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Lipophilicity of Teicoplanin Antibiotics as Assessed by Reversed Phase High-performance Liquid Chromatography: Quantitative Structure-property and Structure-activity Relationships

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Abstract—Structure-lipophilicity relationships of a large series of 63-COX teicoplanin antibiotic derivatives were examined, by correlating their capacity factors (log k_w), measured through reversed-phase high-performance liquid chromatography on Deltabond C_8 stationary phase, with some computed molecular properties such as fragmental log P constants (π_x), molecular volumes (V_x) and factors imparting hydrophilicity (e.g. amino groups in the X chain, *n*N). A number of equations were derived which demonstrate that variations of log k_w are mainly related to changes in bulk (modelled by V_x) and polarity (primarily modelled by *n*N) of X chains of teicoplanin derivatives. QSAR analysis revealed that in-vitro activity against *E. coli* increases as lipophilicity decreases and isoelectric point increases.

Among the different physiocochemical properties related to biological activity, lipophilicity has been repeatedly demonstrated to influence the pharmacokinetic and pharmacodynamic behaviour of many classes of drugs (Topliss 1983; Hansch et al 1987). The logarithm of the octanol-water partition coefficient of a compound, log P_{oct}, is the parameter most frequently used as a measure of lipophilicity in quantitative structure-activity relationship (QSAR) studies. Log P_{oct} encodes two biologically relevant structural contributions, namely a steric or bulk term, reflecting hydrophobic and dispersive forces, and a polar term reflecting dipole–dipole interactions and hydrogen bonds (van de Waterbeemd & Testa 1987; Testa & Kier 1991).

Traditionally, log P_{oct} has been determined by the so-called shake-flask method (Leo et al 1971), but, due to some experimental drawbacks which sometimes limit its reliability, several alternative techniques have recently been exploited (Dearden & Bresnen 1988; El Tayar et al 1991). Among them, techniques based on reversed-phase HPLC continue to be the most commonly used (Braumann 1986; Terada 1986).

In a previous paper we reported on the use of Deltabond C_8 deactivated stationary phase for HPLC measurements of lipophilicity (Altomare et al 1993). Applying the linear solvation energy relationship (LSER) approach (Kamlet & Taft 1976; Kamlet et al 1983, 1986) we demonstrated that the cavity term (modelled by intrinsic molecular volume, V_I) and hydrogen bond acceptor capacity (modelled by the solvatochromic parameter β) of solutes are the most important factors affecting retention on this deactivated phase.

As part of our ongoing research in this field, we report here the use of lipophilicity parameters determined on Deltabond C_8 (i.e. log k_w, the logarithm of the capacity factor extrapolated to 100% of water mobile phase) in the QSAR studies of teicoplanin antibiotics (Altomare et al 1992). The retention data were also correlated with some computed molecular properties, with the aim of assessing physical factors contributing to capacity factors and to derive equations useful for estimating the lipophilicity of new teicoplanin derivatives.

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Materials and Methods

Materials

Analytical grade chemicals and solvents were commercially available and used. The synthesis of the examined teicoplanins has been described elsewhere (Malabarba et al 1989, 1992). The lipophilicity data (log k_w) of the 28 carboxamides of teicoplanin and teicoplanin aglycone listed in Table 1 were taken from our preliminary report (Altomare et al 1992).

Apparatus

All chromatographic measurements were performed at a constant temperature of 30 ± 0.5°C and flow-rate of 1 mL min^{-1} on a Waters HPLC Model 600 Multisolvent delivery system (Waters Associates, Milford, MA, USA) equipped with a Waters 481 variable wavelength detector operating generally at 254 nm.

A 5-μm Deltabond C_8 column (150 × 3.9 mm i.d.; Keystone Sci., Belfonte, PA, USA) was used throughout.

Determination of capacity factors

The capacity factors extrapolated to 100% water eluent (log k_w) were determined as described before (Altomare et al 1989, 1991). The mobile phases consisted of at least five different volume fractions of methanol in 0·05 M sodium acetate buffer (pH 5·0).

Table 1. Antimicrobial activity and physicochemical parameters of derivatives of teicoplanin and teicoplanin aglycone.

Compound	Code	X-chain	log k_w^g	log $k_{w(D)}$[a]	pI[a]	π_x^b	$V_x/100$[c]	I_{NH_2}[d]	nN[d]	mC/nN[d]	$I_{teicoplanin}$[d]	log 1/MIC (*E. coli*)[e]
1	Teicoplanin	—OH	3·82	2·63	5·8	n.c.	0·10	0	0		1	
2	Teicoplanin A_2	—OH	4·02	2·97	5·8	n.c.	0·10	0	0		1	
3	Teicoplanin A44	—$NH(CH_2)_3NH_2$	3·99		8·7	−1·29	0·49	1	1	3	1	
4	Teicoplanin A-50	—$NH(CH_2)_3NHCH_3$	4·30		8·7	−1·14	0·59	0	1	4	1	
5	Teicoplanin A-1/2	—$NH(CH_2)_3N(CH_3)_2$	4·17	2·84	8·7	−0·81	0·68	0	1	5	1	
6	Teicoplanin A-3/2	—$NH(CH_2)_3N(CH_2CH_3)_2$	4·09		8·8	0·08	0·87	0	1	7	1	
7	Teicoplanin A-4	—$NH(CH_2)_3NH(nC_4H_9)_2$	4·69		8·6	2·20	1·26	0	1	11	1	
8	Teicoplanin A-56/2	—$NH(CH_2)_2NH(CH_2)_2NH_2$	3·87	3·39	8·7	−0·80	0·65	1	2	2	1	
9	Teicoplanin A-59/2	—$NH(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$	3·21	2·23	8·9	−2·65	1·20	1	3	3	1	<3·45
10	Teicoplanin A-17	—$NHCH_2COOCH_2CH_3$	4·26		7·6	0·33	0·57	0	0		1	
11	Teicoplanin A-22	—N⟨ ⟩NH	3·71		8·5	−0·19	0·87	0	1	4	1	
12	Teicoplanin A-7	—N⟨ ⟩S	4·29		7·7	0·77	0·56	0	0		1	
13	Aglycone B(T-A3-1)	—OH	2·19	2·70	5·7	n.c.	0·10	0	0		0	<3·20
14	Aglycone C(T-A3-2)	—OH	2·06	3·04	5·6	n.c.	0·10	0	0		0	3·24
15	Aglycone D	—OH	2·23	2·62	5·5	n.c.	0·10	0	0		0	4·27
16	Aglycone D-A-35	—$NH(CH_2)_2NH_2$	2·31		8·1	−0·71	0·39	1	1	2	0	5·49
17	Aglycone D-A-30	—$NH(CH_2)_4NH_2$	2·31		8·2	−0·76	0·59	1	1	4	0	5·20
18	Aglycone D-A-31	—$NH(CH_2)_6NH_2$	2·50		8·6	0·30	0·78	1	1	6	0	5·51
19	Aglycone D-A-24	—$NH(CH_2)_2N(CH_3)_2$	2·44		7·9	0·01	0·57	0	1	4	0	5·50
20	Aglycone D-A-3	—$NH(CH_2)_3N(CH_3)_2$	2·39	1·20	8·0	−0·81	0·68	0	1	5	0	5·20
21	Aglycone D-A-5	—$NH(CH_2)_3N(nC_4H_9)_2$	3·59	2·44	8·0	2·20	1·26	0	1	11	0	5·23
22	Aglycone D-A-28	—$NH(CH_2)_5N(CH_3)_2$	2·51		8·1	0·08	0·87	0	1	7	0	5·21
23	Aglycone D-A-29	—$NH(CH_2)_7N(CH_3)_2$	2·23		8·1	1·14	1·07	0	1	9	0	4·94
24	Aglycone D-A-42	—$NH(CH_2)_3NH(CH_2)_4NH_2$	2·02	0·46	8·5	−1·44	0·94	1	2	3·5	0	5·82
25	Aglycone D-A-58	—$NH(CH_2)_3N[(CH_2)_3NH_2]_2$	1·82	0·64	8·6	−2·63	1·20	1	3	3	0	6·14
26	Aglycone D-A-50	—$NH(CH_2)_2NH(CH_2)_3NH(CH_2)_2NH_2$	2·33	0·29	8·5	−1·49	1·01	1	3	2·3	0	5·53
27	Aglycone D-A-52	—$NH(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$	1·86	0·34	8·6	−2·65	1·20	1	3	3	0	6·44
28	Aglycone D-A-61	—$NH(CH_2)_3NH(CH_2)_9NH(CH_2)_3NH_2$	2·21	0·02	8·6	0·52	1·78	1	3	5	0	<4·05

[a]Values taken from Altomare et al (1992). [b]Lipophilic constant of X-chain derived from log P of CH_3COX, calculated by CLOGP software, according to the following equation: $\pi_x = \log P_{CH_3COX} - (-0{\cdot}62)$, where −0·62 is π_{CH_3CO} for aliphatic systems. n.c. = not calculated. [c]Intrinsic molar volumes of X-chains calculated according to Abraham & McGowan (1987). [d]Discrete variables defined in the text. [e]In-vitro antimicrobial activity against *E. coli* as expressed by MIC (M).

Antimicrobial activity

Activity against *E. coli* expressed as MIC (minimal inhibitory concentration) was determined by a microdilution method in Oxoid Isosensitest broth (Unipath Ltd, Basingstoke, Hampshire, UK). The final inoculum was about 10^4 cfu mL^{-1} (cfu = colony forming units). MIC was taken as the lowest concentration that showed no visible growth after 18–24 h incubation at 37°C.

Physicochemical descriptors and correlation analysis

Calculated log P values were obtained by the fragmental method of Hansch & Leo (1979) using the CLOGP 3·54 software (Pomona College Medicinal Chemistry Project, Claremont, CA, USA). The volumes of the X-carboxamide chains of teicoplanin and teicoplanin aglycone amides (see Fig. 1) were calculated as the characteristic volume V_x by taking into account the atomic volumes and the number of bonds according to Abraham & McGowan (1987). V_x values scaled by 1/100 are reported in Table 1.

Factors imparting hydrophilicity to teicoplanin antibiotics were described by two different kinds of discontinuous descriptors, namely an indicator variable for a terminal primary amino group (I_{NH_2}) and the number of nitrogen atoms (nN) in the X chain. For the polyamine chains, the ratio between the number of carbons in the chain (methylene plus methyl groups) and the number of nitrogen atoms (mC/nN) was also calculated and considered as an additional descriptor of the X-chain lipophilicity in the derivation of structure-retention relationships.

Multiple regression analysis was performed using the QSAR program (Pomona College Medicinal Chemistry Project, Claremont, CA, USA), whereas cross-validation of the regression equations (Dunn et al 1984) was made using the QSAR module of SYBYL 5·5 software (Tripos Associates, St Louis, MO, USA). All the calculations were carried out on a Digital VAX Station 3100.

Molecular graphics analysis

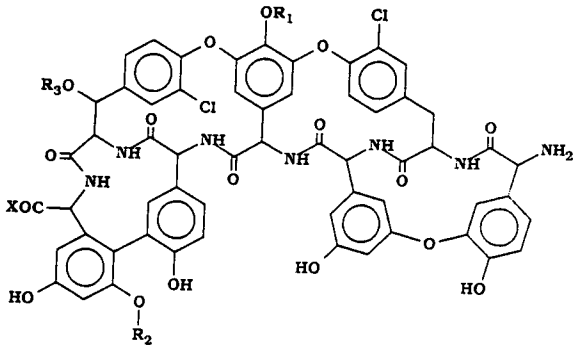
Teicoplanin A_2 in Fig. 2 was built and optimized using the SYBYL software on the basis of the reported stereochemistry (Coronelli et al 1987). Standard bond lengths and angles were used as input for the calculations. Energy minimization was performed by molecular mechanics using the Tripos force field (Clark et al 1989). The lipophilic X-acyl chain was built in the extended conformation.

Results and Discussion

Lipophilicity parameters

Because of the molecular structure complexity of the peculiar pharmacological activity of teicoplanin derivatives shown in Fig. 1, the study of their lipophilicity and antimicrobial properties appeared challenging (Malabarba et al 1989). Log k_w values used in this study were determined and published by us in a preliminary paper (Altomare et al 1992).

Here we report on physical factors contributing to retention of teicoplanin derivatives (i.e. structure-lipo-



Teicoplanin

R_1 = *N*-acyl-β-D-glucosaminyl

N-acyl(NHCOR) side chains

component A_2-1 : R = $(CH_2)_2CH{=}CH(CH_2)_4CH_3$
component A_2-2 : R = $(CH_2)_6CH(CH_3)_2$
component A_2-3 : R = n–C_9H_{10}
component A_2-4 : R = $(CH_2)_6CH(CH_3)CH_2CH_3$
component A_2-5 : R = $(CH_2)_7CH(CH_3)_2$

R_2 = α-D-mannosyl; R_3 = *N*-acetyl-β-D-glucosaminyl

Aglycones B : R_1 = H; R_2 = α-D-mannosyl; R_3 = *N*-acetyl-β-D-glucosaminyl
C : $R_1 = R_2$ = H; R_3 = *N*-acetyl-β-D-glucosaminlyl
D : $R_1 = R_2 = R_3$ = H

Teicoplanin and aglycones : X = OH; teicoplanin and aglycone amides : X = NR′R″

FIG. 1. General structure of teicoplanin antibiotic derivatives.

philicity correlations) and new quantitative structure-activity relationship models (e.g. in-vitro activity against Gram-negative bacteria *E. coli*).

Examining the two lipophilicity data sets in Table 1, i.e. comparing log k_w values determined without and with the addition of *N*,*N*-dimethyloctylamine to the mobile phase (i.e. log $k_{w(D)}$), it emerges that, as a general rule, dimethyloctylamine decreases the retention with three exceptions represented by the acidic pseudoglycones B, C and the aglycone D. This behaviour could be due to the formation of a very lipophilic ion-pair between the acidic aglycones B, C and D and the basic dimethyloctylamine. The formation of a similar ion-pair apparently does not take place in the case of the other acidic compound teicoplanin, for which a positive value of Δ log k_w (log k_w – log $k_{w(D)}$) was observed. This result was interpreted on the basis of possible steric hindrance exerted by the *N*-acyl-glucosaminyl moiety in the ion-pair formation as shown by the molecular model reported in Fig. 2.

A smaller but significant increase of capacity factors of aglycones B, C and D, and not of teicoplanin, was observed also using other pairing ions smaller than dimethyloctylamine (e.g. triethylammonium, n-butylammonium).

Structure-lipophilicity relationships

An inspection of log k_w values in Table 1 reveals that lipophilicity of the acidic pseudoaglycones B and C and the aglycone D does not fluctuate significantly, despite the presence of hydrophilic moieties, *N*-acetyl-β-D-glucosaminyl and α-D-mannosyl and aglycone B, and *N*-acetyl-β-D-glucosaminyl in aglycone C. We may speculate that intramolecular polar interactions hamper the glycidic moieties from expressing entirely their hydrophilic increments (less than −3 log P units for each glycidic fragment, according to the CLOGP fragmental system).

A marked increase of log k_w (more than 1·6 log units) was observed for teicoplanin (compare compounds 1, 13, 14 and 15), due to the highly lipophilic acyl chains in the *N*-acyl-β-D-glucosaminyl moiety.

To interpret the variations of lipophilicity within the teicoplanin amide series (compounds 3–12) and aglycone amide series (compounds 16–28), we compared their log k_w values with the fragmental log P contributions of X-acyl chains (π_x) calculated by CLOGP software and we derived linear relationships with limited statistical significance (r = 0·804 and 0·794 for teicoplanin amides and aglycone amides, respectively). Apparently, besides the hydrophilicity of the flexible X-arms, modelled by π_x, intramolecular interactions must be taken into account in rationalizing log k_w variations. At the experimental pH used for the measurement of retention data (pH 5·0), the amino groups in the X-chain exist almost exclusively in the ionized form (Coronelli et al 1987), and most probably give intramolecular electrostatic and polar interactions, particularly favoured in the apolar environment of the reversed phase, resulting in a hydrophilic increment not being completely expressed.

In an attempt to explore further the structure-lipophilicity relationships within the teicoplanin and aglycone amide series, we tried to place some preliminary qualitative correlations (Altomare et al 1992) on a more quantitative basis.

As for teicoplanin amides (compounds 3–12), whose log k_w values span a range of ca 1·5 log units, some trends were found. In line with expectations, the lipophilicity of polyamine carboxamide derivatives (compare compounds 8 and 9 with 3) depends upon the number of nitrogens (*n*N), and decrease as *n*N increases. The variation of log k_w values of monoamino carboxamide derivatives (compounds 3–7), parallels the increasing bulk of the amine/ammonium

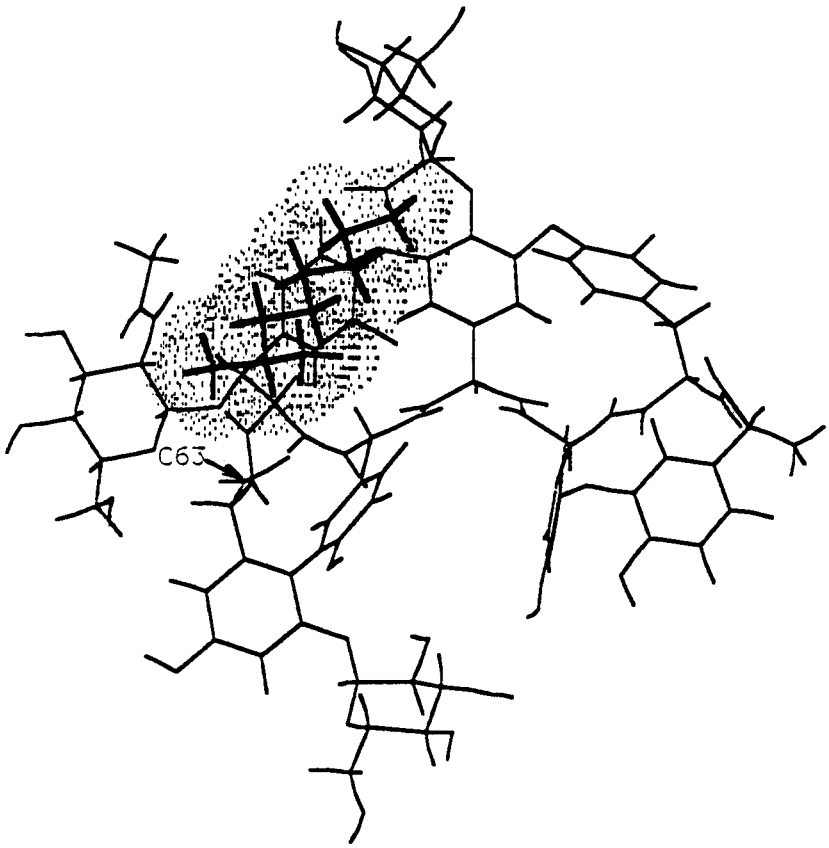


FIG. 2. Three dimensional structure (wire model) of a teicoplanin antibiotic A_2. Dots representing van der Waals surface of *N*-acyl lipophilic side chain of glucosaminyl moiety show a possible masking of the carboxylic acid side-chain.

moieties (compare compounds 3, 5, 7), with two apparent anomalies represented by compounds 4 and 6. Understanding this behaviour is not straightforward. It might be interpreted in the light of some previous findings on molecules containing ammonium moieties which often exhibit anomalous lipophilicity upon *N*-alkylation (Rekker & Mannhold 1992). Very recently, Tsai et al (1991), comparing partition coefficients of glycine and its analogues with secondary and tertiary amines, observed an increase in lipophilicity for the *N*-methyl derivative and, despite the additional methyl group, a decrease in lipophilicity for *N,N*-dimethylglycine. In spite of the different degree of structural complexity of teicoplanin molecules under examination compared with simple amino acids such as glycine derivatives, the inter- and intramolecular interactions leading to lipophilicity expression could be similar. It is possible that increasing the bulk of the amine/ammonium moiety may prevent polar and electrostatic interactions with complementary counterparts to the teicoplanin molecule and hence allow the hydrophilic character to be better expressed. This is evident at least up to the *N,N*-diethylammonium head (compare compounds 4, 5, 6). When substitution of nitrogen with two butyl groups occurs, the hydrophobicity of *N*-alkyl groups dominates the X-chain polarity, and log k_w increases by 0·7 log units (compare compounds 3 and 7).

Also, log k_w values of teicoplanin of aglycone amide (compounds 16–28) significantly reflect structural changes. Log k_w values of homologous monoamine derivatives bearing a terminal primary amino group (compounds 16–18), show that a distance of as much as six CH_2 groups (compound 18) is necessary for one CH_2 group to express its hydrophobic increment. A similar trend, with the not easily interpretable exception of compound 23, was observed for the homologous aglycone monoamines bearing a *N,N*-dimethylamine terminal group (compounds 19, 20, 22, 23).

A comparison amongst log k_w values of mono- (18), di- (24) and triamine (25–28), all having a terminal NH_2 group, indicated that lipophilicity essentially depends upon the ratio of methylene units to the number of nitrogens (nCH$_2$/nN) in the carboxamide chain. With the exception of compound 26, log k_w of the X-polyamine chain correlates well with the nCH$_2$/nN ratio:

$$\log k_w = 0{\cdot}21(\pm 0{\cdot}02)n\mathrm{CH_2}/n\mathrm{N} + 1{\cdot}24(\pm 0{\cdot}09) \quad (1)$$

$$n = 5 \quad r = 0{\cdot}985 \quad r^2_{cv} = 0{\cdot}919 \quad s = 0{\cdot}055 \quad F = 100{\cdot}5$$

where n is the number of compounds, r is the correlation coefficient, r^2_{cv} the cross-validated r^2, s the standard deviation and F is the Fisher-test for significance of the equation; 95% confidence limits are given in parentheses.

Finally, we tried to derive equations to estimate the lipophilicity of novel teicoplanin antibiotics by a simple parameterization of the structural effects observed above.

We started from the assumption that capacity factors of teicoplanin aglycones or teicoplanin amides could be related to their structure by the following general equation:

$$\log k_w = mV - \Sigma F(P) + b \quad (2)$$

where V represents volume effects (cavity term), $F(P)$ represents polar factors imparting hydrophilicity to the molecules, and b is a constant.

We calculated the volume of X-chains and polar factors as described in Materials and Methods and in the footnotes of Table 1. The cross-validated multiple regression analysis (MRA) using the descriptors in Table 1 resulted in the following best three-parameter equation for the whole set of CTA and TD derivatives:

$$\log k_w = 0{\cdot}74(\pm 0{\cdot}47)V_x/100 - 0{\cdot}42(\pm 0{\cdot}19)nN + 1{\cdot}59(\pm 0{\cdot}26)I_{teicoplanin} + 2{\cdot}34(\pm 0{\cdot}34) \quad (3)$$

$$n = 25 \quad r = 0{\cdot}955 \quad r^2_{cv} = 0{\cdot}862 \quad s = 0{\cdot}299 \quad F = 73{\cdot}4$$

In the above equation $I_{teicoplanin}$ represents an indicator variable, which assumes a value of 1 for teicoplanin derivatives and 0 for aglycone derivatives.

Despite their good statistics, the model described by equation 3 loses predictive ability within the teicoplanin and aglycone subgroups ($r^2_{cv} < 0{\cdot}5$). This is most likely due to the unbalanced composition of the data set, as also demonstrated by inspection of the normalized equations (Mager & Barth 1979) (not shown), which revealed that $I_{teicoplanin}$ alone accounts for 54% of the variation of $\log k_w$. Nevertheless, by closely examining the MRA results, we found that, with the exception of a few compounds (11, 23 and 26), a good fit ($r \geqslant 0{\cdot}81$) is provided by the equations of both subsets.

In summary, equation 3 shows that the polar characteristics of X-chains, modelled primarily by the number of nitrogens, as well as their volumes, are the factors mainly contributing to lipophilicity of teicoplanin antibiotics as assessed by reversed-phase HPLC.

Structure-antimicrobial activity relationships

Teicoplanin, a glycopeptide antibiotic of the vancomycin-ristocetin family, is widely used for the parenteral treatment of severe infections caused by aerobic and anaerobic Gram-positive bacteria, including methicillin-resistant Staphylococci (Coronelli et al 1987; Parenti & Cavalleri 1990). Like other antibiotics of this family, teicoplanin is not active in-vivo when administered orally or in-vitro against Gram-negative bacteria (Barna & Williams 1984).

To determine the key structural features responsible for the antibacterial activity and to optimize the pharmacokinetic profile, several derivatives of teicoplanin have been synthesized and tested (Malabarba et al 1984, 1987, 1989, 1992; Malabarba & Parenti 1990). Among them, the positively-charged amide of teicoplanin and its aglycone (D) and pseudoaglycones (B and C) elicited interesting antimicrobial activity. In a previous paper, we derived QSARs demonstrating that the in-vivo antimicrobial activity against *Streptococcus pyogenes*-induced septicaemia in mice mainly depends on lipophilicity, expressed by $\log k_w$ values, and the isoelectric points (pI) of the tested compounds (Altomare et al 1992).

As an extension of the previous study we analysed the activity against *E. coli*, reported in Table 1 as log 1/MIC (M). For the aglycone D amide set, the linear combination of $\log k_w$ and pI led to the following equation:

$$\log 1/MIC = -1{\cdot}12(\pm 0{\cdot}77)\log k_w + 0{\cdot}47(\pm 0{\cdot}21)pI + 4{\cdot}15(\pm 2{\cdot}61) \quad (4)$$

$$n = 12 \quad r = 0{\cdot}908 \quad r^2_{cv} = 0{\cdot}717 \quad s = 0{\cdot}259 \quad F = 21{\cdot}2$$

which fits the data well. In the derivation of equation 4, compound 21 was excluded as an outlier.

The use of CLOGP-calculated π_x instead of $\log k_w$ in equation 4 resulted in the following equation:

$$\log 1/MIC = -0{\cdot}27(\pm 0{\cdot}15)\pi_x + 0{\cdot}35(\pm 0{\cdot}20)pI + 2{\cdot}47(\pm 1{\cdot}60) \quad (5)$$

$$n = 12 \quad r = 0{\cdot}932 \quad r^2_{cv} = 0{\cdot}794 \quad s = 0{\cdot}224 \quad F = 29{\cdot}7$$

which shows a slight improvement in the statistics. The squared correlation matrix in Table 2 shows the degree of collinearity among the independent variables used in the QSAR analysis.

Within the limits of the data set examined, equations 4 and 5 show that activity against *E. coli* increases as the lipophilicity decreases and pI increases. Together with the previously published models (Altomare et al 1992), equations 4 and 5 contribute to a better understanding of the physicochemical properties involved in the modulation of antimicrobial activity of teicoplanin antibiotics and strengthens the teicoplanin QSAR arsenal.

The present study has indicated that silanol-deactivated reversed phases, such as Deltabond C_8, can be successfully used to determine lipophilicity parameters for molecules for which several limitations (low solubility, aggregation phenomena) hamper the accurate measurement of partition coefficients (Malabarba et al 1989). Structure retention-relationships demonstrated that variations of $\log k_w$ are

Table 2. Squared correlation matrix of independent variables used in the regression analysis.

	pI	π_X	$V_x/100$	I_{NH_2}	nN	mC/nN	$I_{teicoplanin}$
$\log k_w$	0·01	0·15	0·01	0·12	0·13	0·10	0·84
pI		0·21	0·55	0·27	0·46	0·08	0·01
π_X			0·01	0·34	0·37	0·72	0·00
$V_X/100$				0·15	0·34	0·14	0·02
I_{NH_2}					0·50	0·46	0·03
nN						0·20	0·05
mC/nN							0·00

related to changes in bulk and polarity (van de Waterbeemd & Testa 1987).

The use of new lipophilic descriptors in the QSAR analyses of in-vivo and in-vitro data has allowed the physicochemical interactions underlying the antimicrobial activity of teicoplanin antibiotics to be detected in more detail.

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References

Abraham, M. H., McGowan, J. C. (1987) The use of characteristic volumes to measure cavity terms in reversed phase liquid chromatography. Chromatographia 23: 243–246

Altomare, C., Carotti, A., Cellamare, S., Ferappi, M. (1989) Lipophilicity measurements of benzenesulfonamide inhibitors of carbonic anhydrase by reversed-phase HPLC. Int. J. Pharm. 56: 273–281

Altomare, C., Tsai, R.-S., El Tayar, N., Testa, B., Carotti, A., Cellamare, S., De Benedetti, P. G. (1991) Determination of lipophilicity and hydrogen-bond donor acidity of bioactive sulphonyl-containing compounds by reversed-phase HPLC and Centrifugal Partition Chromatography and their application to structure-activity relations. J. Pharm. Pharmacol. 43: 191–197

Altomare, C., Carotti, A., Cellamare, S., Contento, A., Ciabatti, R., Malabarba, A., Berti, M., Goldstein, B. (1992) QSAR of teicoplanin antibiotics: influence of lipophilicity and ionic properties of their in vivo antimicrobial activity. Med. Chem. Res. 1: 393–398

Altomare, C., Cellamare, S., Carotti, A., Ferappi, M. (1993) Linear solvation energy relationships in reversed-phase liquid chromatography. Examination of Deltabond C_8 as stationary phase for measuring lipophilicity parameters. Quant. Struct.-Act. Relat. 12: 261–268

Barna, J. C. J., Williams, D. H. (1984) The structure and mode of action of glycopeptide antibiotics of the vancomycin group. Annu. Rev. Microbiol. 38: 339–357

Braumann, T. (1986) Determination of hydrophobic parameters by reversed-phase liquid chromatography: theory, experimental techniques, and application in studies on quantitative structure-activity relationships. J. Chromatogr. 373: 191–225

Clark, M., Cramer III, R. D., Van Opdenbosch, N. (1989) Validation of the general purpose Tripos 5.2 force field. J. Comp. Chem. 10: 982–1012

Coronelli, C., Gallo, G. G., Cavalleri, B. (1987) Teicoplanin: chemical, physico-chemical and biological aspects. Farm. Ed. Sci. 42: 767–786

Dearden, J. C., Bresnen, G. M. (1988) The measurement of partition coefficient. Quant. Struct.-Act. Relat. 7: 133–144

Dunn, W. J., Wold, S., Edlund, U., Hellberg, S. (1984) Multivariate structure-activity relationships between data from a battery of biological tests and an ensemble of structure descriptors: the PLS method. Quant. Struct.-Act. Relat. 3: 131–137

El Tayar, N., Tsai, R.-S., Vallat, P., Altomare, C., Testa, B. (1991) Measurements of partition coefficients by various centrifugal partition chromatographic techniques: a comparative evaluation. J. Chromatogr. 556: 181–194

Hansch, C., Leo, A. (1979) The FRAGMENT method of calculating partition coefficients. In: Substituent Constants for Correlation Analysis in Chemistry and Biology. J. Wiley & Sons, New York, pp 18–43

Hansch, C., Bjorkroth, J. P., Leo, A. (1987) Hydrophobicity and central nervous system agents: on the principle of minimal hydrophobicity in drug design. J. Pharm. Sci. 76: 663–687

Kamlet, M. J., Taft, R. W. (1976) The solvatochromic comparison method. I. The β-scale of solvent hydrogen-bond acceptor (HBA) basicities. J. Am. Chem. Soc. 98: 377–383

Kamlet, M. J., Abboud, J.-L. M., Abraham, M. H., Taft, R. W. (1983) Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters π^*, α, and β, and some methods for simplifying the generalized solvatochromic equation. J. Org. Chem. 48: 2877–2887

Kamlet, M. J., Doherty, R. M., Abboud, J.-L. M., Abraham, M. H., Taft, R. W. (1986) Linear solvation energy relationships: 36. Molecular properties governing solubilities of organic nonelectrolytes in water. J. Pharm. Sci. 75: 338–349

Leo, A., Hansch, C., Elkins, D. (1971) Partition coefficients and their use. Chem. Rev. 71: 525–616

Mager, H., Barth, A. (1979) Problems involved in the specification and interpretation of quantitative structure-activity relationships. Pharmazie 34: 18–25

Malabarba, A., Parenti, F. (1990) Semi-synthetic teicoplanin antibiotics. Curr. Antimicr. Pat. 2: 263–287

Malabarba, A., Strazzolini, P., De Paoli, A., Landi, M., Berti, M., Cavalleri, B. (1984) Teicoplanin, antibiotics from *Actinoplanes teichomyceticus* nov. sp. VI. Chemical degradation: physicochemical and biological properties of acid hydrolysis products. J. Antibiot. 37: 988–999

Malabarba, A., Trani, A., Ferrari, P., Pallanza, R., Cavalleri, B. (1987) Synthesis and biological activity of some esters of the *N*-acetylglucosaminyl aglycone and of the aglycone of teicoplanin. J. Antibiot. 40: 1572–1587

Malabarba, A., Trani, A., Strazzolini, P., Cietto, G., Ferrari, P., Tarzia, G., Pallanza, R., Berti, M. (1989) Synthesis and biological properties of N^{63}-carboxamides of teicoplanin antibiotics. Structure-activity relationships. J. Med. Chem. 32: 2450–2460

Malabarba, A., Ciabatti, R., Retteuring, J., Scotti, R., Candiani, G., Pallanza, R., Berti, M., Goldstein, B. P. (1992) Synthesis and antibacterial activity of a series of basic amides of teicoplanin and deglucoteicoplanin with polyamines. J. Med. Chem. 35: 4054–4060

Parenti, F., Cavalleri, B. (1990) Novel glycopeptide antibiotics of the dalbaheptide group. Drugs of the Future 15: 57–72

Rekker, R. F., Mannhold, R. (1992) Calculation of Drug Lipophilicity. VCH, Weinheim, New York

Terada, H. (1986) Determination of log P_{oct} by high-performance liquid chromatography, and its application in the study of quantitative structure-activity relationships. Quant. Struct.-Act. Relat. 5: 81–88

Testa, B., Kier, L. B. (1991) The concept of molecular structure in structure-activity relationship studies and drug design. Med. Res. Rev. 11: 35–48

Topliss, J. G. (ed.) (1983) Quantitative Structure-Activity Relationships of Drugs. Academic Press, New York

Tsai, R.-S., Testa, B., El Tayar, N., Carrupt, P.-A. (1991) Structure-lipophilicity relationships of zwitterionic amino acids. J. Chem. Soc. Perkin Trans. 2: 1797–1802

van de Waterbeemd, H., Testa, B. (1987) The parametrization of lipophilicity and other structural parameters in drug design. In: Testa, B. (ed.) Advances in Drug Research. Vol. 16, Academic Press, London, pp 85–225