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Recent Developments on Novel Heterocyclic Compounds Thiadiazoles and Heterocyclic Compounds for COVID-19 Targets in Drug Discovery

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

This article mainly reviews the recent developments in the synthesis of novel 1,3,4-Thiadiazoles and also recent development of drug molecules for the treatment of COVID-19. The Thiadiazole heterocycle and its derivatives are the most important class of compounds among various heterocyclic compounds due to their wide range of biological activities and pharmaceutical importance. Thiadiazolemoeity exists as a principal structural pharmacopore in the combination of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antitubercular agents. In this review article, we have attempted to show various synthetic procedures of thiadiazole derivatives along with their pharmacological activities and also the recent studies on Antiviral targets for the discovery of new drugs to combat Covid19 like viruses.

Keywords: Heterocyclic compounds; cyclic compounds; drug discovery; COVID-19.

1. INTRODUCTION

Heterocyclic compounds are the cyclic compounds possessing one or more atom(s) of other elements along with the carbon atoms in the ring system. Nitrogen, sulfur, oxygen are some of the most commonly used heteroatoms.

Thiadiazole is a five-membered cyclic system possessing hydrogenbinding domain, the sulfur

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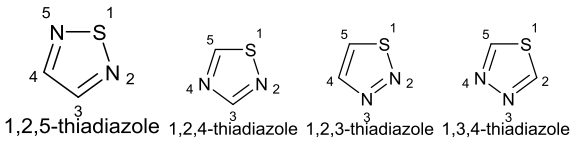
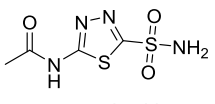
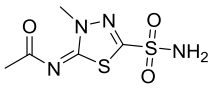
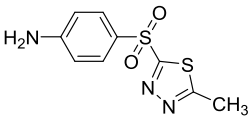
atom, and nitrogen atoms. There are four types of thiadiazoles: 1,2,5-, 1,2,4-, 1,2,3- and 1,3,4-thiadiazole. 1, 3, 4-thiadiazoles have become a versatile class of heterocycles and a great area for academicians and researchers due to their wide range of biological activity [1-5].

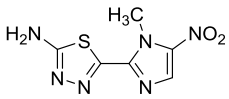


A number of thiadiazole-containing drugs are reported in the literature and marketed as shown below.


acetazolamide


methazolamide

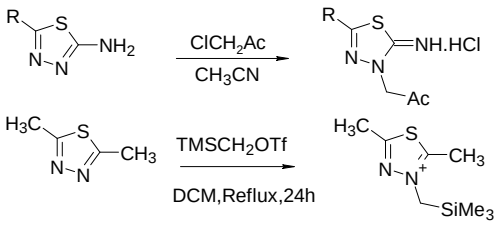

Sulfamethizole


Megazol

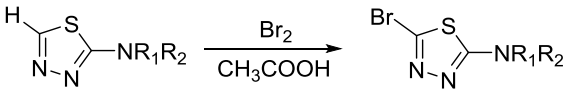
1.1 1,3,4-Thiadiazole and its Reactivity

Several researchers have used different synthetic strategies to obtain the desired target thiadiazole. Some of `the synthetic methodologies are reviewed in this article and shown below [6-9].

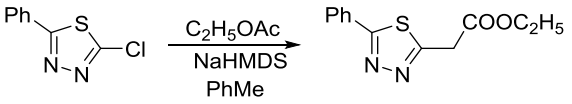
The ring nitrogens react with electrophiles to afford either 1,3,4-thiadiazolium salts or 1,3,4thiadiazol-2(3H)-ones depending on the tautomeric stability of the substituents at the C-2 or C-5 positions. 2-Amino-1,3,4- thiadiazole reacts with chloroacetone to furnish the N-alkylated thiadiazolimine. Reaction with 1-chloro-propan-2-one to provide the N-alkylated thiadiazolimine and reaction with trimethylsilyl methyl trifluoromethane sulfonate to give 1,3,4-thiadiazolium salts respectively.



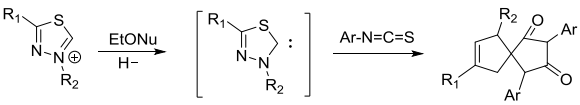
Due to the low electron density at the carbon atoms in 1,3,4-thiadiazole such reactions as nitration, sulphonation, acetylation, halogenations normally do not take place.C-Acylation can be accomplished via rearrangement of intermediate N-acylthiadiazolium salts while radical halogenation can give chlorinated or brominated 2-halo-5-substituted thiadiazoles. 2-aminosubstituted 1,3,4-thiadiazole derivatives react with bromine and acetic acid to give the 5-bromo derivatives.



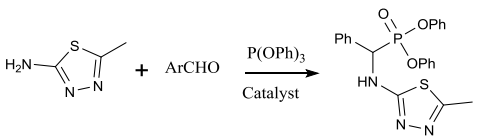
Halo-substituted thiadiazoles are highly activated and react with a variety of nucleophiles. Carbon-based nucleophiles such as malonate have been used in the synthesis of 2-substituted thiadiazoles. When 2-chlorothiadiazole was treated with ethyl acetate in the presence of sodium hexamethyldisilazane (NaHMDS), the 5-phenyl-1,3,4-thiadiazol-2-yl acetic ester was obtained as shown in the following reaction.



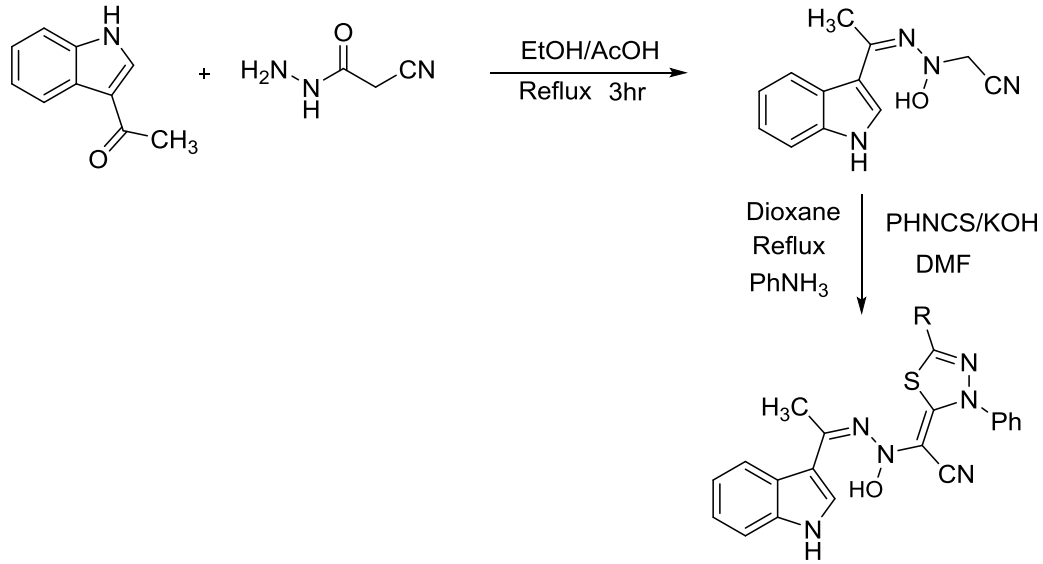
Reaction of various alkylating agents with unsubstituted and 5-substituted thiadiazoles yield 3-alkyl-1,3,4-thiadiazolium salts. These salts were deprotonated with ethoxide to produce carbenes which were then trapped with aromatic isocyanatesto yield spirocyclic compounds as mentioned below.



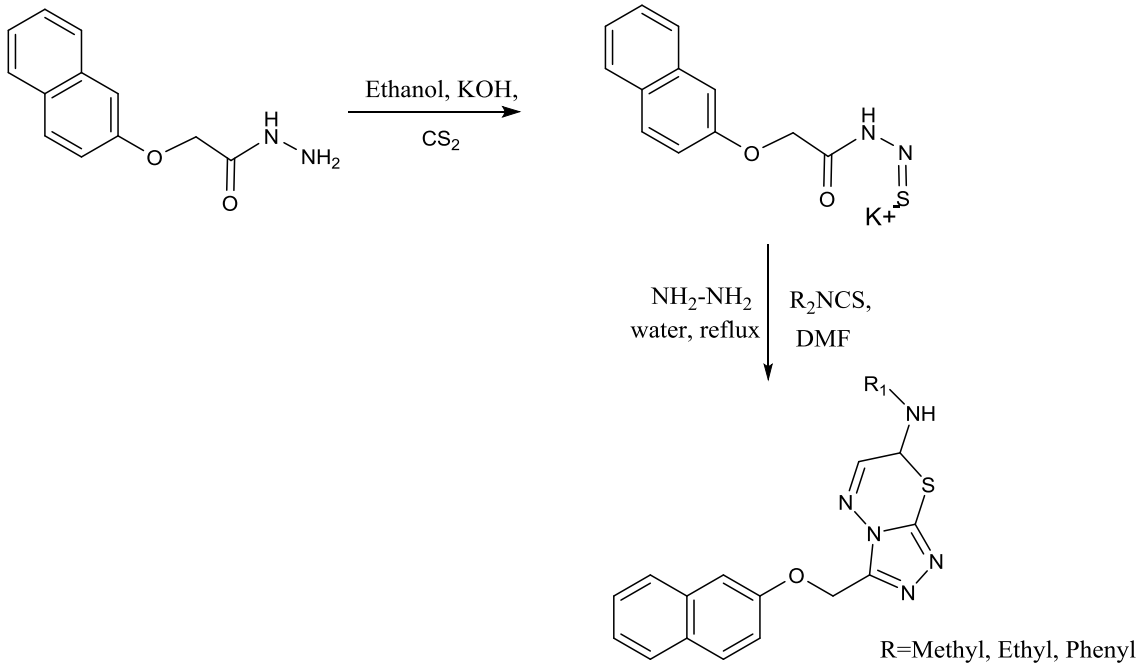
According to Azaam MM et al., [2], an α-aminophosphonate containing thiadiazole was synthesized by reacting 2-amino-5-methyl-1,3,4-thiadiazole with various aldehydes, triphenyl phosphite and mixed valence Cu(I)/Cu(II) inorganic coordination polymer as a catalyst. The products were characterizedand their anticancer activity was carried out on human hepatocellular carcinoma and breast adenocarcinoma cell lines using MTT assay method. These compounds were found to show good anticancer activity.



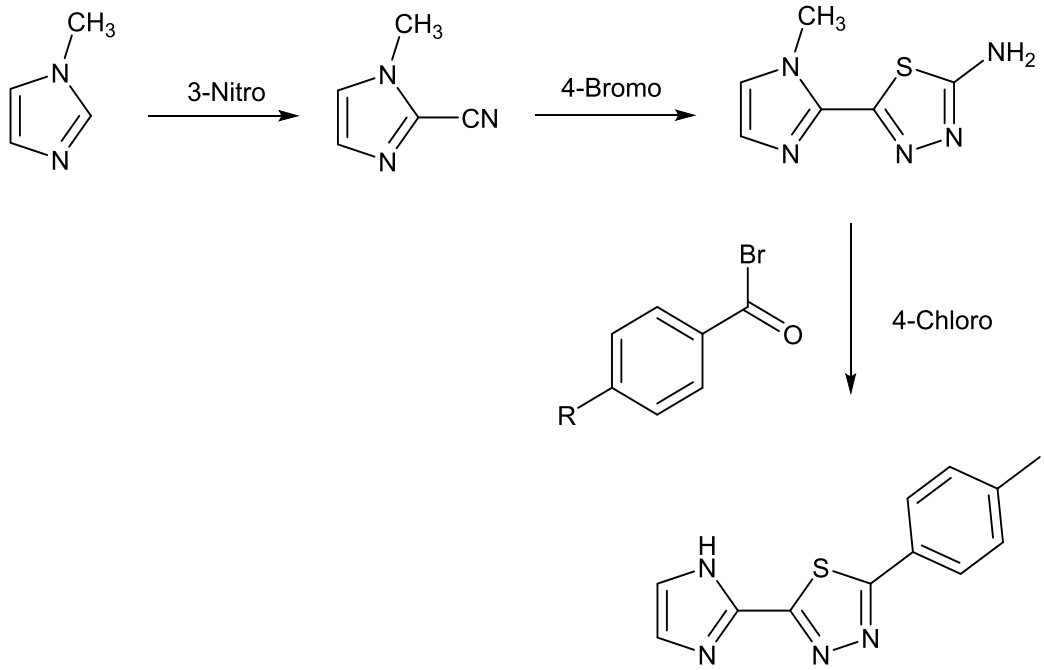
In another report, Abdelhamid A O et al., [1] synthesized some 1, 3, 4-thiadiazole derivatives by the reaction of hydrazonoyl halides with 3-(1H-indol-2-yl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazole1-carbothioamide, hydrazonoyl halides with N'-(1-(1H-indol-3-yl)ethylidene)-2cyano acetohydrazide to form 1,3,4-thiadiazole derivatives. The compounds have been characterized and screened for their antitumor activity against the MCF-7 human breast carcinoma cell line. These compounds are novel and found to show good activity.



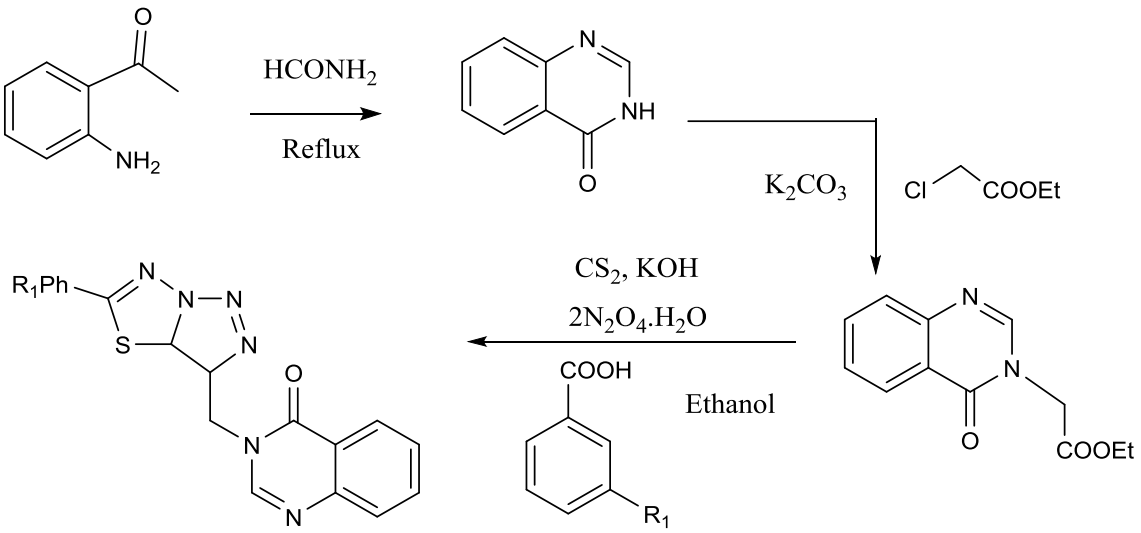
In another approach**,** Amir M et al., in 2017 synthesized 6-substituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazole from naphthoxy acetic acid. The products were characterized and screened foranti-inflammatory activity. These compounds were reported to be showing promising activity.



Patel H M, Noolvi M N, Sethi N S, Gadad A K, Cameotra S S et al., in [3] synthesized imidazo [2, 1-b][1,3,4] thiadiazole derivatives and evaluated for their antitubercular activity.

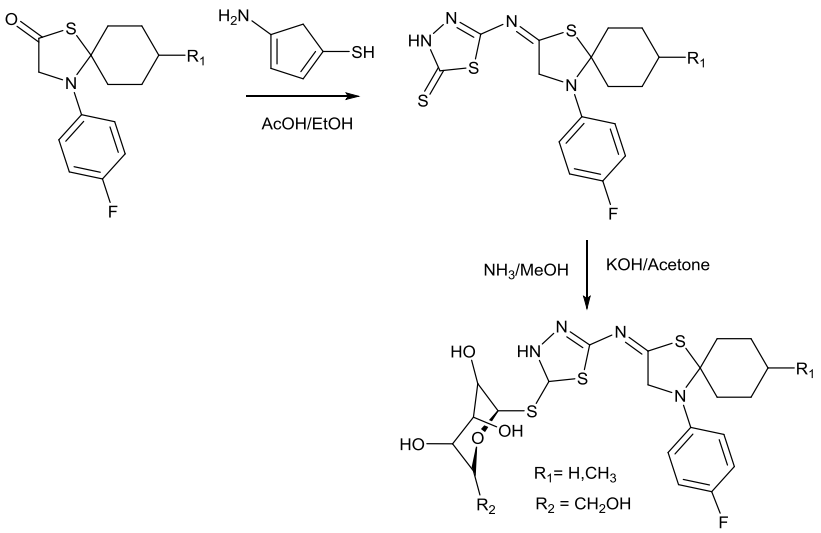


Quinazolin-4 (3H)-one derivatives containing a 1, 2, 4-triazolo [3, 4-b][1, 3, 4] thiadiazole moiety were synthesized by Lv X, Yang L, Fan Z, Bao X et al., in 2017, characterized by the spectral data and evaluated their antimicrobial activities.

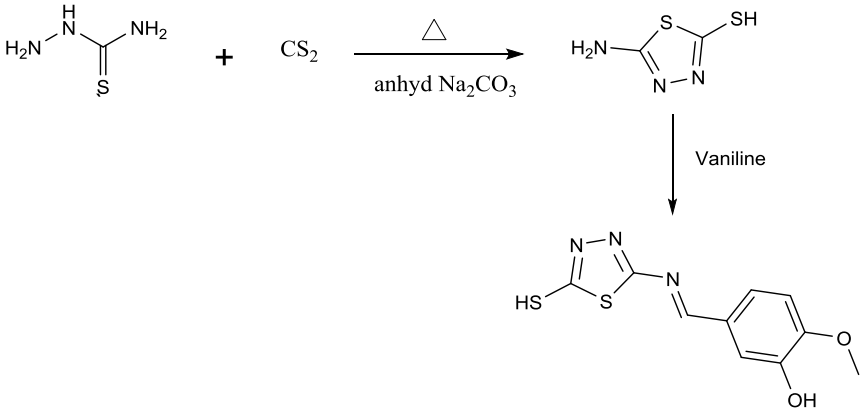


R_1= Phenyl, Methoxy

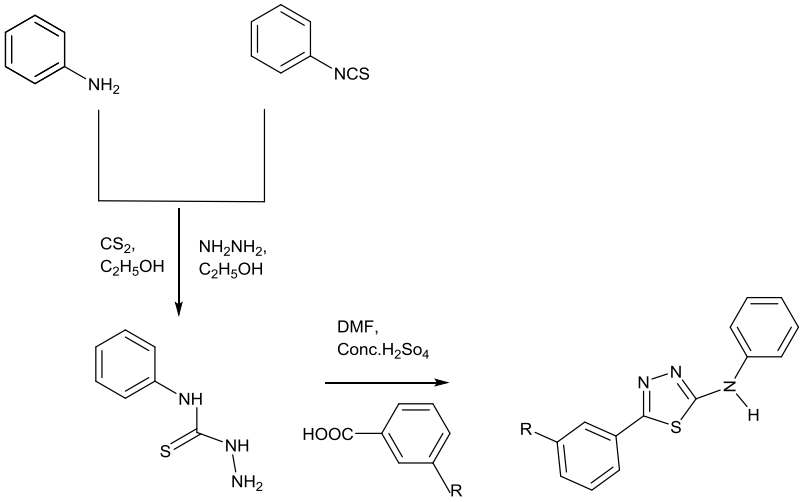
New 1-thia-4-azaspiro [4.5] decane, derived from thiazolopyrimidine and 1, 3, 4thiadiazolethioglycosides were synthesized by Flefel E M et al., in 2017 [4] and evaluated their anticancer activity. These compounds were found to show interesting activity.



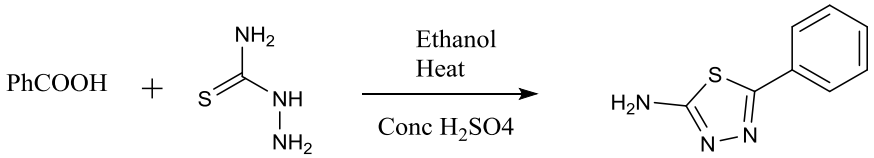
In another approach, Ameen H A, Qasir A J et al., in 2017 have Synthesized 2-amino-5-mercapto-1, 3, 4-thiadiazole derivatives and evaluated them for the antimicrobial activity as shown in the following scheme.



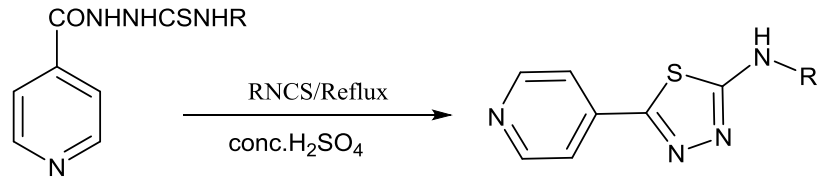
Kumari R, Sharma BB, Dubey V et al., in 2017 [9] synthesized 1, 3,4-thiadiazole derivatives and evaluated for their anti-inflammatory activities.



Kothawade P, Bhalerao R, Kulkarni G et al. in 2017 synthesized the following1, 3, 4- thiadiazole derivatives and evaluated for its antidiabetic and antioxidant activity. The aryl carboxylic acid is treated with thiosemicarbazide in ethanol in the presence of catalytic quantity of sulfuric acid to obtain the respective thiadiazole.

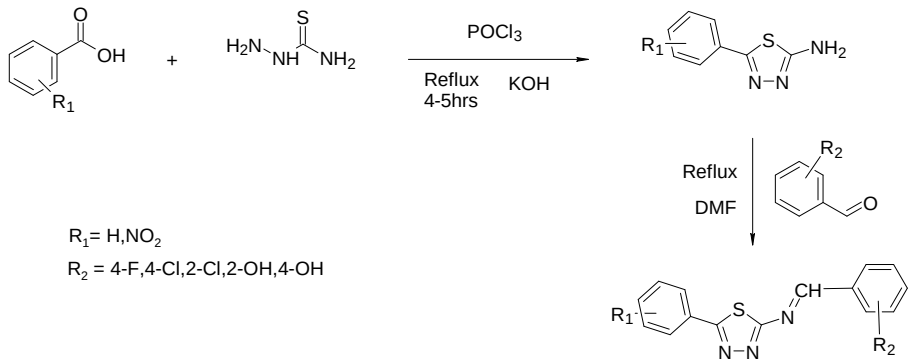


Previously in a slightly different approach,Abdo N Y, Kamel M M. et al.,in 2015 synthesized 1, 3, 4-thiadiazole derivatives and evaluated for its anticancer activity.



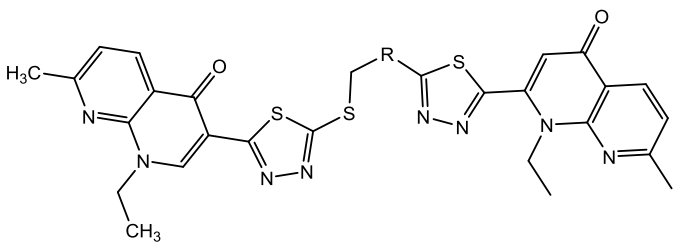
R = Tolune, Anisole

Madhavi B. and Veera Raghava Sharma G. [10] have been focusing on the synthesis of novel thiazolidinoneanalogs as shown in the following scheme for their biological activity studies including their role in treating viral diseases such as Covid 19 and similar viruses.



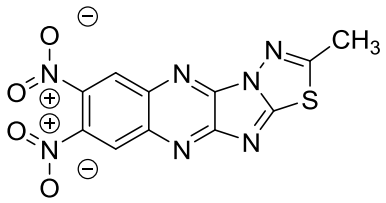
1.2 Antibacterial and Antifungal activity

Aggarwal et al synthesized novel nalidixic acid-based1,3,4-thiadiazoles and demonstrated their antimicrobial activity. The bacterial stain used included gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative bacteria, namely *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Compound with 1,4-bis (methylene) benzene group as a spacer between two 1,3,4-thiadiazoles showed remarkable antibacterial activity (MIC, 31.25–125 lµg/mL) against all the tested organisms.

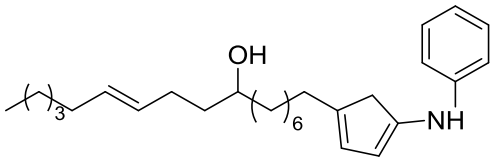


R- -$(CH2)_0$; -$(CH2)_4$; -$(CH2)_6$; -$(CH2)_8$; -$CH_2C_6H_4CH_2$-

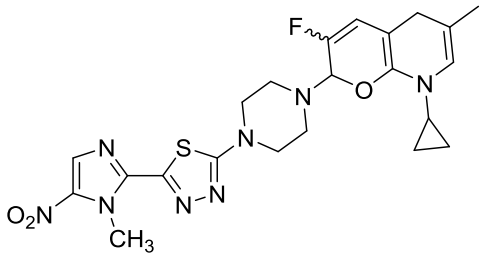
Teja et al synthesized some novel thiadiazolo [2,3] imidazo [4,5-b]quinoxaline derivatives and evaluated their antimicrobial activity against gram positive (*S. aureus* and *Bacillus cereus*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) by paper disc diffusion method. The minimum inhibitory concentrations (MIC) of the compounds were also determined by using the agar streak dilution method. Ciprofloxin was used as reference drug. Many compounds showed good antimicrobial activities.



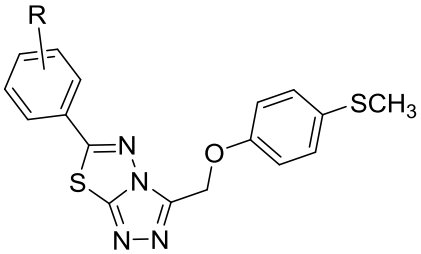
Farshori et al. [8] synthesized a novel series of 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-thiadiazolesand screened for their antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Klebsiella pneumoniae* bacterial strains by disc diffusion method. Minimum inhibitory concentrations (MICs) were determined by broth dilution techniques which were in range of 6.25-12.5µg/ml by using Chloramphenicol and Griseofulvin as standard antimicrobial drugs. Most of the tested compounds depicted excellent antimicrobial activities on comparison with standard drugs.



Foroumadi et al synthesized a series of N-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2yl] and N-[5-(nitrophenyl)-1,3,4-thiadiazole-2-yl]piperazinylquinolone derivatives and evaluated for *in vitro* antibacterial activity against some gram-positive and Gram-negative bacteria. The antibacterial data revealed that all nitroimidazole derivatives showed interesting activity against tested gram-positive bacteria (MIC=0.008-0.03 µg/ml) while they did not show good activity against gram-negative organisms. All nitrophenyl analogues were inactive. Among all of the tested compounds (Ciprofloxacin derivative in nitroimidazole series) exhibited excellent activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*(MIC=0.008 µg/ml).



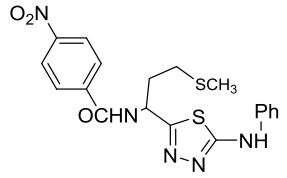
Karabasanagouda et al. synthesized some novel 1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoleswhich were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* bacterial strains and for antifungal activity against *Aspergilus flavus*, *Aspergilus fumigatus, Penicillium marneffei* and *Trichophyton mentagrophytes*. One compound with methyl substitution was found to be the most potent compound of the series by having MIC value of 6.25µg/ml on comparision with Ciprofloxacin and cyclopiroxolamine as standard drug. The good activity is attributed to the presence of pharmacologically active -CH3, OCH3, NH2, and 2,3- dichloro groups attached to phenyl group at position 6 of thethiadiazole ring. Results of antifungal screening showed that the presence of S-CH3 and S-C2H5 groups at position 4 of phenoxy group caused increased activity.



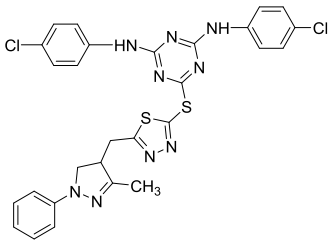
R- 2-Cl; 4-CH_3: 4-OCH_3; 2,3-$(Cl)_2$; 4-NH_2

Pintilie et al synthesized some novel N-(5-(3-(methylthio)propyl)-1,3,4-thiadiazol-2yl) benzamide derivatives and investigated for their antimicrobial activities against five standard bacterial strains *Staphylococcus aureus*, *Bacillus antracis*, *Bacillus cereus*, *Sarcinalutea* and *Escherichia coli* by using double dilution method. Some of the investigated compounds exhibited excellent antimicrobial activities on comparision with their respective standard drugs. The most active compound against *B. antracis* and *B.*

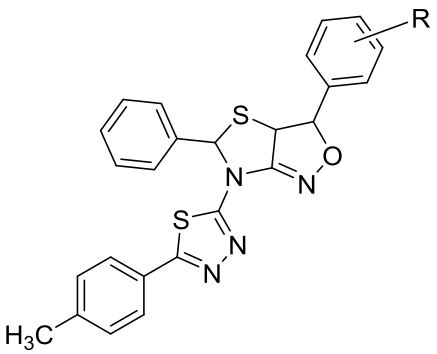
cereus was a compound with a 4-methylphenyl moiety on the heterocyclic ring.



Dubey et al [9] synthesized 1,3,4 thiadiazole-1,3,5-triazine derivatives and evaluated their antimicrobial activity against bacterial strains like *Pseudomonas aeruginosa*, *Bacillus cereus*, *Escherichia coli* and *Bacillus subtilis*. Compounds with chloro-substitution on phenyl amine position connected to 1,3,5-triazine core exhibit significant activity against *Pseudomonas aeruginosa* (6.25 µg ⁄mL), moderate activity against *Bacillus cereus* and *Escherichia coli* (12.5 µg⁄mL).

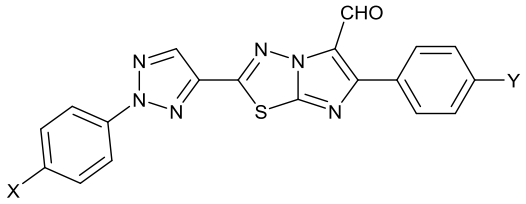


Seelametal synthesized a novel series of 1, 3, 4-thiadiazoles which are incorporated with isoxazolo-thiazole moieties and screened for their antimicrobial activity The screened compounds with chlorine substituted showed high antibacterial activity against all the strains against *B. subtilis* and *B. thuringiensis* with MIC 3.125µg/mlas compared with standard drug Streptomycin. Compound having 4-OCH_3 showed equipotent activity treflucan against all the strains *C. albicans, fabae*, *F. oxysporam* (MIC, 3.125 µg/ml).



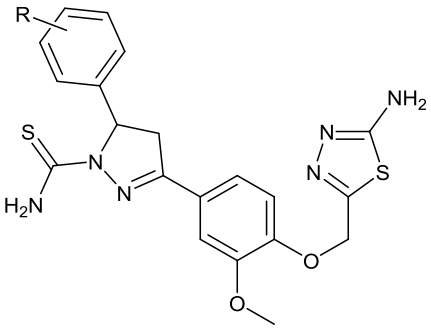
R- 4-Cl; 2-Cl; 4-$N(Me)_2$; 3-NO_2; 4-OCH_3; 4-CH_3

Atta et al synthesized novel imidazo 2,1-b]-1,3,4-thiadiazoles and evaluated for their antimicrobial activity against *Staphylococcus aureus*, Candida albicans, *Pseudomonas aeruginosa* and *Escherichia coli* using agar diffusion method Ampicillin and Clotrimazole were used as reference drugs.



X- H; Br; Cl; I Y- H; Br; Cl

Noolvi et al [3] synthesized 2-(4-formyl-2-methoxyphenoxy) acetic acid and screened for their antimicrobial activity against *S. aureus*, *S. enterica*, *V. cholera*, and antifungal activity against *C. albicans*.

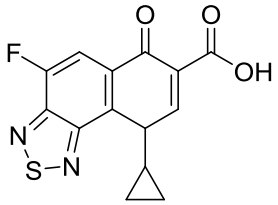


R- H; 2-OCH_3; 3-NO_2; 4-NO_2; 4-Cl; 4-NH_2; 2,4-diOH;4-OH; 3-C

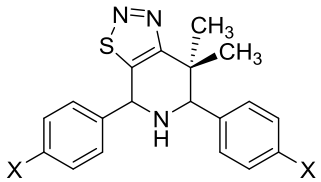
Bhardwaj et al synthesized new pyridine imidazo[2,1b]-1,3,4-thiadiazole derivativesand screened for their antimicrobial activity using cup-plate agar diffusion method against bacteria *B. pumillus*, *S. aureus*, *V. cholera*, *E. coli*, *P. mirabilis*, and *P. aeruginosa* and fungal culture of *C. albicans*. Some compound showed excellent inhibition of *B. pumillus* (95.1%), *P. aeruginosa* (94.6%), *V. cholera* (91.0%), *S. aureus* (88.8%), and one compound demonstrated inhibition of P. mirabilis (87.8%) when compared with standard drug Ampicillin and Amphotericin

Al-Qawasmeh et al. [11] synthesized 9-cyclopropyl-4-fluoro-6-oxo-6, 9-dihydro-[1,2,5] thia- diazolo [3,4-h]quinoline-7-carboxylic acid and ethyl ester derivatives and tested for their antimicrobial activities *in vitro* against a wide spectrum of Gram-positive and Gram-negative

bacteria, yeasts and moulds taking Ciprofloxacin as reference drug. Most of the compounds were active butone compound showed excellent activity against Gram-positive bacilli and staphylococci (MICs= 0.015-1.5µg/mL), including methicillin-resistant *Staphylococcus aureus*, and against most of the Gram-negative bacteria tested (MICs = 0.07-3 µg/mL).

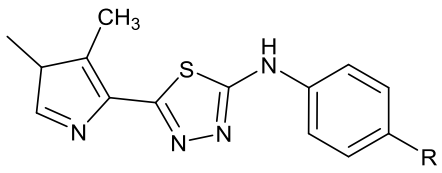


Gopalakrishnan et al. [11] synthesized 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridine [3,4-d]-1,2,3thiadiazoles. All of the newly synthesized novel target molecules were tested for their antibacterial activity *in vitro* against *Staphylococcus aureus*, β-Haemolytic streptococcus, Vibreocholerae, *Salmonella typhii*, Shigella felxneri, *Escherichia coli*, *Klebsiella pneumonia*, and Pseudomonas by using Ciprofloxacin as standard drug for comparison. Synthesized compounds exerteda wide range of modest antibacterial activity and modest *in vitro* antifungal activity against Rhizopus and M. Gypsuem, compared to the standard drug Fluconazole.



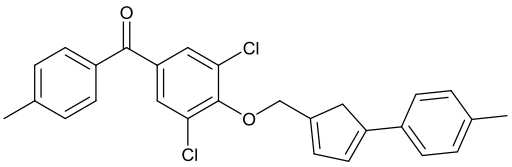
X= halogens

Liesen et al synthesized N-(4-methoxyphenyl)-5-(5-methyl-1H-imidazol-4-yl)-1,3,4-thiadiazole-2amine derivatives. One compound was found to be the most potent compound with MIC value 130µg/ml as compared with standard drug Chloramphenicol and Rifampicin for antibacterial activity.



R- H; Cl; F; OCH_3

Murthy et al supported the synthesis of some new (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2yl)methoxy)phenyl)aryl methanonesand investigated for their antimicrobial activities by agar well diffusion method. Gentamicin (antibacterial drug) and Nystatin (antifungal drug) were used for comparision. The compound with methyl substitution was found to exhibit significant antibacterial activity at lower concentration, against Gram positive bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus cereus* and Gram negative bacteria such as *E. coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumonia*. Results indicate that the compound with electron-donating groups exhibited broad spectrum antimicrobial activity against both bacteria and fungi.



COVID-19: Drug targets and potential treatments

All CoVs enzymes and proteins involved in viral replication are potential drug targets in the search for therapeutic options for SARS-CoV-2. This review provides an overview of the main targets from a structural point of view, together with reported therapeutic compounds with activity against SARS-CoV-2 and/or other Co Vs. Also, the role of immune response to corona virus infection and the related therapeutic option sare presented [12-20].

This novel CoV belongs to the Coronaviridae family as well as SARS CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV). Highly pathogenic CoVs are enveloped, positive polarity single-stranded RNA betacoronavirus and their genomes encode non-structural proteins (nsps), structural proteins and several accessory proteins.

The SARS-CoV-2 infection process starts with the viral entry mediated by the interaction of the spike (S) glycoprotein with the host angiotensin-converting enzyme 2 (ACE2) receptor, and the S protein cleavage by the host transmembrane serine protease 2 (TMPRSS2) prior to the fusion to the host cell membrane. SARS-CoV-2 infection is profoundly inhibited with lysosomotropic drugs (99% and 98% respectively) in cells transduced with pseudovirus [21-28].

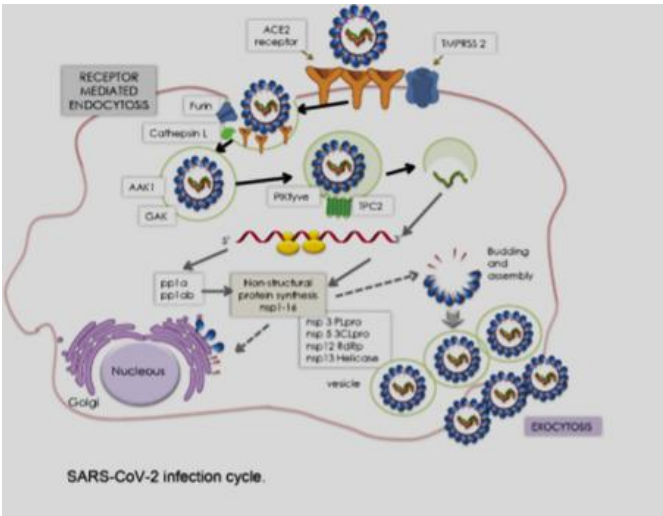
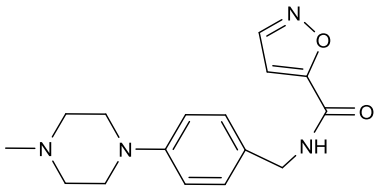


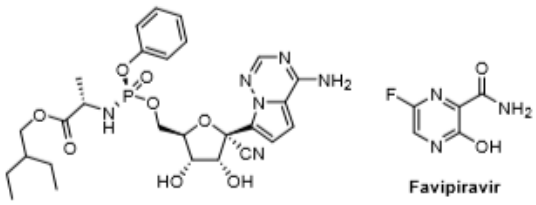
Fig. 1. SARS-Cov-2 Infection Cycle

Systemic peptide mapping on SARS-CoV allowed to discover the peptide CP-1, which binds with high affinity the heptad-repeat 2 region of S2 and interferes with the conformational changes leading to the 6-helix bundle formation and thus blocking Virus cell fusion process. Recently, a pan-corona virus fusion inhibitor lipopeptide (EK1C4) has been designed, targeting a structure formed by two specific regions in the S2 subunit.



Compounds and Peptides directed to S- Protein

GINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYE



Remdesivir

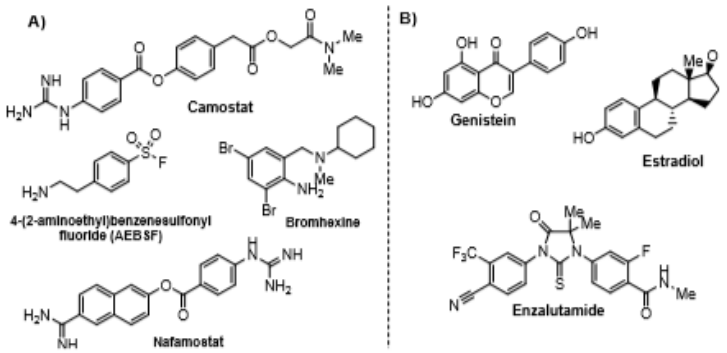
Favipiravir

RdRp inhibitors active against SARS-CoV-2 and under clinical trials

1.3 Host-based Druggable Targets

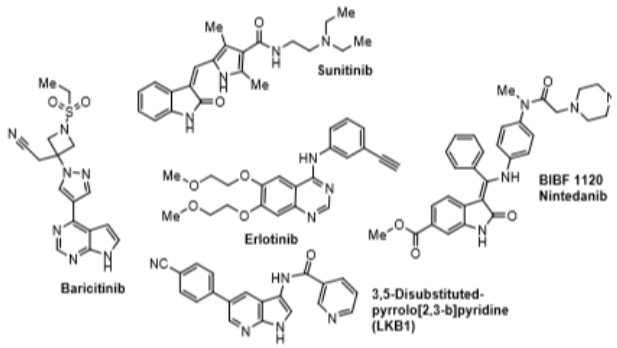
In SARS-CoV-2, the angiotensin I converting enzyme 2 (ACE2) has been recently confirmed as the main virus receptor. Therefore, inhibition or modulation of ACE2 represents one of the proposed host-based strategies for treatment of SARS CoV-2. ACE2 can be found in epithelial cells of lung, liver and testis. ACE2 was already known for mediating infection of the less pathogenic SARS-Co V, in particular, by recognizing the receptor-binding domain of the S protein (S1 RBD) with an helical region located in the peptidase domain.

The host cell surface transmembrane serine protease 2 (TMPRSS2) activates S protein present in the highly pathogenic human corona viruses SARS-CoV and MERS-CoV.1.



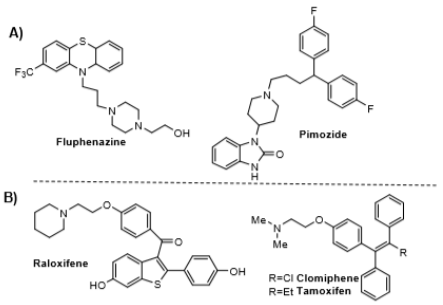
TMPRSS2 modulators. A) Chemical structure of TMPRSS2 inhibitors. B) Some transcriptional inhibitors of TMPRSS2

The adaptor-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK) are host Y8 protein kinases that regulate intracellular viral trafficking during entry, assembly and release of multiple unrelated RNA viruses such as rabies, Ebola, dengue or hepatitis C virus. In the recent past, repurposing marketed drugs or optimizing valuable hits such as 3,5-disubstituted-pyrrolo[2,3-b]pyridines as potent AAK1 and GAK inhibitors could be a good strategy to avoid SARS-CoV-2 entry [29-37].



AAK1 and GAK inhibitors with therapeutic potential for COVID-19.

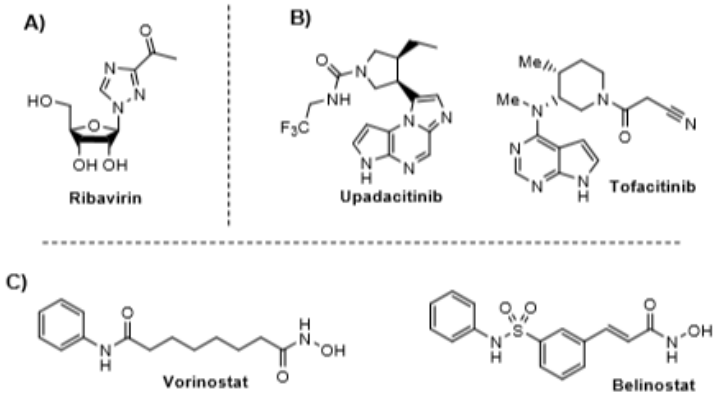
The two-pore channels (TPC1-3) regulate the conductance of sodium and calcium ions across cellular membranes. These are involved in the regulation of endolysosomal trafficking and Ebola entry in the host cell.



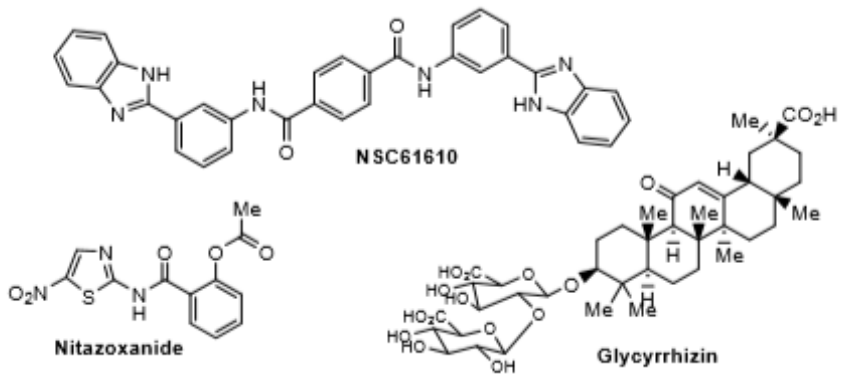
Clinical used drugs blockers of TPC2. A) Dopamine antagonists, B) SERMs

Therapeutic targeting of the innate immune response:

It has been known that a cytokine storm results from an overreaction of the immune system in SARS and MERS patients. Clinical findings showed exuberant inflammatory responses during SARS-CoV-2 infection, further resulting in uncontrolled pulmonary inflammation, likely leading case fatality. The repurposing of host-based therapeutics to control immune response may counterattack COVID-19 [38,39]. Some of these treatments include the use of recombinant IFN-and IFN-] as antiviralcytokines that inhibit viral replication in targeted cells. Some studies have reported that IFN- alone has more effect against SARS-CoV-2 than IFN- *in vitro*. In fact, combinations of IFN- and IFN- with other antivirals such as ribavirinand/ or lopinavir/ ritonavir (HIV treatment) have a synergistic effect *in vitro* and in animal models. *In vitro* and *in vivo* studies show the protective effect of Type III IFN 2L _3 treatment against SARS-CoV infection, that possibly in combination with IFN-I- could be an effective treatment for SARS-CoV-2. It has been shown recently that the potential benefits from low-dose corticosteroids treatment in SARS-CoV-2 critically ill patients. Another immunosuppressor, tocilizumab, an humanized monoclonal antibody against the interleukin IL-6 receptor reduces proinflammatory response in COVID-19 patients. Immunosuppressor treatments successfully used against other viruses, could be also used for COVID-19. These would include JAK inhibitors such as tofacitinib, baricitinib, and the recently approved upadacitinib, previously used in rheumatoid arthritisblinatumomab and HDAC inhibitors such as vorinostat or belinostat. Baricitinib is also a potent inhibitor of AAK1 and may also influence in decreasing viral infectivity, being a good candidate for clinical trials of COVID-19 [40-46].



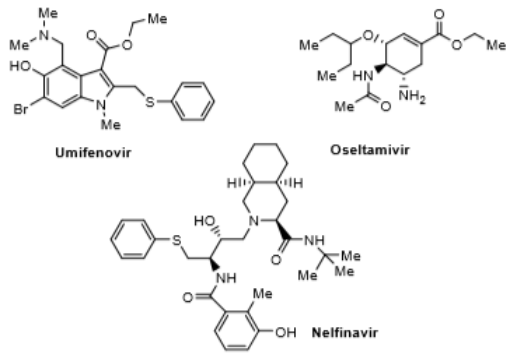
Immunosuppression potential treatments. A) antiviral used in combination with IFN-α and IFN-β B) JAK inhibitors, C) HDAC inhibitors.



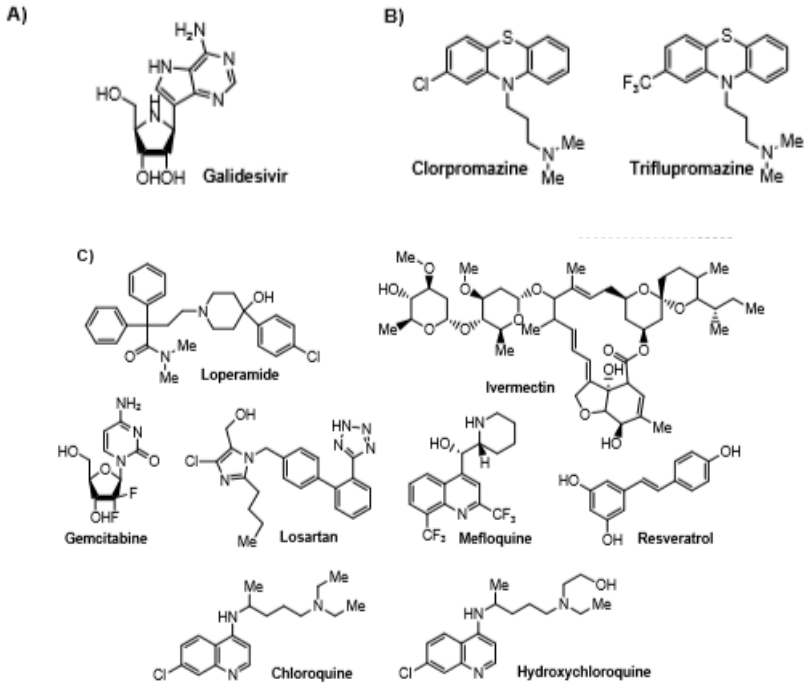
Anti-IFV-A agents with potential therapeutic effects on SARS-CoV-2.

Therapeutic options in clinical trials for COVID-19:

Antivirals lopinavir/ritonavir have been recommended for clinical treatment for COVID-19. However, recent results from clinical trials do not confirm any benefit in hospitalized adult patients with severe COVID-19, but the combination of these two antivirals with interferon is found to be more promising for patients. Remdesivir is an adenosine analogue RdRp inhibitor with antiviral protection against SARS-CoV-2 and other viruses. Intravenous administration has been found to be efficacious in an American patient with COVID 19. Based on these results, Gilead Company provided the compound to China to perform the first clinical trials in SARS-CoV-2-infected individuals (Clinical trials NCT04257654/6). The FDA has approved the emergency use of this drug for COVID-19 patients with severe symptoms.Arbidol (umifenovir) is able to block viral fusion against influenza viruses. The antiviral activity of umifenovir against SARS-CoV-2 has been confirmed *in vitro*. First clinical data from patients with laboratory-confirmed COVID-19 points to a superior efficacy of umifenovir monotherapy to lopinavir/ ritonavit treatment. Also, other drugs used for influenza as Avigan (favipiravir) and Tamiflu (oseltamivir) have been used in patients.



Antivirals used in clinic as potential COVID-19 treatment



Some of the approved drugs in clinical trials for COVID-19. A) Inhibitors of viral RNA polymerase, B) antipsychotics effective in clathrin-mediated endocytosis, C) miscellaneous drugs [47-50,10].

2. CONCLUSIONS

In this report, we have described a brief review on the recent progress in the synthesis and biological activity studies of various Thiadiazole derivatives, an important class of heterocyclic compounds suitable as drug candidates for various drug targets.

Also focused in the present report, the structural druggable sites and determinants of antibodies efficacy against S Protein. The significance of structural spike(S) protein is remarkable due to its main role in the SARS-CoV-2 entry through the host receptor ACE2.Targetting human proteins is an excellent alternative and another promising way is the combination of available antiviral drugs acting through different targets in a multi-target strategy that has proven to increase efficacy during the recent current pandemic. It has been found during the recent pandemic that the repurposing of approved drugs is the only possibility to find a timely effective treatment. However, thecoronavirus outbreaks require thorough preparedness not only for the current situation but also for a future potential reemergence of novel coronaviruses. Hence it is of utmost importance to design drugs acting as pan-coronavirus antivirals or through a multi-target approach to avoid lack of effectiveness by viral mutation escape.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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