ISSN: 2230-9926

*Available online at http://www.journalijdr.com*

IJDR

*International Journal of Development Research*
*Vol. 14, Issue, 09, pp. 66553-66558, September, 2024*
**https://doi.org/10.37118/ijdr.28675.09.2024**


RESEARCH ARTICLE OPEN ACCESS

# PREDICTION OF PHYSICOCHEMICAL, PHARMACOKINETIC AND TOXICOLOGICAL PARAMETERS OF ANTIMICROBIALS IN PHASE III CLINICAL STUDIES

**[1]Ingrid M. de Oliveira and [2]José Luiz C. da Rocha**

[1]Unidade de Ensino Superior de Feira de Santana, Feira de Santana (BA), Brazil; [2]Unidade de Ensino Superior de Feira de Santana, Feira de Santana (BA); Bahia State University, Salvador (BA), Brazil

## ARTICLE INFO

***Article History:***
Received 10th June, 2024
Received in revised form
03rd July, 2024
Accepted 11th August, 2024
Published online 30th September, 2024

***Key Words:***
Traditional Antimicrobials. In silico Analysis. Molecular Prediction. Physicochemical Profile.

****Corresponding Author:***
***Ingrid M. de Oliveira,***

## ABSTRACT

*In silico* analysis importance was recognized. It provides a predictive evaluation of the molecular behavior, revealing physicochemical properties and pharmacokinetic and toxicological informations that determine how much promising is a molecule to advance to other pharmaceutical tests. Therefore, this work aimed to present the traditional antimicrobials in phase III clinical studies, attaching, through *in silico* analysis, their pharmacokinetics, adverse effects and toxicity to their molecular structure and physicochemical properties. Traditional antimicrobials were selected and submited to molecular prediction on the ADMETlab 2.0© platform. The data were exposed into charts and discussed according to informations avaliable in the scientific literature. It was noticed that the physicochemical profile was crucial to the absorption, the distribution, the excretion and the toxicity of the evaluated molecules, which were promising in some aspects but controversial in others, with the nafithromycin presenting the best results. Thus it can be affirmed that the *in silico* studies are not discouraging indeed and they must be considered with good eyes so that all the caracteristics of a potential molecule can be analyzed in order to the studies advance to the next steps properly.



***Citation*: *Ingrid M. de Oliveira and José Luiz C. da Rocha, 2024.*** *"Prediction of physicochemical, pharmacokinetic and toxicological parameters of antimicrobials in Phase iii Clinical Studies". International Journal of Development Research*, 14, (09), 66553-66558.

# INTRODUCTION

The production of new antimicrobials requires a high investment in research and tests to be carried out by the pharmaceutical industry. In these researches, the starting point of the molecular analysis themselves is the *in silico* evaluation, which provides, through computational simulation, previous results regarding the physicochemical behavior, pharmacokinetics and toxicity of molecules. This evaluation is carried out through specialized platforms, which cross-reference a large amount of pre-existing data based on different parameters. So it is possible to select promising molecules for the next phases of the pharmaceutical research, saving time and money during the process. One of the molecular prediction platforms used in this sense is ADMETlab©. It provides information about the pharmacokinetic behavior and toxicity of molecules based on five rules applied in the study of potential drugs, including Lipinski's rule. On the other hand, it allows to deduce how physicochemical properties exert influence on the pharmacokinetic pathways (Dong *et al.*, 2018). Currently, the World Health Organization (WHO) has watching the development of new antimicrobials in all its phases. Recently, some of them were led to the market, where pharmacovigilance studies will take place, while others are still in phase III clinical trials. In 2022, eight traditional antimicrobials were registered in this phase of clinical trials, which means they passed the molecular prediction tests and were promising enough to continue being investigated. Such drugs are aimed at combating priority bacterial pathogens, which comprise a list of species resistant to antimicrobials grouped into three priority categories – critical, high and medium (World Health Organization, 2024). Taking into account the importance of antimicrobial resistance for public health, it is necessary to understand what makes a drug to advance in the pharmaceutical studies and why the scientific community claims that it is effective and reliable. Therefore, knowing that any molecule with a known molecular formula can have its pharmacokinetic and toxicity profile evaluated using ADMETlab©, considering ongoing researches in the pharmaceutical industry, the present work aims to present traditional antimicrobials in phase III clinical trials, assining, through *in silico* analysis, its possible pharmacokinetics and its probable adverse effects and toxicity to its molecular structures and physicochemical characteristics.

# MATERIALS AND METHODS

This study was carried out through the *in silico* analysis of eight traditional antimicrobials (Table 1) in phase III clinical trials, selected from the June 2022 update of the World Health Organization's document 'Antibacterial products in clinical development for priority

pathogens. As inclusion criteria, only this type of antimicrobial was selected, starting from the premise that an antimicrobial is considered traditional according to the pharmaceutical class to which it belongs and how long it is available on the market. Drugs in other phases of pharmaceutical studies were excluded. The *in silico* evaluation was carried out on the ADMETlab 2.0© platform, an update verson of ADMETlab©. The SIMLES number of each antimicrobial, acquired through the PubChem Structure Search platform, was shared on ADMETlab 2.0© so that, by crossing pre-existing data, the profile of each molecule could be generated.

# RESULTS

The data obtained from the *in silico* study allowed to predict important features related to the physicochemical, pharmacokinetic and toxicological behavior of the eight traditional antimicrobials selected for this work. It was possible to determine the physicochemical behavior of each drug according to the molecular structures (figure 1), which were variable in all the points related to Lipinski's Rule of Five.

**Table 1. Phase III clinical trials traditional antimicrobials slected for the *in silico* study**

| Antimicrobial | Class | Developer | Route of administration |
|---|---|---|---|
| Benapenem | Carbapenem | Sichuan Pharmaceutical Holdings Group Ltd. | IV |
| Durlobactam + sulbactam | BLI | Entasis Therapeutics Inc. | IV |
| Enmetazobactam + cefepime | BLI + cephalosporin | Allecra Therapeutics | IV |
| Gepotidacin | Topoisomerase inhibitor | GSK | IV; oral |
| Nafithromycin | Macrolide | Wockhardt Ltd. | Oral |
| Sulopenem | Carbapenem | Interum Therapeutics | IV; oral |
| Taniborbactam + cefepime | BLI + cephalosporin | VenatoRx Pharmaceuticals Inc./GARDP | IV |
| Zoliflodacin | Topoisomerase inhibitor | Entasis Therapeutics Inc./GARDP | Oral |

BLI: Beta-lactamase inhibitor. IV: intravenous

**Table 2. Parameters used on the *in silico* analysis of phase III clinical trials antimicrobials**

| | Parameters | Stablished results | | | |
|---|---|---|---|---|---|
| | | Bad | Medium | Good | Excellent |
| Absorption profile | Caco-2 permeability (log cm/s) | - | - | - | > -5,15 |
| | MDCK permeability (cm/s) | $< 2 \times 10^{-6}$ | $2 - 20 \times 10^{-6}$ | $> 20 \times 10^{-6}$ | $>2 \times 10^{-6}$ |
| | HIA (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| Distribution profile | DV (L/kg) | - | - | - | 0,04 - 20 |
| | PBP (%) | - | - | - | < 90 |
| | PFF (%) | - | - | - | ≥ 5 |
| | BBB permeability (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| Excretion profile | Renal clearance (mL/min/kg) | < 5 | 5 - 15 | > 15 | ≥ 5 |
| | Half-life time (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| Toxicity profile | HHT (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| | DILI (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| | Ames toxicity (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| | Carcinogenicity (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |
| | MRDD (0 - 1) | 0.7 - 1.0 | 0.3 - 0.7 | 0.0 - 0.3 | 0.0 - 0.3 |

MDCK: Madin-Darby canine kidney. HIA: human intestinal absorption. DV: distribution volume. PBP: plasma protein binding. PFF: plasma free fraction. BBB: blood-brain barrier. HHT: human hepatotoxicity. DILI: drug-induced liver injury. MRDD: maximum recommended daily dose.

**Tabela 3. *In silico* prediction of the physicochemical profile of eight phase III clinical trials antimicrobials according to Lipinski's Rule of Five**

| Antimicrobial | Molecular weight (Da) | Oil/water partition coefficient (LogP) | Number of hydrogen acceptors | Number of hydrogen donors |
|---|---|---|---|---|
| Benapenem | 524.14 | -0.247 | 11 | 6 |
| Durlobactam | 299.02 | -1.274 | 9 | 2 |
| Enmetazobactam | 314.07 | -1.887 | 9 | 0 |
| Gepotidacin | 448.22 | 1.033 | 9 | 1 |
| Nafithromycin | 858.42 | 3.308 | 17 | 3 |
| Sulopenem | 349.01 | -0.546 | 6 | 2 |
| Taniborbactam | 389.21 | -0.983 | 8 | 6 |
| Zoliflodacin | 487.15 | 2.429 | 12 | 2 |

The obtained profiles were analyzed according to the guide given by the ADMETlab 2.0© platform itself, with interpretations stablished by Xiong *et al.* (2021). Regarding the physicochemical properties, they were analyzed by applying Lipinski's Rule of Five (Lipinski *et al*., 1997), which includes molecular weight, oil/water partition coefficient, number of hydrogen acceptors and number of hydrogen donors. For the comprehension of absorption, distribution, excretion and toxicity profiles, some paremeters were evaluated according to the data exposed on table 2. Each paremeter can be described as bad, medium or good, but, in some cases, the prediction allows to stablish only the result considered excellent. The platform generated a logarithmic value that varies from 0 to 1 to determine the result and the empirical decision for the molecular prediction of some paremeters. The results were expressed on comparing tables. Cefepime and sulbactam were excluded from this study because both have been available on the market for a long time and have their profiles have been widely studied.

This can be observed on table 3. Among the points of the physicochemical profile that deserve to be highlighted is the oil-water partition coefficient of these drugs. In general, Xiong *et al.* (2021) establish that the optimal partition coefficient of a medicine varies from 0 to 3, with a coefficient of up to 5 being tolerable, as explained by Lipinski *et al.* (1997). Of the drugs presented here, nafithromycin has the highest partition coefficient (3.308), being outside the ideal LogP range, according to Xiong's criteria. Moreover, it has the highest molecular weight among all the tested drugs (858.42), which influences its absorption, so that the good partition coefficient may not be able to compensate for the complexity of the molecule, which could be absorbed in lower rate. Gepotidacin and zoliflodacin, however, are within the range, with LogP of 1.033 and 2.429, respectively.

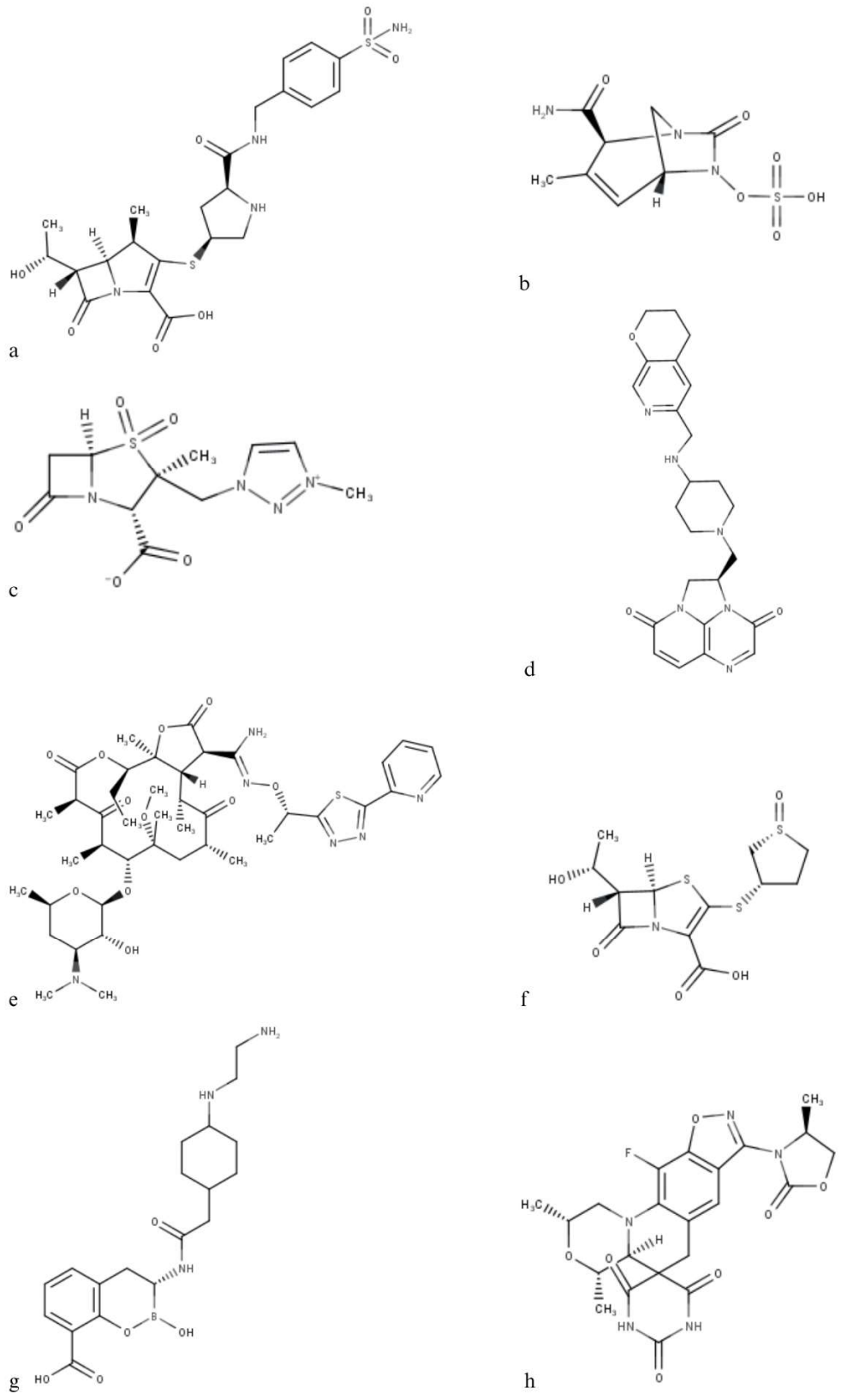


**Figure 1. Molecular structures of eight phase III clinical trials traditional antimicrobials. a: benapenem. b: durlobactam. c: enmetazobactam. d: gepotidacin. e: nafithromycin. f: sulopenem. g: taniborbactam. h: zoliflodacin**

The results regarding the absorption profile of the antimicrobials tested in this work are exposed on table 4, where it is possible to observe that benapenem, durlobactam, enmetazobactam and taniborbactam presented less favorable HIA. Furthermore, benapenem also presented the worse Caco-2 and MDCK permeability (-6.754 log cm/s and 1 x $10^{-6}$ cm/s, respectively). The predicted distribution profile (table 5) showed that zoliflodacin is the antimicrobial with highest PBP rate (91.77%), followed by nafithromycin (78.18%).

In contrast, taniborbactam has the lowest PBP rate (11.10%). Curiously, nafithromycin presented the second highest DV (2.313 L/kg), being the second to gepotidacin (2.568 L/kg). However, all the drugs presented excellent DV and PFF and only gepotidacin did not demonstrate an excellent BBB permeability pattern. Sulopenem, benapenem, zoliflodacin and nafithromycin presented the lowest BBB penetration potential (0.006, 0.023, 0.045 e 0.05, respectively). With regard to the renal excretion of antimicrobials (table 6), it was observed that the renal clearance rate of most of them is lower than

the rate established as ideal in pharmacokinetic prediction, with zoliflodacin demonstrating the lowest rate (0.299 mL/min/ kg). Only gepotidacin, nafithromycin and sulopenem achieved good renal excretion rates (6.189, 5.833 and 5.56 mL/min/kg, respectively). With regard to half-life time, nafithromycin had the longest time (0.012) and sulopenem the shortest time (0.954).

**Tabela 4. *In silico* prediction of the absorption profile of eight phase III clinical trials traditional antimicrobials**

| Antimicrobial | Caco-2 permeability (log cm/s) | MDCK permeability (cm/s) | HIA (0 - 1) |
|---|---|---|---|
| Benapenem | -6.754 | $1 \times 10^{-6}$ | 0.797 |
| Durlobactam | -5.277 | $8.8 \times 10^{-5}$ | 0.843 |
| Enmetazobactam | -5.839 | $8 \times 10^{-5}$ | 0.99 |
| Gepotidacin | -5.037 | $4 \times 10^{-6}$ | 0.702 |
| Nafithromycin | -5.294 | $4.8 \times 10^{-5}$ | 0.032 |
| Sulopenem | -6.111 | $4 \times 10^{-6}$ | 0.75 |
| Taniborbactam | -6.243 | $4 \times 10^{-6}$ | 0.934 |
| Zoliflodacin | -5.111 | $2.1 \times 10^{-5}$ | 0.029 |

**Tabela 5 – *In silico* prediction of the distribution profile of eight phase III clinical trials traditional antimicrobials**

| Antimicrobial | DV (L/kg) | PBP (%) | PFF (%) | BBB permeability (0 - 1) |
|---|---|---|---|---|
| Benapenem | 0.219 | 44.47 | 63.12 | 0.023 |
| Durlobactam | 0.493 | 24.99 | 68.95 | 0.12 |
| Enmetazobactam | 0.408 | 19.70 | 85.53 | 0.064 |
| Gepotidacin | 2.568 | 58.13 | 57.04 | 0.942 |
| Nafithromycin | 2.313 | 76.18 | 29.64 | 0.05 |
| Sulopenem | 0.258 | 58.56 | 50.46 | 0.006 |
| Taniborbactam | 0.864 | 11.10 | 75.43 | 0.061 |
| Zoliflodacin | 0.591 | 91.77 | 5.8 | 0.045 |

DV: distribution volume. PBP: plasma protein binding. PFF: plasma free fraction. BBB: blood-brain barrier.

**Tabela 6. *In silico* prediction of the excretion profile of eight phase III clinical trials traditional antimicrobials**

| Antimicrobial | Half-life time (0 – 1) | Renal clearance (mL/min/kg) |
|---|---|---|
| Benapenem | 0.66 | 1.022 |
| Durlobactam | 0.264 | 1.388 |
| Enmetazobactam | 0.555 | 2.683 |
| Gepotidacin | 0.151 | 6.189 |
| Nafithromycin | 0.012 | 5.833 |
| Sulopenem | 0.954 | 5.56 |
| Taniborbactam | 0.498 | 4.468 |
| Zoliflodacin | 0.277 | 0.299 |

**Tabela 7. *In silico* prediction of the toxicological profile of eight phase III clinical trials traditional antimicrobials**

| Antimicrobial | HHT | DILI | Ames toxicity | Carcinogenicity | MRDD |
|---|---|---|---|---|---|
| Benapenem | 0.975 | 0.995 | 0.003 | 0.054 | 0.903 |
| Durlobactam | 0.98 | 0.987 | 0.992 | 0.967 | 0.208 |
| Enmetazobactam | 0.964 | 0.99 | 0.031 | 0.809 | 0.009 |
| Gepotidacin | 0.964 | 0.733 | 0.141 | 0.936 | 0.97 |
| Nafithromycin | 0.995 | 0.982 | 0.007 | 0.035 | 0.098 |
| Sulopenem | 0.985 | 0.995 | 0.005 | 0.807 | 0.014 |
| Taniborbactam | 0.98 | 0.855 | 0.12 | 0.875 | 0.913 |
| Zoliflodacin | 0.986 | 0.99 | 0.531 | 0.04 | 0.869 |

HHT: human hepatotoxicity. DILI: drug-induced liver injury. MRDD: maximum recommended daily dose.

From table 7, it can be seen that all antimicrobials presented a high risk of HHT and development of DILI. Of the medicines presented here, durlobactam was the one that obtained the most worrying results, in terms of Ames toxicity and carcinogenicity, being close to the maximum limit established by the rate determined by *in silico* prediction. Benapenem and nafithromycin, however, demonstrated low mutagenic and carcinogenic potential. Regarding the MRDD, the results show that enmetazobactam is the antimicrobial whose recommended dose is furthest from the toxic dose limit.

# DISCUSSION

With the results obtained through this work, it was possible to observe that only benapenem and nafithromycin were rejected according to Lipinski's rule, making it clear, through table 3, that, for the first, the molecular weight, the oil/water partition coefficient and the numbers of hydrogen acceptors and donors would be decisive for its rejection. For the second, both the molecular weight and the number of hydrogen donors outside the average considered ideal would contribute to this rejection. However, it is important to say that the oral administration of a drug also depends on its ability to dissolve in an aqueous medium. Therefore, the greater the lipophilicity of a drug, the more difficult it will be to dissolve, and, consequently, its absorption will also be impaired (Loftsson, 2015). By observing the structural formulas of the antimicrobials studied here, it is possible to infer that the low LogP of enmetazobactam (-1.887) is due to the fact that it has a small carbon chain, rich in polar functional groups. The exacerbated polarity would make absorption through the gastrointestinal tract difficult, which justifies the application of enmetazobactam exclusively intravenously. Therefore, the advancement of clinical studies with part of the antimicrobials evaluated here being administered intravenously is justified by their physicochemical and pharmacokinetic profile, since this profile indicates deficient gastrointestinal absorption. The absorption profile

of benapenem, durlobactam, enmetazobactam and taniborbactam explains the fact that they are administered exclusively intravenously. Gepotidacin and sulopenem, despite having an absorption rate greater than 0.7, are very close to the moderate absorption rate, which may justify the option of administering them orally and intravenously, knowing that a molecule with human intestinal absorption lower than 30% is poorly absorbed, which directly affects its bioavailability (Xiong *et al.*, 2021). The permeability in Caco-2 and the MDCK permeability of benapenem are consistent with the fact that the carbapenems available on the market are administered intravenously, with sulopenem being an exception in development, as it can also be administered orally (Koulenti *et al.*, 2019). Zoliflodacin was the only drug that showed an excellent absorption profile in the three aspects evaluated, which justifies its oral administration. The drug distribution profile also follows the standards established in the scientific literature, knowing that the PBP rate is inversely proportional to the PFF, and both affect the DV of the active ingredient (Holt; Nagar; Korzekwa, 2019). Therefore, it is understandable that a lower PFF is generally observed for zoliflodacin and nafithromycin. A high DV indicates that the drug is able to reach the desired target in greater quantities. This influences the determination of the drug dose, as the greater the distribution volume, the greater the dose necessary for the drug to reach an adequate concentration in the blood plasma. Furthermore, the PFF rate is decisive for the therapeutic index of a medicine, as the risk of developing adverse effects is directly proportional to this rate. It indicates that the drug has a greater possibility of interacting with other drugs that also have a high rate of PFF, being displaced by them to reach high concentrations of free fraction in plasma in a shorter time, which can contribute to the toxicity of the drugs. Therefore, drugs with a high PFF rate should be administered with caution, in smaller doses and with a longer interval between doses.

Regarding penetration into the BBB, it is worth highlighting that, for some antimicrobials, it is interesting that they have the ability to cross the BBB, as they are administered with the aim of treating infections that affect the meninges. On the other hand, antimicrobials intended for the treatment of infections other than meningitis should not demonstrate this capacity, as they would represent a risk to the health of the individual, who could have their central nervous system damaged. Sulopenem and benapenem belong to the class of carbapenems, beta-lactam antimicrobials whose ability to cross the inflamed BBB is known, being superior to other beta-lactams in this aspect. However, they do not cross the intact BBB, a fact that may be related to the large number of polar groups in the structure of these drugs. Regarding nafithromycin and zoliflodacin, both have the highest oil/water partition coefficients among all the antimicrobials described in this work, that is, they have a higher degree of lipophilicity. Therefore, knowing that the BBB is a lipid membrane, it is natural that lipophilic drugs cross it more easily (Haddad *et al.*, 2022). However, nafithromycin has a high molecular weight, while zoliflodacin has many polar groups in its structure, which makes it difficult to penetrate the BBB. Gepotidacin, in turn, proved to be the antimicrobial with the highest rate of penetration into the BBB. This may be related to its carbon chain rich in rings and with few high polarity atoms. Furthermore, *in vitro* studies have demonstrated that gepotidacin can act as a reversible inhibitor of the acetylcholinesterase enzyme, acting in a dose-dependent manner. Therefore, the administration of gepotidacin must be done with caution, following the maximum recommended dose, due to the risk of its use causing adverse neurological effects (Perry *et al.*, 2023).

Measuring the renal clearance rate, as well as the volume of distribution and half-life, is essential for setting the dose of a drug, since a low renal excretion rate means the drug stays in the body for longer, where it can reach toxic levels when readministered at shorter intervals than recommended. Furthermore, individuals with chronic kidney disease will need a dose adjustment appropriate to their condition, as, in them, the renal clearance of medications is even more deficient. Therefore, zoliflodacin may not be the most appropriate therapeutic option in these cases. However, the renal route is not the only route of drug excretion, which can also be excreted through bile and feces. In this case, the use of medications with low renal clearance is justified and attention should be paid to physiological or pathological conditions that may affect liver performance. Studies show that the excretion rate of gepotidacin through urine, for example, is 37%, and it can also be eliminated through bile. Furthermore, clearance has shown a significant reduction in individuals with compromised renal function (Hossain *et al.*, 2020). Regarding the half-life, sulopenem was expected to have a short half-life, as this is a common characteristic of carbapenem class antimicrobials, which generally have a half-life of about one hour (Zhao *et al.*, 2019). It is interesting to note the contradiction presented by nafithromycin, since its renal excretion rate is within the range considered excellent, but it still has a long half-life. This may be due to the fact that the renal clearance of this medication is close to the minimum value considered ideal, that is, the renal clearance of nafithromycin is, in fact, moderate. Furthermore, knowing that the lipophilicity of drugs contributes to their slower elimination, the excretion profile presented by nafithromycin is consistent with its physicochemical characteristics.

Regarding the toxicological profile, DILI is known to be responsible for acute liver failure and is often associated with the drug's intrinsic ability to cause liver damage within a few hours or a few days after exposure. This capacity is related to the molecular structure of the drugs themselves, increasing considerably according to their lipophilicity. Therefore, the more lipophilic the drug, the more permeable it will be to the plasma membrane of hepatocytes, where it will cause damage (Hosack; Damry; Biswas, 2023). Such damage results from the biotransformation of drugs into active metabolites, which increase oxidative stress, in addition to activating signal transduction pathways that culminate in mitochondrial stress, resulting in inefficient transport of bile acids and, in more serious situations, cell death (European Association for the Study of the Liver, 2019). The Ames toxicity test evaluates the mutagenic potential of compounds against different bacterial strains and is carried out following the recommendations of the guide made available by the Organization for Economic Cooperation and Development, with its results closely linked to the carcinogenicity of chemical compounds. This test exposes bacterial cells, mutated to prevent the synthesis of amino acids (histidine or tryptophan), to the drugs under study, which, if mutagenic, will promote bacterial growth in agar, even in the absence of said amino acids. (Levy *et al.*, 2019). Regarding the mutagenic and carcinogenic potential of durlobactam, according to the information present in the leaflet registered by the developer of this medicine with the American agency Food and Drug Administration (2023), no carcinogenicity studies were carried out and the mutagenicity studies presented negative results. However, the use of benapenem and nafithromycin may be safer, as both have demonstrated low mutagenic and carcinogenic potential, thus indicating that their use does not represent a potential risk for genomic changes or for the cellular metabolism. However, nafithromycin, with regard to the set of Ames toxicity, carcinogenicity and MRDD, appears to be the most promising antimicrobial, so it is possible to infer that the benefits of its use outweigh the risks. This fact is confirmed through the study by Bhavsar *et al.* (2023), which highlights nafithromycin as a macrolide that has demonstrated good oral tolerability in humans in increasing doses administered to fasting and fed individuals, in addition to having demonstrated, in *in vivo* studies, not to cause serious changes.

# CONCLUSION

Considering the set of characteristics determined through the predictive study carried out in this work, it can be stated that traditional antimicrobials in phase III clinical studies are medicines with great commercialization potential, some demonstrating more favorable characteristics than others. Therefore, the fact that such medicines have advanced to subsequent phases of molecular studies is justified. In general, the physicochemical profile of each of these antimicrobials corroborates their pharmacokinetic as well as toxicological behavior with regard to their hepatotoxicity. This fact

reflects not only the dose at which they must be administered, but also the route of administration chosen for each case. Furthermore, assuming that, due to physiological differences between species and even between individuals of the same species, it is not possible to state that the results established by molecular prediction should always lead to the direct exclusion of a given medicine from subsequent phases of research and development. So developers must consider the degree of disparity between the results obtained and the values considered appropriate for each parameter.

# REFERENCES


Bhavsar, S., Ravikumar, T., Gupta, S., Pawar, S., Dabhade, S., Kayastha, A. K., Deshpande, P., Yeole, R., Nandanwar, M., Bhagwat, S. and Patel M. (2023) WCK 4873 (INN: Nafithromycin): Structure–activity relationship (SAR) identifying a novel lactone ketolide with activity against *Streptococcus pneumoniae* (SPN) and *Streptococcus pyogenes* (SPY). Available online at https://www.sciencedirect.com/science/article/pii/S2211715622004763.

Dong, J., Wang, N., Yao, Z., Zhang, L., Cheng, Y., Ouyang, D., Lu, A. and Cao, D. (2018) ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020094/pdf/13321_2018_Article_283.pdf.

European Association for the Study of the Liver. (2019) EASL Clinical Practice Guidelines: drug-induced liver injury. Available online at https://easl.eu/wp-content/uploads/2019/04/EASL-CPG-Drug-induced-liver-injury-2019-04.pdf.

Food and Drug Administration. (2023) XACDURO-sulbactam and durlobactam. Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216974s000lbl.pdf.

Haddad, N., Carr, M., Balian, S., Lannin, J., Kim, Y., Toth, C. and Jarvis, J. (2022) The Blood-Brain Barrier and Pharmacokinetic/Pharmacodynamic Optimization of Antibiotics for the Treatment of Central Nervous System Infections in Adults. Available online at https://www.mdpi.com/2079-6382/11/12/1843.

Holt, K., Nagar, S. and Korzekwa, K. (2019) Methods to Predict Volume of Distribution. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8221585/pdf/nihms-1601457.pdf.

Hosack, T., Damry, D. and Biswas, S. (2023) Drug-induced liver injury: a comprehensive review. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10031606/pdf/10.1177_17562848231163410.pdf.

Hossain, M., Tiffany, C., Raychaudhuri, A., Nguyen, D., Tai, G., Alcorn Jr., H., Preston, R. A., Marbury, T., and Dumont, E. (2020) Pharmacokinetics of Gepotidacin in Renal Impairment. Available online at https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC7384084/pdf/CPDD-9-560.pdf.

Koulenti, D., Song, A., Ellingboe, A., Abdul-ziz, M. H., Harris, P., Gavey, E. and Lipman, J. (2019) Infections by multidrug-resistant Gram-negative Bacteria: What's new in our arsenal and what's in the pipeline? Available online at https://www.sciencedirect.com/science/article/abs/pii/S0924857918303030?via%3Dihub.

Levy, D. D., Zeiger, E., Escobar, P. A., Hakura, A., van der Leede, B. M., Kato, M., Moore, M. M., and Sugiyama, K. (2019) Recommended criteria for the evaluation of bacterial mutagenicity data (Ames test). Available online at https://www.sciencedirect.com/science/article/pii/S1383571819300774.

Lipinski, C. A., Lombardo, F., Dominy, B. W. and Feeney, P. J. (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Available online at https://www.sciencedirect.com/science/article/abs/pii/S0169409X96004231.

Loftsson, T. (2015) Essential Pharmacokinetics: A Primer for Pharmaceutical Scientists, Academic Press, Cambridge, United Kingdom.

Perry, C. R., Scangarella-Oman, N. E., Millns, H., Flight, W., Gatsi, S., Jakielaszek, C., Janmohamed, S. and Lewi, D. A. (2023) Efficacy and Safety of Gepotidacin as Treatment of Uncomplicated Urogenital Gonorrhea (EAGLE-1): Design of a Randomized, Comparator-Controlled, Phase 3 Study. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10581980/pdf/40121_2023_Article_862.pdf.

World Health Organization. (2024) Antibacterial products in clinical development for priority pathogens. Available online at https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens.

World Health Organization. (2024) WHO Bacterial Priority Pathogens List, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Available online at https://www.who.int/publications/i/item/9789240093461.

Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., Chen, X., Hou, T. and Cao, D. (2021) ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8262709/pdf/gkab255.pdf.

Zhao, C., Lv, Y., Zhu, Y., Wei, M., Liu, M., Ji, X., Kang, Z., Xia, Y., Tian, J., Ma, Y., and Liua, Y. (2019) A First-in-Human Safety, Tolerability, and Pharmacokinetics Study of Benapenem in Healthy Chinese Volunteers. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6395932/pdf/AAC.02188-18.pdf.


*******