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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Correlation study of antibacterial activity and spectrum of Penicillins through a structure-activity relationship analysis

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Abstract

Penicillins are a group of antibiotics of the beta-lactam group, widely used worldwide as first-choice drugs in the treatment of infections caused by sensitive bacteria. Their use is based on an empirical measure of their activity through antibiograms. In this work we have carried out a structure-activity relationship analysis to elucidate the molecular and physicochemical bases that determine the antibacterial activity and the orientation of the antibacterial spectrum of penicillins, employing a set of bacteria that cause common infections. It was found that the antibacterial activity increases as penicillin size increases for both, Gram-negative and Gram-positive bacteria. In the same way, liposolubility affects the activity; water soluble penicillins have greater activity on Gram-negative bacteria, while in some cases liposoluble penicillins present higher activity against Gram-positive bacteria. In addition, it is proposed that electronic properties of the substituent of the penicillin core determine its antibacterial spectrum. The electron donating substituents make the penicillin active against Gram-positive bacteria, while the electron withdrawing substituents gear the activity towards Gram-negative bacteria. In addition, the alpha-carbon (Cα) of the carboxamide side chain is also essential for the activity against Gram-negative bacteria; penicillins that lack it, have higher activity against Gram-positive bacteria.

Keywords Penicillins · Minimal inhibition concentration · Bacteria · Structure-activity relationship

Introduction

Penicillins are very important antibacterial compounds in the medical field; their use amounts to about 50% of the antimicrobial agents currently in use (WHO 2018a, 2018b).

The bacteria sensitive to penicillins are microorganisms involved in common population infections, including nosocomial infections; typical examples are: *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Clostridium perfringens, Escherichia coli, Proteus mirabilis, Serratia marcescens, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Neisseria meningitidis, Salmonella typhi, Haemophilus influenzae*, etc., which are associated to skin, urinary, respiratory and gastrointestinal infections, being the last two the

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primary mortality causes in the world in 2015, according of WHO data (WHO 2018b). The contribution of infectious diseases to population mortality is more frequent in areas with low economic income and limited access to public or private health services. Other susceptible populations are the pediatric and geriatric, as well as hospitalized patients, which belong to sectors of society with high levels of exposition to microorganisms, including exposition to nosocomial infections (Servicios de salud 2018). Although infectious diseases are not the main mortality cause in many world regions, they are still a public health problem, since some infections are difficult to treat due to the high incidence of bacterial resistance (WHO 2015). This represents a serious problem that must be solved in the medium and long-terms, because typical pharmacological treatments are usually ineffective.

Unfortunately, antimicrobial treatments over time tend to become less effective for those microorganisms that adapt to the adverse environment, generating resistance to the drugs. Penicillins are no exception, since they have become less effective (Fair and Tor 2014). Since 1983 the rates of *Staphylococcus aureus* has increased being more of 50% the incidence in nosocomial infection for Methicillin-Resistant *Staphylococcus aureus* (MRSA) (Crosgrove et al. 2003), (Klevens et al. 2007). It is important to point out that the variety of microorganisms sensitive to a given antimicrobial is defined as the *antimicrobial spectrum*, which is an empirical tool based on the clinical experience in the use of antibiotics. This tool it is widely used in the medical field, and penicillins are a typical example of this. In this work, we attempt to elucidate the molecular bases that determine the antibacterial spectrum of penicillins, through correlation of physicochemical properties with their antibacterial activity on the bacteria sensitive to them.

Material and methods

Bibliographic search

The antibacterial spectrum of penicillins was investigated in different sources to obtain the most relevant data on the use of these antibiotics on sensitive bacteria that cause common and nosocomial infections While a thorough review was conducted, it focused on data of Minimal Inhibition Concentration (MIC) reported (Kasper et al. 2015), (Alpuche et al. 2004), (Gilbert et al. 2016) in the last five decades for bacteria sensitive to several penicillins (penicillin G, methicillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, amoxicillin, ticarcillin, carbenicillin, piperacillin, azlocillin and mezlocillin) (Gill et al. 1981), (Eftekhar and Raei 2011), (Adhikari et al. 2017), (Miyazaki et al. 2014), (Andrews 2001), (Haller 1984), (Baker and Thornsberry 1974), (Thijssen and Mattie 1976), (Sutherland et al. 1970), (Brown et al. 1976), (Reimer et al. 1981), (Toshinobu et al. 1993), (Arlet et al. 1993), (Alcaide et al. 1995), (Thomson and Moland 2004), (Fass 1991), (Nicolson et al. 1999), (Smith et al. 2007), (Bornside 1968), (Bou et al. 2000), (Jacobs et al. 1999), (Sahm et al. 2000), (Doern et al. 1996), (Jorgensen et al. 1990), (Hebeisen et al. 2001), (Tanaka et al. 2002), (Álvarez et al. 1985), (Zurenko et al. 1996), (Deshpande and Jones 2003), (Eliopoulos et al. 1985), (Sawai and Yoshida 1982), (Reading and Cole 1977), (Taylor et al. 1983), (Ubukata et al. 1989), (Philippon et al. 1997), (Dowson et al. 1994), (Olsson et al. 1976), (Yotsuji et al. 1983), (Goldstein and Citron 1986), (Takata et al. 1981), (Yang et al. 1990), (Cai et al. 2008), (Osano et al. 1994), (Suh et al. 2010), (Fu and Neu 1978a, 1978b), (Fuchs et al. 1984), (Fass and Prior 1989), (Sutherland et al. 1972), (English et al. 1978), (Williamson et al. 1980), (Kesado et al. 1980), (Neu et al. 1979), (Larsson et al. 1985), (Reimer et al. 1980), (McCracken et al. 1973), (Neu et al. 1981), (White et al. 1979), (Jacobs et al. 2010), (Doern et al. 1998), (Hoban et al. 2001), (McWhinney et al. 1993), (Fass 1983), (Nelson et al. 1994), (Doern et al. 1999), (Andrews 2001), (Quinn et al. 1989), (Poirel et al. 2000), (Jones et al. 1983), (Neu and Winshell 1972), (Endimiani et al. 2009), (Miraglia and Basch 1967), (Chartrand et al. 1983), (Ayers et al. 1982), (Yu et al. 2017), (Neu 1982), (Higgins et al. 2004), (Fernández-Cuenca et al. 2003), (Héritier et al. 2005), (Brown et al. 2005), (Aubert et al. 1996), (Da Silva et al. 1999), (Ikeda 1990), (Neu and Fu 1979), (Toma and Barriault 1995), (Vouillamoz et al. 2006), (Ford et al. 1996), (Fu and Neu 1978a, 1978b), (Teng et al. 1998), (París et al. 1995), (Moody et al. 1985), (Verbist 1978), (Rolston et al. 1982), (Henry et al. 1985), (Sabath et al. 1976), (Lacy et al. 1999), (Neu and Labthavikul 1982), (Chin and Neu 1983), (Monif et al. 1978), (Jones et al. 1977), (Watanakunakorn and Glotzbecker 1979), (Jones et al. 1980), (Overturf et al. 1977), (Sanders 1981), (Baker et al. 1983), (Farber et al. 1983).

The bacteria chosen were Gram-positive (*Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus epidermidis, Streptococcus viridans, Enterococcus spp., Listeria monocytogenes*) and Gram-negative (*Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae, Klebsiella pneumoniae, Bacteroides fragilis, Serratia marcescens*).

Theory

QSAR analysis

All the MIC values obtained from the literature were averaged for each penicillin and each sensitive bacteria. Analysis of the structure-activity relationship was carried out with the experimental data of MIC converted to molar concentration (M) of the penicillins used on infections caused by the corresponding bacteria, according to the antibacterial spectrum summarized in Table 1; and they were correlated with the corresponding partition coefficients and molar refractivities.

The partition coefficient is an important parameter that corresponds to the ratio of concentrations of a substance in a mixture of two immiscible phases at equilibrium; usually the solvents are water and n-octanol. This parameter is often used as a criterion to predict how easily a molecule could cross the blood-brain barrier (Leo et al. 1971), (Hansch and Fujita 1964), (Lipinski et al. 2001):

$$P = \frac{[A]_{oct}}{[A]_w}$$

where P is the partition coefficient, $[A]_{oct}$ is the analyte concentration in the n-octanol phase, $[A]_w$ is the analyte concentration in the aqueous phase.

On the other hand, the molar refractivity is a measure of the total polarizability of a mole of a substance, which is related to molecular size through the Lorentz-Lorenz equation (Padrón and Pellón 2002):

$$MR = \left(\frac{MW}{\rho}\right)\left(\frac{n^2-1}{n^2+2}\right)$$

where MR is the molar refractivity, MW is the molecular weight, ρ is the density and n is de refractive index of the molecule under consideration.

The physicochemical properties of the penicillins (molar refractivity as a criterion of size (ACD/ChemSketch 2015) and partition coefficient as a criterion of liposolubility (Ghose and Crippen 1987) were determined with the ACD/ChemSketch and CS ChemDraw Pro v.6 software.

Molecular volume and dipole moment values were determined through the following procedure: Each penicillin was built in the PC Spartan Pro program A (PC Spartan Pro 1999) conformational search using molecular mechanics (MMFF) was carried out after selecting the most relevant torsions for the molecule. Once the conformer set was obtained, the most stable conformer was optimized at the semi-empirical AM1 level. The molecular volumes and dipole moments were taken from the output file; finally, the dipole moment vector was visualized.

Statistical analysis

The linear correlations were determined by linear least-squares analysis. The slope and intercept thus obtained were validated through Student's t-test for the equation:

$$y = A + Bx$$

Where y is the dependent variable, x the independent variable, A and B correspond to the intercept and the slope, respectively (Marques de Cantú 1998).

Likewise, the parabolic correlations were determined through second order polynomial regression analysis with validation of the coefficients through Student's t-test for the equation:

$$y = Ax^2 + Bx + C$$

where y is the dependent variable, x is the independent variable, A, B and C are the coefficient values for a parabola with the vertex not at the origin (Marques de Cantú 1998).

Table 1 Antibacterial spectrum of penicillins that are most commonly used to treat infections caused by different etiologic agents

Bacteria	PG	Met	Oxa	Clx	Dclx	Amx	Amp	Tic	Car	Pip	Azl	Mez
Staphylococcus aureus	1	1	1	1	1		1			1		
Streptococcus pneumoniae	1			1	1	1	1					
Streptococcus pyogenes	1		1	1	1	1	1					
Staphylococcus epidermidis		1	1	1	1							
Streptococcus viridans	1		1	1		1	1	1	1	1		1
Enterococcus spp.	1					1				1		1
Listeria monocytogenes	1					1	1					
Proteus mirabilis						1	1	1	1		1	
Escherichia coli			1			1	1		1	1	1	
Pseudomonas aeruginosa								1	1	1	1	1
Haemophilus influenzae				1		1	1			1	1	
Neisseria gonorrhoeae				1			1					
Neisseria meningitidis	1					1	1					
Bacteroides fragilis								1	1	1	1	
Klebsiella pneumoniae								1	1		1	1
Serratia marcescens	1					1	1	1	1	1	1	1

1: Bacteria sensitive to penicillins

Differences were considered significant for $p < 0.05$. Statistical tests were run on Sigma Stat 3.5 (Jandel Corp. SPSS Inc. San Rafael, CA., USA).

Results and discussion

The clinical bacterial sensitivity to an antibiotic is defined as the administered dose that leads to a concentration at the infection site that is high enough (in the order of the MIC) to eliminate the microorganism without causing host toxicity (Brunton et al. 2019). A summary of the sensitivity of bacteria to the penicillins most commonly used to treat infections is shown in Table 1. It is very important to note that in general, penicillin G, methicillin, oxacillin, cloxacillin, and dicloxacillin have greater antibacterial activity on Gram-positive bacteria, while carbenicillin, piperacillin, azlocillin, ticarcillin and mezlocillin have greater antibacterial activity on Gram-negative bacteria. Finally, amoxicillin and ampicillin are broad spectrum drugs, since they act on both Gram-positive and Gram-negative bacteria. Based on the above, for each penicillin a bibliographic search of the MIC required to inhibit the growth of Gram-positive and Gram-negative bacteria relevant in clinical use was performed. Table 2 presents these results, which are expressed as the average MIC values ± the standard error of the mean; in this same table some atypical results of MIC that have been reported can be observed. The QSAR analysis of the average antimicrobial activity (expressed as molar concentration) was correlated to the physicochemical properties, partition coefficient and molar refractivity, of each antibiotic under study.

Initially, the correlation analysis between antimicrobial activity and the partition coefficient partition for Gram-positive and Gram-negative bacteria was carried out (Table 3).

The most relevant correlations found in this study are for the *S. aureus* and *S. viridans* bacteria. In the case of *S. aureus*, there is a positive correlation between activity and partition coefficient, so as penicillins become more liposoluble, activity increases (Fig. 1).

In the case of *S. viridans*, the opposite tendency compared to *S. aureus* is observed, so as liposolubility increases, antibacterial activity diminishes (Fig. 2).

For other bacteria we can find some other interesting tendencies: *S. epidermidis, S. pyogenes*, and *S. pneumoniae* display a tendency similar to that of *S. viridans*; the more liposoluble penicillins are, the more they lose activity, meaning that the penicillins commonly used against these bacteria, are hydrophiles (Fig. 3). On the other hand, *Staphylococcus aureus, Listeria monocytogenes* y *Enterococcus spp*. show the opposite behavior (Fig. 4).

It can also be seen in Fig. 3 that most bacteria that show this trend belong to the genus *Streptococcus*, amoxicillin and ampicillin, broad spectrum penicillins, being more active, along with some ureidopenicillins (mezlocillin and piperacillin). It should be noted that penicillin G, methicillin, oxacillin, cloxacillin, and dicloxacillin show good activity against *Streptococcus pneumoniae* and *Staphylococcus epidermidis*, being these penicillins the most commonly used in infections caused by these bacteria.

Figure 4 also shows that the relationship between antibacterial activity and the partition coefficient for *Listeria monocytogenes* and *Enterocuccus spp*. is similar to that shown by *Staphylococcus aureus*, that is, the activity of the penicillin increases as its liposolubility increases. Interestingly, the most active penicillins against *S. aureus* and *Listeria monocytogenes* are penicillin G and the isoxazolyl penicillins (methicillin, oxacillin and cloxacillin dicloxacillin). For *Enterococcus spp*., the most active penicillins are amoxicillin, ampicillin, and piperacillin. It is important to note that for *S. aureus* the antibacterial activity is more sensitive to changes in the partition coefficient than for the other two bacteria (Table 3). For the same group of Gram-positive bacteria, an analysis of antibacterial activity as a function of the size of the molecule, through the physicochemical property molar refractivity (MR, Table 4), was also performed.

The most significant case of the correlation of activity with molar refractivity corresponds to *Staphylococcus aureus*. The relationship is of the parabolic type, that is, for penicillins with small and large volumes, activity is not as high; however, penicillins with intermediate values of molar refractivity present higher activity. Surprisingly, the group of the isoxazolyl penicillins (oxacillin, cloxacillin, and dicloxacillin) correspond to the penicillin group of intermediate size, and from the clinical point of view, they are the first choice in the treatment of infections caused by sensitive strains of *Staphylococcus aureus* (Fig. 5).

The trend observed for the relationship between the size of penicillins and its activity is very interesting; so, the analysis was carried out again, but this time including penicillins atypical in terms of its clinical use (Fig. 6). The trend found was the same as before: the high and low values of molar refractivity reduce activity, while those in the middle are the most active.

Finally, a comparative analysis of the dependence of antibacterial activity on molar refractivity was carried out for the rest of the Gram-positive bacteria (Fig. 7). It can be seen in the graph that, in most cases, larger penicillins present less activity than those with smaller sizes; therefore, the slopes are negative. It is noteworthy that for *Streptococcus viridans* and *Enterococcus spp*., although there is a correlation of activity with the size of the molecule, the

Table 2 Minimal Inhibition Concentration (MIC) of the penicillins on Gram-negative and Gram-positive bacteria. Data presented as Mean ± SEM in [μg/mL]

Bacteria	PG	Met	Oxa	Clx	Dclx	Amx	Amp	Tic	Car	Pip	Azl	Mez
S. aureus	0.300 ± 0.162	1.575 ± 0.305	0.230 ± 0.046	0.6994 ± 0.185	0.229 ± 0.078	46.885 ± 36.429	51.665 ± 13.920	10.387 ± 2.796	34.435 ± 8.582	46.320 ± 42.234	48.077 ± 30.597	128.000
S. pneumoniae	1.464 ± 0.365	9.669 ± 2.288	0.332 ± 0.136	9.327 ± 2.331	9.206 ± 4.738	1.440 ± 0.407	1.842 ± 0.845	0.659 ± 0.301	3.396 ± 1.713	0.157 ± 0.070	0.125	1.380 ± 1.310
S. pyogenes	0.011 ± 0.001	0.175 ± 0.075	0.777 ± 0.414	0.100	0.166 ± 0.089	0.026 ± 0.009	0.138 ± 0.043	0.197 ± 0.053	1.527 ± 0.962	12.444 ± 12.081	97.000	32.395 ± 32.302
S. epidermidis	0.044 ± 0.006	26.665 ± 10.276	0.537 ± 0.355	0.367 ± 0.219	0.347 ± 0.231	3.167 ± 3.111	35.801 ± 15.526	19.840 ± 8.739	38.500 ± 12.895	17.351 ± 10.167	0.113 ± 0.069	31.030 ± 21.320
S. viridans	1.896 ± 0.705	ND	36.405 ± 20.255	ND	ND	0.105 ± 0.095	4.030 ± 3.970	4.542 ± 2.587	5.335 ± 2.937	2.125 ± 1.875	ND	1.592 ± 0.910
Enterococcus spp.	11.500 ± 6.946	ND	64.000	69.333 ± 32.441	49.310 ± 15.611	30.576 ± 15.409	147.092 ± 59.265	75.409 ± 16.050	73.362 ± 12.085	59.680 ± 25.272	ND	32.333 ± 29.339
L. monocytogenes	0.259 ± 0.072	ND	2.062 ± 0.766	1.250	ND	0.462 ± 0.090	0.681 ± 0.240	3.633 ± 0.857	4.343 ± 1.042	2.132 ± 0.621	ND	1.520 ± 1.246
P. mirabilis	9.360 ± 7.630	10.150 ± 2.350	29.286 ± 17.934	357.500 ± 63.031	50.000	2.200	31.721 ± 10.681	51.625 ± 13.451	47.963 ± 13.176	40.512 ± 11.163	43.500 ± 35.500	6.333 ± 4.842
E. coli	64.667 ± 17.359	89.250 ± 56.771	137.806 ± 83.352	461.600 ± 98.816	281.000 ± 133.368	37.311 ± 27.521	132.021 ± 24.619	95.067 ± 29.492	99.762 ± 33.428	112.502 ± 28.676	171.844 ± 94.627	232.687 ± 98.937
P. aeruginosa	413.000 ± 95.042	ND	210.000 ± 82.370	506.000 ± 6.000	512.000	432.800 ± 76.235	510.000 ± 119.243	96.693 ± 14.949	98.703 ± 28.107	68.580 ± 14.824	76.571 ± 35.484	83.210 ± 19.400
H. influenzae	2.250 ± 1.750	ND	17.477 ± 16.512	18.750 ± 6.250	64.000	3.482 ± 2.088	5.039 ± 1.600	2.475 ± 0.963	6.445 ± 2.702	0.538 ± 0.304	1.015 ± 0.985	0.375 ± 0.177
N. gonorrhoeae	20.522 ± 18.141	ND	4.967 ± 3.268	ND	14.187 ± 9.815	0.341 ± 0.170	1.502 ± 1.013	1.151 ± 0.986	5.987 ± 3.223	0.072 ± 0.029	2.032 ± 3.979	0.138 ± 0.060
N. meningitidis	0.077 ± 0.131	ND	6.300	0.100	ND	0.089 ± 0.057	0.099 ± 0.035	0.035 ± 0.005	0.050	0.025 ± 0.005	ND	0.030
S. typhi	6.127 ± 4.942	50.000	38.537 ± 20.395	ND	50.000	113.250 ± 7.674	76.259 ± 25.253	129.800 ± 126.200	40.662 ± 25.672	112.600 ± 51.079	33.000	256.000
B. fragilis	122.830 ± 36.955	63.250 ± 1.974	82.800 ± 10.763	228.833 ± 115.567	ND	102.333 ± 62.179	113.000 ± 36.447	131.085 ± 44.395	96.777 ± 15.418	53.661 ± 12.496	120.167 ± 80.301	98.667 ± 1.333
K. pneumoniae	314.000 ± 186.000	ND	70.250 ± 40.835	433.333 ± 33.333	ND	167.760 ± 169.989	179.543 ± 40.0773	215.753 ± 43.443	143.971 ± 36.546	156.111 ± 28.261	145.700 ± 93.628	102.400 ± 9.609
A. baumanii	80.000 ± 48.000	ND	82.400 ± 27.730	ND	ND	276.571 ± 46.676	272.308 ± 88.190	213.740 ± 34.101	93.571 ± 45.059	216.585 ± 88.381	98.250 ± 16.570	73.500 ± 21.262
S. marcescens	413.200 ± 299.314	ND	76.000 ± 26.000	ND	ND	86.667 ± 28.503	173.467 ± 41.312	117.800 ± 50.570	155.306 ± 57.838	81.560 ± 20.548	139.400 ± 94.236	66.611 ± 14.929

ND Not determined

Table 3 Regression parameters for antimicrobial activity vs. logP in Gram-positive bacteria

Bacteria	Slope ± SEM	Intercept ± SEM	*r*
Staphylococcus aureus	0.753 ± 0.192*	4.653 ± 0.282*	0.868*
Staphylococcus epidermidis	−0.357 ± 0.270	6.849 ± 0.500*	−0.684
Streptococcus pyogenes	−0.179 ± 0.228	6.824 ± 0.353*	−0.365
Listeria monocytogenes	0.200 ± 0.186	5.902 ± 0.111*	0.732
Streptococcus pneumoniae	−0.238 ± 0.063*	5.309 ± 0.099*	−0.908*
Streptococcus viridans	−0.713 ± 0.245*	5.308 ± 0.180*	−0.766*
Enterococcus spp.	0.301 + 0.071*	4.234 + 0.046*	0.948*

*$p < 0.05$, statistically significant

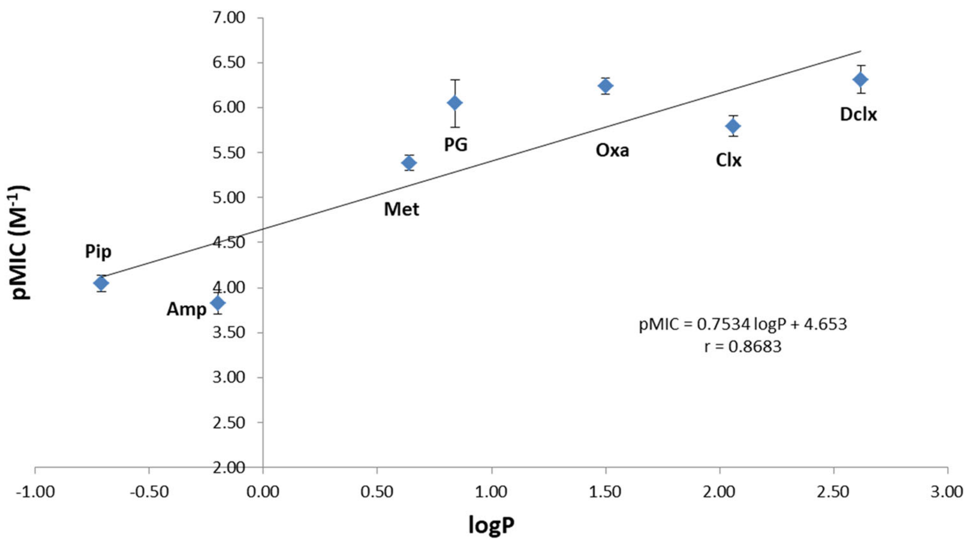

Fig. 1 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins and their partition coefficient for *Staphylococcus aureus* (logP): $b = 4.653 \pm 0.141$ ($p < 0.001$), $m = 0.753 \pm 0.096$ ($p < 0.05$) and $r = 0.8683$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

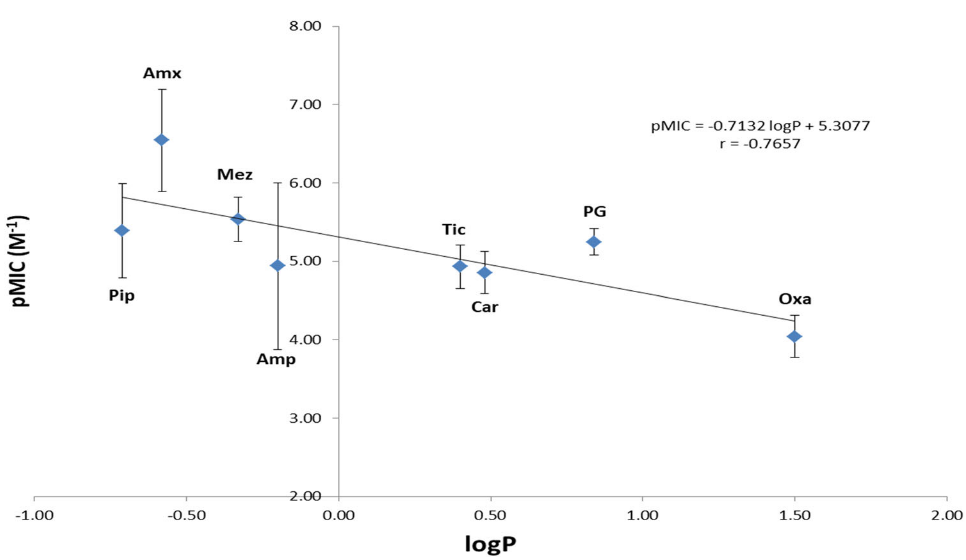

Fig. 2 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins, and their partition coefficient (logP) for *Streptococcus viridans*: $b = 5.307 \pm 0.180$ ($p < 0.001$), $m = -0.713 \pm 0.245$ ($p < 0.05$) and $r = 0.7657$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

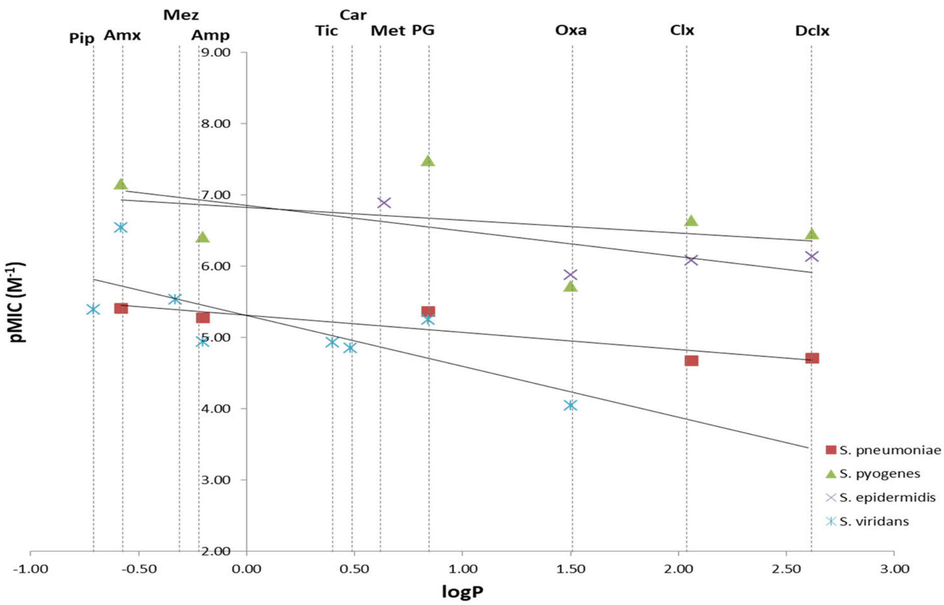

Fig. 3 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins, and their partition coefficient (logP) for *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans*, and *Staphylococcus epidermidis*

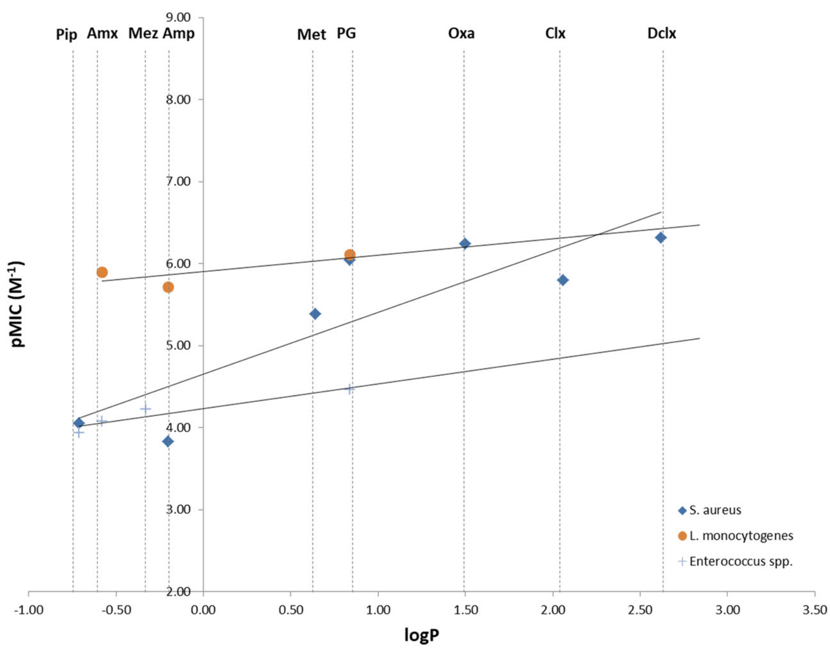

Fig. 4 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins, and their partition coefficient (logP) for *Staphylococcus aureus, Listeria monocytogenes*, and *Enterococcus spp*

Table 4 Regression parameters for antimicrobial activity vs. logMR in Gram-positive bacteria

Bacteria	Slope ± SEM	Intercept ± SEM	*r*
Staphylococcus aureus	−372.740 ± 9.731 1514.200 ± 19.754	−1531.600 ± 19.655	0.965*
Staphylococcus epidermidis	−10.101 ± 7.578	26.573 ± 15.255	−0.686
Streptococcus pyogenes	−7.916 ± 5.826	22.376 ± 11.584	−0.562
Listeria monocytogenes	−11.125 ± 10.912	27.604 ± 21.283	−0.714
Streptococcus pneumoniae	−7.237 ± 1.299*	19.445 ± 2.579	−0.955*
Streptococcus viridans	0.859 ± 4.165	3.465 ± 8.333	0.084
Enterococcus spp.	−1.381 ± 1.414	6.975 ± 2.870	0.568

*$p < 0.05$, statistically significant

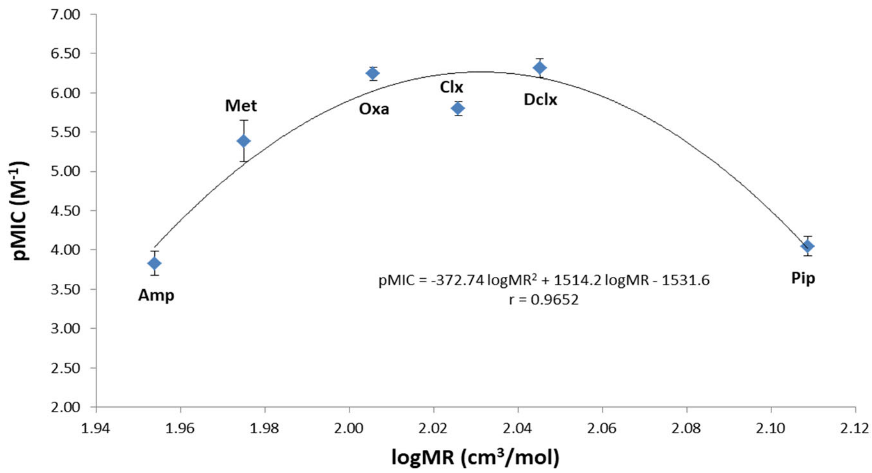

Fig. 5 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins, and molar refractivity (logMR) for *Staphylococcus aureus*: $a = -1531.200 \pm 19.655$ ($p < 0.001$), $b = 1514.200 \pm 19.754$ ($p < 0.05$), $c = -372.740 \pm 9.731$ ($p < 0.05$) and $r = 0.965$ ($p < 0.05$*). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

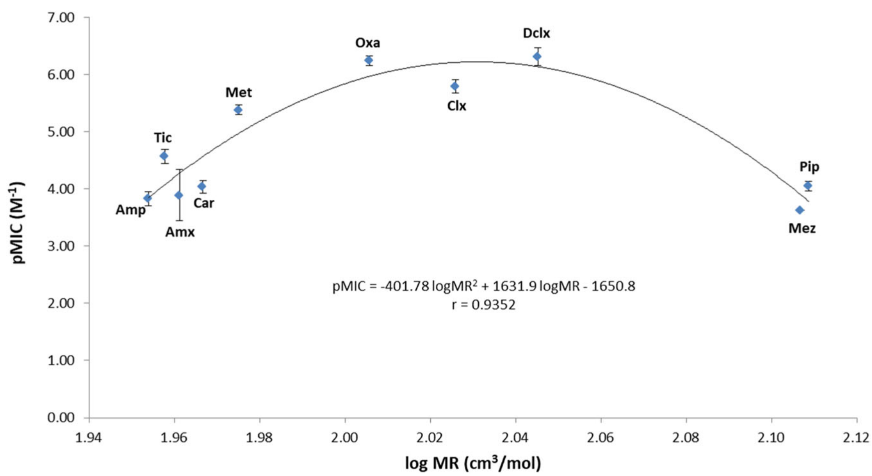

Fig. 6 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins and molar refractivity (logMR) for *Staphylococcus aureus*: $a = -1650.800 \pm 11.780$ ($p < 0.001$), $b = 1631.900 \pm 11.892$ ($p < 0.05$), $c = -401.780 \pm 5.856$ ($p < 0.05$) and $r = 0.9352$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

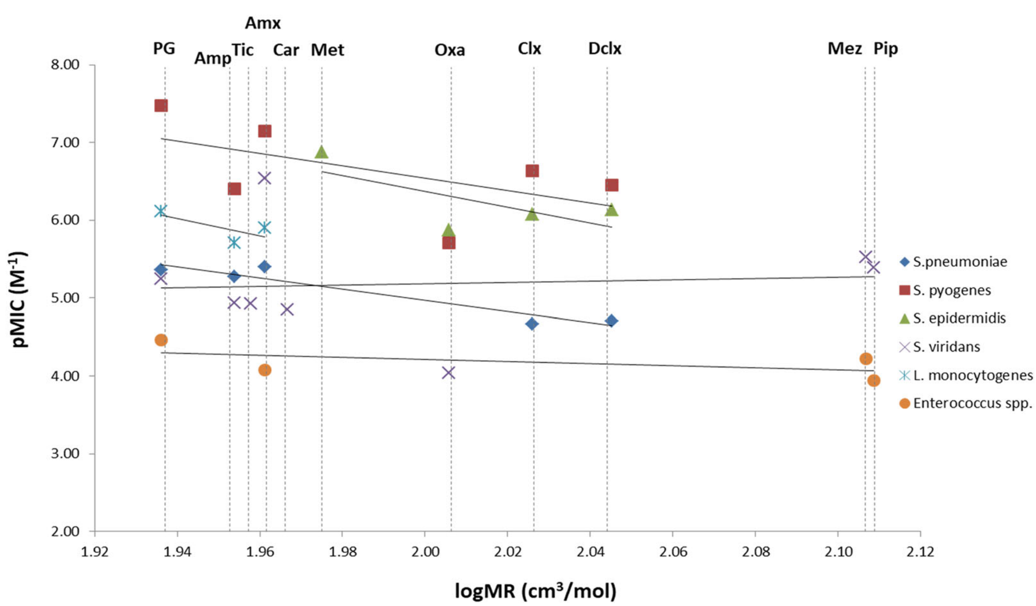

Fig. 7 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins, and molar refractivity (logMR) for *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus epidermidis, Listeria monocytogenes*, and *Enterococcus spp*

slopes of the curves are very small and the linear correlation coefficients are not significant.

In general, the correlation between partition coefficients and antimicrobial activities of penicillins present a consistent and overwhelming trend on Gram-negative bacteria. Derived from the linear regression analysis, biological activity depends on the partition coefficient (Table 5), where the more polar the penicillin is, the higher the activity.

Table 5 Regression parameters for antimicrobial activity vs. logP in Gram-negative bacteri

Bacteria	Slope ± SEM	Intercept ± SEM	*r*
Neisseria gonorrhoeae	−0.385 ± 0.102*	6.237 ± 0.131*	−0.967*
Haemophilus influenzae	−0.422 ± 0.224*	5.209 ± 0.227*	−0.737*
Serratia marcescens	−0.444 ± 0.144*	3.482 ± 0.074*	−0.783*
Proteus mirabilis	−0.238 ± 0.036*	3.991 ± 0.012*	−0.978*
Pseudomonas aeruginosa	−0.260 ± 0.022*	3.714 ± 0.009*	−0.989*
Escherichia coli	−0.125 ± 0.117	3.599 ± 0.087*	−0.473
Bacteroides fragilis	−0.358 ± 0.138*	3.659 ± 0.066*	−0.878*
Neisseria meningitidis	−0.256 ± 0.077*	7.059 ± 0.083*	−0.886*
Klebsiella pneumoniae	−0.417 ± 0.180*	3.515 ± 0.065*	−0.854*

*$p < 0.05$, statistically significant

It is important to note that the slopes in these correlations are actually small, that is, the dependence of the antibacterial activity on liposolubility is moderate but significant (Figs 8 and 9); however, the activity is highest for *Haemophilus influenzae, Neisseria gonorrhoeae*, and *Neisseria gonorrhoeae*. For the rest of the Gram-negative bacteria the antibacterial activity shows a similar behavior. Finally, for *Escherichia coli* the trend of the correlation is the same, but the statistical analysis was not significant.

The correlation between partition coefficient and antibacterial activity in Gram-negative bacteria shows interesting trends that describe fairly well the relationship of the antibacterial spectrum with the clinical use of penicillins in patients. Examples of this can be seen for *Serratia marcescens*, *Bacteroides fragilis*, and *Pseudomonas aeruginosa* (Table 4, Figs 10–12).

Finally, the correlations between activity and molar refractivity for Gram-negative bacteria showed a tendency of higher activity as the size of the penicillin increases (Table 6, Figs 13 and 14). In general, the relationship presents good sensitivity to the change in size, since the values of the slopes range between 1.7 and 3.0.

It is worth mentioning, that for *H. influenzae*, the activity is highly sensitive to the size of the penicillin, being the ureidopenicillins (azlocillin and piperacillin) the most active. In the case of *N. gonorrohoeae* the relationship

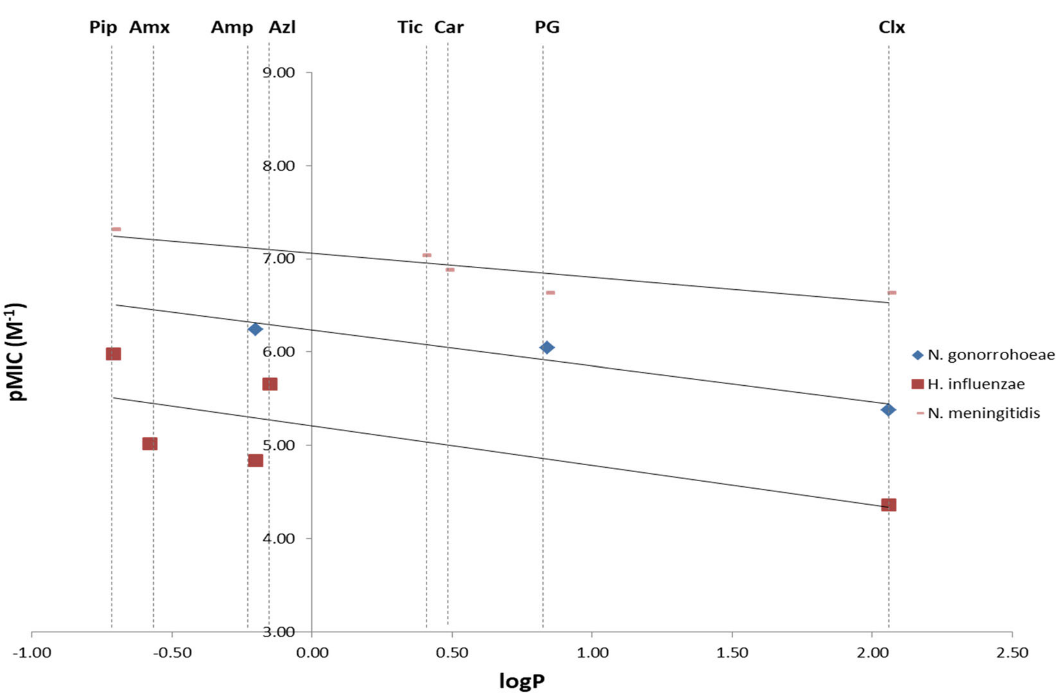

Fig. 8 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins and their partition coefficients (logP) for *Neisseria gonorrhoeae, Haemophilus influenzae*, and *Neisseria meningitidis*

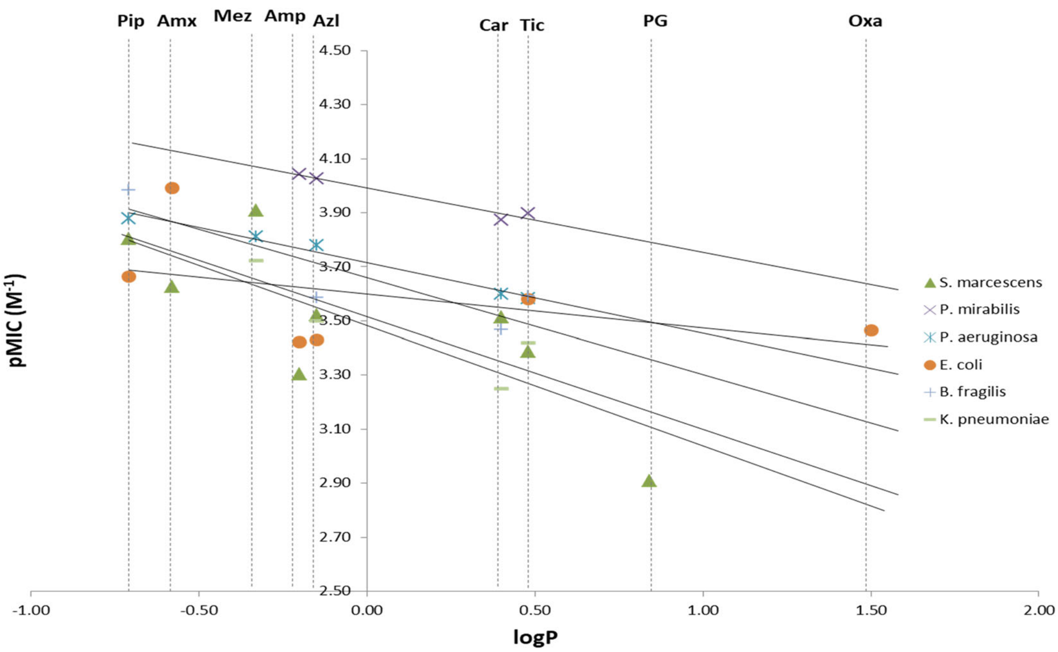

Fig. 9 Quantitative structure-activity relationship between antimicrobial activity (pMIC) of penicillins and their partition coefficients (logP) for *Serratia marcescens, Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli, Bacteroides fragilis*, and *Klebsiella pneumoniae*

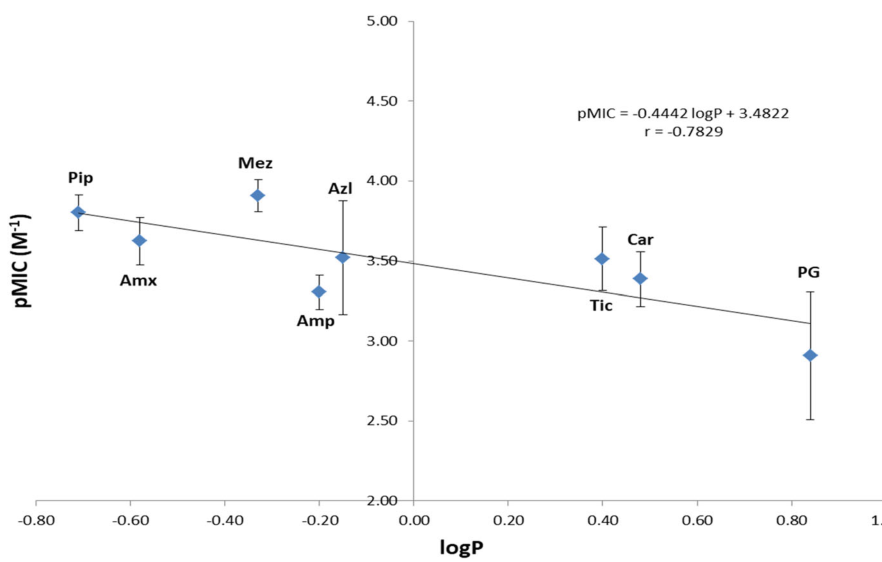

Fig. 10 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins and their partition coefficient (logP) for *Serratia marcescens*: $b = 3.482 \pm 0.074$ ($p < 0.05$), $m = -0.444 \pm 0.144$ ($p < 0.05$) and $r = -0.783$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

between activity and size is inverse, that is, the smaller penicillins are the most active. Finally, *Escherichia coli* does not display a clear relationship with size, as the regression is not significant.

From the structural point of view, the substituents of the core structure of penicillin affect the biological activity; not only that, they also determine the orientation of the antibacterial spectrum. According to the analysis of the correlation of the antimicrobial activity with logP and logMR, a general tendency can be deduced, which is summarized in Fig. 15. According to this, penicillins can be classified into three groups.

Group 1 corresponds to those penicillins that present higher activity towards Gram-positive bacteria: penicillin G, methicillin, oxacillin, cloxacillin, and dicloxacillin. It can be observed that as their size increases, activity increases. In terms of lipophilicity, two tendencies can be observed. For *Streptococcus* penicillins increase their activity as they become more lipophilic, however, the tendency is the opposite for *Staphylococcus* and *Listeria*.

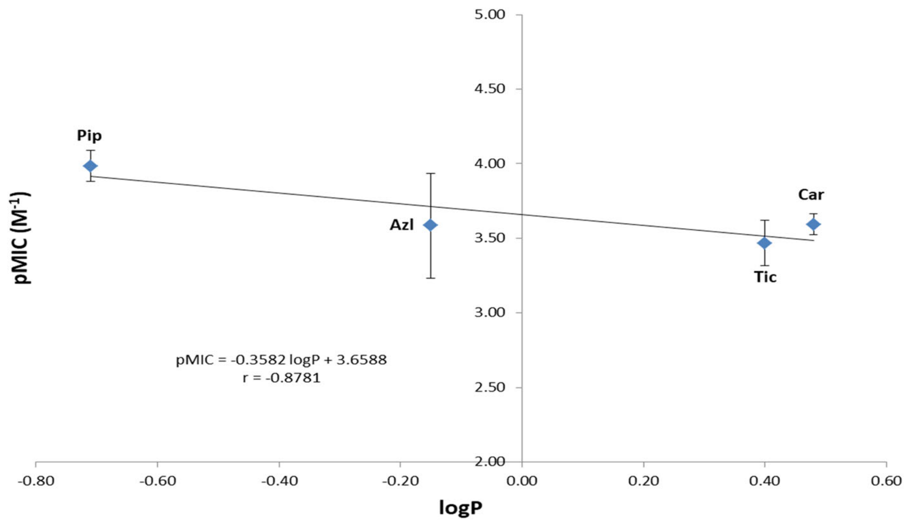

Fig. 11 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins and their partition coefficients (logP) for *Bacteroides fragilis*: $b = 3.658 \pm 0.066$ ($p < 0.05$), $m = -0.358 \pm 0.138$ ($p < 0.05$) and $r = -0.878$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

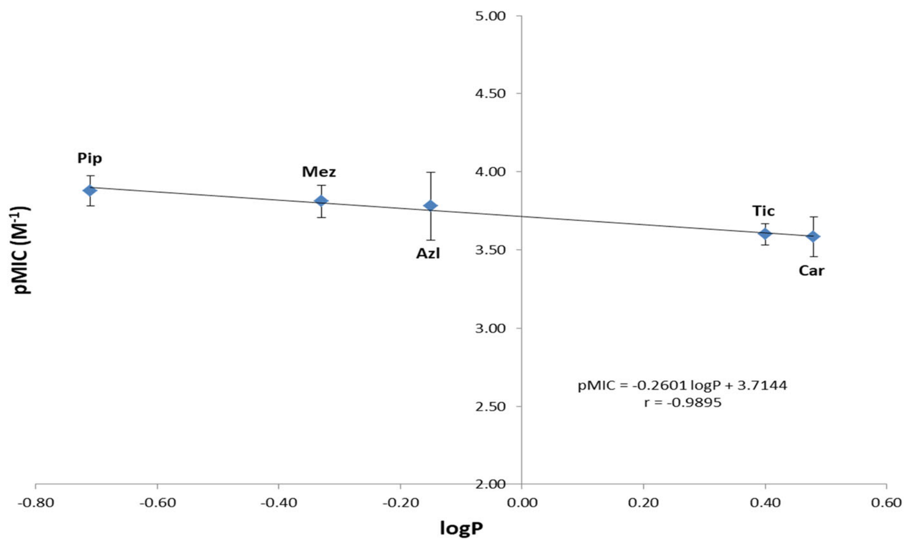

Fig. 12 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins and their partition coefficients (logP) for *Pseudomonas aeruginosa*: $b = 3.714 \pm 0.009$ ($p < 0.05$), $m = -0.260 \pm 0.022$ ($p < 0.05$) and $r = -0.989$ ($p < 0.05$). The $p < 0.05$ value represents a statistically significant difference at 95.0% confidence, assessed with Student's *t*-test

Table 6 Regression parameters for antimicrobial activity vs. logMR in Gram-negative bacteria

Bacteria	Slope ± SEM	Intercept ± SEM	*r*
Neisseria gonorrhoeae	−8.706 ± 3.743*	23.059 ± 7.382	−0.919*
Haemophilus influenzae	6.782 ± 4.154	−8.535 ± 8.400	0.686
Serratia marcescens	3.338 ± 1.096*	−3.201 ± 2.199	0.779*
Proteus mirabilis	0.788 ± 1.115	2.396 ± 2.212	0.447
Pseudomonas aeruginosa	1.756 ± 0.209*	0.148 ± 0.427	0.979*
Escherichia coli	−0.496 ± 1.724	4.589 ± 3.465	−0.143
Bacteroides fragilis	2.602 ± 1.180*	−1.606 ± 2.388	0.842*
Neisseria meningitidis	2.585 ± 1.861	1.734 ± 3.721	0.626
Klebsiella pneumoniae	2.512 ± 0.718*	−1.606 ± 1.454	0.927*

*$p < 0.05$, statistically significant

Group 2 corresponds to those penicillins presenting higher activity on Gram-negative bacteria. In this group, just as it was the case of Gram-positive bacteria, as the size of the molecule increases, activity does as well. Surprisingly, there is a clear tendency in relation to the lipophilicity, as penicillins become more hydrophilic, their activity increases. This group includes: carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin.

Group 3 corresponds to broad spectrum penicillins, those with activity against Gram-positive and Gram-negative bacteria, such as ampicillin and amoxicillin, which show a higher activity with medium sizes and a tendency towards hydrophilicity.

It is important to analyze the molecular aspects that can explain general tendencies for the penicillins on this bacteria. For the general purpose of this paper, it is convenient to analyze the wide spectrum penicillins ampicillin and amoxicillin (Fig. 16).

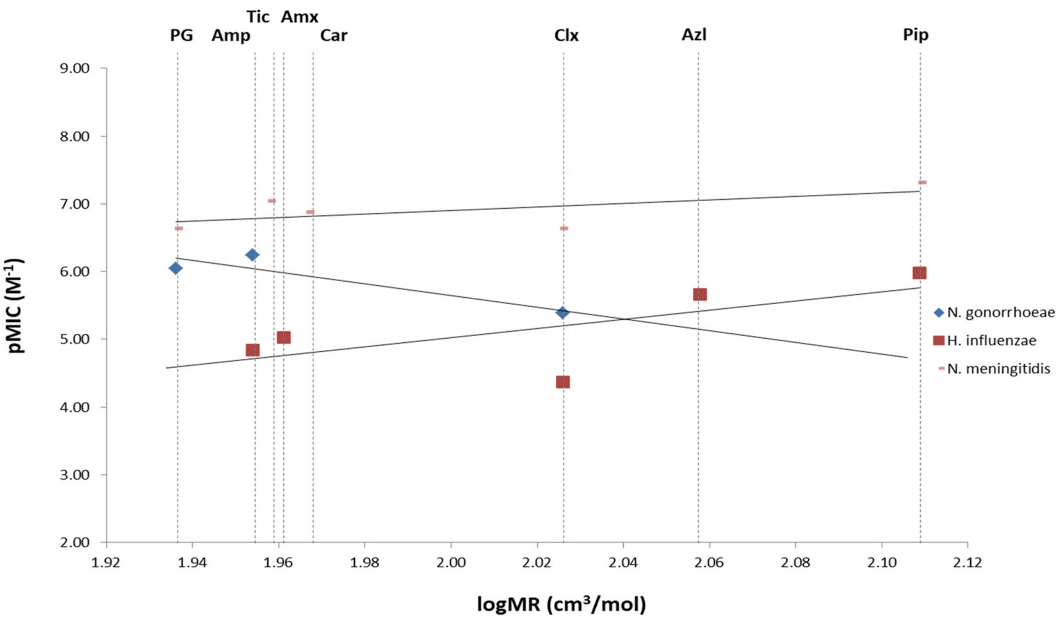

Fig. 13 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins and their molar refractivity (logMR) for *Neisseria gonorrhoeae, Haemophilus influenzae*, and *Neisseria meningitidis*

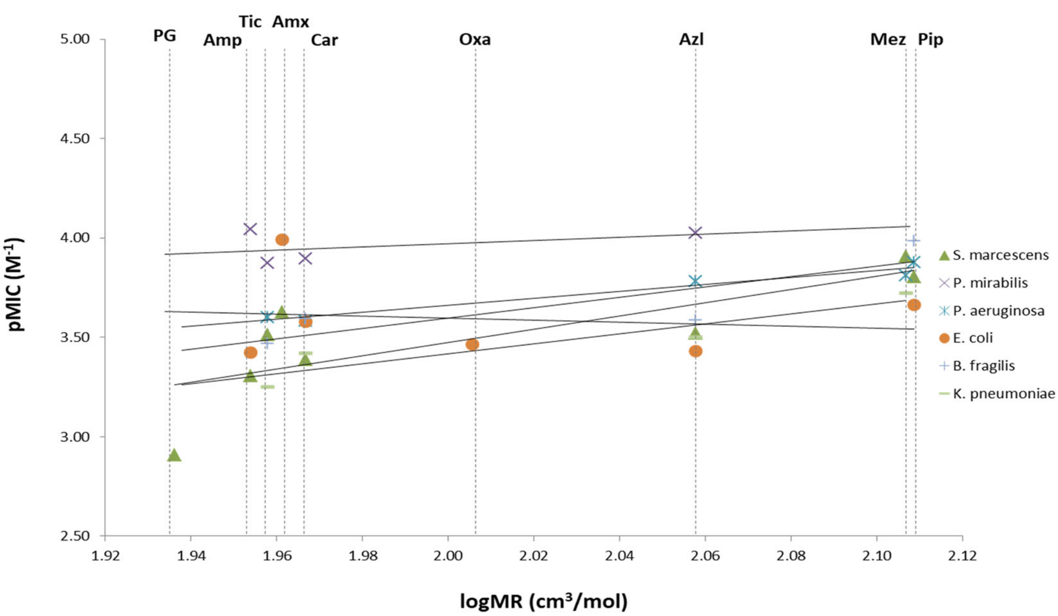

Fig. 14 Quantitative structure-activity relationship between the antimicrobial activity (pMIC) of penicillins and their molar refractivity (logMR) for *Serratia marcescens, Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli, Bacteroides fragilis*, and *Klebsiella pneumoniae*

In the aminopenicillin group there is a stereogenic carbon in the position α (Cα) to the carbonyl of the carboxamide side chain of the penicillin core. The amino group on Cα is electron withdrawing (−*I*) by inductive effect; (Smith and March 1992) other penicillins have substituents with different electronic effects. It is likely that the electron withdrawing or electron donor ability of the Cα substituents determine the antibacterial spectrum of penicillins. Figure 16 illustrates the changes in the substituents on Cα and the overall electronic effects of the R group on the penicillin core structure. The loss of the –*I* group gives rise to natural penicillins, which retain the saturated Cα; this change

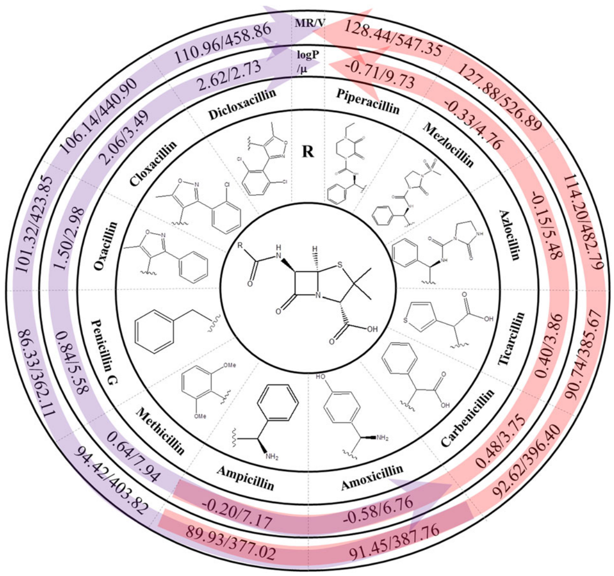

Fig. 15 Diagram of the structure-activity relationship of penicillins. Violet arrow: activity on Gram-positive bacteria. Red arrow: activity on Gram-negative bacteria

apparently induces the loss of the activity against Gram-negative bacteria, although these penicillins are sometimes active on them. Nevertheless, their activity is definitely geared towards Gram-positive bacteria. Therefore, when penicillins lack the Cα, they basically lose the activity against Gram-negative bacteria and become active against Gram-positive. This is displayed in methicillin and its derivatives and in the group of the isoxazolyl-penicillins which are active essentially against bacteria of the *Staphylococcus* genus.

It should be noted that the activity against Gram-positive bacteria seems to be strongly related to the direct union of the aromatic system to the carbonyl of the carboxamide side chain. In the isoxazolyl-penicillins, the isoxazole ring is even more electron donating by resonance (EDG, +*R*) because a high amount of electron density is concentrated on the carbon *ipso* to the carbonyl. As mentioned above, these penicillins have activity against Gram-positive bacteria, primarily of the *Staphylococcus* genus. It is also known that this group of molecules is resistant to penicillinase, (Knox and Smith 1963) and this is probably due to the orientation of the dipole moment

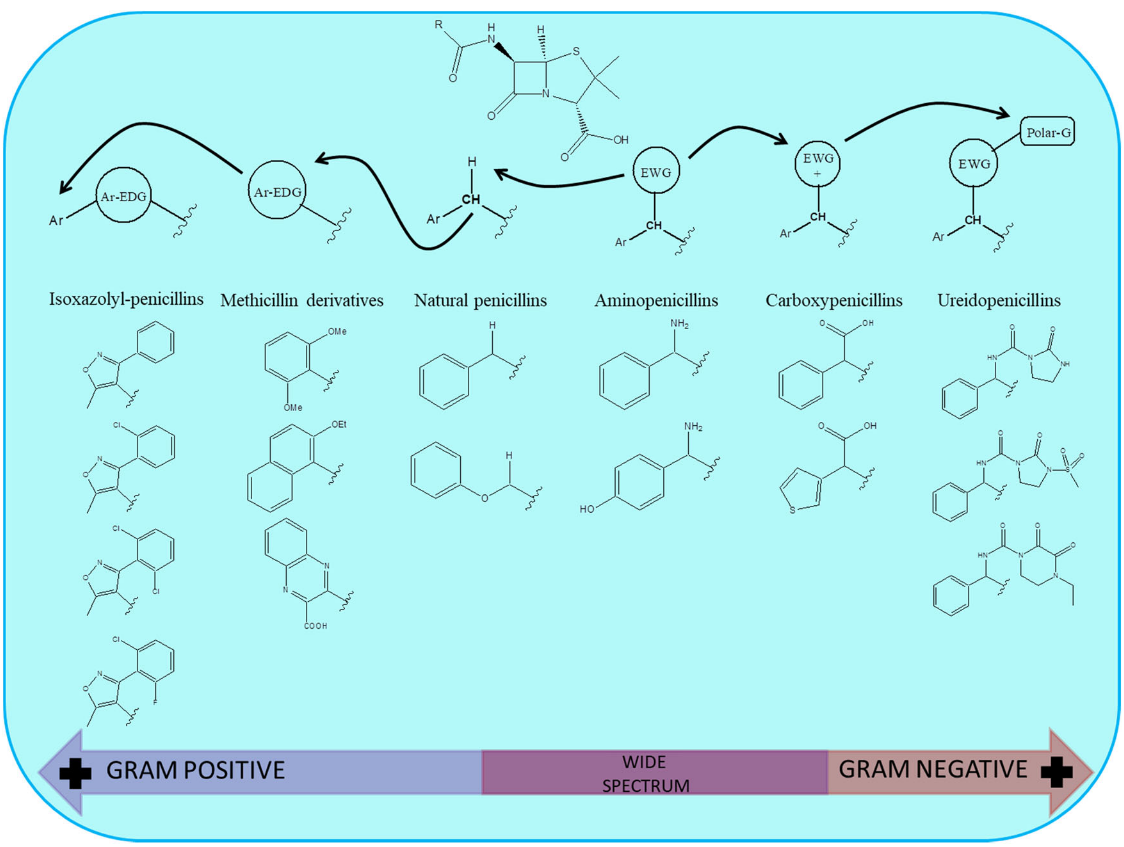

Fig. 16 Diagram of structure-antibacterial spectrum relationship of penicillins. Structural changes on the side-chain of the core structure of penicillins explain the spectrum tendency respect to the aminopenicillins. Ar aryl-substituent, EDG electron-donating group, EWG electron-withdrawing group, Polar-G polar group

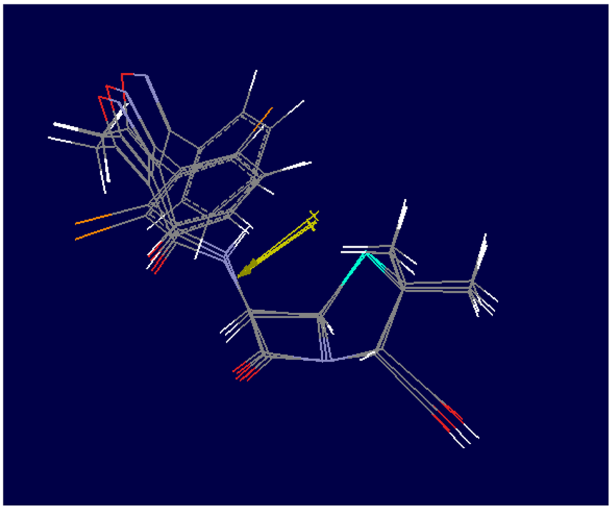

Fig. 17 Orientation of the dipole moment in the group of isoxazolyl penicillins (oxacillin, cloxacillin, and dicloxacillin)

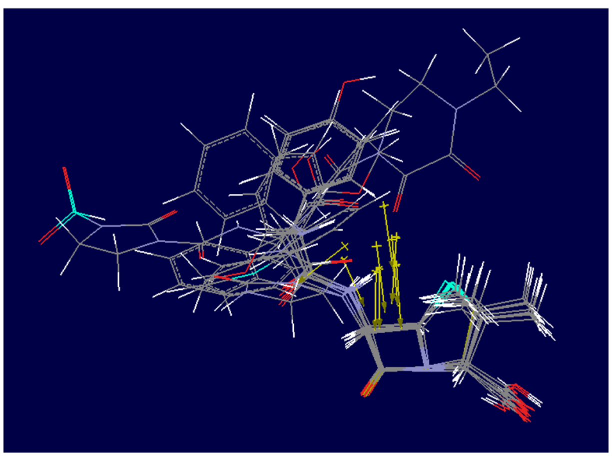

Fig. 18 Orientation of the dipole moment in the methicillin, natural penicillin (penicillin G), aminopenicillins (amoxicillin and aminopenicillin), carboxypenicillins (carbenicillin and ticarcillin), and ureidopenicillins (azlocillin, mezlocillin, and piperacillin)

which is oriented towards the amide side chain (Fig. 17). It is likely that this orientation protects the β-lactam ring from hydrolysis by enzymes and at the same time reduces its antibacterial spectrum, since this ring would be more stable. In the other penicillins the dipole moment is oriented towards the β-lactam ring, and that would be the reason why they are more susceptible to hydrolysis by β-lactamases (Fig. 18).

Furthermore, for the activity against Gram-negative bacteria, it increases in relation to the strength of the electron withdrawing group on Cα: $-NH_2 < -COOH < -NH-CO-$PolarG, corresponding to aminopenicillins, carboxypenicillins, and ureidopenicillins, respectively. Finally, all penicillins have an aromatic group in the side chain which is essential for its antibacterial activity.

Conclusions

Penicillins are still first-choice antibiotics to treat infections acquired under different conditions (common and nosocomial). However, many of them have lost activity against resistant strains of bacteria, requiring the design of more efficient molecules. The main contribution of this work is bringing to light molecular and physicochemical bases that determine the antibacterial activity of penicillins and the orientation of their antibacterial spectrum. This will make it easier to design new molecules by focusing on a specific target according to the requirements. The side chain determines the properties of penicillins, being the Cα, the aromatic ring and the electron withdrawing substituent, structural factors that contribute in an essential way.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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