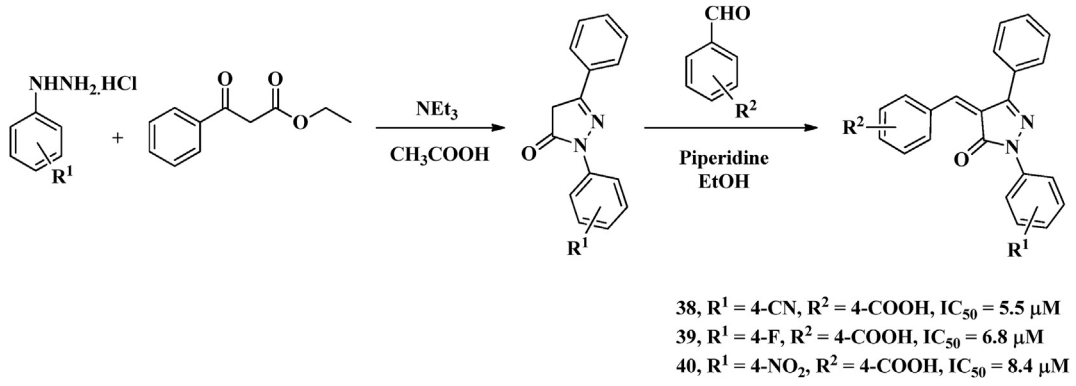


Fig. 21. Preparation scheme and the structure of novel pyrazolone derivatives.

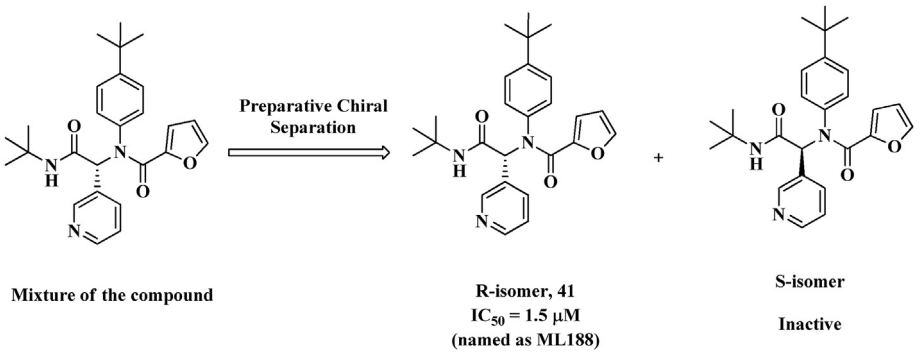


Fig. 22. Structural separation of pyridine containing acetamide analogues.

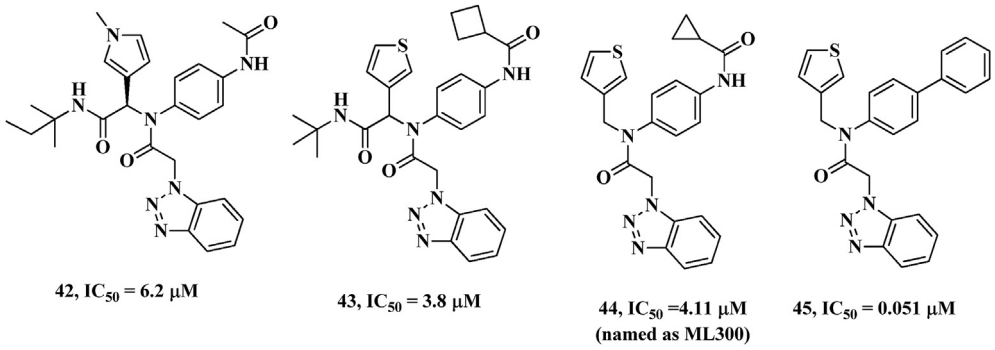


Fig. 23. Structure of benzo-1,2,3-triazolyl ring containing diamaide derivatives.

while S-stereoisomer of the compound was found inactive (Fig. 22).

Jacobs et al. [92] also extended their research for the further development of 3CL protease inhibitors by the simple modification of the previous compound ML188. The new compounds have the same structural moiety containing diamide bonds and the newly introduced benzo-1,2,3-triazolyl ring (**42**–**45**) with the IC_{50} values 0.051–6.2 μM (Fig. 23). In the molecular docking study of the compound **42**, it was observed that N3 atom of the benzotriazolyl ring forms hydrogen bonding interaction with the His-163 while the carbonyl oxygen attached to the benzotriazolyl ring also forms hydrogen bonding interaction with the Glu166 residue of the protease.

Fig. 24. Structure of stilbene derivatives.

Li et al. [93] synthesized various derivatives of stilbenes by Michaelis–Arbuzov reaction followed by Wittig–Horner reaction and then finally demethylated with BBr_3 in dichloromethane. In their study, they found that only two compounds *viz.* [(E)-2′,3,5′,5-tetrthydroxystilben], **46** and [(E)-2′,5,5′,6-tetrahyroxystilbene-2-

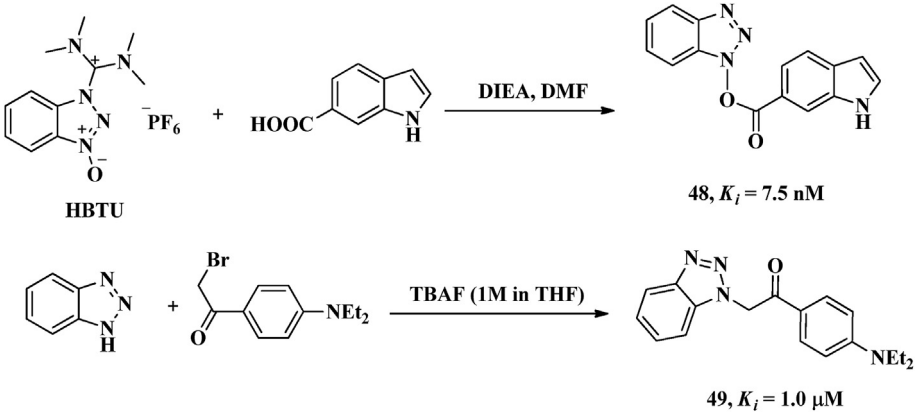


Fig. 25. Preparation scheme and the structure of benzotriazole structure conataining $3CL^{pro}$ inhibitors.

nitrogen], **47** have the potential ability to inhibit the replication of SARS virus in concentration $\leq$ 0.5 mg ml^{-1} with no cytotoxicity (Fig. 24).

Wu et al. [94] reported two different series of stable benzotriazole esters as inactivators of $3CL^{pro}$. One series was synthesized from the well known peptide coupling agent HBTU (1H-Benzotriazolyl Tetramethyl Uronium hexafluorophosphate) along with carboxylic acid derivatives in presence of *N,N*-diisopropylethylamine and *N,N*-diethylformamide while the other series was synthesized by the reaction of benzotriazole with the aromatic α—halo ketone derivatives in presence of TBAF (1M in THF) as catalyst. Herein, they found two benzotriazole esters as the post potent inactivators of $3CL^{pro}$ *viz*. 1H-indole-5-carboxylic acid benzotriazol-1-yl ester, **48** and 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1-(4-(diethylamino)phenyl)ethanone, **49** with the inhibition constant value 7.5 nM and 1.0 μM respectively (Fig. 25).

The molecular docking of compound **48** reveals that the benzotriazole moiety fits into the pocket formed by Cys145, Ser144, and Gly14 residues of $3CL^{pro}$. The carbonyl group of the benzotriazole ester binds the S-atom of Cys145 residue in the course of a nucleophilic attack. Moreover, the indole moiety is situated in the pocket created by Thr25, Thr26, His41, Thr45, Ala46 and Met49 residue while its -NH group was bonded through hydrogen bonding interaction with the side chain -OH group of Thr25 residue of $3CL^{pro}$.

Karypidou et al. [95] synthesized a new library of fused 1,2,3-triazoles and evaluated the biological activity as potential anti-coronavirus agents (against human coronavirus 229E). In their research, they found five most potent compounds with the half maximal effective concentration (EC_{50}) ranging from 8.90 to 11.95 μM (compounds **50**—**54**) (Fig. 26). Furthermore, *in silico* study also showed various molecular binding interactions of the synthesized novel fused 1,2,3-triazoles with the 3-chymotrypsin-like protease.

In the molecular docking of these bioactive fused 1,2,3-triazoles, they observed that compounds **50** and **51** have two hydrogen bond interactions with His163 and Glu166 residues with the fused

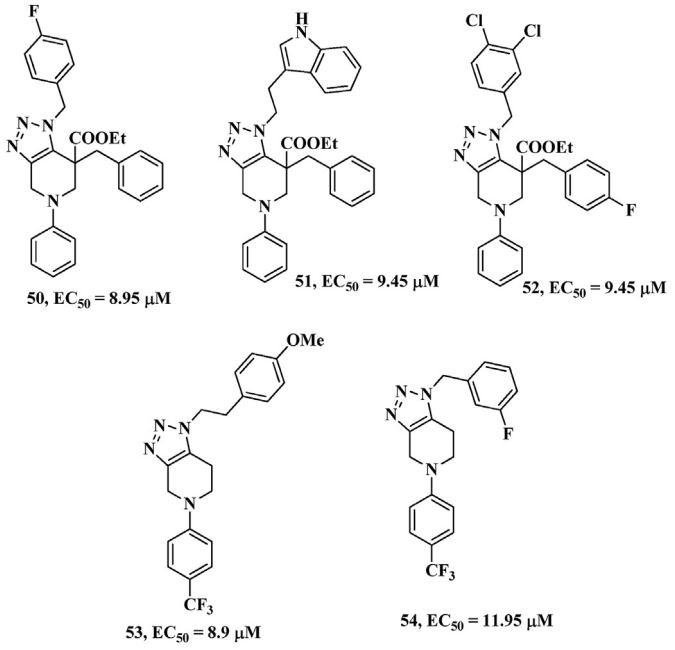


Fig. 26. Structure of fused 1,2,3-triazole derivatives as potential anti-coronavirus agents.

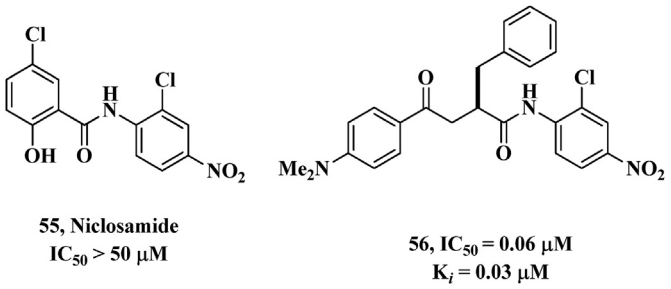


Fig. 27. Structure of Niclosamide and Niclosamide type anilides derivatives.

triazole ring positioning in the close proximities of the catalytic dyad of $3CL^{pro}$. Moreover, in case of other derivatives, **53** and **54** similar behaviors were also observed in the molecular docking study enclosing two established hydrogen bond interactions within the catalytic site of $3CL^{pro}$. In brief, the compound **53** is attached through a stable binding with His163 residue and two additional interactions with Glu166 and Thr25 residues within the catalytic site. Compound **54** established stable hydrogen bonding interaction with both Glu166 and His163 residues and additionally anchored to the Gln189 residue.

Shie et al. [96] developed a series of peptide based anilide derivatives and out of all these, Niclosamide type anilides were found to be potent inhibitors of $3CL^{pro}$. Literature reveals that Niclosamide, **55** itself acts as a $3CL^{pro}$ inhibitor with IC_{50} value > 50 μM [97]. Therefore, the authors designed and synthesized a series of Niclosamide type anilides and the best compound was found by the reaction of 2-chloro-4-nitroaniline, L-phenylalanine and 4-(dimethylamino)benzoic acid, **56** with IC_{50} value of 0.06 μM (Fig. 27).

In the molecular docking study, the pocket created by Thr25, His41, Cys44, Thr45, and Ala46 residues was occupied by the 2-chloro-4-nitroanilide moiety of **56**. In addition to that, the nitro group in **56** is envisaged to be bonded with the -NH of Ala46 residue of $3CL^{pro}$ through hydrogen bonding, while the S-atom of Cys145 and N2 atom of His41 residues was fitted with the chlorine atom of the compound **56**. Similarly, the site formed by Gln189-Gln192 and Met165-Pro68 residues was filled by the dimethylaminophenyl group of the compound.

A series of benzoquinoline compounds were designed, synthesized and evaluated against 3C-like protease ($3CL^{pro}$) inhibitors by Ahn et al. [98] They found that alkylated benzoquinolines with N-phenoltetrazole moieties linked through sulphur atom, **57** was found to be more potent than the non-alkylated derivative, **58** with the IC_{50} values 2.0 and 10.0 μM respectively (Fig. 28). Computer modelling of the compound **57** shows that the benzyl group

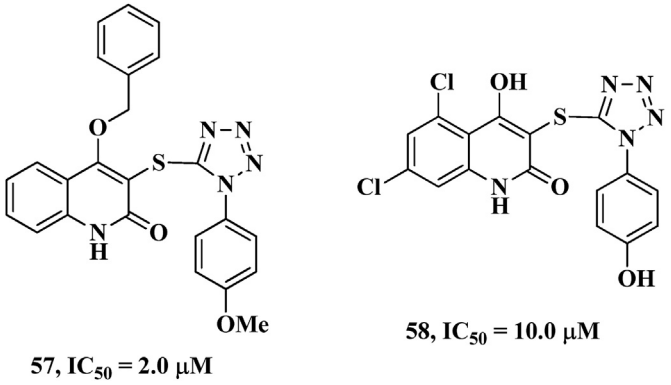


Fig. 28. Structure of benzoquinoline derivatives as SARS-CoV 3CL protease inhibitors.

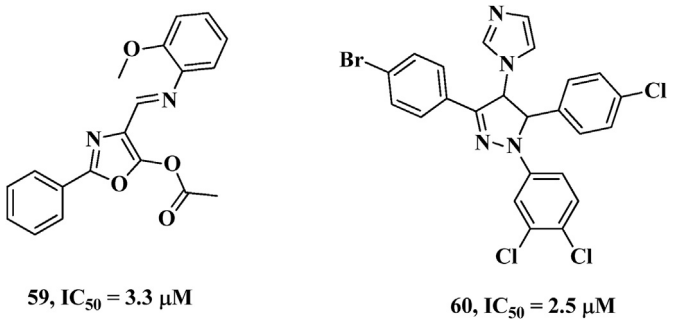


Fig. 29. Structure of oxazole and pyrazole moiety bearing SARS-CoV 3CL protease inhibitors.

attached to the phenyl ring is fitted into the extended S3 subsite and makes interaction with the Glu166 residue through hydrophobic interaction. The other side chain (methoxy group) of **57** is situated between the region of S2 and S3 sites while the benzoquinoline nitrogen and N3 nitrogen of tetrazole ring are located in the S1′and S1 subsite of the 3CL^{pro}. Furthermore the N3 nitrogen of tetrazole ring also binds to the Gly145 residue through hydrogen bonding.

Kuo et al. [99] recognized numerous new inhibitors of SARS-CoV 3CL^{pro} by high throughput screening of over 6000 molecules. They found that an oxazole motif bearing acetate group, **59** and N-aryl imino group and a pyrazole moiety with four different substituents, **60** are found to be most potent inhibitor of SARS-CoV 3CL^{pro} with IC_{50} values of 3.3 and 2.5 μM respectively (Fig. 29).

In the compound bearing oxazole motif, **59** the free rotation of the phenyl and oxazole moiety was restricted by the 1,2-steric interaction between the N-aryl imino group and the acetate group. Based on the molecular modelling interactions, the S1, S2 and S3 sites of 3CL^{pro} are fitted with the N-aryl imino group, phenyl ring and acetate group respectively. Moreover the carbonyl oxygen of the acetate group binds with the Glu166 residue of 3CL^{pro} through hydrogen bonding interaction.

Bacha et al.[46(b)] developed different bifunctional aryl boronic acid derivatives and found that these newly synthesized compounds are predominantly effective at inhibiting the protease. Out of these compounds, one of the bifunctional aryl boronic acids, **61** (named as FL-166) has inhibition constants (K_i) 40 nM (0.04 μM) and considered as the most potent inhibitor for SARS Coronavirus Main Protease 3CL^{pro} (Fig. 30).

The evaluation of well-known possible inhibitory potency of the compounds was identified by the reactivity of hydroxyl group in serine residues with the synthesized bifunctional aryl boronic acid compounds. The boronic acid compounds targeted the nearest active sites of the protease formed by a cluster of serine residues

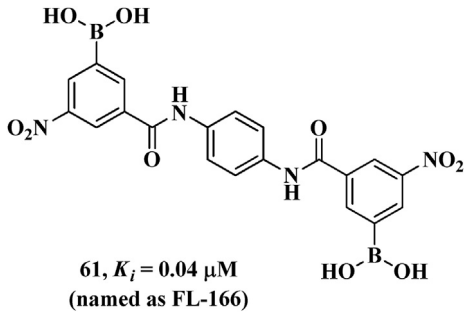


Fig. 30. Structure of bifunctional aryl boronic acid derivatives.

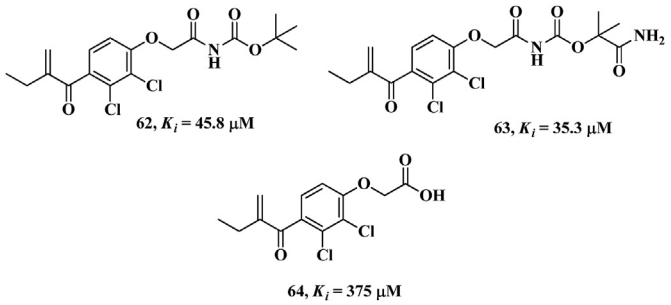


Fig. 31. Structure of Etacrynic acid derivatives against SARS-CoV Main Protease.

such as Ser139, Ser144, and Ser147.

Kaeppler et al. [100] synthesized and evaluated the potent inhibitory activity of etacrynic acid derivatives against SARS-CoV Main Protease. Out of several etacrynic acid derivatives, etacrynic acid tert-butylamide, **62** and etacrynic acid amide, **63** showed the most potent ability against SARS-CoV Main Protease with the inhibitor constants (K_i) 45.8 and 35.3 μM respectively while the parent compound etacrynic acid, **64** was observed with very less amount of the inhibitor constants (K_i) 375 μM (Fig. 31).

In the molecular modeling pose for etacrynic acid tert-butylamide, **62** it was found that the hydrophobic S4 pocket was fitted with tert-butyl group, S3 pocket was situated near to the dichlorobenzyl motif while the terminal ethyl group side chain at the Michael system directing away from the active site of the enzyme residue. Moreover various ligating sites of the molecule bonded to different amino acid residues His163, Glu166, and Gln189 of the protease through hydrogen bonding interaction. Herein, the molecular modelling interactions of etacrynic acid amide, **63** were similar to that of the etacrynic acid tert-butylamide, **62** interactions. In compound **63**, two hydrogen bonds are formed between the terminal amino group and the Thr190 and Gln192 residues whereas in the compound **62** the hydrogen bond interaction was found between the carbonyl group linked to the Michael system and the His163 residue of the protein which make the compound **63** more potent than compound **62**.

Apart from all the synthesized compounds some of the nature derived products are also found to have the inhibitor efficiency against SARS-CoV 3CL^{pro}. Ryu et al. [101] isolated eight diterpenoids and four biflavonoids from the ethanol extract of Torreya nucifera leaves (traditionally used as medicinal plant in Asia, mostly found in Japan and South Korea, for the treatment of several parasitic conditions including hookworm, tapeworms, pinworms and roundworms) and evaluated the SARS-CoV 3CL^{pro} inhibition. Out of all these natural product molecules, the biflavone amentoflavone **65** was found to be the most effective inhibitor against SARS-CoV 3CL^{pro} with IC_{50} 8.3 μM (Fig. 32).

Molecular docking study of amentoflavone **65** indicates the formation of two hydrogen bonds between the C5 hydroxyl group of **A** ring of amentoflavone with the nitrogen atom of the imidazole group of His163 and -OH group of Leu141 residue situated in the S1 site of 3CL^{pro}. Similarly, the hydroxyl group of **B** ring of amentoflavone also forms hydrogen bonding interaction with Gln189 residue and situated in the S2 subsite of 3CL^{pro}. Two more hydrogen bonding interactions were also found between the Val186 residue and the hydroxyl group of the ring **C** and the Gln192 residue with the carbonyl group of the ring D.

Toney et al. [102] developed a non-peptidyl inhibitor of 3CL^{pro} known as Sabadinine, **66** which has the criteria of lowest energy conformers as similar to that of the AG7088, **67** which is a peptidyl molecule with human rhinovirus (HRV) serotype 2 3CL^{pro} inhibitor

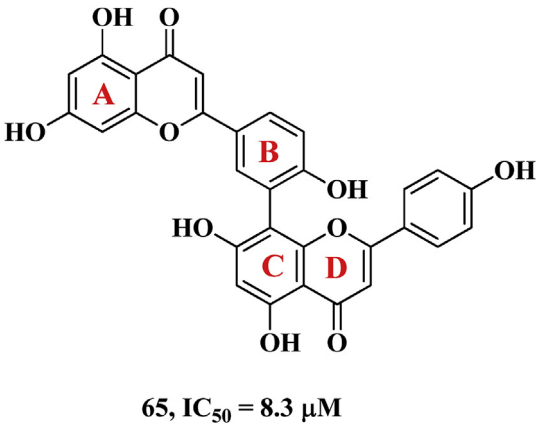


Fig. 32. Structure of amentoflavone isolated from Torreya nucifera leaves.

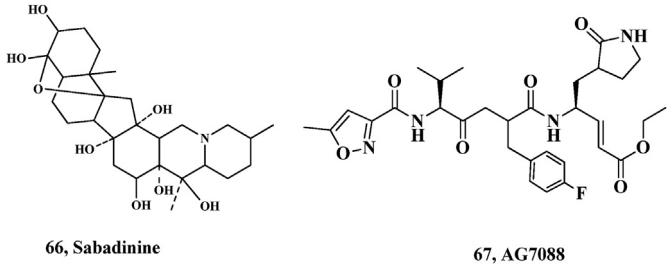


Fig. 33. Structure of sabadinine and AG7088.

efficacy (Fig. 33).

In the molecular docking study, it was found that the molecule (Sabadinine) **66** is sited next to the residues His44 and Cys144 covering the catalytic dyad of the protease. Moreover, hydrogen bonding interactions was also found between the hydroxyl oxygen at C(20) position of sabadinine and the nitrogen atom of His44 residue.

Park et al. [103] isolated seven tanshinone derivatives from ethanol extract of Salvia miltiorrhiza root and examined their biological activity against SARS-CoV $3CL^{pro}$, viral cysteine protease as well as Papain-like protease (PL^{pro}) inhibitors. Out of seven compounds, dihydrotanshinone I, **68**, Methyl tanshinonate, **69** and rosmariquinone, **70** were found to be most potent compounds as cysteine protease inhibitors with the IC_{50} values 14.4, 21.1 and 21.1 μM respectively (Fig. 34).

Lin et al. [104] isolated various polyphenolic compounds from the water extract of different tea leaves and investigated their $3CL^{pro}$ inhibitory activity. Out of different tea leaves, black tea containing polyphenolic compounds showed better inhibitory

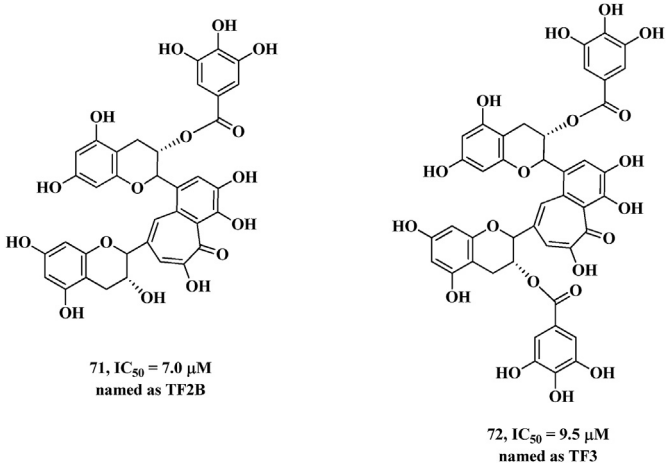


Fig. 35. Structure of polyphenolic derivatives isolated from tea leaves with $3CL^{pro}$ inhibitory activity.

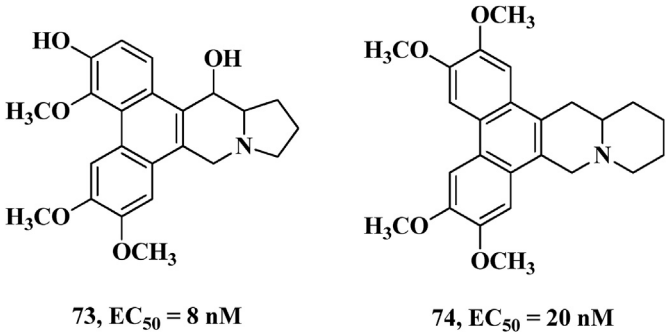


Fig. 36. Structure of phenanthroindolizidines and phenanthroquinolizidines derivatives.

activity against $3CL^{pro}$ and it is mainly due to the presence of theaflavin composition in black tea. Theaflavin derivatives, 3-isotheaflavin-3-gallate (TF2B), **71** and theaflavin-3,3′-digallate (TF_3), **72** have the most potent $3CL^{pro}$ inhibitory activity with the IC_{50} values of 7.0 and 9.5 μM respectively (Fig. 35).

Moreover various other naturally occurring derivatives such as phenanthroindolizidines, **73** and phenanthroquinolizidines, **74** [105], (Fig. 36) Emodin (6-methyl-1,3,8-trihydroxyanthraquinone), **75** [106], (Fig. 37) Cinnamomi Cortex extract and Procyanidin flavonoids, (Procyanidin A2, **76,** Procyanidin B1, **77**, Cinnamtannin B1, **78** [107]), (Fig. 38) along with several nucleoside analogues such as 4-fluorophenylsulfonyl-Val-Leu-CHO (Calpin inhibitor VI), **79** Bn-Val-Phe-CHO (Calpin inhibitor III), **80**, β-D-N [4]-hydroxycytidine, **81** [108], (Fig. 39) are found to act as inhibitors of the SARS

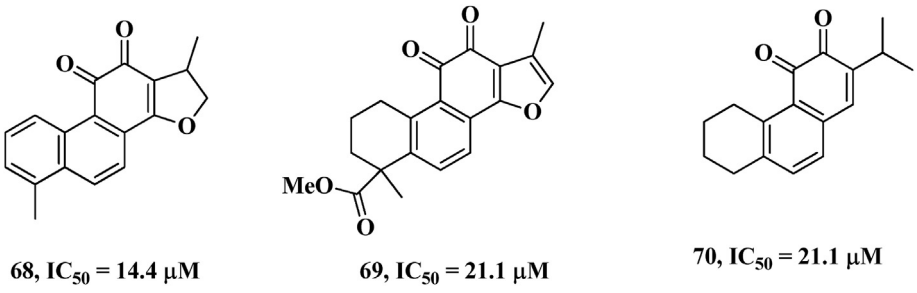
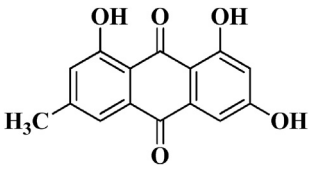


Fig. 34. Structure of tanshinone derivatives isolated from Salvia miltiorrhiza root.



75, Emodin

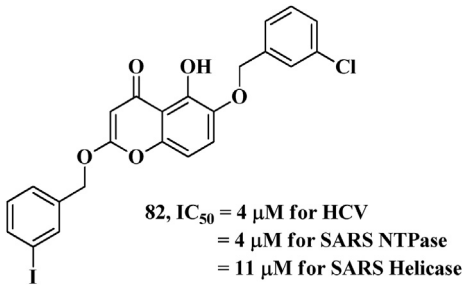
Fig. 37. Structure of Emodin.

coronavirus.

In addition to all these, Kim et al. [109] developed 5-hydroxychromones derivative and evaluated their activity as anti-hepatitis C virus (HCV) agent as well as anti-SARS agent (NTPase and Helicase enzyme, not 3CL protease). Out of different chromone derivatives, 6-(3-chloro-benzyloxy)-5-hydroxy-2-(3-iodobenzyloxy)-chromen-4-one, **82** was observed to exhibit best result in case of both anti-HCV and anti-SARS agent (Fig. 40). The IC_{50} value of the compound **82** was found to be 4.0 μM for HCV while 4.0 and 11.0 μM for SARS NTPase and Helicase respectively.

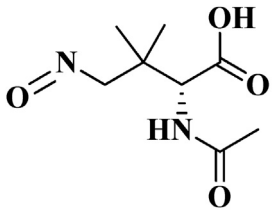
A very interesting literature report by Keyaerts et al. describes organic nitric oxide donor compounds as inhibitors of SARS-CoV in Vero E6 cells [110]. Herein, S-nitroso-N-acetylpenicillamine (SNAP), **83** and is tested for anti-SARS agents with broad concentration range giving efficient IC_{50} values of 222 μM. Moreover the same compound gives CC_{50} values of 587 μM which suggests that the compound, **83** acts as an efficient anti-SARS agent (Fig. 41).

Anthocyanin derivative based anti-SARS agents are reported recently by Fakhar et al. [111] which acquired noteworthy binding



82, IC_{50} = 4 μM for HCV
= 4 μM for SARS NTPase
= 11 μM for SARS Helicase

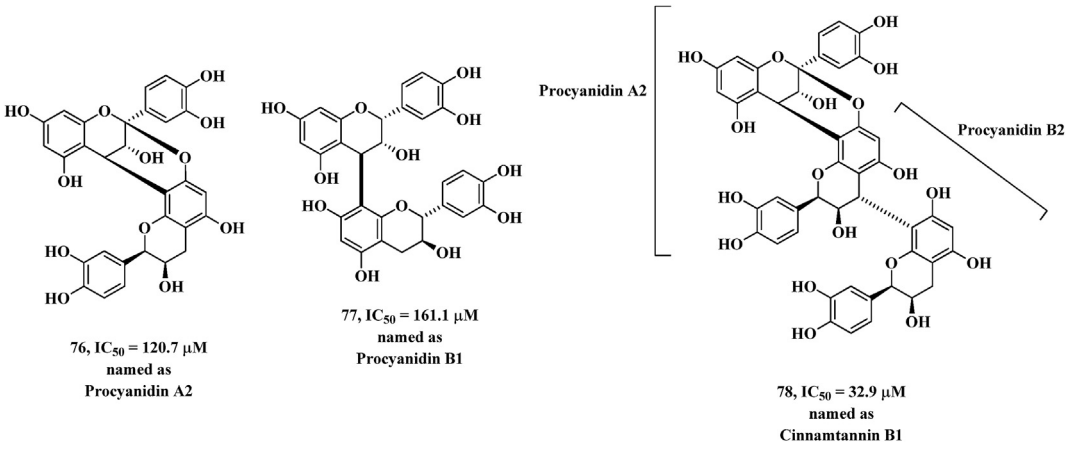
Fig. 40. Structure of hydroxychromones derivatives as anti-SARS agent.



83, IC_{50} = 222 μM

Fig. 41. Structure of S-nitroso-N-acetylpenicillamine (SNAP).

affinity and apparently leads to inhibition of the target. In their study, they observed that the compounds, **84** and **85**, showed the best activity as anti-SARS agents with the binding energies −12.37

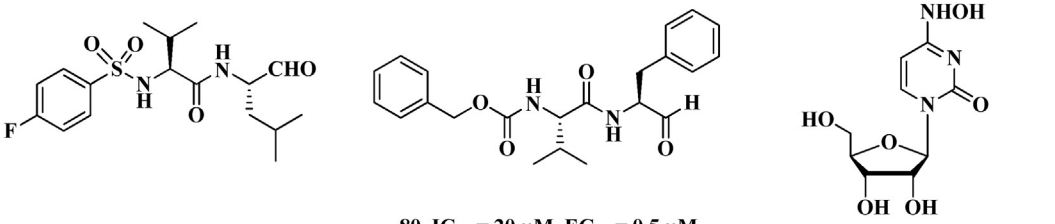


76, IC_{50} = 120.7 μM named as Procyanidin A2

77, IC_{50} = 161.1 μM named as Procyanidin B1

78, IC_{50} = 32.9 μM named as Cinnamtannin B1

Fig. 38. Structure of Cinnamomi Cortex extract and Procyanidin flavonoids.



79, IC_{50} > 100 μM, EC_{50} = 2 μM Calpin inhibitor VI, 4-fluoroohenylsulfonyl-Val-Leu-CHO

80, IC_{50} = 20 μM, EC_{50} = 0.5 μM Calpin inhibitor III, Bn-Phe-Ala-CHO

81, IC_{50} > 100 μM, EC_{50} = 10 μM β-D-N^4-hydroxycytidine

Fig. 39. Structure of different nucleoside analogues.

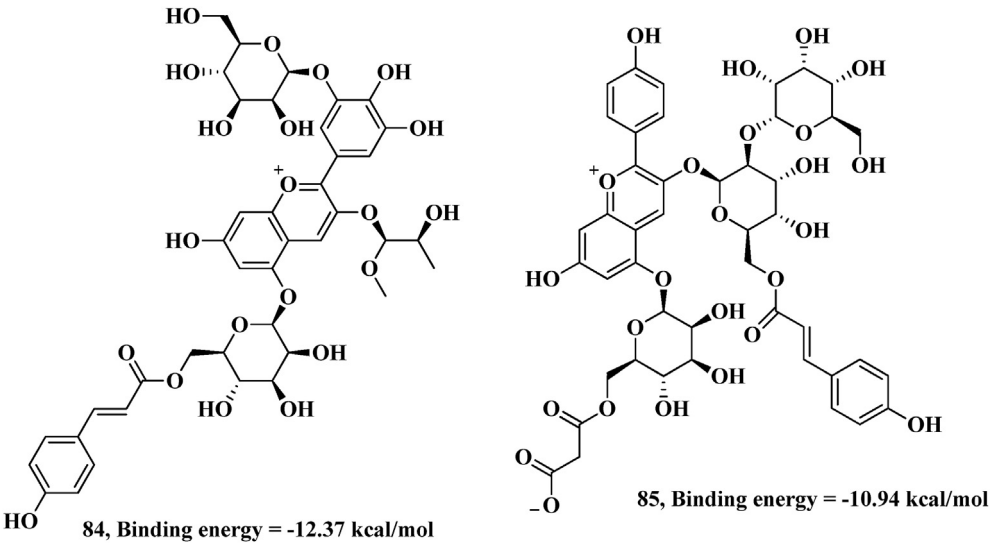


Fig. 42. Structure of anthocyanin derivatives as anti-SARS agents.

and −10.94 kcal/mol respectively. In compound **84**, eight different hydrogen bonding interactions are found which binds with the Asn142, Gly143, Thr190, Gln189, Pro168, Glu166 and His163 active residues of the protease while in compound **85**, ligating sites of the molecule bonded to different amino acid residues Thr190, Gln189, Gly143, Leu141, His163, Glu166, Pro168, Thr24, Asn142 of protease through hydrogen bonding interactions (Fig. 42).

A natural compound known as Hopeaphenol (a resveratrol tetramer) can also act as SARS inhibitor in the recent study carried out by P. Sharma and co-workers through extensive computational studies [112]. Hopeaphenol, **86** binds with various amino acid residues Ser46, Glu47, Met49, Asn142, Gly143, His164, Glu166, Gln189, Thr190 and Gln192 of main protease through hydrogen bonding interactions with binding energy of −14.473 kcal/mol. In their study, they also found that Cobicistat, a common HIV drug also has SARS inhibition ability where Cobicistat, **87** molecule binds with the His41, Cys145, Glu166, Gln189 and Thr190 residues of protease through hydrogen bonding interactions with binding energy of −12.318 kcal/mol (Fig. 43).

A recent in-silico study reveals that the leaves extract of *Justicia adhatoda* can be used as a good inhibitor for SARS-CoV [113]. *Justicia adhatoda* leaves extract contains various organic compounds which are actually available as a drug in market. Among all the organic compounds present in the *Justicia adhatoda* leaves extract, it is found that the compounds *viz.* Vasicoline, **88**, Anisotine, **89** and Pemirolast, **90** act as a good SARS inhibitors with binding energy ranging from −6.9 to −7.8 kcal/mol. The first two compounds, (**88** and **89**) are quinazoline based compounds (vasicine derivatives) while the last compound, **90** is composed of complex fused heterocycles with a tetrazole ring moiety. As vasicine and vasicinone compounds are very well known for their various biological activities therefore these compounds are also able to exhibit as anti-SARS agents (Fig. 44).

Another natural product derived SARS-CoV Papain-like protease (PL^{pro}) inhibitor is reported by Cho et al. [114] by the use of methanol extract of Paulownia tomentosa fruit. This methanol extract mainly contains geranylated flavonoids as well as tomentin compounds which are actually 3,4-dihydro-2*H*-pyran derivatives as

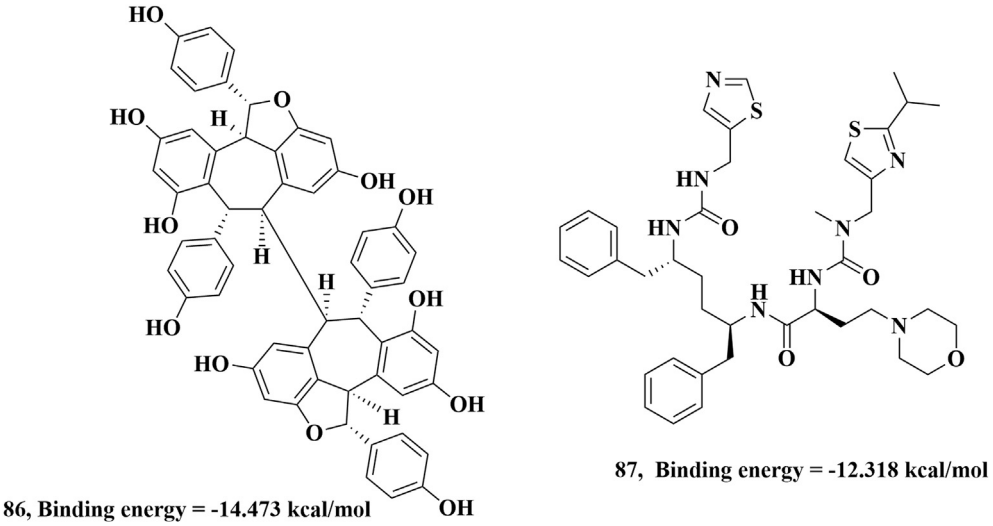


Fig. 43. Structure of natural compound Hopeaphenol and HIV drug Cobicistat.

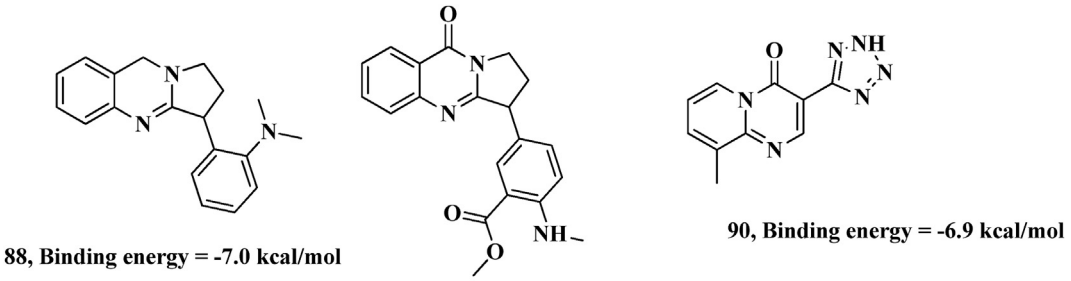
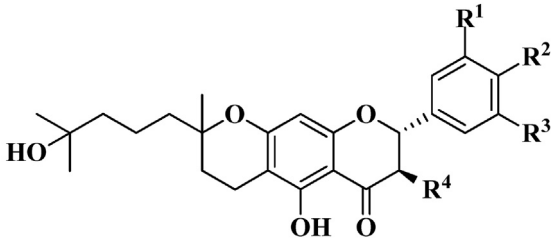


Fig. 44. Structure of compounds derived from *Justicia adhatoda* leaves extract as SARS inhibitors.



91, $R^1 = OH, R^2 = OH, R^3 = H, R^4 = H, IC_{50} = 6.2\ \mu M$
92, $R^1 = OH, R^2 = OCH_3, R^3 = H, R^4 = H, IC_{50} = 6.1\ \mu M$
93, $R^1 = OCH_3, R^2 = OH, R^3 = H, R^4 = OH, IC_{50} = 5.0\ \mu M$

Fig. 45. Structure of geranylated flavonoids and Tomentin E.

confirmed by NMR analyses. There are two geranylated flavonoids, **91** and **92** present in the methanol extract and both of them showed good efficiency as Papain-like protease inhibitor with the IC_{50} values of 6.2 and 6.1 μM respectively. While among the tomentin compounds, tomentin E, **93** showed the best inhibitor efficiency against Papain-like protease with IC_{50} values of 5.0 μM (Fig. 45).

7. Conclusion

In summary, the use of small molecules as cysteine protease inhibitor reduces the feasible replication of SARS corona virus. There is no report of corona virus protease inhibitors developed as drug candidate until now, but the approach of targeting 3CLpro to find novel anti-SARS CoV protease inhibitor with drug like properties is expected to lead the drug discovery approach against COVID-19 and other SARS related disease. Therefore, we hope that the summarization of all these small molecule cysteine protease inhibitors in this review will undeniably help medicinal chemists for further development/modification of the new/existing structures in near future to find effective therapy for corona viruses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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