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Oxazolidinones Antibiotics, Chemistry, Applications and Role in COVID-19 Treatment

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Abstract

Oxazolidinones are groups of synthetic antimicrobial agents, which have a novel chemical structure. Their mechanism of antimicrobial mainly bacteriostatic via inhibition of protein synthesis. Oxazolidinones are used in serious cases of bacterial infections. Their spectrum of action against a lot of microbes, which often infect humans vigorously, like penicillin and cephalosporin-resistant *Streptococcus pneumonia,* methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci*. Oxazolidinones chemical structure possesses a ring called oxazolidone, which is characterized by the *S* configuration of the substituent at C5, the acyl-amino-methyl group connected to C5 and the N-aryl substituent. Some oxazolidinones like linezolid were believed to have a role in COVID-19 treatment. It is also noticed that oxazolidinones have a role in improving clinical status of patients with COVID-19 and in decreasing the risk of mortality caused by co-infections. This review was conducted to discuss the chemistry, mechanism, applications and role of oxazolidinones in the treatment of COVID-19.

Keywords

Oxazolidinones Antibiotics Linezolid Infection COVID-19

1. Introduction

The urgent need for new antibiotics is increasing due to surge of bacterial diseases with resistant strains, in both hospital and community settings. Selman Waksman was the first scientist mentioned the term antibiotic in 1941 which referred to the inhibition effect on the growth of other micro-organisms caused by a small molecule. The golden age of antibiotics is between 1920-1940, penicillin, chloramphenicol, tetracycline and others were developed [1] [2]. Many of these

antibiotics have become ineffective due to the outspread of bacteria resistant to counteracting many bacterial antibiotics [1]. Antimicrobial resistance indicates some changes in micro-organisms, which make the drugs ineffective [3]. Microbial resistance to a wide number of antimicrobial agents is an important international medical problem and the spreading of bacterial multi-drug resistance rapidly is alarming [4] [5]. Recently, bacterial resistance to first-generation drugs reaches a very high level and become more common in second and third-generations. So, one of the important aspect of medical scientific research is to develop agents which capable of overcoming microbial resistance [6]. Thus, researchers basically aim to discover and develop new technologies like new antibiotics, vaccines, understand how antibiotics resistance can be emerged, design new strategies for correct use of antibiotics and decrease the risk of microbial infections [6] [7]. For all that the search for newer antibiotics class and newer strategies to delay the antibiotic resistance is become very important [1]. In the 1990s, new drugs like oxazolidinones were introduced to overcome some infectious disease caused by multi-resistant bacteria either Gram-positive or Gram-negative. The class, Oxazolidinones antibiotics are recent synthetic compounds with special structure characterized by the presence of 2-oxazolidone nucleus (**Figure 1**), which possess broad spectrum activity against resistant bacteria especially gram positive bacterial (GPB), like *Mycobacterium tuberculosis* (Mtb), vancomycin-resistant *Enterococcus* (VRE), MRSA [8]. Oxazolidinones represent one of

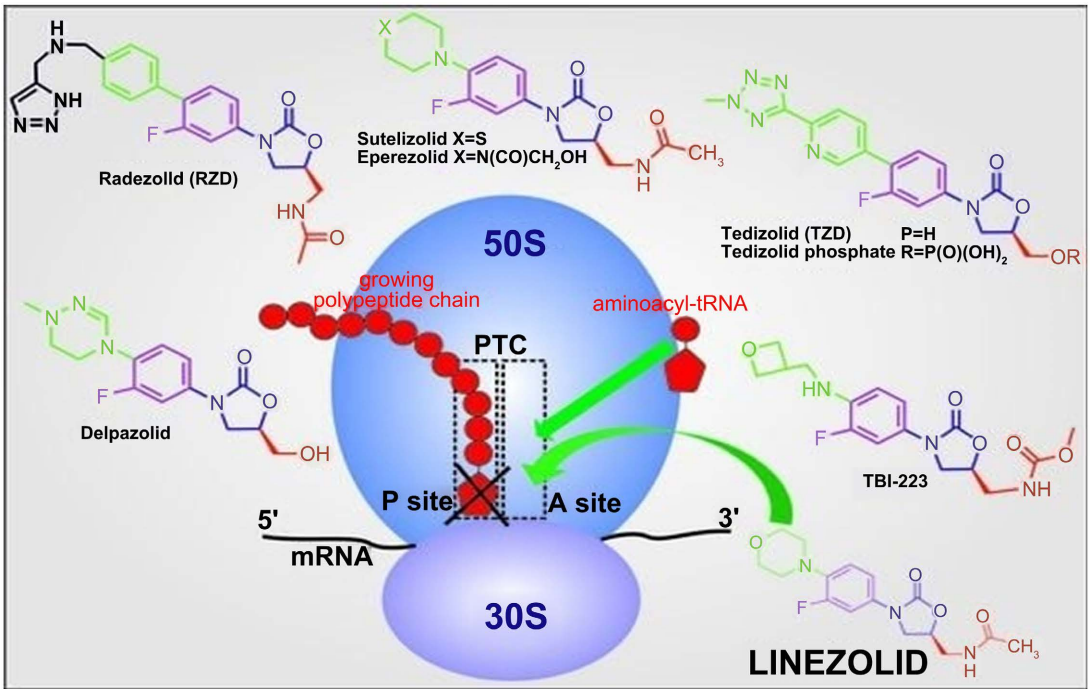

Figure 1. Oxazolidinones antibiotics core structure and structures of main derivatives (Linezolid, Sutezolid, Eperezolid, Delpazolid, Tedizolid, Tedizolid phosphate Radezolid and TBl-223). Ring A: interaction with peptidyltransferase centre (PTC) of 50S ribosome subunit; Side chain: hydrogen bond with the phosphate group on a residue in the upper part of PTC; Ring B: interaction with PTC (π-Stacking); Ring C: modulation of pharmacokinetic; Ring D: improvement of lipophilicity.

the new classes of antibiotics that has entered into clinical application over the past 40 years. Oxazolidinones acted by inhibition of protein synthesis in bacteria through binding at the distinct region of 23S RNA adjacent to peptidyl transferase center of 50S ribosomal subunit [9]. Oxazolidinones have been shown to have great potency for the treatment of infection caused by multidrug-resistant bacteria [10]. Linezolid (LNZ) was the first clinically available antibiotic from oxazolidinone class. LNZ was discovered in 1996 and then approved in 2000 for clinical use by the FDA (U.S. Food and Drug Administration) [11]. LNZ is represented as an efficient antimicrobial for surgical infection and has wide use for GPB infections [12]. LNZ also showed a marked activity against pulmonary infections even with resistant bacteria and against multidrug resistant tuberculosis (MDR-TB). Besides LNZ many oxazolidinones are synthesized and approved like tedizolid, radezolid, sutezolid [13]. LNZ and tedizolid are the only oxazolidinones, which are clinically approved for (MDR-TB) infections. The second generation of oxazolidinones was developed like tedizolid (TZD). This is also indicated for the treatment of skin infections [12]. To overcome resistant LNZ strains, radezolid (RZD), belonging to the biaryl oxazolidinones family was developed and proven its effectiveness. Several oxazolidinones analogs have been synthesized, developed by international pharmaceutical companies, some of which proved efficacy and suitable for treating MDR-TB [13]. One of them is sutezolid (STD), the next analogue after LNZ, TZD and RZD, which has been proven to be promising. Moreover, researchers proposed that Linezolid (LNZ) can act against coronavirus disease 2019 (COVID-19) because it showed an excellent result to treat many bacterial co-infections that accompanies viral infection [14]. In March 2020 Duployes *et al.* used Linezolid to treat covid-19 complications in 30 years old man admitted in ICU with mechanical ventilation [15]. LNZ was included in protocols for the treatment of pneumonia associated with COVID-19 according to national institute for health and care excellence, UK (May 2020). Broad-spectrum antibiotics such as LIN, piperacillin-tazobactam, ceftazidime, levofloxacin, vancomycin and teicoplanin are suspected to the treatment guidance for sever hospital acquired pneumonia in COVID-19 patients [16]. Nelson *et al.* proved their hypothesis which believed that the role of LNZ may be due to an interaction between (R and S)-linezolid with receptor-binding domain (RBD) of SARS-CoV-2 spike protein complexed with human angiotensin converting enzyme2 (ACE2). This opinion was proven using electronic and molecular docking [17]. Shengxian Zhao *et al.* were synthesized 22 compounds of oxazolidinones derivatives (3a-3v) and screened them. They found that compound 3 g displayed the most potent inhibitory activity with an IC_{50} value of 14.47 μmol·L^{-1}. Molecular docking analysis showed the modes of action of compound 3 g with 3-chymotrypsin-like protease (3CLpro) which responsible for cutting at least 11 sites and is extremely important for coronavirus replication [17]. Therefore, 3CLpro is an ideal target for the development of anti-coronavirus drug [17]. Clinical applications showed that LNZ was a good antibiotic in treatment of nosocomial infections in COVID-19 patients. Better

clinical and microbiological efficacy in COVID-19 patients who were suffering from bacterial pneumonia received intravenous dose of 600 mg of linezolid every 12 hours for 7 to 10 days and all patients recovered and discharged from hospital. In addition, Linezolid also showed superiority over other antibiotics may be due to its better penetration into respiratory secretion [18]. This result encourages synthesizing and developing series of new oxazolidinones compounds, including bis-oxazolidinones, and screening of their antibacterial activities as potential anti-tubercular agents [19].

2. Core structure of Oxazolidinones

Oxazolidinones are five-membered ring nitrogen heterocyclic molecules with oxygen in a bridged with a carbonyl group (**Figure 1**). Linezolid is the first member of the 3-aryl-2-oxzalidinones, its antibacterial activity is enhanced by presence of fluorine at 3 positions on phenyl groups and also the hydroxyactetyl group on the heterocyclic nitrogen increases its activity [20].

3. Mechanism of Oxazolidinones Antibacterial Effect

Oxazolidinones posse a novel antimicrobial action through binding to 50S ribosomal subunit then inhibiting the initiation of protein synthesis process [21]. The protein synthesis process in prokaryotic cells focusing on the site and the way by which oxazolidinones make inhibition of this process is described below (**Figure 2**). The component of prokaryotic cells ribosomes has 2 different subunits, the 30S and the 50S subunits. The 30S subunit contains 16S rRNA and 21 polypeptide chains, while the 50S subunit consists of 23S rRNA, 34 polypeptide chains, and 5S [22]. There are 3 steps in protein synthesis process that are: 1st initiation, 2nd elongation and 3rdtermination. Inside the cells, the transcription and releasing of messenger RNA (mRNA) occur [22]. The starting of the translation process is by attaching the initiation factors to the 30S subunit along with the initiator transfer RNA (tRNA)-N-formylmethionine (fMet) and the mRNA then 50S rRNA subunit is attached and completed 70S which is the initiation complex. Studies showed that oxazolidinones don't interfere with termination process of protein; as a result, the protein synthesis inhibition is the expected mechanism [21]. Oxazolidinone binding was reported to be partitioned between both ribosomal subunits. The binding of $tRNA^{fMet}$ to the 70S particle occurs through contacts with the peptidyl transferase region of the 50S particle as well as through codon-anticodon interactions on the 30S subunit [23]. Oxazolidinones were assumed to cause distortion in the binding site for the initiator-tRNA which overlaps both ribosomal subunits Moreover, recent study by Matassova *et al.*, summarized that oxazolidinones able to inhibit elongation process through the influence of the step of translocation in protein synthesis process [24]. Due to the novel oxazolidinones mechanism of action as antibacterial agent, there is no cross-resistance that has been reported between oxazolidinones and other protein synthesis inhibiting antimicrobials [25] [26] [27].

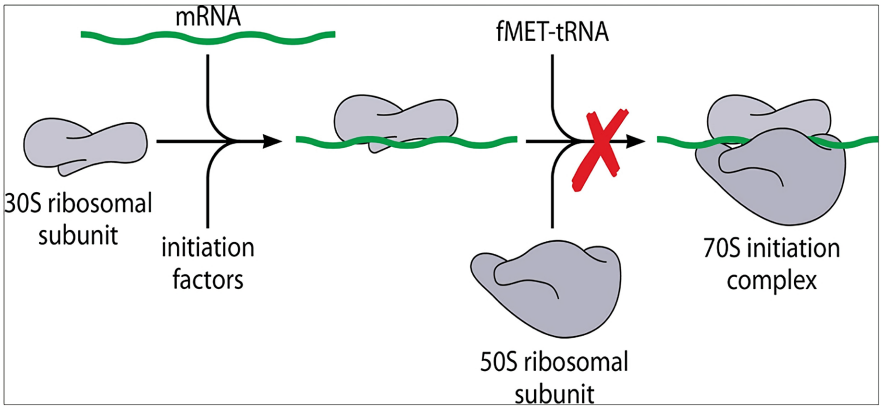

Figure 2. Oxazolidinones inhibition of protein synthesis steps of prokaryotic cells.

4. Mechanism of Anti COVID-19 Effect of Oxazolidinons

Firstly, patients with COVID-19 are at risk of developing serious infections. Clinical applications of LNZ in the treatment of COVID-19 provide good results than other antibiotics like bedaquiline and levofloxacin [28]. Hence, in Covid-19 patients linezolid (LNZ) was considered a useful treatment for associated bacterial nosocomial pneumonia so LNZ is included in covid-19 protocols. LNZ may be considered one of the famous and common antibiotic prescribed and has more superiority over some other antibiotics due to its better availability to penetrate into respiratory secretion [29].

As for anti-corona virus mechanisms, one of the suggested mechanisms which are widely studied in virus invasion of an organism is the formation of spike protein complex of SARS-CoV-2 with ACE2 (29). SARS-CoV is a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to ACE2 receptor [30]. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 trans membrane serine protease (TTSPs) like TMPRSS2, facilitates cell entry by the S protein (28). Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to the completion of assembly and release of viral particles [31] [32]. These viral lifecycle steps provide potential targets for drug therapy (**Figure 3**). For this reason, many researches focused on how to describe how interaction can be done. It is also believed that LZD exhibits activity on the immune response. There is evidence in vitro and pre-clinical, which demonstrated that LZD suppresses the phagocytic ability, cytokine synthesis, and secretion of immune cells as well as the expressions of immune-related genes at the mRNA level under the stimulation of endotoxin or pathogens. Immunomodulatory effects of LZD can not only reduce the inflammatory damage induced by exaggerated or prolonged release of pro-inflammatory cytokines during infections but can also be applied to alleviate the symptoms of non-infectious inflammatory conditions (33). The formers collectively lead to decrease virulence factors of COVID-19.

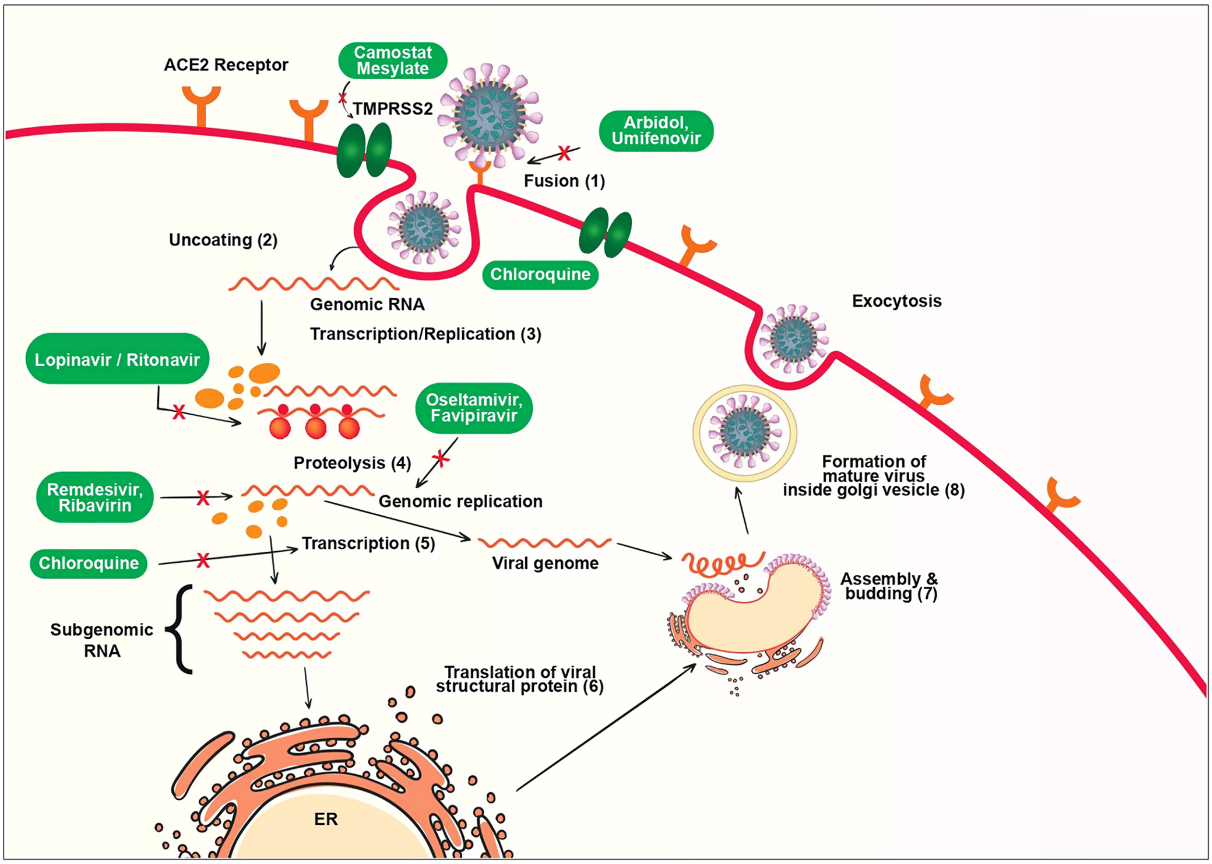

Figure 3. Viral Lifecycle of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) and Potential Drug Targets.

Morgon, N. H *et al.*, explain the mode by which LNZ interfere with viral replications [33]. It was shown that there is an interaction between spike protein of covid-19 and human ACE2, this interaction leads to many dangerous immune disorders. LNZ could interact with ACE2 receptors or interact with spike protein of COVID-19 and prevent spike viral interaction with ACE2 receptors to prevent such fetal immune disorders. This interaction was proved using electronic and molecular docking study. The study revealed that only the (S)-linezolid had a stable interaction with ACE2 with 8.05 Kcal·mol^{-1}, whereas all R-enantiomeric configurations had positive values of binding energy (**Figure 4**).

The stable and low energy complex between (S)-Linezolid and spike protein may represent the main reason for believing that (S)-linezolid has biological activity and not for the (R)-linezolid. Omicron, which is a recent variant of COVID-19 showed a large number of mutations in the receptor-binding domain (RBD) of the spike protein [34]. Assuming (S)-linezolid has the favorability in interacting with the SARS-CoV-2 spike protein ((S)-Linezolid...RBD…ACE2). this interaction could be justified by similar interaction seen on a type of bacterial ribosome unit called Haluarcula marismortui, ((S)-Linezolid…Ribosomal). This interaction revealed the stability and predictive activity of (S)-Linezolid on SARS-CoV-2 protein. This interaction include 3 hydrogen bonding could also be observed in both the Haluarcula morismortui Ribosomal and RBD…ACE2

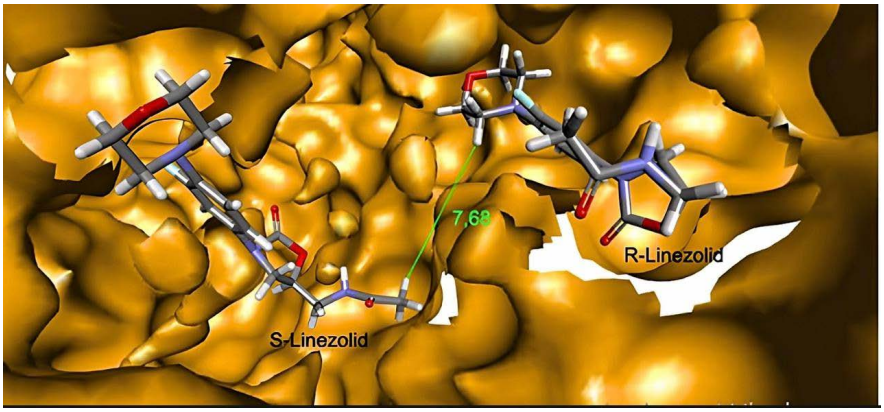

Figure 4. Molecular docking between (R) and (S)-Linezolid with SARS-CoV-2 RBD spike protein with representing of the most stable interaction locations.

complex [33]. Moreover, the coronavirus 3CLpro inhibitors reported in the literature, 3CLpro is 3-chymotrypsin-like protease which is responsible for intra-molecular cleavage to produce multiple non-structure protein of polymeric precursors (pp1) of coronavirus genetic material RNA (ribonucleic acid) after infection. Because the 3CL protease is responsible for cutting at least 11 sites and is extremely important for virus replication, it is also called the main protease (Mpro) [17] [34]. Gene sequence analysis showed that this protease is relatively conserved, and the 3CL protease of SARS-CoV and SARS-CoV-2 are highly similar on the gene sequences and active site [28]. Therefore, 3CLpro is considered as one of the ideal target for the evaluation and development of new anti-coronavirus drugs. The coronavirus 3CLpro inhibitors reported in the literature are mainly divided into peptide inhibitors [35] [36] and non-peptide inhibitors [37] [38]. Oxazolidinones derivatives like (linezolid, tedizolid, and others) are commonly non-peptide inhibitors had shown antibacterial [39], and cholestryl ester transfer protein inhibiting activity [40] [41]. Evaluation of these compounds was done using the fluorescence resonance energy transfer (FRET) based enzymatic assay [18]. Finally, Oxazolidinones like Linezolid can act against covid-19 by showing excellent result to treat various bacterial co-infections that accompanies corona infection [14].

5. Chemistry and Structure Activity Relationship of Oxazolidinones

Oxazolidinones molecules are fully synthesized and doesn't find in nature anymore. They were described firstly in 1980s by El DuPont de Nemours and company that lead to produce Linezolid which was brought in 1990s on markets [42] then they were implemented by (Pfizer. NY.USA). The development history has been discussed in many review [43] [44]. A number of studies identified the essential structural factors and the structure activity relationship (SAR) are very important for their biological action on 1st oxazolidinones derivatives (linezolid and eperezolid) (**Figure 1**). The core of oxazolidinones pharmacophore consist

of oxazolidone ring carrying S configuration substituent at carbon number 5 (C5) and the acyl-amino-methyl group connected to C5 and the N-aryl substituent which is ring B. The basic chemical structure of oxazolidinones, is displayed in (**Figure 5**) [45]. SAR of ring A and B is essential for antimicrobial activity, the potent antimicrobial activity is by the acetamide group at ring B [46], in addition the biological activity increased by fluoro substitution on meta position on ring B while substitution on para position elevates the antibacterial action [43]. Appearance of antimicrobial activity is limited on 5S-acetamidomethyl enantiomer (**Figure 5**). The adverse reaction decreasing, elimination of toxic effects, and enhancement activity are done by alteration of the chemical structure at ring A and by addition of fluorine group on phenyl-3-position (45). Moreover, the size of 3-substitution has a very essential role in determining the antimicrobial activity, the larger one, is the lowest activity [47] [48]. Research in 2008 by using x-ray co-crystal showed that linezolid bounds to 50S ribosomal subunit [49] [50]. Oxazolidinones can inhibit synthesis of protein through interaction with 50S ribosomal subunit at peptide transferase center (PTC) in A-site pocket, and this interaction changes and effects the position or binding of initiator tRNA then inhibit of tRNA binding at the A position that result in prevent the sequence translation. Preclinical studies of both linezolid and eperezolid result from showed almost very similar minimum inhibitory concentration values (MIC), pharmacokinetic parameters and antimicrobial range of efficacy. Linezolid was selected for further development and studied because its half-life in human is relatively prolonged. The large scale synthesis and their chemical strategy of linezolid are described in (**Figure 6**) [51].

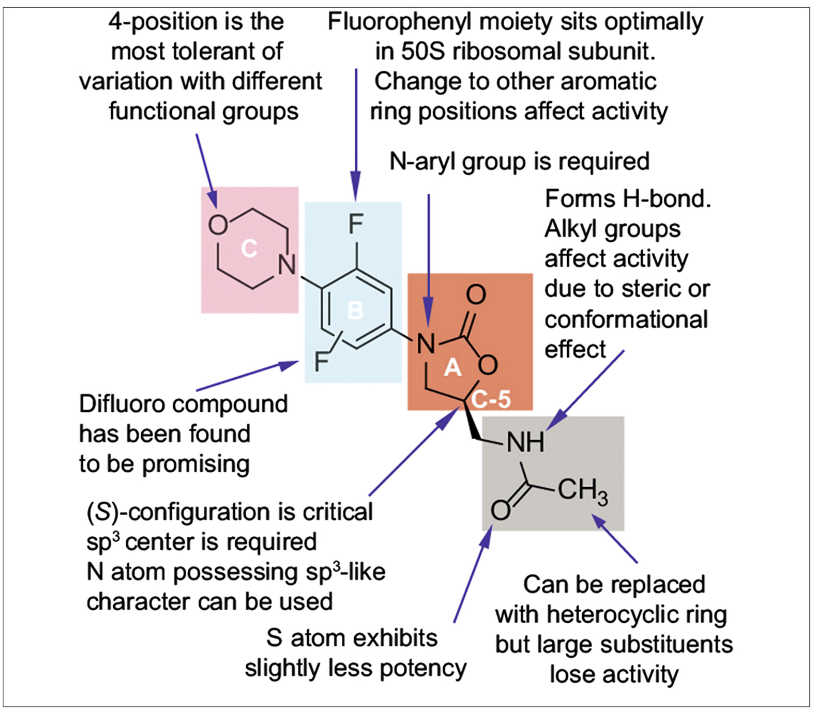

Figure 5. Structure activity relationship of Linezolid.

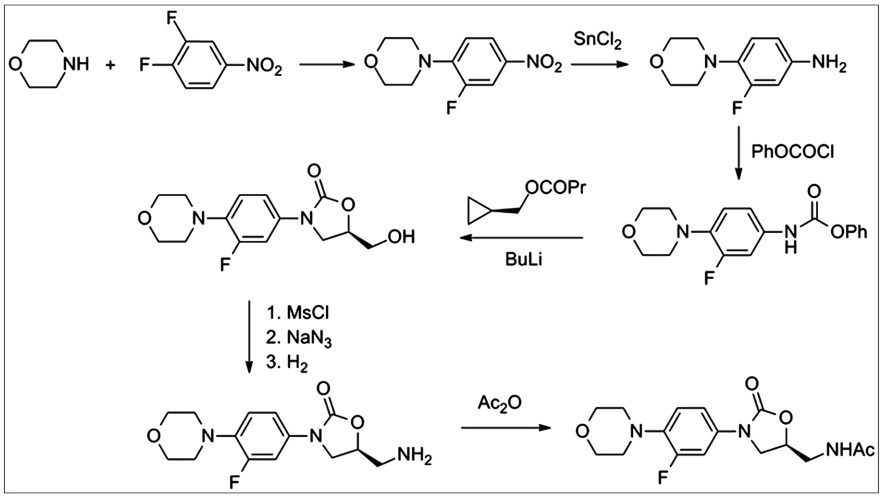

Figure 6. Large scale Linezolid synthesis.

6. Clinical Applications of LNZ in Treatment of COVID-19

In patients with COVID-19, there is a major risk of serious bacterial infections which may cause serious diseases like Pneumonia, meningitis, osteomyelitis and endocarditis [52] [53]. Many clinical studies added antibiotics for the protocol of Covid-19 as macrolids, moxifloxacins and linezolid. Clinical studies suggested that, the early use of prophylactic antibiotics in patients with COVID-19 could help and reduce the risk of co-bacterial infections. It also may decrease the prognosis of the disease in patients of high risk [54]. The study also encouraged the use of LNZ in some complicated cases as diabetic patients with COVID-19 [55]. Treatment of COVID-19 patients with Linezolid should be started to avoid the suspicion of nosocomial pneumonia [56]. The role of LNZ in treatment of Covid-19 is still in need of more studies to up stand and definite the complex role of LNZ.

7. Medical Applications of Oxazolidinones

Oxazolidinones as antibiotics have a wide range of applications in the treatment of many infectious diseases caused by bacterial infections. Wide applications of oxazolidinones in the treatment of many cases of methicillin resistant bacterial infection and vancomycin resistant infection. It is also used for Bacterial infections caused by S. pneumoniae, S. aureus, Streptococcus pyogenes, Streptococcus agalactiae. It is used in the treatment of Community Acquired Pneumonia, Nosocomial Pneumonia, in Skin and Skin Structure infections. It also used for the treatment of is used for meningitis, osteomyelitis and endocarditis [52] [53].

8. Conclusion

Oxazolidinones are an important class of synthetic antibiotics that can treat multi-bacterial infections and many resistant strains of bacteria like methicillin-resistant *Staphylococcus aureus* and many others through inhibits bacterial protein synthesis at earlier steps in mechanism differs than chloramphenicol.

Depending on the unique mechanism of action of oxazolidinones, there was a prediction of the absence of cross-resistance with other antibiotics which act also by protein synthesis inhibition. Early studies suggest that antibiotic class like (Linezolid) can be used to treat coronavirus by contrasting mechanisms or by treating many bacterial co-infections that accompanies corona infection. Further and more studies are required to determine precisely how oxazolidinones work against corona. Moreover, oxazolidinones still represent an interesting media for the synthesis of new oxazolidinones derivatives and for evaluating their antimicrobial effect. Also, more studies are required to up stand and precise the actual role of oxazolidinones in the treatment of COVID-19 and other SARS diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Clardy, J., Fischbach, M.A. and Currie, C.R. (2009) The Natural History of Antibiotics. *Current Biology*, **19**, R437-R441. https://doi.org/10.1016/j.cub.2009.04.001

[2] Da Cunha Ribeiro, B., Fonseca, L.P. and Calado, C.R. (2019) Antibiotic Discovery: Where Have We Come from, Where Do We Go? *Antibiotics* (*Basel*, *Switzerland*), **8**, Article 45. https://doi.org/10.3390/antibiotics8020045

[3] World Health Organization (2021) Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report.

[4] Ayukekbong, J.A., Ntemgwa, M. and Atabe, A.N. (2017) The Threat of Antimicrobial Resistance in Developing Countries: Causes and Control Strategies. *Antimicrobial Resistance & Infection Control*, **6**, Article No. 47. https://doi.org/10.1186/s13756-017-0208-x

[5] Jampilek, J. (2018) Design and Discovery of New Antibacterial Agents: Advances, Perspectives, Challenges. *Current Medicinal Chemistry*, **25**, 4972-5006. https://doi.org/10.2174/0929867324666170918122633

[6] Cassini, A., Högberg, L.D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G.S., Colomb-Cotinat, M., Kretzschmar, M.E., Devleesschauwer, B., Cecchini, M. and Ouakrim, D.A. (2019) Attributable Deaths and Disability-Adjusted Life-Years Caused by Infections with Antibiotic-Resistant Bacteria in the EU and the European Economic Area in 2015: A Population-Level Modelling Analysis. *The Lancet Infectious Diseases*, **19**, 56-66. https://doi.org/10.1016/S1473-3099(18)30605-4

[7] Zignol, M., Dean, A.S., Falzon, D., van Gemert, W., Wright, A., van Deun, A., Portaels, F., Laszlo, A., Espinal, M.A., Pablos-Méndez, A. and Bloom, A. (2016) Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *New England Journal of Medicine*, **375**, 1081-1089. https://doi.org/10.1056/NEJMsr1512438

[8] Jiang, J., Hou, Y., Duan, M., Wang, B., Wu, Y., Ding, X. and Zhao, Y. (2021) Design, Synthesis and Antibacterial Evaluation of Novel Oxazolidinone Derivatives Nitrogen-Containing Fused Heterocyclic Moiety. *Bioorganic & Medicinal Chemistry Letters*, **32**, Article ID: 127660. https://doi.org/10.1016/j.bmcl.2020.127660

[9] Shinabarger, D. (1999) Mechanism of Action of the Oxazolidinone Antibacterial Agents. *Expert Opinion on Investigational Drugs*, **8**, 1195-1202. https://doi.org/10.1517/13543784.8.8.1195

[10] Schlünzen, F., *et al.* (2001) Structural Basis for the Interaction of Antibiotics with the Peptidyl Transferase Centre in Eubacteria. *Nature*, **413**, 814-821. https://doi.org/10.1038/35101544

[11] Bozdogan, B. and Appelbaum, P.C. (2004) Oxazolidinones: Activity, Mode of Action, and Mechanism of Resistance. *International Journal of Antimicrobial Agents*, **23**, 113-119. https://doi.org/10.1016/j.ijantimicag.2003.11.003

[12] Dorn, C., Schießer, S., Wulkersdorfer, B., Hitzenbichler, F., Kees, M.G. and Zeitlinger, M. (2020) Determination of Free Clindamycin, Flucloxacillin or Tedizolid in Plasma: Pay Attention to Physiological Conditions when Using Ultrafiltration. *Biomedical Chromatography*, **34**, e4820. https://doi.org/10.1002/bmc.4820

[13] Hoagland, D.T., Liu, J., Lee, R.B. and Lee, R.E. (2016) New Agents for the Treatment of Drug-Resistant *Mycobacterium tuberculosis*. *Advanced Drug Delivery Reviews*, **102**, 55-72. https://doi.org/10.1016/j.addr.2016.04.026

[14] Brenciani, A., Morroni, G., Schwarz, S. and Giovanetti, E. (2022) Oxazolidinones: Mechanisms of Resistance and Mobile Genetic Elements Involved. *Journal of Antimicrobial Chemotherapy*, **77**, 2596-2621. https://doi.org/10.1093/jac/dkac263

[15] Duployez, C., Le Guern, R., Tinez, C., Lejeune, A.L., Robriquet, L., Six, S., Loïez, C. and Wallet, F. (2020) Panton-Valentine Leukocidin-Secreting Staphylococcus Aureus Pneumonia Complicating COVID-19. *Emerging Infectious Diseases*, **26**, Article 1939. https://doi.org/10.3201/eid2608.201413

[16] Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., *et al.* (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *New England Journal of Medicine*, **382**, 1199-1207. https://doi.org/10.1056/NEJMoa2001316

[17] Zhao, S.X., Wang, C.J., Lu, Y.M., Zhang, X., Wu, S.Y. and Mao, H. (2022) Synthesis and SARS-CoV-2 3CL Protease Inhibitory Effects of Oxazolidinone Derivatives. *Journal of the Brazilian Chemical Society*, **33**, 1134-1143. https://doi.org/10.21577/0103-5053.20220033

[18] Moghadam, V.D. Momenimovahed, Z., Khodadadi, J. and Ghorbani, M. (2021) Linezolid a Potential Treatment for COVID-19 Coinfections. *Brazilian Journal of Anesthesiology*, **71**, 198. https://doi.org/10.1016/j.bjane.2020.12.019

[19] Ang, W., Ye, W., Sang, Z., Liu, Y., Yang, T., Deng, Y., Luo, Y. and Wei, Y. (2014) Discovery of Novel Bis-Oxazolidinone Compounds as Potential Potent and Selective Antitubercular Agents. *Bioorganic & Medicinal Chemistry Letters*, **24**, 1496-1501. https://doi.org/10.1016/j.bmcl.2014.02.025

[20] Shinabarger, D.L., Marotti, K.R., Murray, R.W., Lin, A.H., Melchior, E.P., Swaney, S.M., Dunyak, D.S., Demyan, W.F. and Buysse, J.M. (1997) Mechanism of Action of Oxazolidinones: Effects of Linezolid and Eperezolid on Translation Reactions. *Antimicrobial Agents and Chemotherapy*, **41**, 2132-2136. https://doi.org/10.1128/AAC.41.10.2132

[21] Lin, A.H., Murray, R.W., Vidmar, T.J. and Marotti, K.R. (1997) The Oxazolidinone Eperezolid Binds to the 50S Ribosomal Subunit and Competes with Binding of Chloramphenicol and Lincomycin. *Antimicrobial Agents and Chemotherapy*, **41**, 2127-2131. https://doi.org/10.1128/AAC.41.10.2127

[22] Samaha, R.R., Green, R. and Noller, H.F. (1995) A Base Pair between tRNA and 23S rRNA in the Peptidyl Transferase Centre of the Ribosome. *Nature*, **377**, 309-314. https://doi.org/10.1038/377309a0

[23] Cundliffe, E. and McQuillen, K. (1967) Bacterial Protein Synthesis: The Effects of Antibiotics. *Journal of Molecular Biology*, **30**, 137-146.

https://doi.org/10.1016/0022-2836(67)90249-5

[24] Matassova, N.B., Rodnina, M.V., Endermann, R., Kroll, H.P., Pleiss, U., Wild, H. and Wintermeyer, W. (1999) Ribosomal RNA Is the Target for Oxazolidinones, a Novel Class of Translational Inhibitors. *RNA*, **5**, 939-946. https://doi.org/10.1017/S1355838299990210

[25] Swaney, S.M., Aoki, H., Ganoza, M.C. and Shinabarger, D.L. (1998) The Oxazolidinone Linezolid Inhibits Initiation of Protein Synthesis in Bacteria. *Antimicrobial Agents and Chemotherapy*, **42**, 3251-3255. https://doi.org/10.1128/AAC.42.12.3251

[26] Murray, R.W., Schaadt, R.D., Zurenko, G.E. and Marotti, K.R. (1998) Ribosomes from an Oxazolidinone-Resistant Mutant Confer Resistance to Eperezolid in a Staphylococcus Aureus Cell-Free Transcription-Translation Assay. *Antimicrobial Agents and Chemotherapy*, **42**, 947-950. https://doi.org/10.1128/AAC.42.4.947

[27] Zurenko, G.E., Yagi, B.H., Schaadt, R.D., Allison, J.W., Kilburn, J.O., Glickman, S.E., Hutchinson, D.K., Barbachyn, M.R. and Brickner, S.J. (1996) *In Vitro* Activities of U-100592 and U-100766, Novel Oxazolidinone Antibacterial Agents. *Antimicrobial Agents and Chemotherapy*, **40**, 839-845. https://doi.org/10.1128/AAC.40.4.839

[28] Vilbrun, S.C., Mathurin, L., Pape, J.W., Fitzgerald, D. and Walsh, K.F. (2020) Case Report: Multidrug-Resistant Tuberculosis and COVID-19 Coinfection in Port-au-Prince, Haiti. *The American Journal of Tropical Medicine and Hygiene*, **103**, 1986-1988. https://doi.org/10.4269/ajtmh.20-0851

[29] Bertram, S., Heurich, A., Lavender, H., Gierer, S., Danisch, S., Perin, P., Lucas, J.M., Nelson, P.S., Pöhlmann, S. and Soilleux, E.J. (2012) Influenza and SARS-Coronavirus Activating Proteases TMPRSS2 and HAT Are Expressed at Multiple Sites in Human Respiratory and Gastrointestinal Tracts. *PLOS ONE*, **7**, e35876. https://doi.org/10.1371/journal.pone.0035876

[30] Huang, Y., Yang, C., Xu, X.F., Xu, W. and Liu, S.W. (2020) Structural and Functional Properties of SARS-CoV-2 Spike Protein: Potential Antivirus Drug Development for COVID-19. *Acta Pharmacologica Sinica*, **41**, 1141-1149. https://doi.org/10.1038/s41401-020-0485-4

[31] Brufsky, A. (2020) Distinct Viral Clades of SARS-CoV-2: Implications for Modeling of Viral Spread. *Journal of Medical Virology*, **92**, Article 1386. https://doi.org/10.1002/jmv.25902

[32] Fehr, A.R., Perlman, S., Maier, H.J., Bickerton, E. and Britton, P. (2015) An Overview of Their Replication and Pathogenesis. In: Maier, H., Bickerton, E. and Britton, P., Eds., *Genomic Organization. Methods in Molecular Biology*, Humana Press, New York, 1-23. https://doi.org/10.1007/978-1-4939-2438-7_1

[33] Morgon, N.H., Grandini, G.S., Yoguim, M.I., Porto, C.M., Santana, L.C., Biswas, S. and de Souza, A.R. (2021) Potential Activity of Linezolid against SARS-CoV-2 Using Electronic and Molecular Docking Study. *Journal of Molecular Modeling*, **27**, Article No. 222. https://doi.org/10.1007/s00894-021-04828-8

[34] Gal-Mor, O., Boyle, E.C. and Grassl, G.A. (2014) Same Species, Different Diseases: How and Why Typhoidal and Non-Typhoidal Salmonella Enterica Serovars Differ. *Frontiers in Microbiology*, **5**, Article 391. https://doi.org/10.3389/fmicb.2014.00391

[35] Han, P., Li, L., Liu, S., Wang, Q., Zhang, D., Xu, Z., Han, P., Li, X., Peng, Q., Su, C., Huang, B., Li, D., Zhang, R., Tian, M., Fu, L., Gao, Y., Zhao, X., Liu, K., Qi, J., Gao, G.F. and Wang, P. (2022) Receptor Binding and Complex Structures of Human ACE2 to Spike RBD from Omicron and Delta SARS-CoV-2. *Cell*, **185**, 630-640. https://doi.org/10.1016/j.cell.2022.01.001

[36] Dai, W.H., Zhang, B., Jiang, X.M., Su, H.X., Li, J., Zhao, Y., Xie, X., *et al.* (2020) Structure-Based Design of Antiviral Drug Candidates Targeting the SARS-CoV-2 Main Protease. *Science*, **368**, 1331-1335. https://doi.org/10.1126/science.abb4489

[37] Yang, K.S., Ma, X.R., Ma, Y., Alugubelli, Y.R., Scott, D.A., Vatansever, E.C., *et al.* (2021) A Quick Route to Multiple Highly Potent SARS-CoV-2 Main Protease Inhibitors. *ChemMedChem*, **16**, 942-948. https://doi.org/10.1002/cmdc.202000924

[38] Shimamoto, Y., Hattori, Y., Kobayashi, K., Teruya, K., Sanjoh, A., Nakagawa, A., Yamashita, E. and Akaji, K. (2015) Fused-Ring Structure of Decahydroisoquinolin as a Novel Scaffold for SARS 3CL Protease Inhibitors. *Bioorganic & Medicinal Chemistry*, **23**, 876-890. https://doi.org/10.1016/j.bmc.2014.12.028

[39] Kumar, V., Tan, K.P., Wang, Y.M., Lin, S.W. and Liang, P.H. (2016) Identification, Synthesis and Evaluation of SARS-CoV and MERS-CoV 3C-Like Protease Inhibitors. *Bioorganic & Medicinal Chemistry*, **24**, 3035-3042. https://doi.org/10.1016/j.bmc.2016.05.013

[40] Deshmukh, M.S. and Jain, N. (2017) Design, Synthesis, and Antibacterial Evaluation of Oxazolidinones with Fused Heterocyclic C-Ring Substructure. *ACS Medicinal Chemistry Letters*, **8**, 1153-1158. https://doi.org/10.1021/acsmedchemlett.7b00263

[41] Liu, C., Luo, C., Hao, L., Wu, Q., Xie, H., Zhao, S., Hao, C., Zhao, D. and Cheng, M. (2016) Design, Synthesis and Biological Evaluation of Novel Cholesteryl Ester Transfer Protein Inhibitors Bearing a Cycloalkene Scaffold. *European Journal of Medicinal Chemistry*, **123**, 419-430. https://doi.org/10.1016/j.ejmech.2016.07.065

[42] Crowe-McAuliffe, C. and Wilson, D.N. (2022) Putting the Antibiotics Chloramphenicol and Linezolid into Context. *Nature Structural & Molecular Biology*, **29**, 79-81. https://doi.org/10.1038/s41594-022-00725-7

[43] Zhanel, G.G., Shroeder, C., Vercaigne, L., Gin, A.S., Embil, J. and Hoban, D.J. (2001) A Critical Review of Oxazolidinones: An Alternative or Replacement for Glycopeptides and Streptogramins? *Canadian Journal of Infectious Diseases and Medical Microbiology*, **12**, Article ID: 260651. https://doi.org/10.1155/2001/260651

[44] Barbachyn, M.R. and Ford, C.W. (2003) Oxazolidinone Structure-Activity Relationships Leading to Linezolid. *Angewandte Chemie International Edition*, **42**, 2010-2023. https://doi.org/10.1002/anie.200200528

[45] Mukhtar, T.A. and Wright, G.D. (2005) Streptogramins, Oxazolidinones, and Other Inhibitors of Bacterial Protein Synthesis. *Chemical Reviews*, **105**, 529-542. https://doi.org/10.1021/cr030110z

[46] Brickner, S.J., Hutchinson, D.K., Barbachyn, M.R., Manninen, P.R., Ulanowicz, D.A., Garmon, S.A., Grega, K.C., Hendges, S.K., Toops, D.S., Ford, C.W. and Zurenko, G.E. (1996) Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections. *Journal of Medicinal Chemistry*, **39**, 673-679. https://doi.org/10.1021/jm9509556

[47] Chellat, M.F., Raguž, L. and Riedl, R. (2016) Targeting Antibiotic Resistance. *Angewandte Chemie International Edition*, **55**, 6600-6626. https://doi.org/10.1002/anie.201506818

[48] Ippolito, J.A., Kanyo, Z.F., Wang, D., Franceschi, F.J., Moore, P.B., Steitz, T.A. and Duffy, E.M. (2008) Crystal Structure of the Oxazolidinone Antibiotic Linezolid Bound to the 50S Ribosomal Subunit. *Journal of Medicinal Chemistry*, **51**, 3353-3356. https://doi.org/10.1021/jm800379d

[49] Wilson, D.N., Schluenzen, F., Harms, J.M., Starosta, A.L., Connell, S.R. and Fucini,

P. (2008) The Oxazolidinone Antibiotics Perturb the Ribosomal Peptidyl-Transferase Center and Effect tRNA Positioning. *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 13339-13344. https://doi.org/10.1073/pnas.0804276105

[50] Fines, M. and Leclercq, R. (2000) Activity of Linezolid against Gram-Positive Cocci Possessing Genes Conferring Resistance to Protein Synthesis Inhibitors. *Journal of Antimicrobial Chemotherapy*, **45**, 797-802. https://doi.org/10.1093/jac/45.6.797

[51] Barbachyn, M.R., Brickner, S.J., Gadwood, R.C., Garmon, S.A., Grega, K.C., Hutchinson, D.K., *et al.* (1998) Design, Synthesis, and Evaluation of Novel Oxazolidinone Antibacterial Agents Active against Multidrug-Resistant Bacteria. In: Rosen, B.P. and Mobashery, S., Eds., *Resolving the Antibiotic Paradox*, Springer, Boston, MA, 219-238. https://doi.org/10.1007/978-1-4615-4897-3_12

[52] Stevens, D.L., Smith, L.G., Bruss, J.B., McConnell-Martin, M.A., Duvall, S.E., Todd, W.M. and Hafkin, B. (2000) Randomized Comparison of Linezolid (PNU-100766) versus Oxacillin-Dicloxacillin for Treatment of Complicated Skin and Soft Tissue Infections. *Antimicrobial Agents and Chemotherapy*, **44**, 3408-3413. https://doi.org/10.1128/AAC.44.12.3408-3413.2000

[53] Stevens, D.L., Herr, D., Lampiris, H., Hunt, J.L., Batts, D.H. and Hafkin, B. (2002) Linezolid versus Vancomycin for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections. *Clinical Infectious Diseases*, **34**, 1481-1490. https://doi.org/10.1086/340353

[54] Bode, C., Muenster, S., Diedrich, B., Jahnert, S., Weisheit, C., Steinhagen, F., *et al.* (2015) Linezolid, Vancomycin and Daptomycin Modulate Cytokine Production, Toll-Like Receptors and Phagocytosis in a Human *in Vitro* Model of Sepsis. *The Journal of Antibiotics* (*Tokyo*), **68**, 485-490. https://doi.org/10.1038/ja.2015.18

[55] Fan, L., Liu, H., Li, N., Liu, C., Gu, Y., Liu, Y. and Chen, Y. (2021) Medical Treatment of 55 Patients with COVID-19 from Seven Cities in Northeast China Who Fully Recovered: A Single-Center, Retrospective, Observational Study. *Medicine* (*Baltimore*), **100**, e23923. https://doi.org/10.1097/MD.0000000000023923

[56] Alegre-González, D., Herrera, S., Bernal, J., Soriano, A. and Bodro, M.(2021) Disseminated Cryptococcus Neoformans Infection Associated to COVID-19. *Medical Mycology Case Reports*, **34**, 35-37. https://doi.org/10.1016/j.mmcr.2021.10.001