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(REVIEW ARTICLE)

Novel potential heterocyclic compounds as potent anti covid drug candidates

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Abstract

The present review lays emphasis on the anticipated role of heterocyclic scaffolds in the design and discovery different heterocyclic moieties as targeting SARS, MERS and SARS COV-2 coronaviruses.

Keywords: Heterocyclic compounds; Anti-covid Activities; COVID-19.

1 Introduction

Coronavirus disease (COVID-19) became a serious pandemic in 2020 the world over which was responsible for millions of deaths worldwide and still, the numbers are increasing. Further, despite the availability of vaccines, mutation in the virus continuously poses a threat of re-emergence of the more lethal form of the virus. The approved drugs failed to achieve a significant clinical outcome.

A lot of work has been done and still going on to explore heterocyclic compounds as potent Anti-COVID-19 drugs. The heterocyclic scaffolds have been explored exhaustively for their anticancer, antimalarial, anti-inflammatory, antitubercular, antimicrobial, antidiabetic, antiviral and many more treatment capabilities since many decades.

The present review shows that the heterocyclic motifs candidates can serve as crucial resources for the development of SARS coronaviruses treatment strategies.

Hence, this review discusses the evidence of rationally designed and tested heterocyclic compounds acting on different targets against COVID-19 tested by molecular docking.

2 Anti Covid Activity

Abu-Melha et al. synthesized a novel series of some hydrazones bearing thiazole moiety via solvent-drop grinding of thiazole carbohydrazide with various carbonyl compounds. Also, dehydrative-cyclocondensation with active methylene compounds or anhydrides gave the respective pyrazole or pyrazine derivatives. The structures of the newly synthesized compounds were established based on spectroscopic evidence and their alternative syntheses. Additionally, the anti-viral activity of all the products was tested against SARS-CoV-2 main protease (M^{pro}) using molecular docking combined with molecular dynamics simulation (MDS). The average binding affinities of the compounds (−8.1 ± 0.33 kcal/mol, −8.0 ± 0.35 kcal/mol, and −8.2 ± 0.21 kcal/mol, respectively) are better than that of the positive control Nelfinavir (−6.9 ± 0.51 kcal/mol). This shows the possibility of these three compounds to effectively bind to SARS-CoV-2 Mpro and hence, contradict the virus life cycle.

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Chalkha et al. synthesized new functionalized pyrazoles using a simple and accessible approach. The synthesized aminobenzoyl pyrazoles [1] and pyrazole-sulfonamides were obtained in good yields and were evaluated in vitro for their antimicrobial and antioxidant activities. The structures of the synthesized compounds were determined using IR, NMR, and mass spectrometry. The results of the in vitro screening show that the synthesized pyrazoles exhibit promising antimicrobial and antioxidant activities. Among the tested compounds, pyrazoles have exhibited remarkable antimicrobial activity against some microorganisms. In addition, compounds have shown significant antioxidant activity in comparison with the standard butylhydroxytoluene (BHT). Hence, some compounds represent interesting dual acting antimicrobial and antioxidant agents. In fact, pyrazole derivatives bearing sulfonamide moiety have displayed an important antimicrobial activity compared to pyrazoles, this finding could be attributed to the synergistic effect of the pyrazole and sulfonamide pharmacophores. Furthermore, Molecular docking results revealed a good interaction of the synthesized compounds with the target proteins and provided important information about their interaction modes with the target enzyme. The results of the POM bioinformatics investigations (Petra, Osiris, Molinspiration) show that the studied heterocycles present a very good non toxicity profile, an excellent bioavailability, and pharmacokinetics. Finally, an antiviral pharmacophore was evaluated in the POM investigations and deserves all our attention to be tested against Covid-19 and its Omicron and Delta mutants.

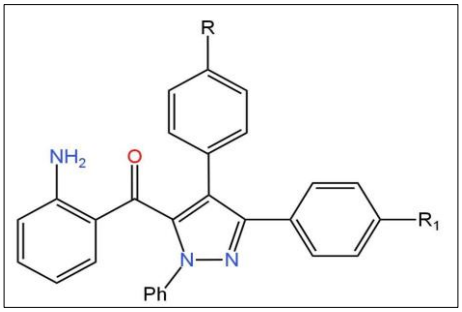

Figure 1 Aminobenzoyl Pyrazoles

Alzahrani et al. synthesized some benzo fused 1,2,3 triazole sulfonamide hybrids and evaluated for their anti- SARS-CoV-2 activity using *in silico* prediction, then the most potent compounds were assessed using *in-vitro* analysis. The *in-Silico* study was assessed against RNA dependent RNA polymerase, Spike protein S1, Main protease (3CLpro) and 2′-O-methyltransferase (nsp16). It was found that compounds showed high binding scores against RNA dependent RNA polymerase reached −8.40 and −8.75 kcal/mol, respectively compared to the approved antiviral (ramdesivir −6.77 kcal/mol). Upon testing the binding score with SARS-CoV-2 spike protein, it was revealed that it exhibited the highest score (−7.22 kcal/mol) compared to the reference antibacterial drug Ceftazidime (−6.36 kcal/mol). Surprisingly, the two compounds showed the highest binding scores against SARS-CoV-2 3CLpro (−8.75, −8.48 kcal/mol, respectively) and nsp16 (- 8.84 and – 8.89 kcal/mol, respectively) displaying many types of interaction with all the enzymes binding sites. The derivatives were examined *in vitro* for their potential anti-SARS-CoV-2 and it was revealed that compound [2] was the most promising compound with IC_{50} reached 758.8108 mM and complete (100%) inhibition of the binding of SARS-CoV-2 virus to human ACE2 can be accomplished by using 0.01 mg.

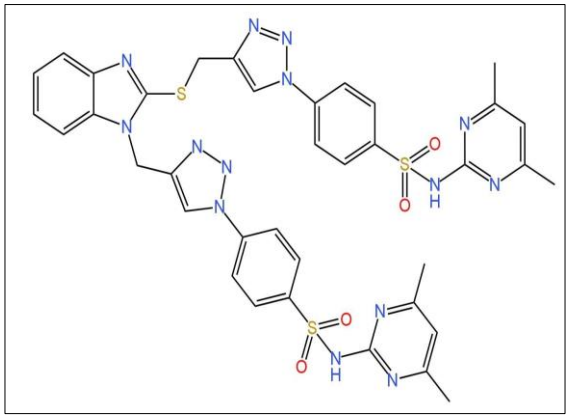

Figure 2 Structures of bis-(1,2,3-triazole-sulfa drug hybrids) carrying benzimidazole moiety

Ramalingam et al. synthesized Isopropyl 1-benzoyl-4-(benzoyloxy)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (IDPC) and characterized via spectroscopic (FT-IR and NMR) techniques. Hirshfeld surface and topological analyses were conducted to study structural and molecular properties. The energy gap (Eg), frontier orbital energies (EHOMO, ELUMO) and reactivity parameters (like chemical hardness and global hardness) were calculated using density functional theory with B3LYP/6–311++G (d,p) level of theory. Molecular docking of IDPC at the active sites of SARS-COVID receptors was investigated. IDPC molecule crystallized in the centrosymmetric triclinic space group. The topological and Hirshfeld surface analysis revealed that covalent, non-covalent and intermolecular H-bonding interactions, and electron delocalization exist in the molecular framework. Higher binding score (-6.966 kcal/mol) of IDPC at the active site of SARS-COVID main protease compared to other proteases suggests that IDPC has the potential of blocking polyprotein maturation. H-bonding and π-cationic and interactions of the phenyl ring and carbonyl oxygen of the ligand indicate the effective inhibiting potential of the compound against the virus.

Ghasemi et al. synthesized two new mixed-ligand complexes with general formula [Cu(SB)(L')]ClO4 and characterized by different spectroscopic and analytical techniques including Fourier transform infrared (FT-IR) and UV–Vis spectroscopy and elemental analyses. The SB ligand is an unsymmetrical tridentate NN'O type Schiff base ligand that was derived from the condensation of 1,2-ethylenediamine and 5-bromo-2-hydroxy-3-nitrobenzaldehyde. The two complexes were used as anticancer agents against leukemia cancer cell line HL-60 and showed considerable anticancer activity. The anticancer activity of these complexes was comparable with the standard drug 5-fluorouracil (5-FU). Molecular docking and pharmacophore studies were also performed on DNA (PDB:1BNA) and leukemia inhibitory factor (LIF) (PDB:1EMR) to further investigate the anticancer and anti-COVID activity of these complexes. The experimental and theoretical results showed good correlation. Molecular docking and pharmacophore studies were also applied to study the interactions between the synthesized complexes and SARS-CoV-2 virus receptor protein (PDB ID:6LU7).

Abu-Zaied et al. synthesized a class of pyrimidine thioglycoside analogs from a reaction of 2-cyano-3,3-dimercapto-N-aryl acrylamide and thiourea to produce the corresponding 4-amino-2-mercapto-*N*-arylpyrimidine-5-carboxamide derivatives [3], and stirring of compounds [3] with peracetylated α-D-*gluco*- and galacto-pyranosyl bromides in DMF–sodium hydride gave the corresponding pyrimidine thioglycosides. Deacetylation of the pyrimidine thioglycosides via a reaction with dry NH3/MeOH gave the corresponding free pyrimidine thioglycosides. The compounds have been characterized by ^{13}C NMR, ^{1}H NMR, and IR. Pharmacological evaluation of compounds in vitro against SARS-COV-2 and Avian Influenza H5N1 virus strains revealed that some compounds possess interesting activity.

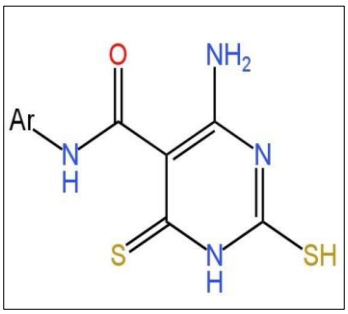

Figure 3 4-amino-2-mercapto-*N*-arylpyrimidine-5-carboxamide derivatives

Alshammari et al. synthesized a new series of *N*-substituted-2-quinolonylacetohydrazides aiming to evaluate their activity towards SARS-CoV-2. The structures of the obtained products were fully confirmed by NMR, mass, IR spectra and elemental analysis as well. Molecular docking calculations showed that most of the tested compounds possessed good binding affinity to the SARS-CoV-2 main protease (Mpro) comparable to Remdesivir.

Muhammad et al. synthesized new azoloazines from the reaction of fluorinated hydrazonoyl chlorides with heterocyclic thiones, 1,8-diaminonaphthalene, ketene aminal derivatives, and 4-amino-5-trifluoromethyl-1,2,4-triazole-2-thiol. The mechanistic pathways and the structures of all synthesized derivatives were discussed and assured based on the available spectral data. The synthesized azoloazine derivatives were evaluated for their antifungal and antibacterial activities through zones of inhibition measurement. The results revealed promising antifungal activities for compounds against the pathogenic fungal strains used; *Aspergillus flavus* and *Candida albicans* compared to ketoconazole. Molecular docking studies of the promising compounds were carried out on leucyl-tRNA synthetase active site of *Candida albicans*, suggesting good binding in the active site forming stable complexes. Moreover, docking of the synthesized compounds

was performed on the active site of SARS-CoV-2 3CLpro to predict their potential as a hopeful anti-COVID and to investigate their binding pattern.

Missioui et al. synthesized new quinoxaline derivative, N-(4-methyl-2-nitrophenyl)-2-(3-methyl-2-oxo quinoxaline-1(2H)-yl)acetamide (NMPOQA= disordered molecules NMPOQAa(50.3% and NMPOQAb(49.7%)) and characterized by ESI-MS, IR, ^{1}H & ^{13}C NMR. The geometric parameters of NMPOQA compound whose crystallographic structure has been defined by X-ray diffraction have been calculated by Density Functional Theory (DFT), B3LYP, 6-311++G(d,p) basis set. Additionally, Molecular Electrostatic Potential (MEP) and Hirshfeld studies have been conducted to analyze intermolecular interactions. Interesting molecular docking of NMPOQA and Remdesivir drug with 6M03 was conducted using the same parameters for a fair comparison. A low binding affinity of the NMPOQA (−6.9 kcal/mol) compared to the Remdesivir drug, (−7.1 kcal/mol) and other good reasons make NMPOQA a good candidate against COVID-19. A similar study was calculated with 1EVE producing evidences that suggest NMPOQA may serve as a potential drug for developing Alzheimer's disease (AD) treatment.

Said et al. synthesized Schiff bases encompassing a 1,2,3-triazole [4] motif using an efficient multi-step synthesis. The formations of targeted Schiff base ligands were confirmed by different spectroscopic techniques (FT-IR, ^{1}H NMR, ^{13}C NMR, and CHN analysis). The spectral data analysis revealed that the newly designed hydrazones exist as a mixture of *trans-E* and *cis-E* diastereomers. Density Functional theory calculations (DFT) for the Schiff bases showed that the trans-trans form has the lowest energy structure with maximum stability compared to the other possible geometrical isomers that could be present due to the orientation of the amidic NH–C=O group. The binding affinities of the newly synthesized bases are, maybe, attributed to the presence of hydrogen bonds together with many hydrophobic interactions between the ligands and the active amino acid residue of the receptor. The superposition of the inhibitor N3 and an example ligand into the binding pocket of 7BQY is also presented. Further interesting comparative docking analyses were performed. Quantitative structure-activity relationship calculations are presented, illustrating possible inhibitory activity. Further computer-aided cytotoxicity analysis by Drug2Way and PASS online software was carried out for Schiff base ligands against various cancer cell lines. Overall, the results of this study suggest that these Schiff base derivatives may be considered for further investigation as possible therapeutic agents for COVID-19.

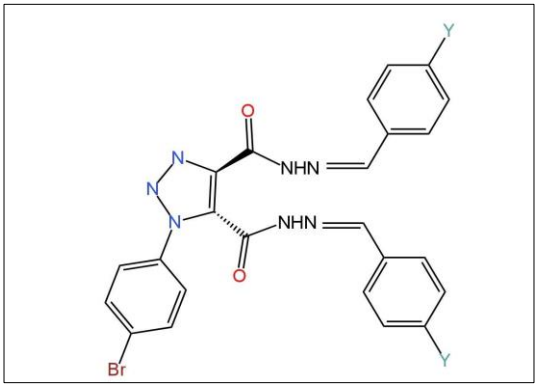

Figure 4 1,2,3-triazole compound

Devasia synthesized a new series of 3-aryl/heteroaryl-2-(1*H*-tetrazol-5-yl) acrylamides [5] through catalyst-free, one-pot cascade reactions, utilizing click chemistry approach and evaluated for their anti-COVID activities against two proteins *in silico*. The structural properties of the synthesized molecules were evaluated based on DFT calculations. Total energy of the synthesized tetrazole compounds were obtained through computational analysis which indicate the high stability of the synthesized compounds. The Frontier Molecular Orbitals (FMO) and associated energies and molecular electrostatic potential (MEP) surfaces were generated for the compounds. Spectral analysis by DFT gave additional evidence to the structural properties of the synthesized molecules. All tetrazole analogues come under good ADMET data as they follow the standard value for ADMET parameters. Docking studies offered evidence of the molecules displaying excellent biological properties as an *anti-Covid* drug. Compound 5g exhibited excellent *anti-COVID*-19 properties with four hydrogen binding interactions with amino acids GLN 2.486 Å, GLN 2.436 Å, THR 2.186 Å and HSD 2.468 Å with good full-fitness score (–1189.12) and DeltaG (–7.19). Similarly, compound 5d had shown potent activity against anti-COVID-19 mutant protein (PDB: 3K7H) with three hydrogen binding interactions, *i.e.*, SER 2.274 Å, GLU 1.758 Å and GLU 1.853 Å with full-fitness score of –786.60) and DeltaG (–6.85). The result of these studies revealed that the compounds have the potential to become lead molecules in the drug discovery process.

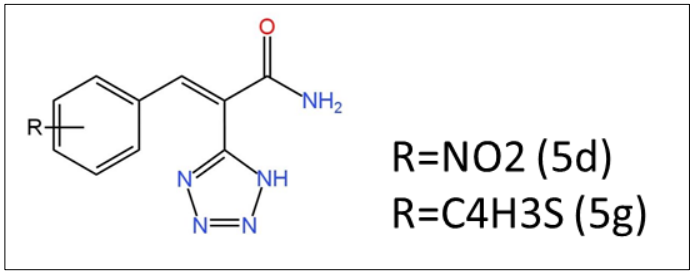

Figure 5 3-aryl/heteroaryl-2-(1*H*-tetrazol-5-yl) acrylamides

Hosny et al. described the cytotoxicity in HEPG-2 cells and studied the COVID-19 activities of the novel H2L ligand [6] and its Cr and Cu nano-complexes. In this paper novel Schiff base, N-(4, 6-dimethyl pyrimidin-2-yl)-4-(((2-hydroxyl naphthalene-1-y l) methylene) amino) benzene—sulfonamide sulfonyl) amide has been synthesized. The novel Schiff base H2L is used to synthesize novel nano and micro-complexes with CrCl2.6H2O and CuCl2.2H2O. The prepared ligand and micro complexes were interpreted by different spectroscopic techniques. The nano-sized Cr and Cu complexes were synthesized in an environmentally friendly manner using *Coriandrum sativum* (CS) media extract in ethanol. The structure, morphologies and particle size of the nano-sized complexes were determined using FT-IR, TEM, and PXRD. Furthermore, using TGA, we studied the effect of heat on the size of newly prepared nano-complexes. The findings revealed that the metal complexes investigated are more stable than the free ligand. The antitumor activity was examined before and after heating the nano-complexes at 200 °C. The results reveal the Cr nano complex, after heating, exhibited strong antitumor activity with IC50 value (3.349 µg/ml). The tested Cu nano-complex shows good DNA cleavage. The liver cancer and COVID19 proteins were examined using molecular docking to identify the potential binding energy of inhibitors.

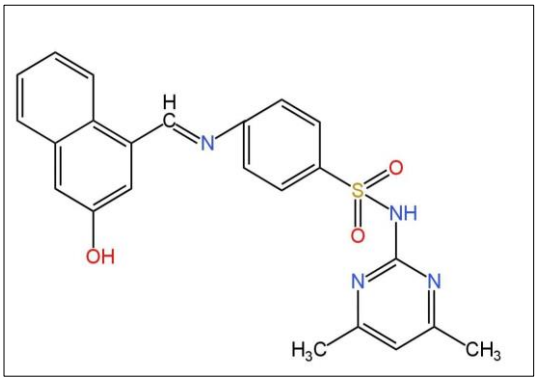

Figure 6 N-(4, 6-dimethyl pyrimidin-2-yl)-4-(((2-hydroxyl naphthalene-1-y l) methylene) amino) benzene—sulfonamide sulfonyl) amide

Tarika et al. synthesized novel antiviral compound 4-(Dimethylamino) Pyridinium, 5-dichlorosalicylic (DADS) and characterized by UV–vis, FT-IR, FT-Raman, ^{1}H NMR and ^{13}C NMR spectra. Quantum chemical computations were carried out by Density functional theory methods at B3LYP level. Frontier molecular orbital energy gap affirms the bioactivity of the molecule and NCI analysis gives information about inter and intra non covalent interactions. The reactive sites of the compound were studied from the Fukui function calculations and chemical descriptors define the reactivity of the molecule. Molecular docking done with SARS and MERS proteins endorses the bioactivity of molecules and drug likeness factors were calculated to comprehend the biological assets of DADS. Molecular docking of DADS is carried out with SARS-CoV-2 and MERS virus proteins affirms that DADS act as a good antiviral agent and further drug likeness studies also supports that DADS can be used as an active drug to treat certain viral diseases including Covid-19 virus disease.

Abbas et al. synthesized four new ferrocene Schiff bases [7] to understand the active sites and biological activity of ferrocene derivatives by employing various molecular descriptors, frontier molecular orbitals (FMO), electron affinity, ionization potential, and molecular electrostatic potential (MEP). A theoretical insight on synthesized ferrocene Schiff bases was accomplished by molecular docking, frontier molecular orbitals energies, active sites, and molecular descriptors which were further compared with drugs being currently used against COVID-19, i.e., dexamethasone, hydroxychloroquine, favipiravir (FPV), and remdesivir (RDV). The inhibitions of ferrocene derivatives were recorded on the core protease (6LU7) protein of SARS-CoV-2 and the effect of substituents on the anti-COVID activity through the

molecular docking approach. The docking results for L1-L4 highlighted that the L1 might have better anti-oxidant and anti-COVID19 ability than other currently used drugs. The computational outcome indicated that such compounds have powerful 6LU7 inhibition of SARS-CoV-2. These findings could be helpful for further exploration of new ferrocene derivatives and their potential applications in the prevention and treatment of SARS-CoV-2.

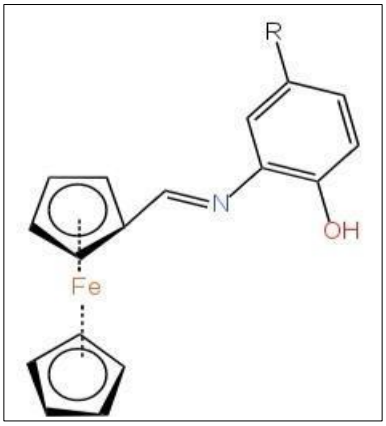

Figure 7 Ferrocene derivative

L_1=Ph, L_2=No_2, L_3=SO_3H, L_4=Cl

Alshammari et al. synthesized a new series of *N*-substituted-2-quinolonylacetohydrazides aiming to evaluate their activity towards SARS-CoV-2. The structures of the obtained products were fully confirmed by NMR, mass, IR spectra and elemental analysis as well. Molecular docking calculations showed that most of the tested compounds possessed good binding affinity to the SARS-CoV-2 main protease (Mpro) comparable to Remdesivir.

Musa et al. designed and synthesized nineteen novel compounds containing 1,2,3-triazole [8] side chains linked to phenyl pyrazolone scaffold and terminal lipophilic aryl parts with prominent substituent functionalities via a click reaction based on our previous work. The novel compounds were assessed using an in vitro effect on the growth of SARS-CoV-2 virus-infected Vero cells with different compound concentrations: 1 and 10 μM. The data revealed that most of these derivatives showed potent cellular anti-COVID-19 activity and inhibited viral replication by more than 50% with no or weak cytotoxic effect on harboring cells. In addition, in vitro assay employing the SARS-CoV-2-Main protease inhibition assay was done to test the inhibitors' ability to block the common primary protease of the SARS-CoV-2 virus as a mode of action. The obtained results show that the one non-linker analog 8h and two amide-based linkers 8i and 8q were the most active compounds with IC_{50} values of 5.08, 3.16, and 7.55 μM, respectively, against the viral protease in comparison to data of the selective antiviral agent GC-376. Molecular modeling studies were done for compound placement within the binding pocket of protease which reveal conserved residues hydrogen bonding and non-hydrogen interactions of 8i analog fragments: triazole scaffold, aryl part, and linker. Moreover, the stability of compounds and their interactions with the target pocket were also studied and analyzed by molecular dynamic simulations. The physicochemical and toxicity profiles were predicted, and the results show that compounds behave as an antiviral activity with low or no cellular or organ toxicity. All research results point to the potential usage of new chemotype potent derivatives as promising leads to be explored in vivo that might open the door to rational drug development of SARS-CoV-2 Main protease potent medicines.

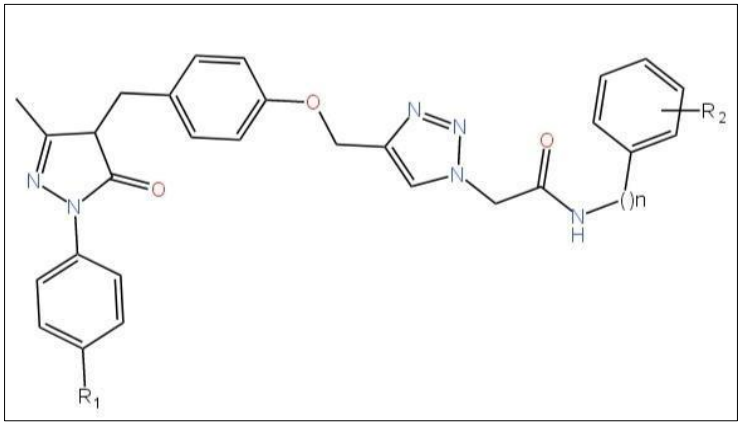

Figure 8 1,2,3-triazole derivative

8h R_1=Cl, R_2=3-F, 4-CH_3

8i R_1=Cl, R_2=4-COOH

8q R_1=Cl, R_2=4-F

Rashdan and Abdelmonsef synthesized and characterized a new series of 1,3,4-thiadiazole derivatives and theoretically evaluated as Covid-19 inhibitors against four SARS-CoV-2 targets namely, main protease (Mpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp), and receptor-binding domain (RBD) of the spike protein. The molecular docking studies and molecular dynamics simulations exhibited the promising binding affinity of compound [9] with all targets. Therefore, it could be selected as a promising chemical moiety for designing of future inhibitors as anti-Covid-19 agents.

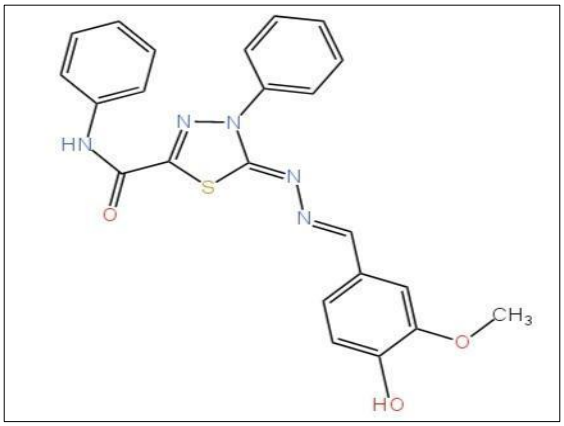

Figure 9 1,3,4-thiadiazole derivative

Horchani synthesized a new series of pyrazole, 2,5-pyrrolidinedione, and carboxylic acid linked pyrazolopyrimidinones [10] and evaluated theoretically in silico study of molecular docking and ADMET properties in order to predict their inhibition of Mpro which characterizes the Omicron variant designed for SARS-CoV-2. Significant results were obtained, and some of these compounds showed interesting binding energies and types of interactions compared to nirmatrelvir that was employed as a reference drug. These results showed that pyrazolopyrimidinone linked to 2,5-pyrrolidinedione and the unconjugated carboxylic acid could have interesting applications against the Omicron variant of SARS-CoV-2, and therefore encourages to expand this series via the synthesis of more analogues, and to test them all experimentally in order to draw the right conclusions.

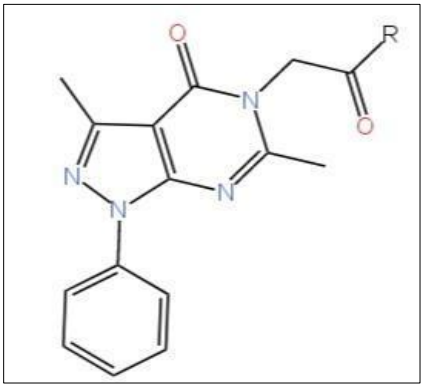

Figure 10 Pyrazolopyrimidinones

Mary et al. characterized antiviral molecule (2E)-N-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide using Fourier transform infrared (FTIR), FT-Raman and quantum chemical computations. The geometry equilibrium and natural bond orbital analysis have been carried out with density functional theory employing the Becke, 3-parameter, Lee-Yang-Parr method with the 6-311G++(d,p) basis set. The vibrational assignments pertaining to different modes of vibrations have been augmented by normal coordinate analysis, force constant and potential energy distributions. Drug likeness and oral activity have been carried out based on Lipinski's rule of five. The inhibiting potency of 2(2E)-methyl-2-[(4-oxo-4H-chromen-3-yl)methylidene]-hydrazinecarbothioamide has been investigated by docking simulation against SARS-CoV-2 protein.Drug likeness predicts the oral activity and ADMET property analysis gives an idea about the pharmacokinetic properties of the title molecule. The binding energy of −8.8 kcal/mol and the binding affinity of MCMH with Histidine and Cysteine with nonbonding interactions present a clear view that MCMH can irreversibly interact with SARS-CoV-2 protease and claims to be an excellent antiviral inhibitor.

Al-Humaidi et al. synthesized a series of 1,2,3-triazole/1,2,4-triazole either from benzimidazole/isatin precursors. Molecular docking studies and in vitro enzyme activity revealed that most of the investigated compounds demonstrated promising binding scores against the SARS-CoV-2 and Omicron spike proteins, in comparison to the reference drugs. In particular, compound [11] has the highest scoring affinity against the SARS-CoV-2 and Omicron spike proteins in vitro with its IC50 reaching 75.98 nM against the Omicron spike protein and 74.51 nM against the SARS-CoV-2 spike protein. The possible interaction between the synthesized triazoles and the viral spike proteins was by the prevention of the viral entry into the host cells, which led to a reduction in viral reproduction and infection. A cytopathic inhibition assay in the human airway epithelial cell line (Vero E6) infected with SARS-CoV-2 revealed the effectiveness and safety of the synthesized compound [11] (EC50 and CC50 reached 80.4 and 1028.28 μg/mL, respectively, with a selectivity index of 12.78). Moreover, the antiinflammatory effect of the tested compound may pave the way to reduce the reported SARS-CoV-2-induced hyperinflammation.

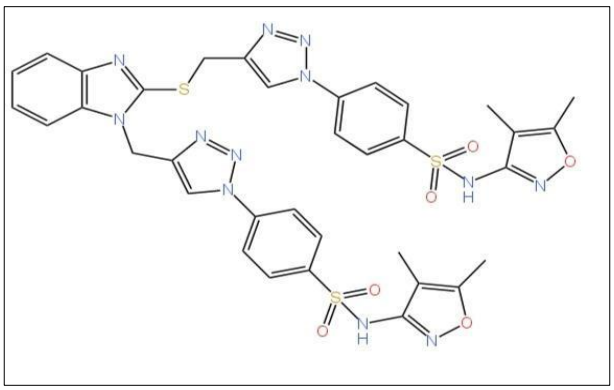

Figure 11 Synthesis of benzimidazole-1,2,3-triazole hybrid carrying sulfaoxazole

Tretyakova et al carried out the one-pot three-component CuCl-catalyzed aminomethylation of the abietane diterpenoid propargyl derivatives by formaldehyde and secondary amines (diethylamine, pyrrolidine, morpholine, and homopiperazine). All compounds were tested for cytotoxicity and antiviral activity against influenza virus A/Puerto

Rico/8/34 (H1N1) in MDCK cells and SARS-CoV-2 pseudovirus in BHK-21-hACE2 cells. Minimal toxicity with the highest antiviral activity against influenza virus A was demonstrated by compound [12] bearing a pyrrolidine fragment. The compound [12] appeared to be most effective when added at the time points 0–10 and 1–10 h of the viral life cycle, and the possible target was M2-protein. Molecular docking and dynamics modeling investigated the binding mode of compound [12] into the binding pocket of influenza A virus M2 protein.

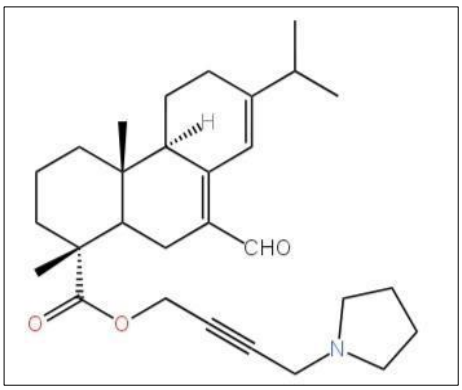

Figure 12 one-pot three-component CuCl-catalyzed aminomethylation of the abietane diterpenoid propargyl derivatives

Nepolraj et al. synthesized novel 3-(hydroxymethyl)-2-phenyl-2,3 dihydroquinolin-4(1*H*)-one and its *in-silico* evaluation as inhibitor of COVID-19 main protease. The one-pot synthesis of an established procedure Claisen ester condensation reaction was sodium hydride mediated with intramolecular cyclization with solvent free conditions. The structures of the synthesized compound were confirmed by IR, ^{1}H,^{13}C NMR, and EI-MS spectral studies. Chemo-informatics study showed that the compound obeyed Lipinski's rule, PASS, Swiss ADME. Computational docking analysis was performed using PyRx, AutoDock Vina option based on scoring functions. In-silico molecular docking study results demonstrated greater binding energy and affinity to the active pocket, the N3 binding site of the Coronavirus primary protease.

Rashdan and Abdelmonsef synthesized 1,3,4-Thiadiazole analogues *via* the reaction of 1-(5-methyl-1-(5-(methylthio)-1,3,4-thiadiazol-2-yl)-1*H*-1,2,3-triazol-4-yl)ethan-1 one 2 with vanillin or thiophene-2-carboxaldehyde, respectively through chalcone reaction. Meanwhile, all the newly synthesized compounds have been screened for their ability to prevent the proliferation of different pathogens named *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus*, and *Candida albicans* in vitro*.* As a result the newly synthesized compounds showed potent antimicrobial activities against the tested pathogens, especially compound [13], which showed the highest activity against all the tested microbes at low MIC concentration. Additionally, the ability of these compounds to inhibit Covid-19 TMPRSS2 enzyme was investigated through a structure-based docking study to identify potent anti-Covid-19 drug candidates. It has been observed that compound [13] has the highest binding affinity toward the target enzyme. Therefore, it could be used as a potential therapeutic agent to combat Coronavirus.

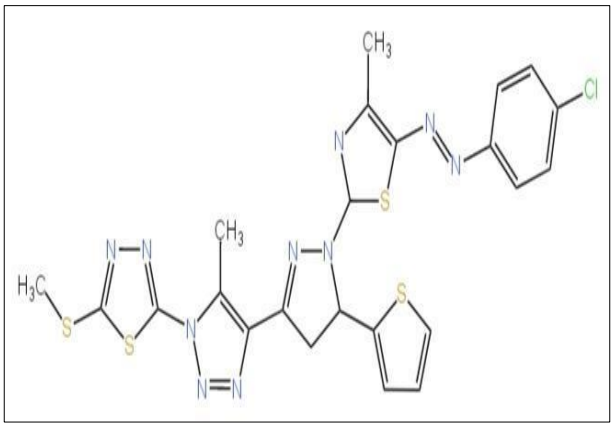

Figure 13 1,3,4-Thiadiazole analogues

Gomes et al. synthesized a series of β-amino chalcogenides, through a reaction without solvent, accelerated by microwaves, and catalyzed by molecular iodine in the presence of 2 equivalents of DMSO. In general, a wide variety of differently substituted β-amino chalcogenides were prepared, and obtained in moderate to good yields.The potential antiviral activity against SARS-CoV-2 revealed two promising compounds among the 10 selected for potency and cytotoxicity tests, [14] and [15] which showed a low cytotoxicity profile and a promising selectivity index. Computational modeling also showed that these compounds were predicted to bind in the active site of the key pharmacological target of SARS-CoV-2, the main protease Mpro, providing a rationale for their biological activity. Overall, the results provide a proof of concept of a complete pipeline to obtain compounds with potential applications against COVID-19, by applying an efficient and fully eco-friendly methodology.

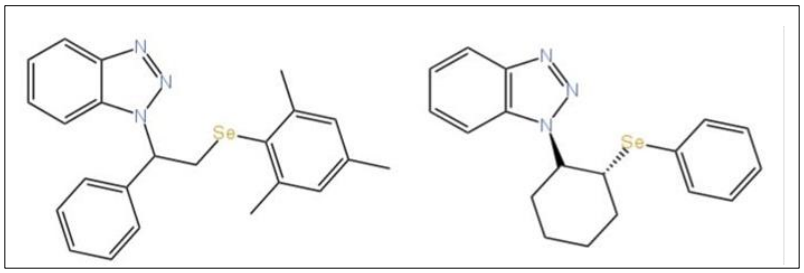

Figure 14 and 15 β-amino chalcogenides

3 Conclusion

The coronavirus disease continues to spread across the world following a trajectory that is difficult to predict. Effective treatment strategies that can be inexpensively and conveniently applied are still needed to tackle COVID-19. We studied in this review that pyrazole drugs may help in fighting COVID-19, further studies should be carried out to evaluate the clinical usefulness of such drugs against COVID-19 infection.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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