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Research paper

Applying pattern recognition methods and structure property correlations to determine drug carrier potential of nicotinic acid and analogize to dihydropyridine

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Abstract

Multivariate methods are utilized to compare nicotinic acid and dihydropyridine as a drug carrier. Nicotinic acid and dihydropyridine form ester groups on 10 β-lactam antibiotics with an oxymethyl group forming a linkage between the antibiotic and the drug carrier (nicotinic acid or dihydropyridine). Calculated molecular properties are analyzed by self-organizing tree algorithm (SOTA), bivariate regression, cluster analysis, factor analysis, discriminant analysis, hierarchical classification, and principal coordinates analysis. Ten important pharmacological properties for each of the nicotinic acid and dihydropyridine antibiotic derivatives are numerically similar and highly correlated. Calculated molecular properties include molar refractivity, molar volume, parachor, index of refraction, partition coefficient (log P), polarizability, and polar surface area. Dermal permeability coefficients (K_p) for nicotinic acid derivatives are similar to values for dihydropyridine derivatives. Dermal permeabliity coefficients analyzed by hierarchical classification and SOTA analysis were shown to be closely interrelated and highly correlated. Ten properties of the nicotinic acid and dihydropyridine were compared by Passing–Bablok regression analysis and shown to be highly correlated ($r = 0.9879$). Box plot analysis of 10 properties, inclusive of both groups of derivatives, showed narrow ranges in values. Cluster analysis of derivative properties showed the nicotinic acid derivatives to be highly similar to the dihydropyridine derivatives of the same antibiotics. Cluster analysis was performed by single linkage, complete linkage, and centroid linkage. Factor analysis showed the nicotinic acid derivatives to be interrelated and similar to the dihydropyridine derivatives. Discriminant analysis performed on all derivatives formed a single highly cohesive and non-differentiated cluster, demonstrating strong similarity among nicotinic acid and dihydropyridine derivatives. Principal coordinates analysis (determines similarity) of K_p values showed high similarity between the nicotinic acid and dihydropyridine antibiotic derivatives.

Keywords: Nicotinic acid; Dihydropyridine; Pattern recognition; Antibiotics; Multivariate methods

1. Introduction

Chemical delivery systems (CDSs) utilizing dihydropyridine as a drug carrier have been previously studied. The synthesis of dihydropyridine derivatives of semisynthetic penicillins has been achieved previously, and the procedure actually passes through steps which connect the nicotinic acid compound by an oxymethyl linkage to the β-lactam antibiotic [1]. The final step of such synthesis is the methylation of the nitrogen atom within the pyridine ring by CH_3I, forming the dihydropyridine carrier [1]. Therefore, the actual synthesis of the nicotinic acid derivatives of β-lactam antibiotics (nicotinic acid present as nicotinate ester group) has been accomplished [1]. Previous studies have shown that dihydropyridine-based pharmaceuticals are water-soluble [2] and can be formed into tablets for clinical applications [3]. The treatment of bacterial infections of the brain have necessitated the use of CDSs because many active antibiotics are unable to cross the blood–brain barrier (BBB) [1]. An important application of dihydropyridine-based pharmaceuticals are as water-soluble CDSs for brain penetrating formulations [4–6]. Dihydropyridine CDSs have been shown capable of delivering peptides to the brain as HIV protease inhibitors [7]. Dihydropyridine CDSs have been shown to deliver β-lactam antibiotics specifically

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to the brain [8,9] and function as vehicles for gene delivery [10].

Nicotinic acid has structural similarity to dihydropyridine (i.e. it contains a nitrogen atom within a ring and a carboxyl group (–COOH)). Nicotinic acid is a B vitamin which has shown useful clinical applications for treating hyperlipidemia [11]. Nicotinamide (the amide version of nicotinic acid) has been studied previously as a drug carrier for centrally acting thyrotropin-releasing hormone analogs [12]. Previous studies have determined that the metabolic processing of nicotinic acid irreversibly produces nicotinamide, *N*-methyl-nicotinamide, and finally *N*-methyl-2-pyridone-5-carboxylamide in sequence [13]. Use of nicotinic acid as a treatment for hyperlipidemia [11] has shown that considerable amounts of the vitamin (1500 mg per day) can be beneficial and tolerated by patients.

The work presented here shows nicotinic acid to have strong potential as a drug carrier and to be highly analogous to dihydropyridine when applied in a similar manner with β-lactam antibiotics. The synthesis of nicotinic acid CDSs of β-lactam antibiotics has been achieved previously as by-products of dihydropyridine CDS synthesis [1]. Methods of numerical analysis such as self-organizing tree algorithms, bivariate regression, cluster analysis, factor analysis, discriminant analysis, hierarchical classification, and principal coordinates will show clearly that nicotinic acid has high potential as a drug carrier of antibiotics and is analogous to a dihydropyridine carrier. Application of multivariate methods to evaluate potential drug carriers will provide novel tools beneficial for clinical application.

2. Materials and methods

2.1. Software

Calculation of molar volume, parachor, molar refractivity, formula weight, and polarizability were accomplished by ChemSketch (Toronto, Ontario, Canada). Structure modeling was accomplished by MDL ISIS DRAW 2.5 (Copyright 1990–2002, MDL Information Systems Inc) and ChemSketch. Hierarchical classification analysis was accomplished by OpenStat 3 v. 3.1.0 (Copyright 2003, William G. Miller).

Discriminant analysis and factor analysis were performed KyPlot v. 2.0 beta 15 (Copyright 1997–2001 Koichi Yoshioka). Principal coordinates analysis was accomplished by PAST v. 0.45 (D.A.T. Harper May 2001, Øyvind Hammer). Cluster analysis was accomplished by AMADA v. 2.0.3 [14], KyPlot, and StatBox v 2 (Grimmersoft Logiciels, Paris France). Values of water solubility, log K_{ow}, and dermal permeability coefficient (K_p) were calculated by EPISUITE (Copyright 2000 US Environmental Protection Agency, Washington DC). Passing–Bablok regression analysis was accomplished by Method Validator analysis program (P. Marquis, Biologiste des hopitaux, Metz France). Box plots and means plot were accomplished by GraphPad Prism 4 (GraphPad Software, www.graphpad.com).

2.2. Computer-based algorithms

Values of $m_i \log P$, number of nitrogens, oxygens, hydroxyls (–OH), and amines (–NH) were determined by Molinspiration Cheminformatics (Bratislava, Slovak Republic). Self-organizing tree algorithm (SOTA) analysis was accomplished by GEPAS v. 1.0 [15]. Descriptive statistics and general scatter plot graphing were accomplished by Quattro Pro 10 (Copyright 2001 Corel Corporation).

3. Results and discussion

CDSs have been utilized to facilitate drug concentrations at therapeutic levels where tissue and organs present barriers (i.e. Membranes) that deter beneficial applications of clinical pharmaceuticals. The BBB presents obstacles to the beneficial applications of some drugs. Dihydropyridine has been shown to be a successful vehicle to enhance brain delivery of penicillin antibiotics [8,9]. Utilizing an oxymethyl linkage between the drug carrier (dihydropyridine) and the antibiotic, the final derivative is readily acquired [1] and this synthesis actually generates the nicotinate compound (nicotinic acid as an ester group) prior to the final steps producing the dihydropyridine derivative.

Examples of the structures of antibiotic derivatives which are examined by multivariate methods are shown in Fig. 1 with the drug carrier indicated by inset rectangle, the β-lactam group indicated by inset circle, and oxymethyl linkage indicated by inset arrow. The penicillin-type antibiotics utilized for this study include the following: methicillin, oxacillin, benzylpenicillin, penicillin F, dihydro F, propicillin, carbenicillin, penicillin K, penicillin X, and ampicillin. Molecular properties of these 10 penicillins are calculated after incorporating an oxymethyl-linked dihydropyridine or nicotinate carrier group in the position of the former carboxyl group (–COOH) of the parent compound.

Various pharmacological parameters of nicotinic acid ($C_6H_5NO_2$) are highly correlated with those of dihydropyridine ($C_7H_9NO_2$), which include parachor, formula weight, molar volume, polar surface area, and partition coefficient. Demonstrating this result is a Passing–Bablok regression plot of nine molecular properties that is presented in Fig. 2 (dihydropyridine on *y*-axis and nicotinic acid on *x*-axis). A Passing–Bablok regression analysis makes no presumptions of the normality or instrumental techniques of gathering the data and is a means of method validation. It is clearly seen that there is a strong correlation between molecular properties of dihydropyridine and nicotinic acid (Spearman rank correlation $r = 0.9879$) which strongly supports the contention that these two compounds are highly similar.

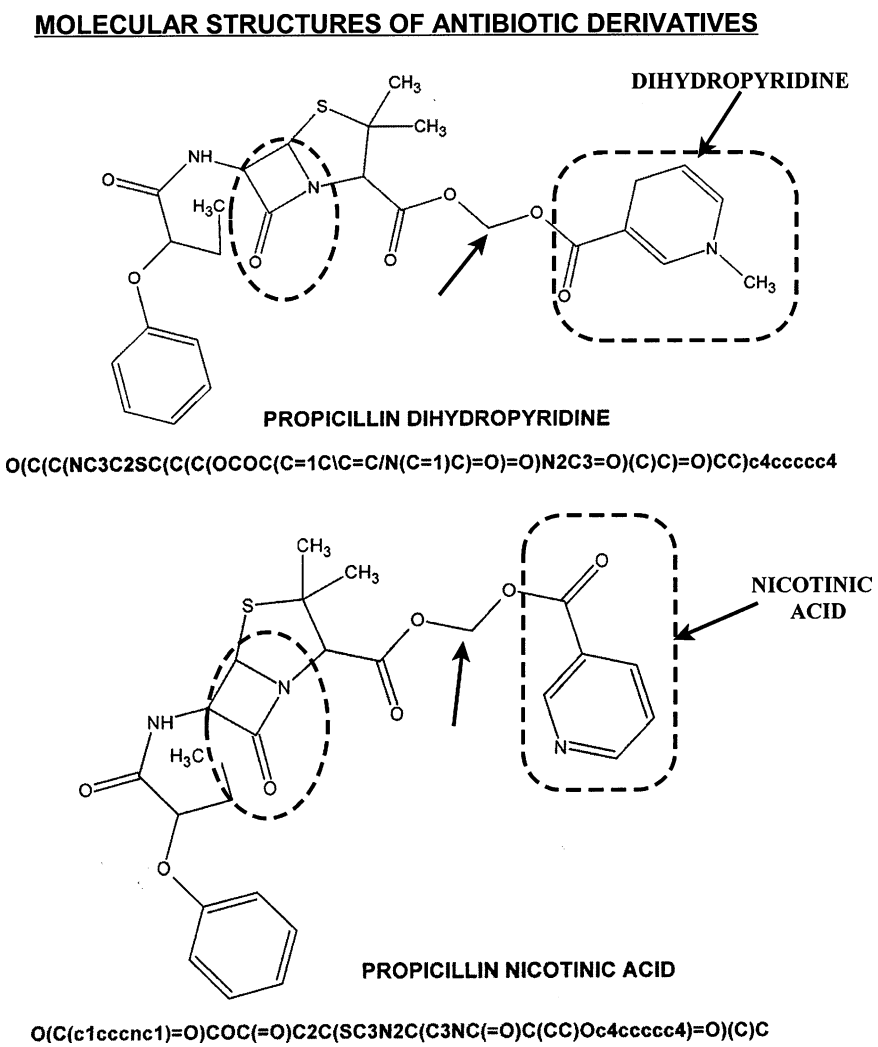

Fig. 1. Examples of molecular structures for each group of nicotinate derivatives and dihydropyridine derivatives. The oxymethyl linker is indicated by inset arrow, β-lactam group indicated by inset circle, and drug carrier (nicotinic acid or dihydropyridine) by inset rectangle. The SMILES designation is given for each example shown here.

These properties and others will be utilized to compare these two groups of antibiotic derivatives designed to penetrate the BBB.

Table 1 presents for both the nicotinic acid group and dihydropyridine group of antibiotic derivatives the 10 molecular properties used for comparison by multivariate methods. Note the antibiotic name listed with each group designation and the number assigned given to the right of the name for purposes of identification in cluster analysis, factor analysis, and discriminant analysis. Units for molar refractivity, molar volume, parachor, and polarizability are cm^3 (polar surface area is $Å^2$). Visual inspection of the numerical values of these properties show the high similarity between the nicotinic acid and dihydropyridine derivatives. An effective manner of visualizing the mean and numerical range for each parameter is by box plot. These are presented in Fig. 3 for these molecular properties and inclusive of BOTH groups of derivatives. The top half of Fig. 3 shows box plots for polar surface area, polarizability, parachor, molar volume, molar refractivity, and formula weight values inclusive of both nicotinic acid and dihydropyridine derivatives. The line bisecting the box indicates the mean value of both groups and box whiskers (extensions) indicate the ranges of numerical values. Note that all property values lie within a small numerical range which strongly supports the contention that antibiotic derivatives of nicotinic acid and dihydropyridine are highly similar. Numerical values for polarizability, molar refractivity, and index of refraction (lower half) fall into an extremely narrow range. This type of data representation allows medicinal chemists the ability to determine novel molecular structures which have appropriate numerical values for these important parameters (i.e. values which fit inside the numerical range presented by the box plots and whiskers). The lower half of Fig. 3 shows numerical ranges for $m_i \times \log P$, index of refraction, numbers of oxygens (O), nitrogens (N), amines (–NH), and hydroxyls (–OH).

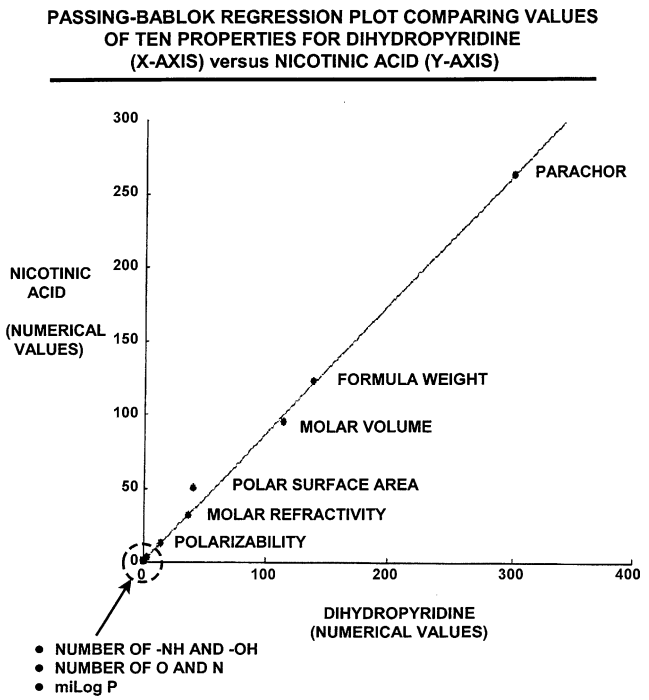

Fig. 2. Passing–Bablok regression analysis for molecular properties of nicotinic acid ($C_6H_5NO_2$) and dihydropyridine ($C_7H_9NO_2$). High linearity from dihydropyridine values (*x*-axis) plotted versus nicotinic acid values (*y*-axis) clearly show high similarity of these two compounds.

Taking into account the small numerical range of the *x*-axis to be 0–12, again it is clearly seen that the small range of these parameters is inclusive of BOTH nicotinic acid and dihydropyridine-type derivatives.

Polar surface area of pharmaceuticals has been shown to be an accurate and useful tool for prediction of absorption into tissues [16–19]. In particular, it has been shown to be effective in predicting penetration of the BBB into the brain [20,21]. A means plot is an effective method to compare values of numerical data and ranges for analogous categorical variables. A means plot of polar surface area values for nicotinic acid derivatives is shown in a vertical scale in Fig. 4 and compared to those values for dihydropyridine derivatives (Fig. 4). Group means (indicated by inset arrow) lie numerically close to one another and the range of values overlap into each group. Polar surface area values range from 105.26 to 152.21 $Å^2$ (Table 1), which indicates intestinal absorption of these 20 compounds will range from 37 to 5%, respectively [19]. This again demonstrates similarity and overlap of the nicotinic acid group with the dihydropyridine group of antibiotic derivatives.

Hierarchical cluster analysis determines subgroups of data having high similarity within a larger group. The approach applied here is a divisive method in which all data begins in one large cluster and euclidean distance which is the mathematical shortest distance between subjects. Fig. 5 shows the results of cluster analysis of all 20 compounds and all 10 properties shown in Table 1. Individual antibiotic compounds are identified by number assignment shown in Table 1 to the right of the drug name (Table 1). Single linkage analysis is given in the top dendogram and represents the results of distance measurements between the two closest subjects with the clusters. Complete linkage

Table 1
Molecular properties of derivative compounds

		Formula weight	Molar refractivity	Molar volume	Parachor	Index of refraction	Polarizability	Number of oxygens and nitrogens	Number of amine and hydroxyl groups	m_i Log *P*	Polar surface area
Nicotinic acid structures											
Methicillin	11	515.54	128.28	357.7	1030.5	1.636	50.85	11	1	2.563	133.28
Oxacillin	12	538.57	138.11	358.7	999.6	1.696	54.75	11	1	3.232	136.51
Benzylpenicillin	13	469.51	120.18	330.6	953.4	1.647	47.64	9	1	2.801	114.91
Penicillin F	14	447.51	113.9	329.9	927.4	1.606	45.15	9	1	2.88	114.91
Dihydro F	15	449.52	113.99	336.6	939.8	1.592	45.19	9	1	3.12	114.91
Propicillin	16	513.56	131.16	369.4	1051.8	1.628	51.89	10	1	3.629	124.143
Carbenicillin	17	513.52	126.44	341.3	1013.6	1.662	50.12	11	2	1.734	152.21
Penicillin K	18	477.58	123.25	368.8	1019.9	1.582	48.86	9	1	3.988	114.91
Penicillin X	19	485.51	121.71	327.4	968.6	1.665	48.25	10	2	2.417	135.137
Ampicillin	20	484.53	123.78	334.7	981.1	1.661	49.07	10	3	1.12	140.93
Dihydropyridine structures of penicillins											
Methicillin	1	531.58	134.98	377	1069.9	1.634	53.51	11	1	2.339	123.723
Oxacillin	2	554.62	143.43	379.9	1045.1	1.679	56.86	11	1	3.008	126.853
Benzylpenicillin	3	485.55	126.88	349.9	992.7	1.645	50.3	9	1	2.577	105.26
Penixillin F	4	463.55	120.6	349.2	966.8	1.607	47.81	9	1	2.436	105.26
Dihydro F	5	465.56	120.69	355.9	979.2	1.593	47.84	9	1	2.676	105.26
Propicillin	6	529.61	137.86	388.6	1091.2	1.627	54.65	10	1	3.405	114.49
Carbenicillin	7	529.56	133.14	360.6	1052.9	1.66	52.78	11	2	1.51	142.55
Penicillin K	8	493.62	129.96	388.1	1059.3	1.584	51.52	9	1	3.544	105.26
Penicillin X	9	501.55	128.41	346.7	1007.9	1.662	50.9	10	2	2.194	125.48
Ampicillin	10	500.57	130.49	354	1020.4	1.658	51.73	9	3	0.896	131.28

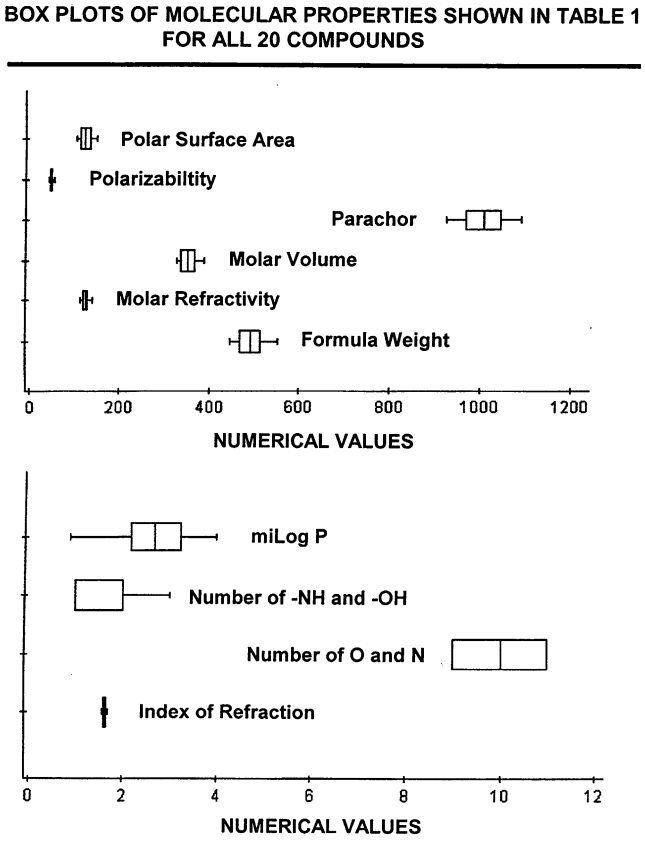

Fig. 3. Box plots with whiskers clearly show the narrow ranges of 10 molecular properties for all 20 compounds shown in Table 1. This observation supports the contention that nicotinate derivatives are highly similar to dihydropyridine derivatives.

is distance between the farthest pair of points within two clusters. Centroid linkage is analysis of data in which distances are measured between mean positions within clusters. With all cluster analysis methods, the dihydropyridine derivatives (**1**–**10**) are completely interdispersed with the nicotinic acid derivatives (**11**–**20**), thus indicating very high similarity. Intergroup clustering of members are consistent with single, complete, and centroid analysis. Examples of consistent intergroup clustering include the following combinations: **1** and **11**, **8** and *18*, **2** and **12**, **7** and **17**, **9** and **19**. This consistent pairing of intergroup members occurs as secondary or tertiary nodes within higher clusters. In summary, the cluster analysis results showed the nicotinic acid derivatives to be well interdispersed and analogous to the dihydropyridine derivatives.

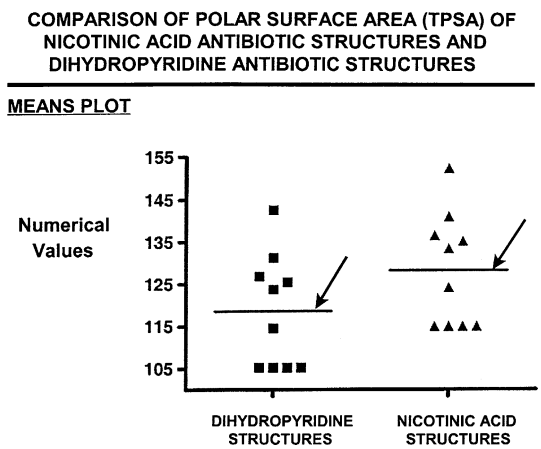

Fig. 4. Polar surface area (TPSA) is an important parameter for predicting the membrane permeability of a drug. Average TPSA is indicated by inset arrows and clearly shows close proximity and overlap of TPSA for both groups.

The main applications of factor analysis techniques are: (A) reduce the number of variables; (B) detect structure in the relationships; and (C) classify variables. Data is reduced to two factors designated Factors 1 and 2, which contain the majority of variance within the entire data. Factor analysis was accomplished utilizing all variables and subjects shown in Table 1. Fig. 6 presents results of factor analysis and reveals the pattern of relationship between nicotinic acid derivatives (**11**–**20**) and dihydropyridine derivatives (**1**–**10**). Dihydroypridine derivatives are indicated in Fig. 6 by inset arrows. In general, the nicotinic acid derivatives are shifted higher (more positive) along Factor 2 axis in relation to dihydropyridine derivatives. This is high interdispersion of derivative groups along the Factor 1 axes which will generally contain greater content of data variance than Factor 2. Although individual derivatives are not highly interdispersed when considering both factor axis, it is clearly seen that the two groups of derivatives overlap strongly in this dimensionality.

Discriminant analysis is performed to predict group membership and determine the relationship between group membership. Greater discrimination between groups is achieved if the groups have considerable difference between their group means. If low discrimination exists between groups, then they have large overlapping regions. Fig. 7 shows discriminant analysis of all 20 compounds and 10 properties shown in Table 1. It is clearly seen that no significant discrimination exists along DA 1 and DA 2. The 20 compounds are grouped around a single principal cluster, which indicates that there is no significant difference of the group means for the nicotinic acid derivatives and dihydropyridine derivatives. Identified by number designation given in Table 1, the data points correspond to derivatives (from left to right): **14**, **15**, **13**, **4**, **12**, **19**, **5**, **20**. **3**, **9**, **2**, **17**, **10**, **18**, **11**, **7**, **16**, **8**, **1**, and **6**. The results of this analysis clearly show that dihydropyridine ester derivatives are extremely similar to nicotinic acid derivatives of the same penicillin antibiotics.

Penetration of dermal layers can be measured in terms of dermal permeability coefficient (K_p) in centimeters per hour (cm/h). Dihydropyridine has been used previously to facilitate drug penetration through dermal layers. Values of K_p calculated by EPISUITE software are presented in Table 2 for all antibiotic derivatives. Visual inspection of numerical values indicates that the values are comparable across derivative types (for the same antibiotic). For each type of antibiotic, the intergroup K_p values are correlated

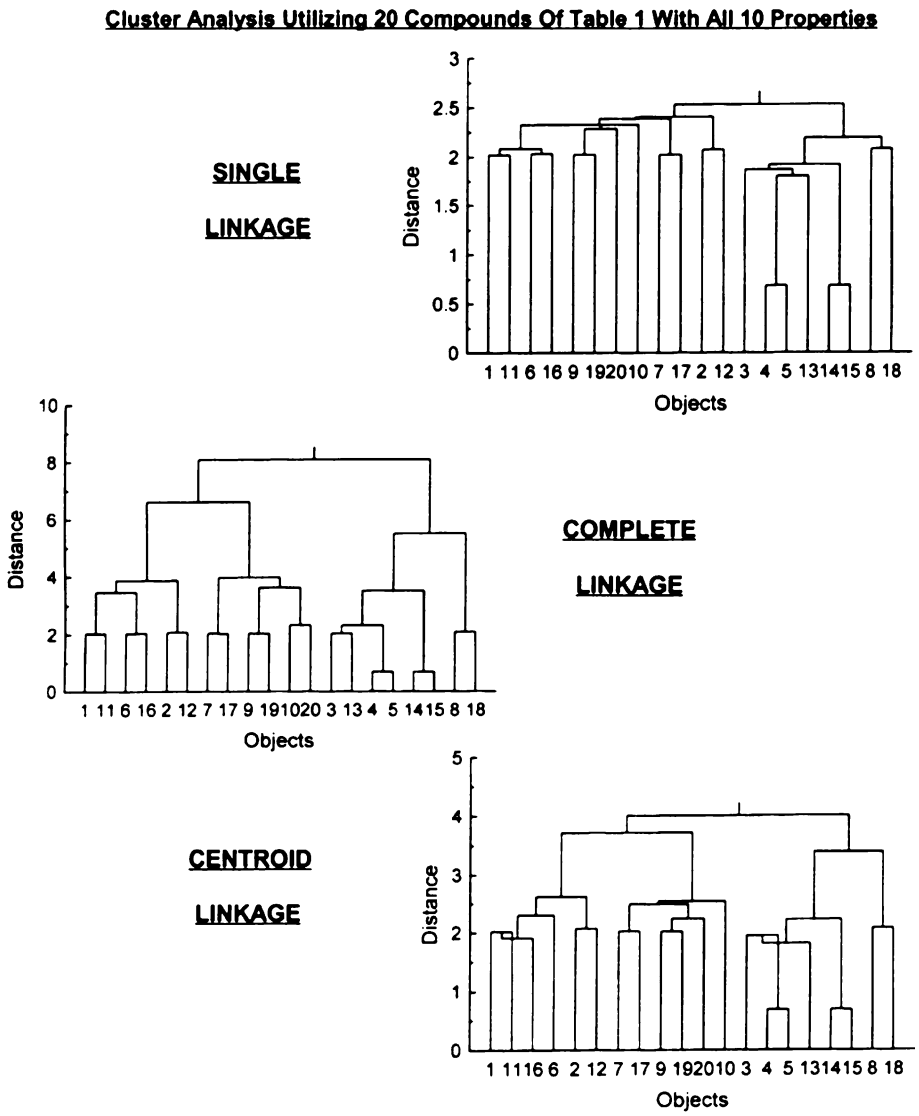

Fig. 5. Dendograms of cluster analysis of all properties and compounds presented in Table 1 (note numerical identification numbers adjacent to drug names). Cluster analysis is calculated under Euclidean distance with single, complete, or centroid linkage. Note consistent grouping of the following compounds in identical clusters: **1** and **11**, **8** and **18**, **2** and **12**, **7** and **17**, **9** and **19**.

(non-parametric Spearman $r = 0.6606$). For K_p values on matched antibiotic types the Wilcoxon matched pairs signed ranks test resulted in a two-tailed P value of 0.0020 (considered very significant) and verified that matching by derivative type (dihydropyridine or nicotinic acid) was effective. Overlap of average values of K_p for each group, based on standard deviation (Table 2), further supports the contention that these derivative types are similar. Hierarchical classification of K_p values as matched pairs according to antibiotic type is presented in Fig. 8. The matched pairs of derivatives are identified by designated number as indicated to the left of the antibiotic name as shown in Table 2. The 10 matched pairs are designated into three primary nodes (labeled as A) indicated in Fig. 8. The methicillin and dihydro F derivatives (**1** and **5**) are combined in an identical group; benzylpenicillin, penicillin F, and ampicillin derivatives (**3**, **4**, and **10**) are combined in an identical group; oxacillin, penicillin K, propicillin, penicillin X, and carbenicillin (**2**, **8**, **6**, **9**, **7**) are combined in an identical group. Principal coordinates analysis will determine the distances within data arranged in a matrix and organize the subjects so that similarities are maximized. The similarities among subjects can be visualized in a 2D plot in which close proximities are indicative of similarity. Fig. 9 shows the 2D plot of principal coordinates in which close proximities of derivative pairs **6**, **5**, **4**, **1**, **3**, **9**, **7**, and **10** (enclosed in inset rectangle) are indicated as highly similar.

SOTA analysis of all 20 compounds and 10 properties shown in Table 1 produced two clusters with derivatives identified by number identification and formula weight as shown in Table 3. Results of SOTA analysis indicate similarity among subjects analogous to the method of cluster analysis and will report results in terms of clusters. It is readily seen that members of each group of derivatives are

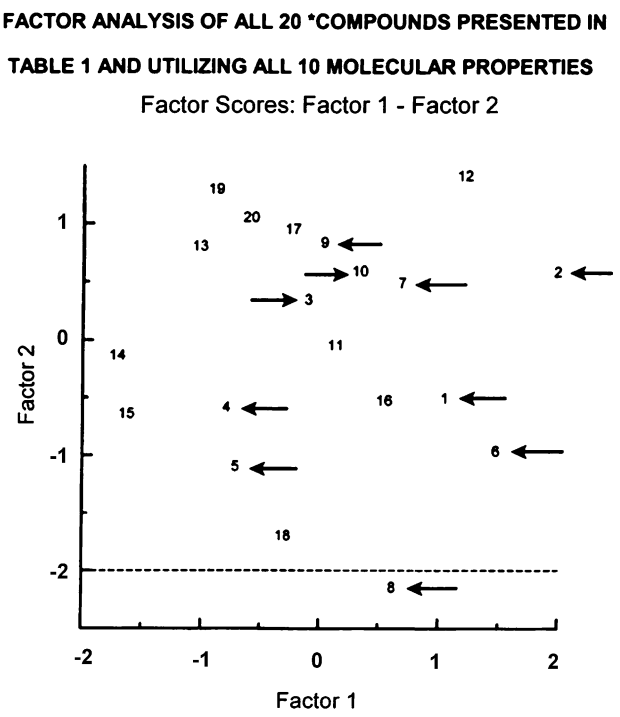

Fig. 6. 2D plot of Factors 1 and 2 for all compounds and molecular properties given in Table 1 (note numerical identification adjacent to drug names in Table 1). Inset arrow designates dihydropyridine derivatives. High overlap is observed for the two groups of derivatives.

interdispersed and therefore determined to be similar. Cluster analysis (single linkage) performed by StatBox of all compounds and properties given in Table 1 produced three clusters of similar compounds as follows: Cluster 1: **4**, **5**, **13**, **14**, **15**, **19**, **20**; Cluster 2: **3**, **9**, **10**, **11**, **12**, **17**, **18**; Cluster 3: **1**, **2**, **6**, **7**, **8**, **16**. These results show high interdispersion of members of these two groups of derivatives and consequently very high similarity.

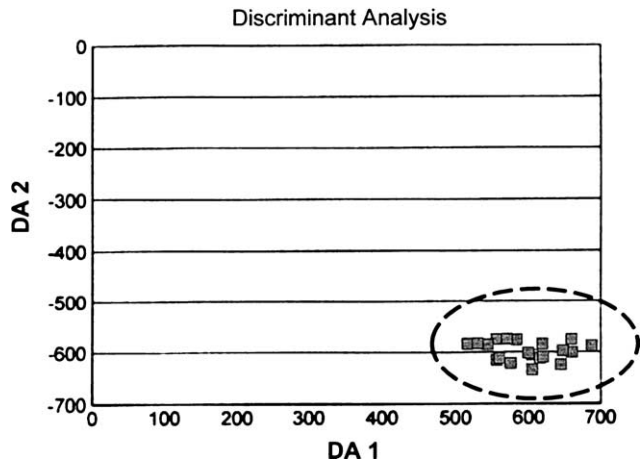

Fig. 7. Discriminant analysis of all compounds and properties given in Table 1. Note all compounds are located in close proximity within a single cluster. Identification of compounds is from left to right: **14**, **15**, **13**, **4**, **12**, **19**, **5**, **20**. **3**, **9**, **2**, **17**, **10**, **18**, **11**, **7**, **16**, **8**, **1**, and **6** . This result strongly supports the similarity between these two groups of antibiotic derivatives.

Table 2
Dermal permeability coefficient (K_p)

Number	Antibiotic type	Dihydropyridine structures (cm/h)	Nicotinic acid structures (cm/h)
1	Methicillin	1.87×10^{-5}	1.05×10^{-5}
2	Oxacillin	0.000195	4.88×10^{-6}
3	Benzylpenicillin	2×10^{-5}	1.12×10^{-5}
4	Penicillin F	2.92×10^{-5}	1.63×10^{-5}
5	Dihydro F	4.03×10^{-5}	2.25×10^{-5}
6	Propicillin	4.92×10^{-5}	2.76×10^{-5}
7	Carbenicillin	9.63×10^{-6}	5.38×10^{-6}
8	Penicillin K	0.000135	7.57×10^{-5}
9	Penicillin X	7.29×10^{-6}	4.08×10^{-6}
10	Ampicillin	8.5×10^{-6}	4.75×10^{-6}

Mean of dihydropyridine derivatives: 5.13×10^{-5} cm/h, standard deviation: 6.31×10^{-5} cm/h, mean of nicotinic acid derivatives: 1.83×10^{-5} cm/h, standard deviation: 2.17×10^{-5} cm/h.

Other important pharmacological parameters include water solubility, log K_{ow}, and violations of Rule of 5. Previous studies have shown that two violations of the Rule of 5 indicate a drug will be poorly absorbed in vivo [22]. Good drug absorption in vivo and bioavailability are more likely if the following are traits: (a) less than five hydrogen bond donors; (b) formula weight is less than 500; (c) log P is less than 5; (d) there is less than 10 hydrogen bond acceptors. Log K_{ow} values describe the partitioning between an organic and water layer when all compounds are neutral. Values for log K_{ow}, violations of Rule of 5, and water solubility for all 20 derivatives are presented in Table 4.

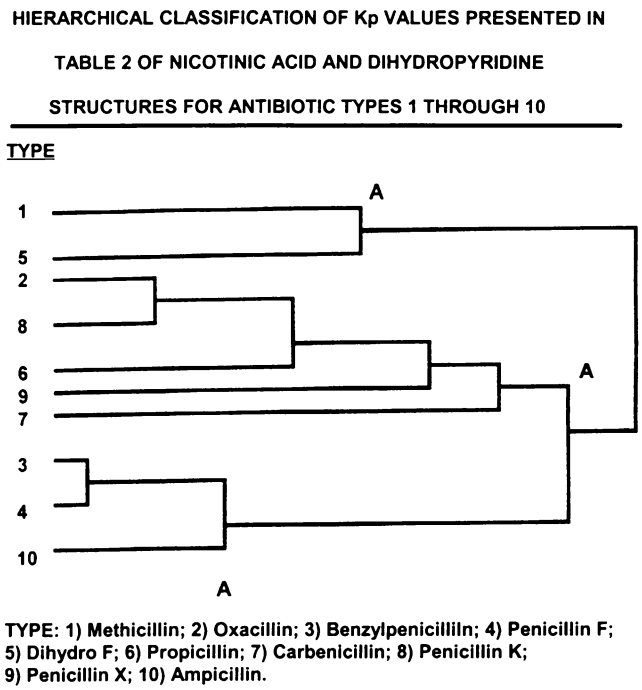

Fig. 8. Hierarchical classification of K_p values given in Table 2 (note numerical identification adjacent to drug names). Compounds are highly interdispersed with grouping within just three primary nodes (designated by A) and therefore analogous.

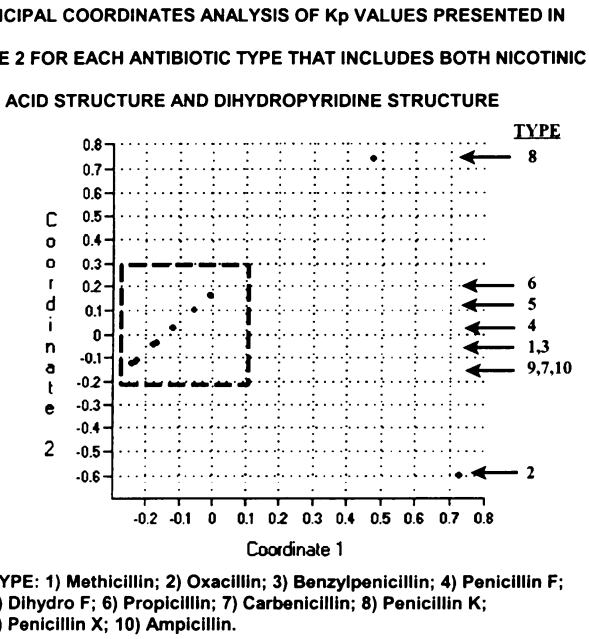

Fig. 9. Principal coordinates analysis of antibiotic type derivatives given in Table 2 clearly shows strong similarity of sets **6**, **5**, **4**, **1**, **3**, **9**, **7**, and **10**. See inset key for identification of numbered pairs.

Mean log K_{ow} value for dihydropyridine derivatives is 1.77 compared to the mean of 1.088 for nicotinic acid derivatives. Average water solubility of dihydropyridine derivatives is 79.02 mg/l which is much less than average solubility of 269.48 mg/l for nicotinic acid derivatives. Greater water solubility may be considered beneficial and enhances blood solubility. No greater than two violations of Rule of 5 are determined by Molinspiration for members of each group of derivatives and overall violations are similar from group to group.

Table 3
SOTA[a] analysis of all 20 compounds[b] of Table 1 by GEPAS

Cluster 1	531.58	**1**
	554.62	**2**
	529.61	**6**
	529.56	**7**
	493.62	**8**
	500.57	**10**
	515.54	**11**
	513.56	**16**
	513.52	**17**
	477.58	**18**
Cluster 2	485.55	**3**
	463.55	**4**
	465.56	**5**
	501.55	**9**
	538.57	**12**
	469.51	**13**
	447.51	**14**
	449.52	**15**
	485.51	**19**
	484.53	**20**

[a] SOTA, Self-organizing tree algorithm.
[b] Compounds identified by formula weight values. Utilizing all 10 properties.

Table 4
Properties of antibiotic compounds

	Log K_{ow}	Violations of Rule of 5	Water solubility (mg/l)
Nicotinic acid structures			
Carbenicillin	0.82	2	116.4
Propicillin	1.82	2	16.32
Penicillin X	0.41	0	1502
Penicillin K	2.13	0	15.11
Penicillin dihydroF	1.15	0	157
Penicillin F	0.93	1	246.7
Oxacillin	0.98	2	59.18
Benxylpenicillin	0.89	0	194.3
Methicillin	1.25	0	49.14
Ampicillin	0.5	0	338.6
Dihydropyridine structures			
Carbenicillin	1.32	2	34.79
Propicillin	2.31	2	4.877
Penicillin X	0.9	0	449.6
Penicillin K	2.62	0	4.525
Penicillin dihydroF	1.64	0	47.12
Penicillin F	1.43	1	74.57
Oxacillin	3.37	2	0.4212
Benxylpenicillin	1.38	0	58.22
Methicillin	1.74	1	14.68
Ampicillin	0.99	1	101.4

4. Conclusion

Penicillin derivatives which contain either a nicotinic acid or dihydropyridine group linked by an oxymethyl moiety to a carbonyl carbon were compared by multivariate methods. Cluster analysis by single, complete, and centroid linkage clearly showed that members of each group of derivatives were highly similar and determined to be in identical clusters. Factor analysis of all 20 antibiotic derivatives utilized for this study, and with 10 molecular properties, produced a 2D plot of Factor 1 versus Factor 2 having interdispersed subjects (indicating similarities in properties). Penetration of dermal layers as indicated by dermal permeability coefficient (K_p) were calculated for each class of derivatives (nicotinic acid and dihydropyridine) and found to be comparable. Hierarchical classification of derivative pairs matched by the same parent compound clearly showed similarities with derivatives derived from different parent compounds. Also, principal coordinates analysis of K_p for same matched pairs of derivatives resulted in a 2D coordinates plot showing 80% of the derivatives being highly similar. SOTA analysis of all 20 compounds via 10 properties produced two clusters showing clearly the interdispersion of nicotinic acid and dihydropyridine derivatives, and thereby high levels of

similarity between the two groups of derivatives. The number of violations of Rule of 5 for each group of penicillin derivatives were comparable, as were values of $\log K_{ow}$. Nicotinic acid derivatives had greater water solubility in general than did the dihydropyridine derivatives. Numerical values of 10 important molecular properties were calculated for each member of nicotinic acid and dihydropyridine derivatives and found to be comparable by box plot. A means plot showed similarity of polar surface area values for each group (this property being important in estimating membrane penetration). A Passing–Bablok regression analysis of nine properties for nicotinic acid and dihydropyridine themselves showed extremely high correlation ($r = 0.9879$). These results strongly support the contention that nicotinic acid is comparable and highly similar to dihydropyridine as a drug carrier. These results suggest that nicotinic acid has good potential as a useful and beneficial clinical tool.

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