



Prioritisation of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics

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Abstract

There is a rapidly expanding literature on the *in vitro* antiviral activity of drugs that may be repurposed for therapy or chemoprophylaxis against SARS-CoV-2. However, this has not been accompanied by a comprehensive evaluation of the target plasma and lung concentrations of these drugs following approved dosing in humans. Accordingly, EC_{90} values recalculated from *in vitro* anti-SARS-CoV-2 activity data was expressed as a ratio to the achievable maximum plasma concentrations (C_{max}) at an approved dose in humans (C_{max}/EC_{90} ratio). Only 14 of the 56 analysed drugs achieved a C_{max}/EC_{90} ratio above 1. A more in-depth assessment demonstrated that only nitazoxanide, nelfinavir, tipranavir (ritonavir-boosted) and sulfadoxine achieved plasma concentrations above their reported anti-SARS-CoV-2 activity across their entire approved dosing interval. An unbound lung to plasma tissue partition coefficient ($K_p U_{lung}$) was also simulated to derive a lung C_{max}/EC_{50} as a better indicator of potential human efficacy. Hydroxychloroquine, chloroquine, mefloquine, atazanavir (ritonavir-boosted), tipranavir (ritonavir-boosted), ivermectin, azithromycin and lopinavir (ritonavir-boosted) were all predicted to achieve lung concentrations over 10-fold higher than their reported EC_{50} . Nitazoxanide and sulfadoxine also exceeded their reported EC_{50} by 7.8- and 1.5-fold in lung, respectively. This analysis may be used to select potential candidates for further clinical testing, while deprioritising compounds unlikely to attain target concentrations for antiviral activity. Future studies should focus on EC_{90} values and discuss findings in the context of achievable exposures in humans, especially within target compartments such as the lung, in order to maximise the potential for success of proposed human clinical trials.

Introduction

Coronavirus 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Fever, a persistent cough and respiratory symptoms are common, with some patients reporting vomiting, nausea, abdominal pains and diarrhoea (1). To date, no specific treatment is available, and this has resulted in significant morbidity and mortality globally. According to the International Clinical Trials Registry Platform search portal, 927 clinical trials for COVID-19 have been registered (2). This rapidly expanding pandemic warrants the urgent development of strategies, particularly to protect people at high risk of infection. Repurposing currently available drugs that have been utilised clinically with a known safety profile, is the quickest way to address this serious unmet clinical need. Antiviral drugs are urgently required for treatment of patients with mild/moderate disease to prevent the worsening of symptoms and reduce the burden upon healthcare systems. However, a different approach is likely to be needed for patients that are already in a critical state, due to the immune dysregulation which is so apparent in severe cases (3).

Previous investigations have shown that the entry by SARS-CoV-2 occurs via the angiotensin converting enzyme 2 (ACE2) receptor (4). A study on normal lung tissue showed that 83% of ACE2-expressing cells were alveolar epithelial type II cells (5), highlighting the lungs as the primary target organ that facilitate viral invasion and replication. Furthermore, the ACE2 receptor is also highly expressed in gastrointestinal epithelial cells, with SARS-CoV-2 RNA observed to be present in stool specimens of patients during infection (1, 6). A recent retrospective analysis of 85 patients with laboratory-confirmed COVID-19 also indicated that SARS-CoV-2 infects human kidney tubules and induces acute tubular damage in some patients (7). Furthermore, 2–11% of patients with COVID-19 exhibit liver comorbidities (8). Of note is an observation of SARS and Middle East respiratory syndrome (MERS) having a tropism to the gastrointestinal tract (9) and causing liver impairment in addition to respiratory disease. The genomic similarity between SARS-CoV-2 and SARS-CoV (79.6% sequence identity) would imply that the current virus would act in a similar manner and be present within the body systemically (10-12). Therefore, treatment options that provide therapeutic concentrations of drug(s) within the systemic circulation and other affected organs are likely to be required.

In the absence of a vaccine, antiviral drugs could also be deployed as chemoprophylaxis to protect against infection and would present an essential tool for protecting healthcare staff and other key workers, as well as household contacts of those already infected. For chemoprevention drugs will need to penetrate into the multiple sites where SARS-CoV-2 infection occurs, and do so in sufficient concentrations to inhibit viral replication (13). This may include the mucous membranes present in the nasal cavity and throat, the

ocular surface, tears and the upper respiratory tract/lungs (14, 15). However, therapeutic concentrations may not be needed in the systemic circulation for chemoprophylaxis, but this is yet to be determined. Although difficult and scarcely studied, work in animals has shown that the size of the inoculum of other respiratory viruses such as influenza is associated with the severity of the resultant disease (16, 17). Reports with SARS-CoV-2 indicate that higher viral loads are indicative of poorer prognosis and correlate with the severity of symptoms, with viral load in severe cases reported to be 60 times higher than that of mild cases (18, 19). In light of this, even if a chemoprophylactic drug reduced inoculum size without completely blocking transmission, major benefits for morbidity and mortality may still be achievable.

Many ongoing global research efforts are focussed on screening the activity of existing compounds *in vitro* in order to identify candidates to repurpose for SARS-CoV-2. However, current data have not yet been systematically analysed in the context of the plasma and target site exposures that are achievable after administration of the approved doses to humans. The purpose of this work was to evaluate the existing *in vitro* anti-SARS-CoV-2 data to determine and prioritise drugs capable of reaching antiviral concentrations within the blood plasma. Accepted physiologically based pharmacokinetic (PBPK) equation were also used to predict the expected concentration in lung (20-22), in order to assess the potential of these drugs for therapy in this key disease site and the potential for chemoprevention.

Methods

Candidate analysis

To identify compounds and their relevant potency and pharmacokinetic data, we performed a literature search on PubMed, Google Scholar, BioRxiv, MedRxiv, and ChemRxiv. The following search terms were used for *in vitro* activity data – (COVID-19 OR SARS-CoV-2) AND (EC50 OR IC50 OR antiviral). For pharmacokinetic data (Cmax OR pharmacokinetics) was used along with the drug name for drugs with reported anti-SARS-CoV-2 activity (up to 13th April 2020). Further clinical pharmacokinetic data were obtained from the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and through publications available online. Inhaled medications were excluded from all analyses because the purpose was to assess systemically administered medicines.

Lung accumulation prediction

An indication of the degree to which candidate drugs are expected to accumulate in lung (a presumed site of primary efficacy and for prevention of SARS-CoV-2 infection) was provided by calculation of unbound

lung to plasma tissue partition coefficient ($K_{p,U_{lung}}$) according to the methodology of Rodgers and Rowland (20-22). Equations therein were implemented in the R programming environment (version 3.6.3) and are replicated in the supplementary methods. Briefly, the physicochemical properties of the drug (pKa, log P, classification as acid/base/neutral) and *in vitro* drug binding information (fraction unbound in plasma, blood to plasma ratio), in combination with tissue-specific data (lipid content, volumes of intra/extracellular water etc.) were used to predict tissue $K_{p,U}$ values. Measured log P and pKa values were used where available but substituted with calculated values where necessary and all parameter values used for the calculations for each drug, and their references/sources, are provided in Supplementary Table 1. $K_{p,U_{lung}}$ values were converted to $K_{p,lung}$ by multiplying by fraction unbound in plasma to allow estimation of lung exposure from *in vivo* measurements of plasma C_{max} concentration. A similar analysis was conducted to assess the tissue distribution into other tissues. In the absence of observed tissue distribution data, the Rodgers and Rowland method is an accepted means to provide initial estimates of tissue partitioning for PBPK modelling. However, there are known limits on accuracy with predicted $K_{p,U}$ by the Rodgers and Rowland method generally reported to be within 2-3 fold of observed tissue $K_{p,U}$ values (20-22). This was confirmed for a limited number of drugs within the current dataset for which measure K_p values for lung were available from animal studies in the literature (see data analysis below).

Data analysis and interpretation

Since in the majority of papers only an EC₅₀ value was available, concentration-response data were digitised using the Web Plot Digitizer® software. Graphs were then replotted in SigmaPlot 14.0 (Systat Software, Inc.) and curves were fitted to confirm EC₅₀ values and determine EC₉₀ values. A C_{max}/EC₅₀ and C_{max}/EC₉₀ ratio was then calculated for each drug for which previous evidence of clinical use in humans and availability of human pharmacokinetic data were available. Lung and other tissue $K_{p,U}$ values were used in combination with reported C_{max} values to derive an estimate of lung exposure at C_{max} for each drug. For a subset of molecules, the absence of available physicochemical or plasma protein binding parameters prohibited derivation of a $K_{p,U}$ estimate. For the remaining drugs, a lung (or other tissue) C_{max}/EC₅₀ and lung C_{max}/EC₉₀ was calculated. Published plasma concentration-time data for the most promising candidates were then digitised (where available) and replotted to visually represent human pharmacokinetics relative to the calculated EC₅₀ and EC₉₀ data. Equivalence between values for the predicted lung K_p and those observed *in vivo* was undertaken for drugs with available animal lung and plasma concentration data. For this analysis, animal lung concentration data were available for anidulafungin (rat), bazedoxifene (rat), chloroquine (three albino rat studies), favipiravir (monkey), hydroxychloroquine (two albino rat studies), nitazoxanide (mouse), tamoxifen (rat),

cyclosporine (rat), ritonavir (rat), azithromycin (mouse), dolutegravir (mouse), gilteritinib (albino rat), and lopinavir (rat) (23-32). Agreement between the predicted and measured K_p was assessed by simple linear regression and by constructing Bland-Altman plots, the limits of agreement (mean \pm 2 standard deviation) were included in these plots as previously described (33).

Results

Identified papers and methods

We identified 14 key studies that detailed the antiviral activity of 71 compounds (34-48). The majority of the *in vitro* SARS-CoV-2 infection experiments were performed in Vero E6 cells (ATCC 1586) maintained in either DMEM or MEM. Other studies utilised Vero-hSLAM cells, Vero E6 cells expressing TMPRSS2 and the CACO-2 cell line to cultivate the virus. The following SARS-CoV-2 strains were used across studies; WA-1 strain – BEI #NR-52281; Brazil/RJ-314/2020; C-Tan-nCoV Wuhan strain 01; Wuhan/WIV04/2019; USA-WA1/2020; nCoV-2019BetaCoV/Wuhan/WIV04/2019; BetaCoV/Hong Kong/VM20001061/2020; Australia/VIC01/2020; β CoV/KOR/KCDC03/2020 and BavPat1/2020. Cells across all studies were infected with the virus with a multiplicity of infection (MOI) of 0.002, 0.01, 0.0125, 0.02, 0.05 and 0.1. Drugs were added at concentrations varying between 0.01 μ M - 500 μ M. A summary of the differences in methodologies between studies reporting SARS-CoV-2 antiviral activity is presented in Supplementary Table 2. A ranking of included drugs based just on their EC₅₀ and recalculated EC₉₀ is presented in Supplementary Figure 1.

Identification of candidates achieving plasma concentrations expected to exert antiviral activity (C_{max}/EC₅₀ ratio)

Seventeen molecules had a reported C_{max} value greater than at least one of the reported EC₅₀ values against SARS-CoV-2 and these were nelfinavir, chloroquine, remdesivir, lopinavir (ritonavir boosted), eltrombopag, hydroxychloroquine, atazanavir (ritonavir boosted), indomethacin, favipiravir, sulfadoxine, niclosamide, mefloquine, tipranavir (ritonavir boosted), ritonavir, merimepodib, anidulafungin and nitazoxanide. However, it should be noted that for amodiaquine, atazanavir, chloroquine, hydroxychloroquine, lopinavir, mefloquine, nelfinavir, remdesivir and toremifene, more than one EC₅₀ value had been reported across the available literature and these were not always in agreement (Figure 1A). Moreover, this variability in reported EC₅₀ values sometimes resulted in C_{max}/EC₅₀ ratios giving a different estimation of the likely value of the molecule. Meaning that for the same drug, the C_{max}/EC₅₀ ratio could be above or below 1 (Figure 1B). For amodiaquine and toremifene, all reported EC₅₀ values were below their reported C_{max} and only for nelfinavir was the reported C_{max} value expected to exceed both reported EC₅₀ values. For atazanavir, chloroquine, hydroxychloroquine, lopinavir, mefloquine and remdesivir, some EC₅₀ values were above the C_{max} whereas others were below. This observation

dramatically highlights the sensitivity of the current analysis to the reported antiviral activity data, and this should be taken into account when interpreting the data presented hereafter.

Identification of candidates achieving plasma concentrations exceeding the SARS-CoV-2 EC₉₀ (C_{max}/EC₉₀ ratio)

For 56 of the reported antiviral activities, data covering a sufficient concentration range were available for digitisation and subsequent calculation of an EC₉₀ value. For the remainder it was not possible to calculate an EC₉₀. Drugs with an available EC₉₀ were ranked according to their C_{max}/EC₉₀ ratio (Figure 2). Drugs with a value above 1.0 achieved plasma concentrations above the concentrations reported to inhibit 90% of SARS-CoV-2 replication. Only eltrombopag, favipiravir, remdesivir, nelfinavir, niclosamide, nitazoxanide and tipranavir were estimated to exceed at least one of their reported EC₉₀ by 2-fold or more at C_{max} concentrations. Anidulafungin, lopinavir, chloroquine and ritonavir were also reported to exceed at least one of their reported EC₉₀ values at C_{max} but by less than 2-fold. It was not possible to calculate an EC₉₀ value for sulfadoxine or indomethacin.

Detailed interrogation of the plasma pharmacokinetics in relation to reported anti-SARS-CoV-2 activity

For drugs with C_{max} concentrations above at least one of their reported EC₉₀ values that are not already in clinical trials for COVID-19, a detailed evaluation of concentrations across their approved dosing interval was undertaken. For this, published pharmacokinetics data were digitised and replotted relative to the calculated EC₅₀ and EC₉₀ data for SARS-CoV-2 (Figure 3). For tipranavir (ritonavir boosted), nelfinavir, sulfadoxine and nitazoxanide, plasma concentrations after administration of the approved dose remained above SARS-CoV-2 effective concentrations across the entire dosing interval. For anidulafungin, eltrombopag, lopinavir (ritonavir boosted), mefloquine and chloroquine, C_{max} values were above EC₉₀ at 2, 6, 8 and 24 hours post dose, respectively, but concentrations would be expected to dip below the EC₅₀ at 3, 8, 10, 72 and 120 hours post dose, respectively, when given at approved doses and schedules. An overview of these drugs is presented in Table 1.

Simulated exposure relative to reported anti-SARS-CoV-2 activity in lung and other tissues

Lung K_pU was simulated for all molecules for which the necessary physicochemical properties and *in vitro* drug binding information were available. Regression and Bland–Altman plots were first used to assess the agreement between predicted lung K_p and that observed in previously published animal studies for drugs with available prior data. Good agreement was observed across the available drugs with the exception of chloroquine. An $r^2 = 0.86$ was observed in linear regression when chloroquine was excluded, but decreased to $r^2 = 0.22$ when included (Supplementary Figure 2A). Similarly, good agreement between measured and predicted K_p was observed by Bland-Altman analysis for all data points with the exception of one chloroquine measurement (Supplementary Figure 2B). K_pU_{lung} was then used along with fraction unbound in plasma (F_u) and plasma C_{max} values to calculate a predicted C_{max}/EC_{50} (Figure 4) and C_{max}/EC_{90} in lung (data not shown). Tissue C_{max}/EC_{50} ratios are also shown for other tissues in Figure 5. For 4 drugs, ebselen, merimepodib, niclosamide and remdesivir, the fraction unbound data were unavailable. For 6 other drugs, benztropine, indinavir, loperamide, nelfinavir, saquinavir and toremifene, the blood to plasma ratios were unavailable. For a further 4 drugs, camostat, emetine, fluspirilene and umifenovir, both fraction unbound and blood to plasma ratios were unavailable. Therefore, these drugs were excluded from the analysis. A total of 18 drugs with available data were predicted to give concentrations in lung above at least one of their reported EC_{50} against SARS-CoV-2 (Figure 4) and 8 of these were predicted to exceed their EC_{50} by more than 10-fold. The rank order of lung C_{max}/EC_{90} ratio was chloroquine > atazanavir (ritonavir boosted) > tipranavir (ritonavir boosted) > hydroxychloroquine > mefloquine > ivermectin > lopinavir (ritonavir boosted) > azithromycin > nitazoxanide > ritonavir > gilteritinib > amodiaquine > imatinib > oxprenolol (data excluded due to this analysis only being possible for 33 of the 56 drugs).

Discussion

The systematic development of mechanism-based inhibitors for key targets involved in viral replication or pathogenesis is likely to result in highly effective and safe medicines in the coming years. However, the repurposing of already approved medicines in antiviral treatment or chemoprevention strategies is undoubtedly the fastest way to bring forward therapeutic options against the urgent unmet need posed by SARS-CoV-2. A range of different drugs and drug classes have been demonstrated to display varying degrees of antiviral activity against SARS-CoV-2 *in vitro*, and many of these drugs are already licenced for use in humans for a range of indications. However, currently the data emerging from global screening efforts are not being routinely benchmarked and prioritised against achievable concentrations after administration of doses proven to have acceptable safety profiles in humans.

The current analysis indicates that only 12 drugs with reported antiviral activity are likely to achieve plasma exposures above that required for antiviral activity for at least some of their dosing interval. Notably, neither chloroquine, hydroxychloroquine nor lopinavir/ritonavir exhibited a sustained plasma concentration above their reported SARS-CoV-2 EC₉₀ across their reported dosing interval. Ultimately, the implications of this for therapy will depend upon whether systemic suppression is a prerequisite for a reduction in morbidity or mortality, but this does raise some concern for ongoing trials with these drugs (chloroquine: NCT04323527; NCT04333628, hydroxychloroquine: NCT04316377; NCT04333225; NCT04307693 and lopinavir/ritonavir: NCT04331834; NCT04255017; NCT04315948). However, the predicted lung accumulation rather than plasma exposure may provide some therapy advantage and/or give more reassurance for ongoing chemoprevention trials.

At least 7 of the 13 candidates achieving C_{max} above one of their reported EC₅₀ and derived EC₉₀ are already in clinical evaluation for treatment of SARS-CoV-2. These include remdesivir (NCT04292730; NCT04292899; NCT04257656; NCT04252664; NCT04315948), favipiravir (NCT04310228; NCT04319900), niclosamide (NCT04345419), mefloquine (NCT04347031), lopinavir/ritonavir and chloroquine. No robust antiviral activity data were found for galidesivir on which to conduct an analysis but it is also under clinical investigation (NCT03800173). A recent trial for favipiravir demonstrated some success with an improvement over arbidol from 56% to 71% ($p = 0.02$) in patients without risk factors (but not critical cases or patients with hypertension and/or diabetes) (49). The results of compassionate use of remdesivir in severely ill patients was also recently reported, and if confirmed in ongoing randomised, placebo-controlled trials, will serve as a further validation of the other candidates presented here (50). Of particular interest, nitazoxanide, tipranavir, sulfadoxine and nelfinavir may be expected to sustain their

plasma pharmacokinetic exposure above their lowest reported EC_{50} and derived EC_{90} (where available) for the duration of their approved dose and dosing interval.

Nitazoxanide is an antiprotozoal drug that has previously been demonstrated to display broad antiviral activity against human and animal coronaviruses (51) as well as various strains of influenza (52, 53). Importantly, nitazoxanide is rapidly metabolised to tizoxanide in humans and this active metabolite is being investigated against SARS-CoV-2 (NCT04341493 and NCT04343248). Tizoxanide has been reported to exhibit similar activities to nitazoxanide for other viruses as well as other pathogens (54-56). The mechanism of antiviral action is not fully understood for nitazoxanide, but it has been reported to affect viral genome synthesis, prevent viral entry and interfere with the N-glycosylation and maturation of the influenza hemagglutinin (57-60). Notably, the SARS-CoV-2 spike protein is also highly N-glycosylated (61). This drug has also been shown to elicit an innate immune response that potentiates the production of type 1 interferons (57, 62) and a phase 2b/3 clinical trial demonstrated a reduction in symptoms and viral shedding in patients with uncomplicated influenza (53). The safety of nitazoxanide is well understood, but it has not been fully investigated during renal or hepatic impairment. The antiviral activity of nitazoxanide for SARS-CoV-2 requires further study but the existing data for this drug are encouraging. Niclosamide is another antiprotozoal drug that exhibits broad antiviral activity due to its ability to perturb the pH-dependent membrane fusion required for virus entry (63), but it was reported to have no impact upon the attachment and entry of SARS-CoV-2 (64). For MERS-CoV, niclosamide was observed to inhibit SKP2 activity impairing viral replication (65). Niclosamide has been reported to be well tolerated and does not influence vital organ functions (66). However, it has low aqueous solubility and poor oral bioavailability (67) and, despite a higher reported SARS-CoV-2 potency (39) than nitazoxanide (38), the C_{max}/EC_{90} ratio was slightly lower. There is a paucity of published pharmacokinetic data for niclosamide and this prohibited a thorough investigation of exposures in relation to activity over its entire dosing interval. Both nitazoxanide and niclosamide have also been reported to be potent antagonists of TMEM16A, calcium-activated chloride channels that modulate bronchodilation (68).

Tipranavir and nelfinavir are HIV protease inhibitors (69) and both drugs ranked highly in terms of their C_{max}/EC_{90} ratio. Moreover, a more in-depth analysis demonstrated that the concentrations across the dosing interval for both these drugs remained above the calculated EC_{90} values at approved doses and schedules. Unlike nelfinavir, tipranavir has to be co-administered with a low dose of ritonavir to boost its pharmacokinetics via CYP3A4 inhibition (70). Since ritonavir itself has been reported to exert anti-SARS-CoV-2 activity, this could be advantageous, but would need to be balanced against the much higher risk of drug-drug interactions that could negatively impact patient management. The implications of drug

interactions have already been raised for this reason with lopinavir/ritonavir use for COVID-19 (71) and are likely to be exacerbated with the higher ritonavir dose needed for tipranavir. Moreover, tipranavir has a black box warning from the FDA for fatal and nonfatal intracranial haemorrhage as well as severe hepatotoxicity (72-74). The major route of metabolic clearance for nelfinavir is via CYP2C19 and this pathway generates the M8 metabolite that retains activity against the HIV protease (75). No data are available for inhibition of SARS-CoV-2 replication by the M8 metabolite but if active, this could provide an advantage for nelfinavir over tipranavir for COVID-19. Conversely, while the analysis of pharmacokinetics relative to potency of these molecules against SARS-CoV-2 is encouraging, it should be noted that the reported *in vitro* activity for HIV (69, 76) is far higher than that against SARS-CoV-2 and both drugs are highly protein bound (77, 78). Given that tipranavir and nelfinavir are associated with long-term toxicities (69, 79-81), there will be concern over giving even short-term exposure for COVID-19.

Sulfadoxine is another antimalarial drug that is usually administered in combination with pyrimethamine as a folic acid antagonist combination (82). Sulfadoxine inhibits the activity of dihydropteroate synthase within the malaria parasite, but its mechanism of action for SARS-CoV-2 is unclear. It should also be noted that the authors can find no data describing antiviral activity of this drug against other viruses. Also, the concentrations used in the *in vitro* activity used in this analysis (37) were not high enough to reach or calculate an EC_{90} value. Therefore, like other molecules described in this manuscript, *in vitro* anti-SARS-CoV-2 activity should be repeated. Notwithstanding, sulfadoxine plasma concentrations far above the reported EC_{50} are maintained in patients receiving a single 1500 mg dose (with 75 mg pyrimethamine) for over 40 days (83). Compared to some other reported molecules, sulfadoxine is not expected to have as high an accumulation in the lungs, but concentrations higher than its EC_{50} are estimated from the analysis of its lung K_pU . Therefore, if the reported antiviral activity is confirmed, this drug may offer opportunities for therapy and/or chemoprophylaxis.

Indomethacin is a nonsteroidal anti-inflammatory drug that is indicated for rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder or acute gouty arthritis. The recommended dose for acute gouty arthritis is 50 mg three times a day and the pharmacokinetic exposure for this is shown in Figure 3 relative to the reported EC_{50} . Indomethacin mechanism of action for SARS-CoV-2 remains elusive, but it was shown to inhibit translation of the vesicular stomatitis virus by activating protein kinase R leading to the phosphorylation of eukaryotic initiation factor-2 α -subunit (84). This abrogated viral protein translation, leading to a dramatic inhibition of viral replication and infectious viral particle production. The reported *in vitro* antiviral activity data for indomethacin were insufficient to calculate an EC_{90} and this activity requires confirmation in other studies (40). Furthermore, the drug has a

black box warning for serious cardiovascular and gastrointestinal events from FDA so its use should be managed with caution (85).

Considering that most of the impact of severe disease occurs in the lung and that this tissue may be a key site for transmission, the potential of candidate drugs to accumulate in lung tissue was considered. The lung K_p predictions were validated across 13 drugs for which previously reported animal plasma and lung concentrations were available, and showed good agreement for all agents other than chloroquine. The poor fit for chloroquine does highlight that the predictions may not be accurate for all of the drugs listed and this should be considered in interpretation. Notwithstanding, the analysis of predicted lung C_{max}/EC_{50} ratio revealed more candidates expected to exceed the concentrations needed for antiviral activity in this tissue. Hydroxychloroquine, chloroquine, mefloquine, atazanavir (ritonavir boosted), tipranavir (ritonavir boosted), ivermectin and lopinavir were all predicted to achieve lung concentrations over 10-fold higher than their reported EC_{50} . All of these drugs were also predicted to exceed their EC_{90} in lung by at least 3.4-fold (data not shown). The lung prediction was not possible for nelfinavir because insufficient data were available to calculate $K_p U_{lung}$, but nitazoxanide and sulfadoxine were also predicted to exceed their reported EC_{50} by 7.8- and 1.5-fold in lung, respectively. Nitazoxanide was predicted to exceed its EC_{90} by 3.6-fold in lung but an EC_{90} was not calculable from the available data for sulfadoxine.

Predictions for C_{max}/EC_{50} ratio were also made for other tissues, and were generally in agreement with observations in the lung with some important exceptions. Gliteritinib, amodiaquine, imatinib, indomethacin, oxprenolol, and sulfadoxine were predicted to be subtherapeutic in brain and bone, with indomethacin and sulfadoxine being predicted to be subtherapeutic across most of the tissues in which C_{max} was estimated.

During inflammation or injury, changes to the vascular microenvironment could have a profound effect on the ability of these drugs to accumulate in lung cells. Due to the recruitment of neutrophils and leaky endothelial cells (86), the lung inflammatory microenvironment is characterised by increased body temperature, excessive enzymatic activity and, most importantly, by a low interstitial pH (87). In the case of chloroquine and hydroxychloroquine, these diprotic weak bases are exquisitely dependent on a pH gradient to drive lysosomal uptake as a mechanism of lung accumulation. It has been demonstrated that cellular chloroquine uptake is diminished 100-fold for every pH unit of external acidification (88). This situation is likely to deteriorate further on mechanical ventilation, which also induces acidification of the lung tissue, independently of inflammation (89, 90). Therefore, the benefits of lung accumulation for many of these drugs may be lost during treatment of severe SARS-CoV-2 infection. Conversely, mefloquine is monoprotic and more lipophilic than chloroquine, which may make it much less reliant on

the pH gradient to drive cellular accumulation in lung. It is likely that the charged form of the drug is sufficiently lipophilic to allow movement across biological membranes along a concentration gradient (91). Only two studies have described mefloquine uptake into cells, one study suggested that mefloquine uptake is not energy dependent and the other suggested that mefloquine uptake is mediated by secondary active transport, rather than passive proton trapping (92, 93). Mefloquine is known to cause severe psychiatric side effects in some patients and so use of this drug should be managed with care (94). Therefore, mefloquine may offer opportunities for treatment during severe disease that are not available with other drugs currently being tested for COVID-19 therapy. If the high lung exposures are proven empirically for the drugs on this list, then some may also prove to be valuable for chemoprevention strategies.

Limitations of this analysis

This study represents the first holistic view of drugs with reported activity against SARS-CoV-2 in the context of their achievable pharmacokinetic exposure in humans. While the analysis does provide a basis to rationally selected candidates for further analysis, there are some important limitations. Firstly, C_{max} was the only pharmacokinetic parameter that was universally available for all of the candidate drugs, but C_{min} values are generally accepted as a better marker of efficacy since they represent the lowest plasma concentration over the dosing interval. However, C_{max} was only used to assess whether plasma concentration would exceed those required at any point in the dosing interval, and this was followed by a more in-depth analysis of the most promising candidates.

Secondly, an EC_{50} value only equates to a concentration required to suppress 50% of the virus, and data were unavailable to calculate EC_{90} values for some of the drugs. EC_{90} values are a preferred marker of activity because the slope of the concentration-response curve can vary substantially between different molecules and between different mechanisms of action. Although EC_{90} values were not calculable for all drugs the authors deemed it appropriate to deprioritise molecules not achieving EC_{50} at C_{max} in this analysis. Thirdly, the reported antiviral activities were conducted under different conditions (Supplementary Table 2) and in several cases varied between the same molecule assessed in different studies (Figure 1). Also, some of the studied drugs (e.g. nitazoxanide and amodiaquine) are rapidly metabolised such that the major species systemically is a metabolite that has not been investigated for anti-SARS-CoV-2 activity. No mitigation strategy was possible for these limitations and the data should be

interpreted in the context that the quality of the available data may profoundly impact the conclusions. *In vitro* activity should be confirmed for the promising candidates and/or relevant metabolites.

Fourthly, plasma protein binding can be an important factor in determining whether sufficient free drug concentrations are available to exert antiviral activity (95) and insufficient data were available across the dataset to determine protein binding-adjusted EC_{90} values. This is important because for highly protein bound drugs the antiviral activity in plasma may be lower than reported *in vitro* activity because protein concentrations used in culture media are lower than those in plasma. Fifthly, robust pharmacokinetic data were not available for all the molecules and subtle differences have been reported in the pharmacokinetics in different studies. Where possible, this analysis utilised the pharmacokinetics described at the highest doses approved for other indications and checked them to ensure that profound differences were not evident between different studies. However, in some cases, higher doses and/or more frequent dosing has been investigated for some of the drugs mentioned so higher exposures may be available for some drugs with off-label dosing. Sixthly, the digitised pharmacokinetic plots presented in this manuscript represent the mean or median profiles depending on what was presented in the original manuscripts. Many of the drugs presented are known to exhibit high inter-individual variability that is not captured within the presented analysis and it is possible that even for promising candidates, a significant proportion of patients may have sub-therapeutic concentrations despite population mean/median being higher than the C_{max} . Advanced pharmacokinetics modelling approaches will be needed to unpick the exposure-response relationship and these studies are currently underway by the authors.

Seventhly, the presented predictions for lung accumulation may offer a basis for ranking molecules for expected accumulation in that organ, but ultimate effectiveness of a chemoprophylactic approach will likely depend upon penetration into other critical matrices in the upper airways, for which there are currently no robustly validated methods of prediction. Also, while a generally accepted method for assessing KpU was employed, the predictions were only validated for a subset of drugs for which previous animal lung accumulation data were available. In addition, the KpU method assumes all the processes are passive and perfusion limited, and the complexity of pulmonary tissue pharmacokinetics is not captured in this analysis. The lungs include different structures including airways, bronchioles and alveoli with different blood flow perfusion and more detailed modelling validated through animal experiments will be required to capture this complexity.

Finally, this analysis assumes that drugs need to be active within the systemic compartment in order to have efficacy against SARS-CoV-2. Since current evidence suggests that the virus is widely disseminated

throughout the body this is a logical assumption. However, ultimate efficacy of any drug can only be demonstrated with robust clinical trial designs.

Summary

The current analysis reveals that many putative agents are never likely to achieve target concentrations necessary to adequately suppress SARS-CoV-2 under normal dosing conditions. It is critical that candidate medicines emerging from *in vitro* antiviral screening programmes are considered in the context of their expected exposure in humans where possible. Clinical trials are extremely time consuming and expensive, and it is critical that only the best options are progressed for robust analysis as potential mono- or combination therapy or prevention options. Finally, it would be highly beneficial for activity data for SARS-CoV-2 to be performed with standardised protocol and with activity reported as EC₉₀ values as a better marker of the concentrations required to suppress the virus to therapeutically relevant levels. Based upon the currently reported data, atazanavir, chloroquine, favipiravir, hydroxychloroquine, indomethacin, lopinavir, mefloquine, nitazoxanide, ritonavir, sulfadoxine, and tipranavir are predicted to have mean/median C_{max} concentrations above their reported EC₅₀ in both plasma and lung. Anidulafungin, eltrombopag, merimepodib, nelfinavir, niclosamide and remdesivir also had mean/media C_{max} above available EC₅₀ in plasma but a lung prediction was not possible. Only atazanavir, indomethacin, nelfinavir, nitazoxanide, sulfadoxine, and tipranavir were predicted to have mean/median plasma C_{max} concentrations above their reported EC₅₀ for the duration of their dosing interval, but full concentration-time profiles were not available to make this judgement for favipiravir, niclosamide, and remdesivir.

Study Highlights

What is the current knowledge on the topic?

COVID-19 is an acute infectious respiratory disease caused by infection with the coronavirus subtype SARS-CoV-2, first detected in Wuhan, China, in December 2019. There are currently no available treatments or chemopreventative options, but several are being explored preclinically and clinically. Most publications reporting *in vitro* activity have focussed on 50% maximum effective concentrations (EC_{50}) and not considered the achievable concentrations in plasma or relevant compartments for COVID-19, which may be an insufficiently robust indicator of antiviral activity because of marked differences in the slope of the concentration-response curve between drugs.

What question did this study address?

The manuscript describes a comprehensive analysis of literature reported anti-SARS-CoV-2 activity for approved medicines in the context of their known pharmacokinetic exposure. A combination of physiochemical and pharmacological parameters was used to predict the accumulation of these drugs within lung tissues using a widely accepted modelling approach. Plasma and lung pharmacokinetic parameters were then used to rank the reported molecules according to whether they would provide therapeutic or chemopreventative exposures with the plasma or lung tissue.

What does this study add to our knowledge?

Of the identified molecules with reported anti-SARS-CoV-2 activity, the overwhelming majority are not expected to reach active concentrations within the key target compartments. However, a number of candidates were identified that are expected to exceed the concentrations necessary to provide viral suppression at doses approved for use in humans.

How might this change clinical pharmacology or translational science?

The manuscript identifies key drug repurposing opportunities and dramatically highlights the importance of considering pharmacokinetic exposure when interpreting the emerging candidacy of drugs for COVID-19 treatment and prevention.

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Author contributions

All authors wrote the manuscript. A.O. designed the research. U.A., H.B., L.T., H.P. and A.O. performed the research. R.R., H.P., U.A., and A.O. analysed the data.

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Figure legends

Figure 1. Assessment of the variation in reported EC_{50} values for SARS-CoV-2 across the drugs for which more than one value was available in the literature (A). The consequences of this variability in reported EC_{50} in terms of the C_{max}/EC_{50} ratio is also provided (B). Amodiaquine and toremifene were estimated to exhibit sub-therapeutic pharmacokinetics irrespective of which EC_{50} value was used. Similarly, nelfinavir was estimated to have C_{max} value higher than its EC_{50} irrespective of which EC_{50} was used in the analysis. For the other drugs, interpretation was highly dependent upon which reported EC_{50} was utilised and this underscores the caution that should be taken in interpreting the available data.

Figure 2. A bar chart displaying C_{max}/EC_{90} ratio for compounds studied for *in vitro* antiviral activity against SARS-CoV-2 for which data were available to recalculate an EC_{90} . Drugs with a ratio below 1 were deemed not to provide plasma concentrations at their approved doses to exert sufficient systemic antiviral activity. Those drugs with a ratio above 1 (shown in orange) were deemed to have potential to provide plasma concentrations sufficient to exert at least some antiviral activity for at least some of their dosing interval at their approved dose. Drugs shown in green were predicted to exceed plasma concentrations over their EC_{90} by more than 2-fold.

Figure 3. Digitised pharmacokinetic interrogation of all drugs calculated to have a C_{max}/EC_{50} ratio above 1. The lowest reported SARS-CoV-2 EC_{50} (dashed orange lines) and associated recalculated EC_{90} (dashed green lines) are also highlighted. References for the utilised data are nitazoxanide 500 mg BID and 1000 mg BID (96), tipranavir 500 mg BID with 200 mg ritonavir (97), sulfadoxine 1500 mg with 75 mg pyrimethamine (83), nelfinavir 1250 mg BID (98), indomethacin 50 mg TID (99), atazanavir 300 mg QD with 100 mg ritonavir (100), hydroxychloroquine 2000 mg hydroxychloroquine sulfate/1550 mg base administered over 3 days (101), eltrombopag 75 mg single dose (102), lopinavir 400 mg with 100 mg ritonavir (103), chloroquine 1500 mg administered over 3 days (104), mefloquine 1200 mg over 3 days (105), anidulafungin 100 mg QD (106). Robust pharmacokinetic data were unavailable for niclosamide 500 mg, ritonavir 600 mg and merimepodib 300 mg in order to conduct this digitised interrogation of these molecules.

Figure 4. A bar chart displaying the simulated lung C_{max}/EC_{50} . Drugs with a ratio below 1 were deemed not to provide lung concentrations at their approved doses to exert sufficient pulmonary antiviral activity for treatment or prevention strategies. Those drugs with a ratio above 1 (shown in orange) were estimated to provide lung concentrations sufficient to exert at least some antiviral activity at their

approved dose. Drugs shown in green were predicted to exceed lung concentrations over their EC_{50} by more than 10-fold.

Figure 5. A heatmap displaying the simulated tissue C_{max}/EC_{50} values for all drugs with available data. Those drugs with a ratio above 1 (shown in orange) were estimated to provide tissue concentrations sufficient to exert at least some antiviral activity at their approved dose. Drugs shown in green were predicted to exceed tissue concentrations over their EC_{50} by more than 10-fold.

Supplemental Information

Figure S1

Figure S2

Table S1

Table S2

Supplemental Figure Legends

Supplemental Methods

Supplemental References

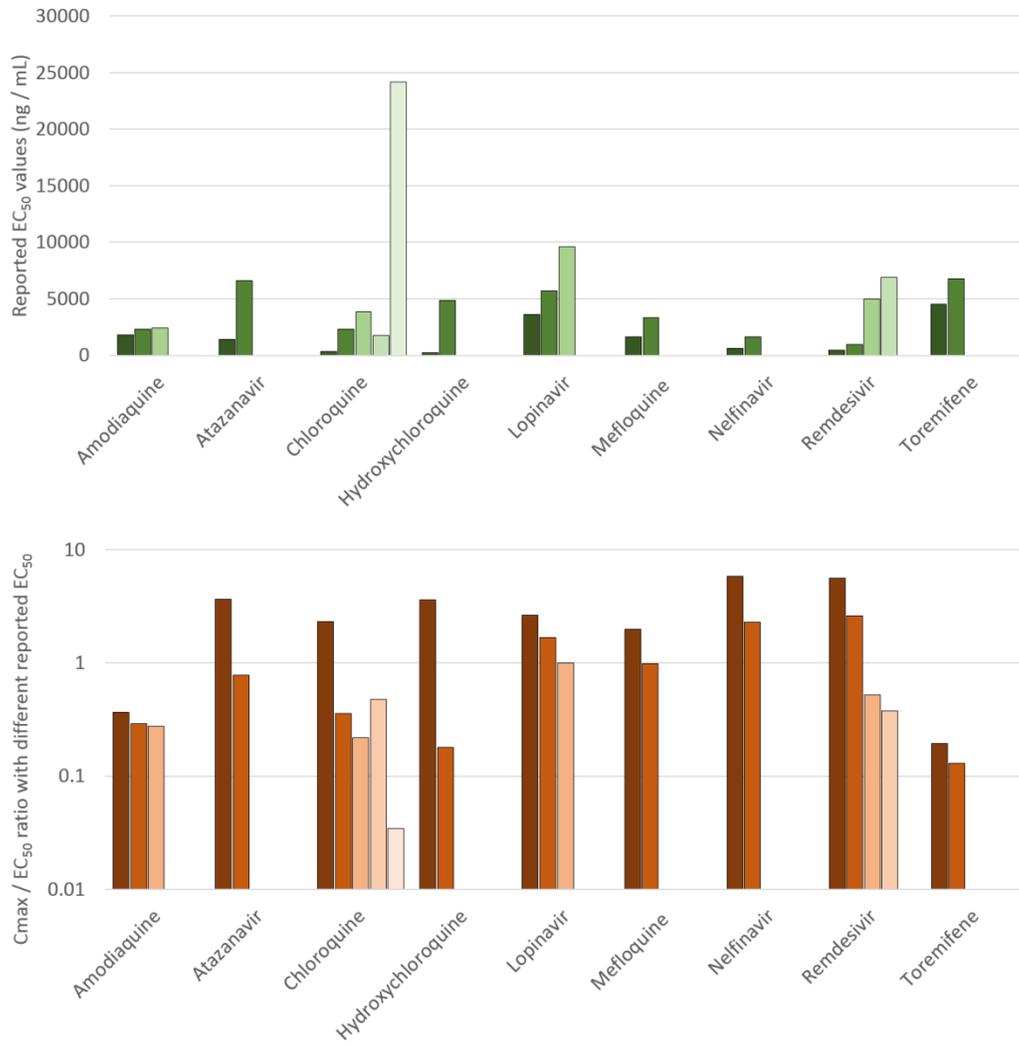
Table 1. Summary of the top leads identified

| Drug | C _{max} :EC ₅₀ | C _{max} :EC ₉₀ | Approval | Indications | Route of administration | Dosage | Ref |
|---|------------------------------------|------------------------------------|--------------|---|-------------------------|--------------------------|------------|
| Atazanavir & Ritonavir REYATAZ® (Bristol-Myers Squibb) | 3.643 | 0.728 | EMA FDA | HIV-1 | Oral | 300/100 mg | (107, 108) |
| Anidulafungin Eraxis®/Ecalta® (Pfizer) | 1.323 | 1.192 | EMA FDA | Invasive fungal infections | Intravenous infusion | 200 mg QD + 100 mg QD | (109) |
| Chloroquine Aralen® (Sanofi Aventis) | 2.318 | 1.261 | FDA | Malaria Extraintestinal amebiasis | Oral | 1500 mg | (110) |
| Eltrombopag Promacta®/Revolade® (Novartis) | 3.416 | 2.029 | EMA FDA | Primary immune thrombocytopenia Acquired severe aplastic anaemia | Oral | 75 mg QD | (111) |
| Favipiravir Avigan® (Fujifilm Toyama Chemical Co) | 6.326 | 2.469 | PMDA - Japan | Influenza | Oral | 600 mg BID | (112) |
| Hydroxychloroquine Plaquenil® (Sanofi Aventis) | 3.598 | 0.101 | EMA FDA | Malaria | Oral | 400 mg | (113) |

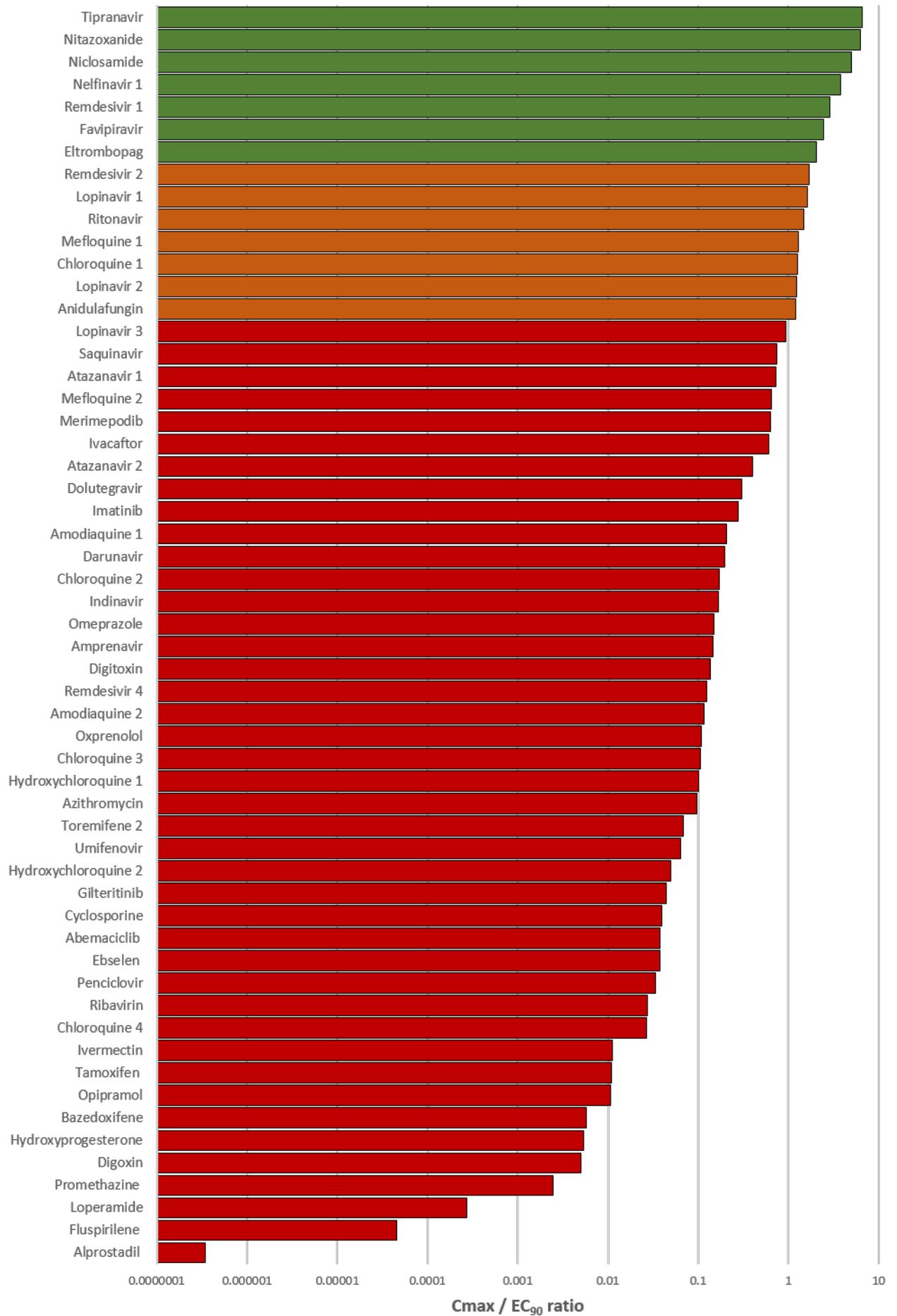
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|--|---------------|---------------|-----------------------------|---|-------------|-----------------------|-------|
| Indomethacin Indocin® (Merck & Co) | 5.366 | - | EMA FDA | Rheumatoid arthritis | Oral | 50 mg TID | (114) |
| Lopinavir & Ritonavir Kaletra® (AbbVie) | 2.660 / 1.671 | 1.630 / 1.240 | EMA FDA | HIV-1 | Oral | 400/100 mg BID | (115) |
| Mefloquine Lariam® (Roche) | 1.350 | 1.284 | EMA FDA | Malaria | Oral | 250 mg | (116) |
| Merimepodib (Vertex Pharmaceuticals) | 1.629 | 0.638 | Not clinically approved | HCV | Oral | 300 mg TID | (117) |
| Nelfinavir VIRACEPT® (Roche) | 5.849 / 2.287 | 3.755 | EMA FDA | HIV-1 | Oral | 1250 mg BID | (118) |
| Niclosamide Yomesan® (Bayer) | 8.286 | 4.936 | EMA FDA | Infestation with tapeworms | Oral | 2000 mg | (119) |
| Nitazoxanide Alinia® (Romark Pharmaceuticals) | 13.823 | 6.315 | FDA | Diarrhoea caused by Giardia lamblia or Cryptosporidium parvum | Oral | 1000 – 2000 mg BID | (120) |
| Remdesivir (Gilead) | 5.603 / 2.614 | 3.755 / 1.712 | *Not clinically approved | Ebola | Intravenous | 200 mg + 100 mg | (38) |
| Ritonavir Norvir® | 1.800 | | EMA FDA | HIV-1 | Oral | 600 mg | (121) |

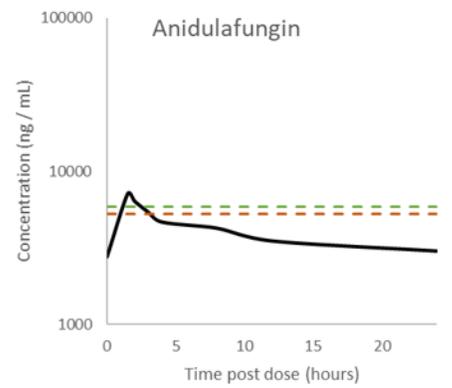
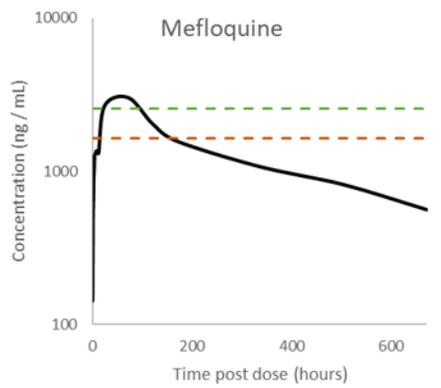
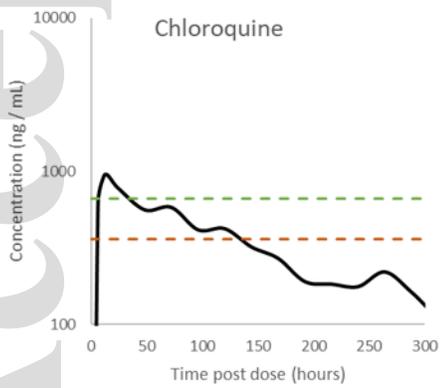
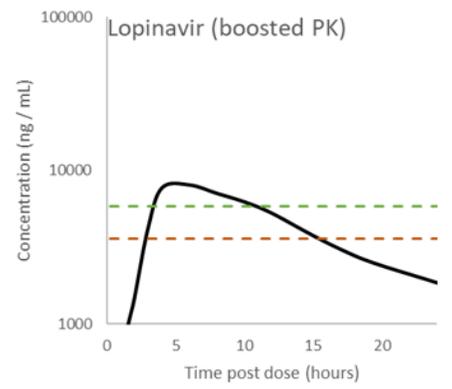
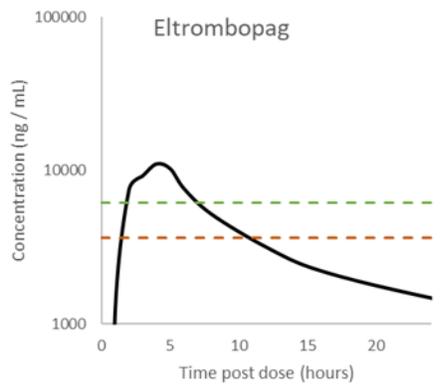
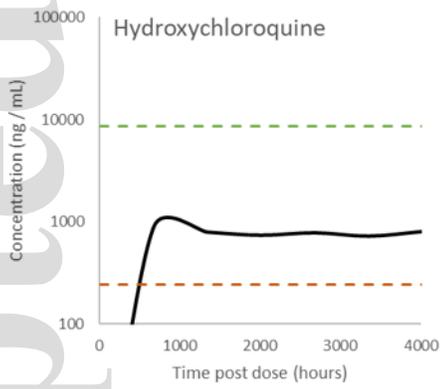
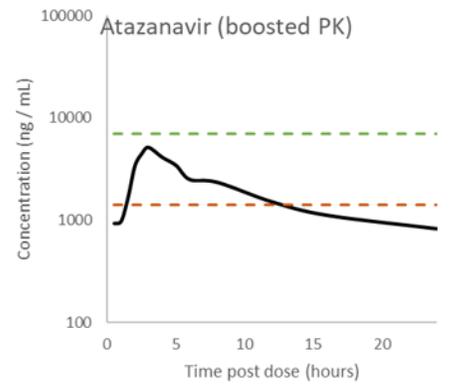
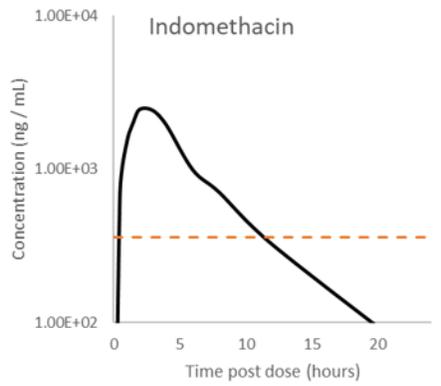
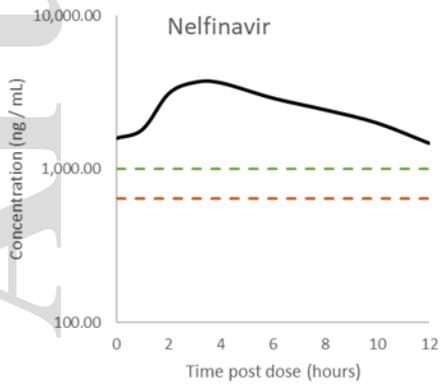
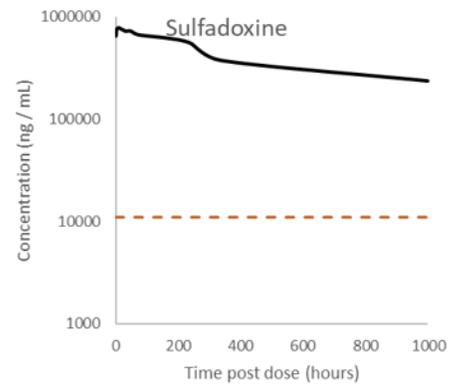
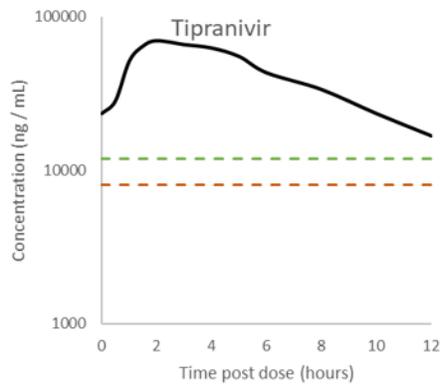
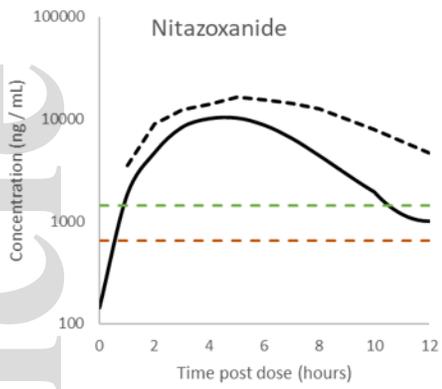
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|---|-------|-------|--------------------|---------|------|-------------------|-------|
| (AbbVie) | | | | | | | |
| Sulfadoxine & pyrimethamine | 6.577 | | FDA - discontinued | Malaria | Oral | 1500/75 mg | (122) |
| Fansidar® | | | | | | | |
| (Roche) | | | | | | | |
| Tipranavir & Ritonavir | | | | | | | |
| Aptivus® | 9.647 | 6.559 | EMA FDA | HIV-1 | Oral | 500/200 mg BID | (123) |
| (Boehringer Ingelheim Pharmaceuticals, Inc.) | | | | | | | |

*compassionate use programme

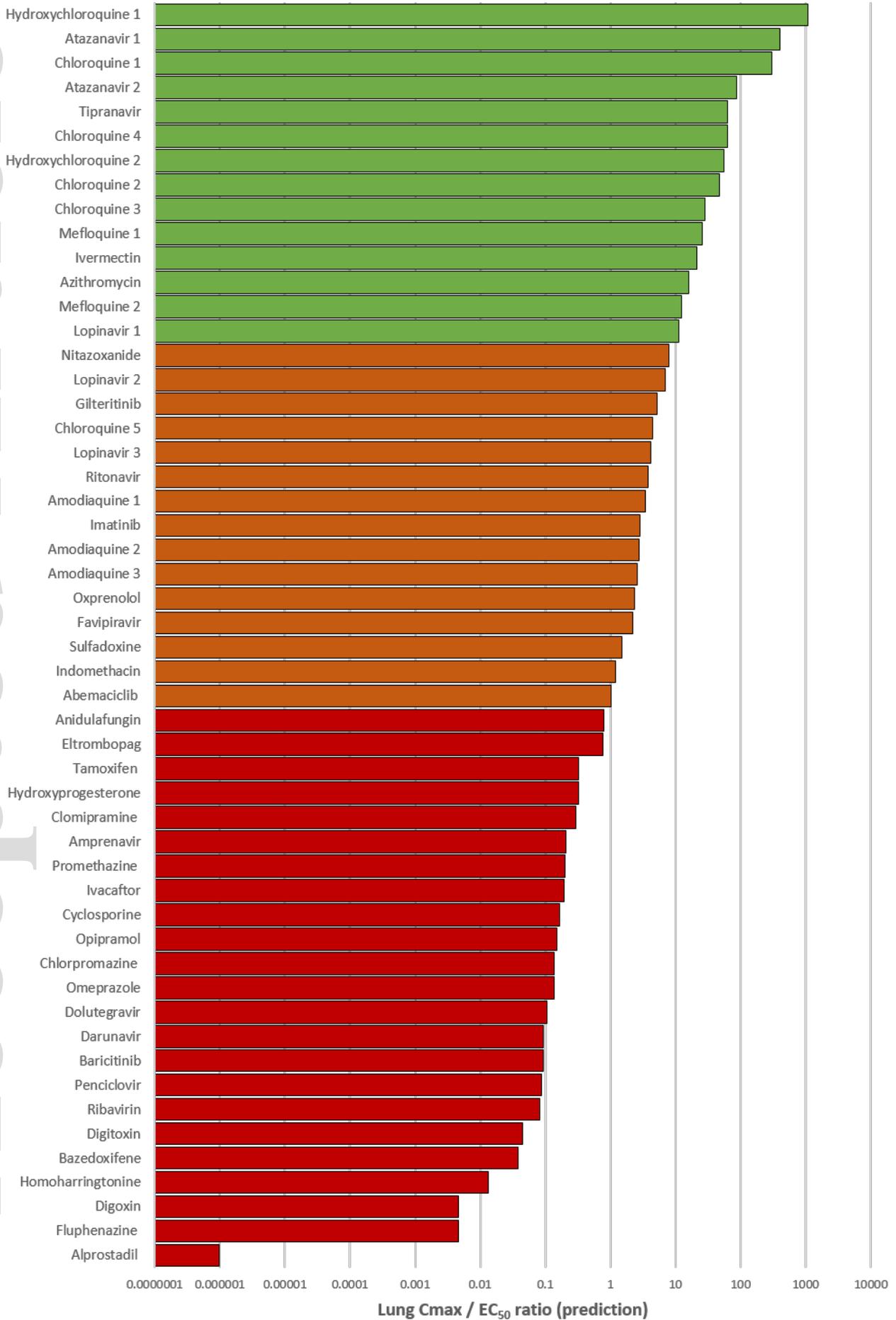


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| | Tissue C _{max} /EC ₅₀ ratio | | | | | | | | | | | |
|---------------------------|---|---------|--------|---------|--------|--------|--------|--------|----------|--------|--------|--------|
| | Lung | Kidney | Gut | Liver | Brain | Heart | Bone | Muscle | Pancreas | Skin | Spleen | Thymus |
| Abemaciclib | 1.03 | 1.18 | 0.92 | 1.11 | 0.52 | 0.62 | 0.33 | 0.43 | 0.80 | 0.94 | 0.73 | 0.66 |
| Alprostadil | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Amodiaquine 1 | 3.42 | 4.38 | 2.13 | 3.98 | 0.41 | 1.99 | 0.61 | 1.38 | 1.50 | 1.18 | 2.80 | 2.04 |
| Amodiaquine 2 | 2.73 | 3.50 | 1.70 | 3.18 | 0.33 | 1.59 | 0.49 | 1.10 | 1.20 | 0.94 | 2.23 | 1.63 |
| Amodiaquine 3 | 2.59 | 3.32 | 1.61 | 3.02 | 0.31 | 1.51 | 0.46 | 1.04 | 1.14 | 0.89 | 2.12 | 1.55 |
| Amprenavir | 0.21 | 0.17 | 0.28 | 0.18 | 0.24 | 0.16 | 0.12 | 0.11 | 0.26 | 0.36 | 0.14 | 0.15 |
| Anidulafungin | 0.79 | 0.60 | 0.97 | 0.57 | 0.83 | 0.59 | 0.45 | 0.42 | 0.90 | 1.40 | 0.43 | 0.55 |
| Atazanavir 1 | 406.68 | 311.65 | 665.21 | 333.28 | 638.29 | 269.42 | 288.61 | 196.51 | 693.93 | 994.19 | 166.69 | 315.87 |
| Atazanavir 2 | 86.90 | 66.60 | 142.14 | 71.21 | 136.39 | 57.57 | 61.67 | 41.99 | 148.28 | 212.43 | 35.62 | 67.49 |
| Azithromycin | 16.04 | 20.26 | 10.59 | 18.50 | 2.85 | 9.45 | 3.23 | 6.63 | 7.85 | 6.72 | 12.96 | 9.77 |
| Baricitinib | 0.09 | 0.08 | 0.10 | 0.09 | 0.10 | 0.08 | 0.05 | 0.07 | 0.10 | 0.11 | 0.08 | 0.08 |
| Bazedoxifene | 0.04 | 0.03 | 0.06 | 0.03 | 0.06 | 0.03 | 0.03 | 0.02 | 0.07 | 0.09 | 0.02 | 0.03 |
| Chloroquine 1 | 300.78 | 386.01 | 187.12 | 350.74 | 35.03 | 174.47 | 53.46 | 120.52 | 131.88 | 103.54 | 245.72 | 179.19 |
| Chloroquine 2 | 46.69 | 59.92 | 29.04 | 54.44 | 5.44 | 27.08 | 8.30 | 18.71 | 20.47 | 16.07 | 38.14 | 27.81 |
| Chloroquine 3 | 28.32 | 36.35 | 17.62 | 33.03 | 3.30 | 16.43 | 5.03 | 11.35 | 12.42 | 9.75 | 23.14 | 16.87 |
| Chloroquine 4 | 62.14 | 79.74 | 38.66 | 72.46 | 7.24 | 36.04 | 11.04 | 24.90 | 27.24 | 21.39 | 50.76 | 37.02 |
| Chloroquine 5 | 4.50 | 5.78 | 2.80 | 5.25 | 0.52 | 2.61 | 0.80 | 1.80 | 1.97 | 1.55 | 3.65 | 2.68 |
| Chlorpromazine | 0.14 | 0.12 | 0.20 | 0.12 | 0.19 | 0.09 | 0.09 | 0.07 | 0.21 | 0.29 | 0.07 | 0.10 |
| Ciclesonide | 0.00 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| Clomipramine | 0.29 | 0.37 | 0.21 | 0.34 | 0.07 | 0.17 | 0.06 | 0.12 | 0.16 | 0.15 | 0.23 | 0.18 |
| Cyclosporine | 0.17 | 0.13 | 0.26 | 0.14 | 0.25 | 0.12 | 0.11 | 0.08 | 0.27 | 0.38 | 0.08 | 0.13 |
| Darunavir | 0.09 | 0.08 | 0.11 | 0.09 | 0.07 | 0.08 | 0.04 | 0.04 | 0.08 | 0.12 | 0.09 | 0.06 |
| Digitoxin | 0.04 | 0.03 | 0.04 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.06 | 0.02 | 0.02 |
| Digoxin | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 |
| Dolutegravir | 0.11 | 0.09 | 0.09 | 0.10 | 0.03 | 0.10 | 0.03 | 0.04 | 0.04 | 0.06 | 0.13 | 0.06 |
| Eltrombopag | 0.77 | 0.48 | 0.60 | 0.33 | 0.23 | 0.57 | 0.37 | 0.24 | 0.27 | 1.03 | 0.36 | 0.29 |
| Favipiravir | 2.22 | 1.80 | 1.92 | 1.43 | 1.36 | 2.00 | 1.04 | 1.30 | 1.33 | 2.40 | 1.61 | 1.42 |
| Fluphenazine | 0.00 | 0.00 | 0.01 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| Glitteritinib | 5.28 | 6.79 | 3.27 | 6.16 | 0.57 | 3.04 | 0.92 | 2.07 | 2.28 | 1.81 | 4.29 | 3.11 |
| Homoharringtonine | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.01 | 0.01 | 0.02 | 0.02 | 0.01 | 0.01 | 0.02 |
| Hydroxychloroquine 1 | 1096.26 | 1408.93 | 678.16 | 1278.66 | 118.97 | 633.33 | 191.01 | 434.11 | 473.61 | 372.29 | 893.89 | 648.90 |
| Hydroxychloroquine 2 | 54.69 | 70.29 | 33.83 | 63.79 | 5.94 | 31.60 | 9.53 | 21.66 | 23.63 | 18.57 | 44.59 | 32.37 |
| Hydroxyprogesterone | 0.32 | 0.25 | 0.53 | 0.26 | 0.51 | 0.21 | 0.23 | 0.16 | 0.55 | 0.79 | 0.13 | 0.25 |
| Imatinib | 2.82 | 3.58 | 1.84 | 3.26 | 0.46 | 1.65 | 0.55 | 1.14 | 1.35 | 1.15 | 2.28 | 1.70 |
| Indomethacin | 1.18 | 0.74 | 0.92 | 0.50 | 0.33 | 0.88 | 0.57 | 0.37 | 0.39 | 1.57 | 0.55 | 0.44 |
| Ivacaftor | 0.20 | 0.13 | 0.18 | 0.10 | 0.09 | 0.14 | 0.10 | 0.07 | 0.11 | 0.29 | 0.09 | 0.09 |
| Ivermectin | 21.01 | 16.10 | 34.39 | 17.22 | 32.99 | 13.92 | 14.92 | 10.14 | 35.87 | 51.40 | 8.60 | 16.32 |
| Lopinavir 1 | 11.18 | 8.59 | 18.07 | 9.20 | 17.21 | 7.49 | 7.83 | 5.39 | 18.73 | 26.83 | 4.80 | 8.61 |
| Lopinavir 2 | 7.02 | 5.40 | 11.36 | 5.78 | 10.81 | 4.70 | 4.92 | 3.38 | 11.77 | 16.96 | 3.02 | 5.41 |
| Lopinavir 3 | 4.20 | 3.22 | 6.78 | 3.45 | 6.46 | 2.81 | 2.94 | 2.02 | 7.03 | 10.07 | 1.80 | 3.23 |
| Mefloquine 1 | 25.54 | 32.81 | 15.84 | 29.76 | 2.78 | 14.73 | 4.44 | 10.05 | 11.04 | 8.79 | 20.76 | 15.07 |
| Mefloquine 2 | 12.51 | 16.07 | 7.76 | 14.58 | 1.36 | 7.22 | 2.18 | 4.92 | 5.41 | 4.31 | 10.17 | 7.38 |
| Nitazoxanide (Tizoxanide) | 7.80 | 5.57 | 10.20 | 5.25 | 8.43 | 5.42 | 4.85 | 3.31 | 9.26 | 15.73 | 3.39 | 4.90 |
| Omeprazole | 0.14 | 0.11 | 0.17 | 0.12 | 0.14 | 0.11 | 0.07 | 0.07 | 0.15 | 0.22 | 0.11 | 0.09 |
| Opipramol | 0.15 | 0.19 | 0.10 | 0.17 | 0.03 | 0.09 | 0.03 | 0.06 | 0.08 | 0.07 | 0.12 | 0.09 |
| Oxprenolol | 2.36 | 3.02 | 1.48 | 2.75 | 0.31 | 1.38 | 0.44 | 0.97 | 1.06 | 0.82 | 1.94 | 1.42 |
| Penciclovir | 0.09 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.05 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 |
| Promethazine | 0.20 | 0.25 | 0.14 | 0.23 | 0.04 | 0.12 | 0.04 | 0.08 | 0.10 | 0.10 | 0.16 | 0.12 |
| Ribavirin | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.07 | 0.08 | 0.08 |
| Ritonavir | 3.85 | 2.97 | 6.10 | 3.19 | 5.73 | 2.62 | 2.63 | 1.83 | 6.25 | 8.96 | 1.78 | 2.92 |
| Sulfadoxine | 1.52 | 1.00 | 1.17 | 0.69 | 0.47 | 1.18 | 0.72 | 0.55 | 0.53 | 1.92 | 0.78 | 0.63 |
| Tamoxifen | 0.33 | 0.25 | 0.54 | 0.27 | 0.52 | 0.22 | 0.23 | 0.16 | 0.56 | 0.80 | 0.13 | 0.26 |
| Tipranavir | 62.52 | 47.80 | 101.73 | 50.96 | 97.29 | 41.45 | 44.22 | 30.07 | 105.80 | 152.20 | 25.62 | 48.28 |