Review Article

A review of the Structure-Activity Relationships (SAR) of selected drugs with potential to be repurposed against SARS-COV-2

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Abstract

Background: The pandemic caused by the novel SARS-CoV-2 virus has escalated rapidly and impacted human health worldwide, in addition to causing severe disruptions to socioeconomic life. There is presently no effective treatment for the disease and this underscores the urgent need for new therapeutic options against this life threatening disease. The traditional strategy for the development of new drugs is a slow and expensive process. Drug repurposing is a valuable alternative strategy that can be used to bypass some of the limitations of traditional drug discovery in order to rapidly develop new therapeutic agents for the management of Covid-19. **Objectives:** The present review x-rays recent efforts to re-purpose some antiviral drugs for the treatment of SARS-Cov-2 with an emphasis on the structure activity relationships (SAR) of the compounds. **Methods:** A systematic internet search of three academic databases of published literature was undertaken using relevant keywords and search terms which focused on drug re-purposing against SARS-CoV-2. **Results:** A total of 853 results were generated and evaluated. The results of the search were screened and relevant articles identified, yielding a total of 83 articles. Some of the drugs identified with potential for re-purposing against SARS-CoV-2 include: Arbidol, Favipiravir, Ribavirin, Nitazoxanide etc. **Conclusion:** It is hoped that the information generated in this review will help deepen understanding of the potential mechanism of anti-SARS-CoV-2 action of the compounds and also draw attention to opportunities that exist for structural modification of these molecules with the aim of improving and enhancing their selectivity and efficacy against SARS-CoV-2.

Keywords: Drug repurposing, drug design, SARS-CoV-2, Structure-activity-relationship (SAR), antiviral

Introduction

Coronavirus disease 2019 (COVID-2019) is a viral disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Grifoni et al., 2020). The virus is a novel, single stranded RNA virus belonging to the beta corona virus sub class (Xie & Chen, 2020). It is thought to have originated in China in late 2019 but has subsequently spread to almost all countries of the world (Hoffmann et al., 2020). The rapid global spread of the disease resulted in its declaration as a public health emergency by the World Health Organization (WHO) (Zhang et al., 2020). As at February 2021, the pandemic has resulted in over a hundred (100) million infections and about 2.5 million deaths worldwide, with the number of infection on a steady and

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rapid rise (WHO, 2021). According to the official release by the Nigerian Centres for Disease Control, on 23rd February, 2021, Nigeria has had about 152,074 confirmed cases of COVID-19 with 1,839 deaths (NCDC, 2021).

Traditionally, drug discovery and development is a very demanding, expensive and time consuming process. Drug repurposing or repositioning is a drug discovery strategy which involves the identification of new uses for already approved or investigational new drugs that are outside the scope of the original disease or condition it is indicated for (Fetro & Scherman, 2020). Interestingly, about 30% of new drug approvals by the United States Food and Drug Administration (FDA) are repurposed agents (Jin & Wong, 2014). Repurposing represents a promising drug discovery strategy that may have the advantages of shorter time for approval than de novo drug discovery in addition to been cost effective due to the lower development costs (Gelosa, Castiglioni, Camera, & Sironi, 2020). It has been reported that in some instances, the drug research and development process has been significantly accelerated by repurposing old drugs for the treatment of different diseases than originally planned leading to cost savings of as much as 40% of the overall cost (Chong & Sullivan, 2007). Other major advantages of drug repurposing include established methods for chemical synthesis and manufacturing of the drug, availability of reliable safety data in addition to information on the pharmacokinetic profile of the drug obtained from earlier pre-clinical and clinical studies (Andersen et al., 2020). Some instances of drugs been successfully repurposed for new indications include the case of Sildenafil which was initially designed to treat Pulmonary arterial hypertension but is presently indicated for the management of erectile dysfunction (Salentin et al., 2017). Also, Miltefosine which is an alkylphosphocholine drug was initially developed as an anti-tumour drug but was later repositioned for the treatment of visceral leishmaniasis for which it is currently the only orally available drug treatment (Dorlo, Balasegaram, Beijnen, & de Vries, 2012). Another example is Thalidomide which was originally approved as a sedative but has been repurposed for the management of Leprosy (Kim and Scialli, 2011).

There is presently no cure for Covid-19 and most cases are being managed symptomatically together with supportive care (Wu et al., 2020). In this light and considering the urgency of the situation, it may therefore be sensible to explore the option of repurposing previously approved drugs for their potential in the treatment of Covid-19. Several studies have reported that some clinically available drugs have shown anti-Covid 19 activity *in vitro, in silico* or even clinically. Some of these include the antimalarial agents; Chloroquine and hydroxychloroquine (Geleris et al., 2020), the protease inhibitors; Lopinavir/ Ritonavir (Cao et al., 2020) and the nucleoside analogue antiviral agent; Remdesivir which has received emergency use authorization for the treatment of Covid-19 by the United States Food and Drug Administration (FDA). The drug has the advantage of shortening recovery time but does not improve survival rates in infected patients and this is a serious limitation (Singh, Singh, Singh, & Misra, 2020). Other molecules that have shown some activity against the virus include the RNA polymerase inhibitor, Favipiravir (Zhang, Xie, & Hashimoto, 2020); angiotensin converting enzyme 2 (ACE2) inhibitors, and the anti-influenza drug; Umifenovir. Furthermore, a number of vaccines are presently in development against the virus (Groneberg et al., 2005) but if successful, they may not be available for mass vaccination campaigns in the near future, hence the need to accelerate the development of new drugs as a strategy to combat the virus.

The present review is therefore aimed at highlighting the structure activity relationships (SAR) of some of the above classes of compounds with the aim of deepening understanding of their anti-SARS-COV-2 activity. A study of their SAR may also reveal some regions in these compounds where structural modification can be done to enhance their anti-SARS-COV-2 activity.

Methods

A review of published literature was carried out in a systematic manner by searching the PubMed, Google Scholar and ScienceDirect databases. Relevant articles were located using the following combination of terms: (Covid-19 OR SARS-CoV-2) AND (drug repurposing OR repositioning) AND (Structure Activity Relationship OR SAR). Every paper reporting data on drugs repurposed for the treatment of Covid-19 including clinical trials and studies where drug screening were done *in vitro* or *in silico* against various SARS-CoV-2 targets were considered together with papers detailing the structure activity relationships of the drugs. Furthermore, the reference list from eligible papers were examined in order to identify other related or potentially relevant articles. A total of 853 results were generated and evaluated. The results of the search were screened and relevant articles identified, yielding a total of 83 papers which were found to be relevant and therefore included in this review.

Structure Activity Relationships (SAR) of drugs for potential repurposing against SARS-COV-2

Arbidol (Umifenovir)

Arbidol is a synthetic antiviral agent that is licensed to treat Influenza A and B virus infection in Russia and China (Leneva, Russell, Boriskin, & Hay, 2009). Chemically, it features an indole core which is functionalized with a

variety of substituents at all but one position and it interacts preferentially with aromatic amino acids affecting multiple stages of virus life cycle. Arbidol possesses broad spectrum activity, being active against both enveloped and non-enveloped viruses including Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Ebola Virus, human herpes virus and Polio virus (Pécheur et al., 2016). Recent studies have also detailed its activity against the novel SARS-CoV-2 virus (Vankadari, 2020; Wang et al., 2020). Its mechanism of anti SARS-CoV-2 action is thought to be by inhibition of the spike (S) protein/ Angiotensin converting enzyme 2 (ACE 2) thereby inhibiting membrane fusion of the viral envelope. A number of Arbidol derivatives have been synthesized and tested in recent times with the aim of getting better understanding of the structural attributes that are important for its antiviral activity, improving its safety profile and identifying new lead compounds that may possess activity against emerging viral diseases and some of those studies are discussed below.

In an effort to enhance the activity of Arbidol against the Chikunguya virus (a mosquito borne alpha virus), a series of derivatives were synthesized and tested. The most potent analogues were those in which the Bromine atom had been removed from the indole nucleus and further optimization done by converting the Sulfide into a sulfoxide while introducing electron withdrawing substituents such as halogens and trifluoromethyl (-CF_3) on the Benzene ring (Di Mola et al., 2014). It had earlier been demonstrated that cytotoxicity of Arbidol derivatives can be reduced by oxidation of the Sulfide with no negative effect on the antiviral activity of the compounds (Zhao et al., 2006). Another study showed that addition of a hydroxy group at the meta position of the thiophenol moiety of Arbidol led to a remarkable increase in affinity of the compounds for hemagglutinin thereby blocking viral entry (Wright et al., 2017). It has also been shown that the amine at position 4 and the hydroxyl moiety in position 5 are important for antiviral action, whereas insertion of a methyl (-CH_3) group between the 5-hydroxyl group and the indole ring substantially increased the antiviral potency of the resultant molecule (Blaising et al., 2014; Brancato et al., 2013). Other studies demonstrated that introduction at position four (4) of certain azole-based heterocyclic moieties improved anti-Hepatitis B virus activity while substitution of the thiophenyl group at position 2 with a phenyl-sulfonyl group increased the anti-HBV activity of the compound and also reduced its cytotoxicity (Chai et al., 2006; Zhao et al., 2006). Finally, the indole ring, S-phenyl group, ester group and amino group have all been shown to be essential for interaction of Arbidol with viral membranes (Sellitto et al., 2010) and any changes that radically change their nature may be detrimental to antiviral activity.

From the foregoing, it can be gleaned that it is possible through a combination of *in silico* modelling and *in vitro* experimentation, to refine the SAR of Arbidol in order to improve its specificity for its molecular targets in the SARS-CoV-2 virus since the 3D structure of most of its viral proteins have been elucidated and deposited in various data banks (Walls et al., 2020; Zhang et al., 2020).

Favipiravir

Favipiravir is a broad-spectrum antiviral with activity against RNA viruses. It is approved for the treatment of Influenza virus infection in Japan, China and other parts of Asia (Shiraki & Daikoku, 2020). Chemically, it is a pyrazinecarboxamide derivative and it undergoes intracellular phosphoribosylation to the active form, favipiravir-RTP (favipiravir ribofuranosyl-5′-triphosphate), which is recognized as a substrate by RNA-dependent RNA polymerase (RdRp). Its mechanism of action is via inhibition of RNA-dependent RNA polymerase (RdRp) which leads to inhibition of viral RNA synthesis. (Furuta et al., 2017).

Favipiravir possesses broad spectrum antiviral activity and in addition to its anti-influenza virus activity, it is able to inhibit the replication of flavi-, alpha-, filo-, bunya-, arena- and noro- viruses. One of its off label use is in the treatment of Ebola and Lassa virus infected patients (Delang, Abdelnabi, & Neyts, 2018). The drug has also been shown to be active against the SARS-CoV-2 virus (Cai et al., 2020; Wang et al., 2020).

Structurally, Favipiravir has three substituents (–F, –OH, –$CONH_2$) attached at various position around the pyrazine core. The compound exhibits acidic properties due to the hydroxyl group which can undergo tautomerism to the keto form (El-Nahas and Hirao, 1999). A look at the synthetic landscape shows that only a few studies have been carried out to prepare new derivatives of Favipiravir. In one such study, a series of novel pyridine, pyridazine, and pyrimidine C-nucleoside favipiravir analogues were synthesized and found to have enhanced potency together with an expanded spectrum of antiviral activity (G. Wang et al., 2016). In another study, a class of 1,3-oxathiolane nucleoside derivatives of Favipiravir were designed and tested and some of the analogues were found to have good anti-HIV and anti-H1N1 activity (Mingming et al., 2018). The brominated and defluorinated derivatives of Favipiravir have also been prepared and found to be highly stable when subjected to extended stability studies at 37°C (Huchting et al., 2017).

Nitazoxanide

Nitazoxanide is a Nitrothiazole Benzamide derivative antiinfective agent with broad spectrum activity against

several microbial species (Shakya et al., 2018). It is rapidly hydrolyzed *in vivo* to the active circulating metabolite, tizoxanide (Lam et al., 2012). The drug is approved in the United States for the treatment of giardiasis and cryptosporiodiosis. It has also been successfully been repurposed against Influenza virus infection (Rossignol et al., 2009). The drug has also shown remarkable activity against several viral pathogens such as the Chikunguya virus (Wang et al., 2016), Human immunodeficiency virus (Tan et al., 2012), Vaccinia virus (Hickson, Margineantu, Hockenbery, Simon, & Geballe, 2018), Hepatitis B and C viruses (Korba et al., 2008), Rubella virus (Perelygina et al., 2017), Middle East Respiratory Syndrome (MERS) coronavirus (Rossignol, 2016) and the Ebola virus (Jasenosky et al., 2019). Nitazoxanide has been shown to inhibit the SARS-CoV-2 virus *in vitro* with an EC_{50} of 2.12μM (M. Wang et al., 2020). The molecular mechanism of its anti-viral activity is still unclear but has been linked to interference with host mediated pathways for viral replication. Some of the pathways implicated include interferon or mammalian target of rapamycin complex 1 (mTORC1) signaling pathways. It may also block the post translational maturation of viral hemagglutinin (Rossignol, 2014; Rossignol, 2016).

With respect to the structure activity relationship of the thiazolides, substitution of the nitro group on the 5-position of the thiazole ring with a chloride substituent diminished activity of the derivative (RM-5038) against bacteria and anaerobic protozoa but enhanced its activity against Hepatitis B and C viruses (Korba et al., 2008; Stachulski et al., 2011). Also, replacement of the Nitro group on the thiazole heterocycle and changing the position of the ethanoate group from the 2 to 3 position of the Benzene ring led to a change in activity of the derivative which demonstrated enhanced anti-alzheimers activity (Li et al., 2020). Recently, a series of amino-acid ester thiazolide prodrugs were synthesized and tested with the aim of improving bioavailablity of the compound class. Those prodrug derivatives possessing L-tertiary-leucine as the amino acid exhibited greater stability than the Valine and Iso-leucine analogues and this was attributed to the increased steric bulk of the amino acid side chain of L-tertiary-leucine (Stachulski et al., 2017). Hybridization of the nitazoxanide pharmacophore with the N-methylbenzimidazole nucleus produced a series of conjugates with good antiprotozoal activity (Soria-Arteche et al., 2013). Benzologue derivatives of Nitazoxanide have also been designed using the vinylogy principle whereby a Benzene ring was inserted in between the Nitro and Thiazole group, in the ortho and para positions on the aromatic ring in relation to one another and the compounds obtained were found to have multiple fold increase in antiprotozoal activity especially against *Leishmania mexicana* and *Giardia sp.* (Navarrete-Vazquez et al., 2011). In another study, a set of urea and amide based analogues of Nitazoxanide were prepared and they demonstrated low micromolar activity *in vitro* against *Mycobacterium tuberculosis*. The authors however observed that while the Salicylate and amide linker regions of Nitazixanide can accommodate changes, any modification to the Nitrothiazole led to a loss of activity in most cases (Odingo et al., 2017). One important inference that can be made from the above is that the pharmacological activity of Nitazoxanide depends on the presence of the 5-nitrothiazole ring which is essential for activity (i.e. the pharmacophore) and this has to be kept intact during chemical modification and optimization efforts.

Others

There are a number of other antiviral agents which have been postulated to have some activity against Covid-19 but a survey of the literature available shows that there is a lot of conflicting information regarding their inhibitory efficacy against the SARS-CoV-2 virus. They may therefore require additional and more detailed investigation before a definate position can be taken concerning the prospects of repurposing them for the treament of Covid 19. These agents are briefly discussed below.

Ribavirin

Ribavirin is a broad spectrum antiviral agent used in the treatment of Hepatitis C virus infection (Pawlotsky, 2003), Lassa Fever (Haas et al., 2003) and respiratory syncytial virus (Cooper et al., 2003). It is a purine (guanosine) nucleoside analogue with a modified base and a D-ribose sugar moiety and is phosphorylated intracellularly by host enzymes (Graci & Cameron, 2006). A number of mechanisms have been suggested for its antiviral action and these include: inhibition of inosine monophosphate dehydrogenase (IMP) which is essential for the synthesis of guanosine triphosphate, inhibition of viral capping and inhibition of viral polymerase by the 5′-triphosphate metabolite of ribavirin (Hong and Cameron, 2002).

Ribavirin has been shown to have the ability to inhibit the SARS-CoV-2 virus *in silico* (Elfiky, 2020; Kandeel and Al-Nazawi, 2020; Shah et al., 2020) but when evaluated *in vitro*, inconsistent results have been obtained. Some investigators found that the drug can inhibit SARS-CoV-2 replication *in vitro* at high concentration (Wang et al., 2020), while another group of investigators obtained opposing results (Choy et al., 2020). Some workers have also suggested that the ability of the cell line used in the assay to phosphorylate Ribavirin is a major determinant of the inhibitory efficacy observed (Cinatl et al., 2005) and this may account for the contradictory results obtained in the different studies. Hence, the question still remains open as to the ability of ribavirin to inhibit SARS-CoV-2. Severe

adverse effects such as anaemia, bradycardia and the risk of teratogenicity (Knowles et al., 2003) associated with ribavirin may however limit its potential to be re-directed for the management of Covid-19.

Lopinavir/ Ritonavir Combination

They are both protease inhibitors used in the management of HIV infection. In formulation, Lopinavir is usually boosted with ritonavir which substantially increases lopinavir bioavailability through inhibition of a cytochrome P450 isoenzyme (Mangum and Graham, 2001). Among the Orthocoronavirinae family, these protease inhibitors are believed to target papain-like protease and 3-Chymotrypsin-like protease in exerting their anti-viral action (Zumla et al., 2016).

A number of molecular docking studies showed that Ritonavir is capable of inhibiting the main protease (Mpro) of SARS-CoV-2 (Choudhury and Mazumder, 2020; Nutho et al., 2020). This was further supported by results from *in vitro* studies (Choy et al., 2020; Costanzo & Roviello, 2020). Several studies have similarly shown that Lop/r combination was effective in resolving clinical symptoms in Covid 19 patients (Lim et al., 2020; Liu et al., 2020). Conversely, other groups in Asia reported that the combination of Lopinavir/ritonavir was not beneficial clinically in the management of SARS-CoV-2 patients (Cao et al., 2020; Cheng et al., 2020). The picture is therefore still hazy regarding the usefullness of this combination for Covid-19 management.

Oseltamivir

Oseltamivir is an orally bioavailable antiviral agent approved for the treatment and prevention of Influenza A and B virus infections (Moscona, 2005). It acts by competitive inhibition of neuraminidase enzyme which ultimately prevents the release of new virions (Lew et al., 2012). It is a prodrug and has to undergo ester hydrolysis to Oseltamivir carboxylate which is the active form (Agrawal et al., 2010).

In silico evaluation of Oseltamivir binding to a SARS-CoV-2 protease showed good inhibitory potential which was improved by combination with Lopinavir/ritonavir (Muralidharan et al., 2020). A recent paper detailing the management of a group of patients for Covid-19 showed that about 90 % of the patients received Oseltamivir (Wang et al., 2020) as part of a cocktail of medications and favourable treatment outcome was obtained in majority of the patients. In contrast to the foregoing, *in vitro* evaluation of the drug revealed that it was unable to inhibit SARS-CoV-2 activity even at very high concentrations (Choy et al., 2020; Wang et al., 2020) and this has cast serious doubt as to the role and benefit (if any) of Oseltamivir in the management of Covid-19 patients.

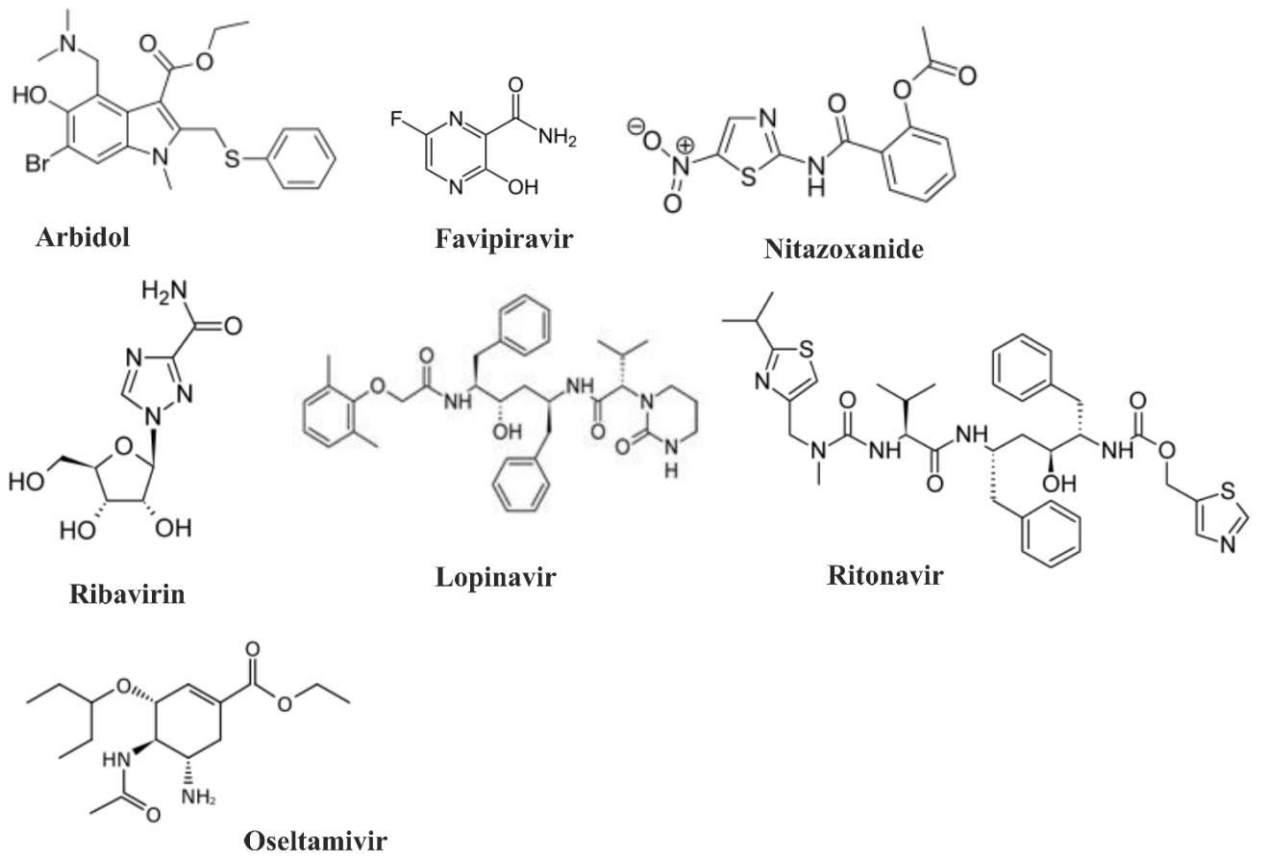

Figure 1. Structure of selected drugs for potential repurposing against SARS-COV-2

Conclusion

Drug repurposing has the prospect of making drug discovery less expensive, less laborious and can lead to faster approval of new drug treatment for new and emerging viral infections. This review has thrown light on several approved drugs in the market that have the potential to be rapidly developed, optimized and repositioned as candidates for the management of SARS-CoV-2.

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