# Application of the Hypersurface Iterative Projection Method to Bicyclic Pyrazolidinone Antibacterial Agents

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Bicyclic pyrazolidinones are a class of synthetic antibacterial agents in which the β-lactam ring is replaced by a five-membered ring. These compounds possess electronic and shape properties required for inhibiting penicillin-binding proteins essential for bacterial cell growth. A novel approach called the hypersurface iterative projection (HIP) method, which is based on three-dimensional computer graphics, allows available structure–activity information to be extrapolated to new synthetic targets. By updating the data set as the SAR evolves, the computer graphics reveal regions of parameter space to explore for optimum activity and regions yet unexplored. A large substituent parameter database is used to propose appropriate substituents. For the bicyclic pyrazolidinones, lipophilicity and particularly electron-withdrawing properties of the 3-substituent are shown to correlate strongly with minimum inhibitory concentrations (MIC). Antibacterial potency is intimately related to the activating effect of 3-substituents on chemical reactivity. The HIP method succeeded in proposing the most potent member of the series prior to synthesis and also showed when all of parameter space was reasonably well explored to the extent the chemistry allowed.

The field of quantitative structure–activity relationships (QSAR) has seen the development of numerous techniques to explore the space measured by the electronic, structural, and lipophilic parameters of substituents on a parent compound.[1,2] These techniques have as their primary purpose the discovery of structural variations that optimize a property, such as biological activity, for a set of compounds. Of all the approaches in computer-aided chemistry, QSAR is best suited for substituent optimization. In the case of drug design, an additional advantage of QSAR is that there is no requirement for a three-dimensional structure of the receptor molecule. Also, the calculations are fast and need not be compute-intensive.

The hypersurface iterative projection (HIP) method was developed with these goals in mind and proved well suited for achieving them. It is based on three-dimensional computer graphics and has applicability to many molecular series. Its success rests on the active interplay of synthetic chemistry, biological (or other) testing, and computations. The method allows the scientist to extrapolate quantitatively from structure–property information at hand to what chemical modifications to try next. The HIP method is thus applicable to the rational development of a structure–activity series and optimization of biological activity (or other molecular property) by variation of substituents at a position on a molecular framework.

The method was first conceived and applied during the study of bicyclic pyrazolidinone antibacterial agents. The β-lactam ring, which is the hallmark of the well-studied penicillin and cephalosporin classes of antibiotics,[3] is replaced by a pyrazolidinone ring[4,5] (Figure 1). Recent computations and chemistry have shown that the four-membered ring could be replaced by a γ-lactam ring,[6,7] while retaining at last a very low level of antibacterial activity. Introducing a second nitrogen into the five-membered ring significantly boosted activity to a useful range.[8–12] The advantages of this ring bioisostere are that it opens up a novel structural series and it could in principle afford antibacterial or pharmacokinetic properties not achievable with traditional β-lactam antibiotics. In fact,

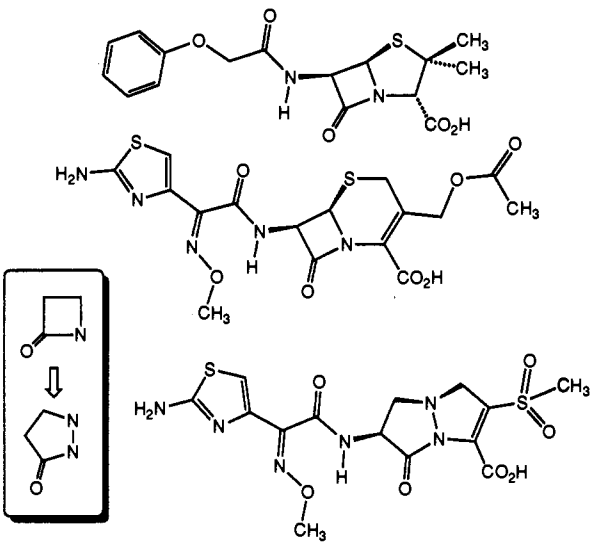

**Figure 1.** Example of a penicillin (pencillin V) and a third-generation cephalosporin (cefotaxime). The pyrazolidinone ring is able to function as a bioisostere of the β-lactam ring.

the new synthetic compounds exhibited broad spectrum activity and resistance to β-lactamases.[11]

Concepts related to the HIP method can be traced back to the well-known Craig plots.[13] In these, the location of substituents in parameter space are visualized by two-dimensional plots; any two (preferably noncollinearly related) substituent descriptors can be plotted along the two axes. The value of these plots is to show the relationship of substituents so that synthetic targets can be selected on the basis of similarity or dissimilarity strategies.

In the late 1970s, Cramer et al. used a Craig plot with a few hand-sketched contours to highlight regions of parameter space yielding the best biological activity for a series of antiallergic compounds.[14] In effect, this "relief map" added a third dimension. The plot was used only at the beginning of that QSAR analysis, and thereafter traditional Hansch-type regression analysis was used to

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process the structure–activity relationship (SAR) data. In contrast, the HIP method, as its name states, involves an iterative use of three-dimensional plots through the whole course of an SAR as it evolves. The HIP is intended to be used dynamically so that it can supply useful information before the SAR table is complete. Also, in the HIP method the computer is used to fit and form the contours through the data points.

The HIP method is different from the parameter focusing and cluster significant analysis methods.[15-17] They attempt to find a two-dimensional plot of physicochemical data wherein the active compounds tend to fall in one region and the inactive ones elsewhere. In contrast, the HIP method uses trends and gradations in the biological data to extrapolate the SAR to regions which have not yet been explored.

The HIP method will be illustrated by showing how it was applied as the SAR of the bicyclic pyrazolidinone series evolved. The electron-withdrawing power of the substituent at the 3 position was shown to play an important role in determining activity. The optimum compound, which achieved impressive antibacterial activity as good as third-generation cephalosporins, was one of those suggested by the method prior to synthesis.

## Methods

Properties of compounds will depend on a large number of variables related to molecular structure. It is useful to the scientist to be able to visualize as many of these variables as possible and thereby gain an appreciation of which variables to modify. A three-dimensional contour surface (hypersurface) can be fit through data points. From these surfaces and inspection of scatter plots of the data, one can project to regions of parameter space for exploration. In the HIP method, analysis and visualization of the data are done iteratively; that is, as more compounds are synthesized and the SAR evolves, the data set is updated with more compounds and biological data. By the end of the process, a hopefully complete picture of the effect of substituents on the property of interest will be secured.

The first step in the HIP method is to plot in three dimensions the property of interest as a function of two (or more) molecular descriptors. To do this requires, of course, that at least a small set of related compounds has already been made and tested. This is not usually a problem because the medicinal chemists will generally have started investigating a lead before a computational chemist becomes involved in a project. The descriptors can be any of the usual physicochemical parameters describing lipophilic, electronic, steric, or other tabulated or computed properties of substituents or molecules. Presenting the data as a multidimensional scatter plot[18] is essential for showing which regions of descriptor space have not been explored by the structural modifications already synthesized. Next a three-dimensional surface is fitted through the data with appropriate smoothing, thereby emphasizing trends in the data. Then examination of the surface as either a surface map[18] or contoured map reveals extrema-determining regions of descriptor space where the most promising activity is to be found, as well as those regions that are least promising. Of course, as the SAR develops and more compounds (and information) are added to the data set, the shape of the surface will change and further define the most promising regions.

SAS/GRAPH software can be programmed to produce scatter plots with up to six dimensions (variables) in a single plot, which is useful for seeing complex interrelationships in the data.[18] The software was also programmed to produce a topographical surface fitted to the data.[19] The bivariate spline procedure was used to interpolate between irregularly distributed data points. Only three variables at a time can be displayed in the contour and surface plots.

A large substituent parameter database is an important component of the HIP method. A huge relational database that we designed and created[20] was used to propose new synthetic targets. The database has over 17 000 physicochemical parameters for 3000 substituents. Hence it is possible for the computer to suggest substituents that might not be thought of otherwise. Searchable parameters include Hansch $\pi$ values for lipophilic contributions of substituents, several steric descriptors, such as the Taft, Charton, and Verloop parameters, and over 30 electronic constants, such as Hammett $\sigma_p$, $\sigma_{ms}$, and $\sigma_I$. The System 1032 database management software[21] allows queries to retrieve substituents with parameter values in specified ranges. The medicinal chemist can consider substituents in the hit lists on the basis of synthetic feasibility and other requirements such as the absence of obvious toxic potential.

The iterative process is terminated when all regions of parameter space (and all positions in the molecule) are explored and optimized and no further substituents can improve activity, at least to the extent that the chemistry allows.

## Results

The HIP method was applied to the bicyclic pyrazolidinones to improve their initially modest level of antibacterial activity. Biological activity of the compounds was expressed in the form of minimum inhibitory concentration (MIC) against pathogenic strains used for screening antibiotics. MICs (in units of $\mu$g/mL) were determined by the 2-fold serial agar dilution method.[11] For the QSAR analysis, MICs against various individual organisms and MICs averaged over several organisms were found to give correlations, although generally MICs against the Gram-negative organisms gave better correlations.

Because both Gram-positive and Gram-negative activities were important in the evaluation of the compounds, we show results from using geometric mean of MICs against 10 important organisms in the screen. Four Gram-positive organisms, *Staphylococcus aureus* X1.1, *Streptococcus pyogenes* C203, *Haemophilus influenzae* C.L. (ampicillin sensitive), and *Haemophilus influenzae* 76 (ampicillin resistant), and six Gram-negative organisms, *Escherichia coli* EC14, *Klebsiella pneumoniae* X26, *Enterobacter aerogenes* C32, *Salmonella typhi* X514, *Shigella sonnei* N9, and *Providencia rettgeri* C24, were included. These organisms were being used by the medicinal chemists to make decisions on the course of the SAR. Not included in the mean were MICs against *Pseudomonas* sp. because these were generally $\geq$128 $\mu$g/mL for all compounds in the series.

Using a geometric mean has the advantage that it is a single quantitative measure that would reflect the overall relative activity of the compounds. Also, a mean will tend to minimize the effects of the usual experimental uncertainty in MICs. The microbiological data were put in the form of log MIC of racemic material. More active compounds have smaller values. Because the medicinal chemists were used to thinking in terms of *lowering* MICs, it was more ergonomic to use log MIC rather than log(1/MIC) in the analysis.

$$\log \mathrm{MIC} = [\sum_{\text{organism } i}^{10} \log \mathrm{MIC}_i]/10$$

The compounds investigated are shown in Figure 2. The substituent at the 3 position was varied, while the (aminothiazolyl)methoximinoacetamido (ATMO) side chain at the 7 position was held constant for purposes of having a related set of compounds to compare. The ATMO side chain is characteristic of third-generation cephalosporins and imparts impressive potency on $\beta$-lactam antibacterial agents.[22] Figure 2 groups the 3-R substituents on the dihydropyrazole ring in chronological order of their synthesis and testing. Thus set A compounds

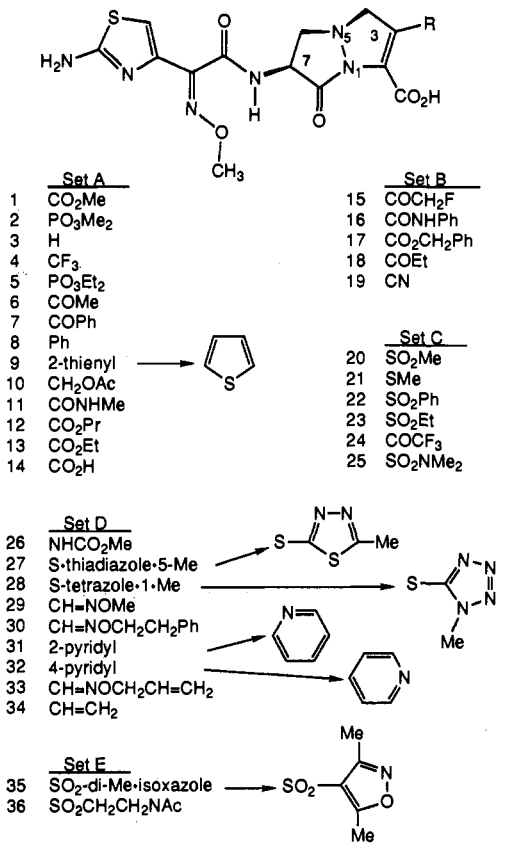


**Figure 2.** Structures of 3-substituted 7-aminothiazole methoxime acetamido bicyclic pyrazolidinones.

were those available at the start of the QSAR study. Subsequently, the data set was enlarged when data for the compounds in set B became available. The data set continued to grow until all the compounds in sets A–E had been made and tested. One structure ($COCF_3$) was included in set C, although attempts to synthesize it proved futile because of chemical instability. It was felt that it would be useful to include this data point in the analyses because the high $\sigma_p$ value (0.80) helps define the upper limit of parameter space that would be accessible to synthesis. The MIC of this structure was taken to be 256 μg/mL for graphing purposes.

It was obvious from the outset that we would want to explore the electronic, lipophilic, and steric characteristics of the substituents. Indeed, two of the more interesting variables were $\sigma_p$ and $\pi$. The $\pi$ value increases with lipophilicity; the $\sigma_p$ value increases as a substituent becomes more electron-withdrawing. Formally, $\sigma_p$ values are for substituents on an aromatic ring; however, they are useful here because a conjugated system links the 3 position and the γ-lactam amide bond. It has also been shown previously that Hammett $\sigma$ values correlate with reactivity of cephalosporins, where an analogous delocalization occurs.[23] Inductive $\sigma_I$ parameters (as a replacement for $\sigma_p$) and molar refractivity (MR) parameters were also found to be useful, whereas the Verloop sterimol length L1 and group dipole moment[24] were less useful. There were no parameter values for some of the derivatives that were synthesized; in these cases parameters were estimated from closely analogous substituents in the database or were computed by running R-phenyl models in the CLOGP and CMR programs.[25]

Results are plotted in Figures 3–7 showing how the hypersurface evolved as additional compounds became available to be added to the data sets. Contours in each of these figures are in log units corresponding to the usual 2-fold dilutions used in MIC assays, i.e., 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 μg/mL. The final set of data used in the figures is given in Table I, which also has some notes on the parameters.

Table I. Data for Bicyclic Pyrazolidinones with 3-R Substituents

| no. | π | $\sigma_p$ | MR | log MIC | R |
|---|---|---|---|---|---|
| 1 | −0.01 | 0.45 | 12.87 | 1.05 | $CO_2Me$ |
| 2 | −1.18 | 0.53 | 21.87 | 1.66 | $PO_3Me_2$ |
| 3 | 0.00 | 0.00 | 1.03 | 2.32 | H |
| 4 | 0.88 | 0.54 | 5.02 | 1.87 | $CF_3$ |
| 5 | −0.10 | 0.60 | 31.16 | 2.29 | $PO_3Et_2$ |
| 6 | −0.55 | 0.50 | 11.18 | 0.39 | COMe |
| 7 | 1.05 | 0.43 | 30.33 | 1.08 | COPh |
| 8 | 1.96 | −0.01 | 25.36 | 2.41 | Ph |
| 9 | 1.61 | 0.05 | 24.04 | 2.41 | 2-thienyl |
| 10 | −0.17 | 0.05 | 16.48 | 2.41 | $CH_2OAc$ |
| 11 | −1.27 | 0.36 | 14.57 | 1.99 | CONHMe |
| 12 | 1.03 | 0.45 | 21.33 | 1.35 | $CO_2Pr^a$ |
| 13 | 0.51 | 0.45 | 17.47 | 1.26 | $CO_2Et$ |
| 14 | −4.36 | 0.00 | 6.05 | 1.78 | $CO_2H$ |
| 15 | −0.39 | 0.70 | 9.78 | 1.66 | $COCH_2F^{a,b}$ |
| 16 | 0.49 | 0.38 | 35.35 | 1.35 | CONHPh |
| 17 | 1.84 | 0.45 | 37.20 | 1.84 | $CO_2CH_2Ph$ |
| 18 | 0.06 | 0.48 | 15.83 | 0.63 | COEt |
| 19 | −0.57 | 0.66 | 6.33 | −0.03 | CN |
| 20 | −1.63 | 0.72 | 13.49 | −0.39 | $SO_2Me$ |
| 21 | 0.61 | 0.00 | 13.82 | 2.26 | SMe |
| 22 | 0.27 | 0.68 | 33.20 | 0.03 | $SO_2Ph$ |
| 23 | −1.11 | 0.77 | 18.14 | −0.21 | $SO_2Et$ |
| 24 | 0.02 | 0.80 | 11.17 | 2.41 | $COCF_3$ |
| 25 | −0.78 | 0.65 | 21.88 | 0.39 | $SO_2NMe_2$ |
| 26 | −0.38 | −0.17 | 15.74 | 2.41 | $NHCO_2Me^a$ |
| 27 | 0.29 | 0.02 | 32.57 | 1.81 | S-thiadiazole-5-$Me^{a,c}$ |
| 28 | −0.50 | 0.02 | 26.66 | 2.05 | S-tetrazole-1-$Me^{a,c}$ |
| 29 | 0.40 | 0.30 | 15.73 | 1.87 | CH=NOMe |
| 30 | 2.49 | 0.30 | 46.40 | 1.81 | $CH{=}NOCH_2CH_2Ph^{a,d}$ |
| 31 | 0.50 | 0.09 | 23.03 | 2.11 | 2-pyridyl[e] |
| 32 | 0.46 | 0.18 | 23.03 | 2.20 | 4-pyridyl[e] |
| 33 | 0.90 | 0.30 | 25.67 | 1.87 | $CH{=}NOCH_2CH_2{=}CH_2^{a,d}$ |
| 34 | 0.82 | −0.04 | 10.99 | 2.38 | $CH{=}CH_2$ |
| 35 | −0.48 | 0.77 | 34.03 | 0.27 | $SO_2$-di-Me-isoxazole$^{a,f}$ |
| 36 | −2.14 | 0.77 | 32.21 | 0.27 | $SO_2CH_2CH_2NAc^{a,f}$ |

[a] π and MR from Medchem software; π of X = (CLOGP value of Ph-X) − (CLOGP value of Ph-H), which is analogous to the definition of π given in ref 24; MR of X = 10[(CMR value of Ph-X) + (CMR value of H) − (CMR value of Ph-H)], which accounts for the additive, constitutive way the CMR program computes molar refractivity. [b] $\sigma_p$ from C=O(F). [c] $\sigma_p$ from S-Ph. [d] $\sigma_p$ from CH=NOMe. [e] $\sigma_p$ from hydrolysis rate at pH 10, μ = 0.5, 35 °C using interpolation of the correlation between hydrolysis rate and $\sigma_p$ for bicyclic pyrazolidinones in ref 28; the new values of $\sigma_p$ are generally lower than those compiled in ref 24. [f] $\sigma_p$ from $SO_2Et$.

At the beginning of the HIP analysis of the bicyclic pyrazolidinones (set A), the derivatives that had been made were primarily concentrated in two regions of parameter space: one with substituents that were poorly electron-withdrawing $0.0 < \sigma_p < 0.2$ and the second with strongly electron-withdrawing characteristics, $0.4 < \sigma_p < 0.6$. All the derivatives except the ionized carboxylate had π values between −2 and +2. The π value for R = COOH, which is the only ionizable group in the series, was for the ionized form because the group would be ionized under test conditions. The scatter plot of the data for set A is given in the preliminary report of the HIP method.[18] The contour surface fit through this parameter space (Figure 3) shows that most regions of the map are rather undefined, except for the broad valley centered near $\sigma_p = 0.5$ and $\pi = -0.3$. The minimum of this valley would be the obvious region in which to attempt to locate additional derivatives. In addition, more widely spaced data points would better

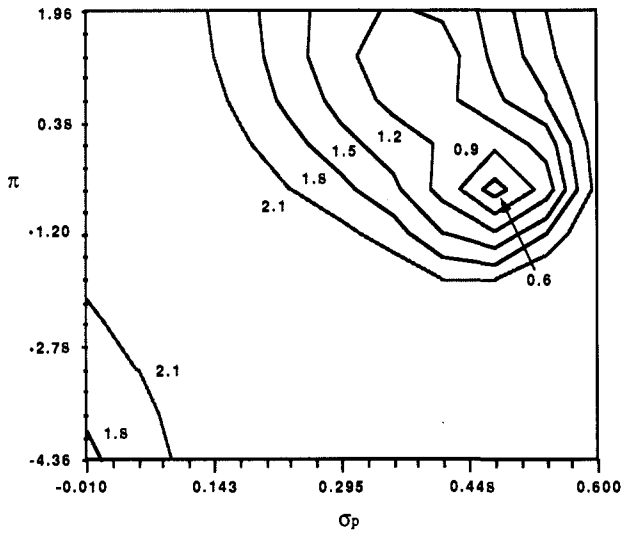


**Figure 3.** Contour surface showing the effect of lipophilicity and electron withdrawal of 3-X substituents on geometric mean MICs for compounds in set A. Contours are at $\log_{10}$ of 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 μg/mL, which are the usual 2-fold dilutions used in MIC assays.

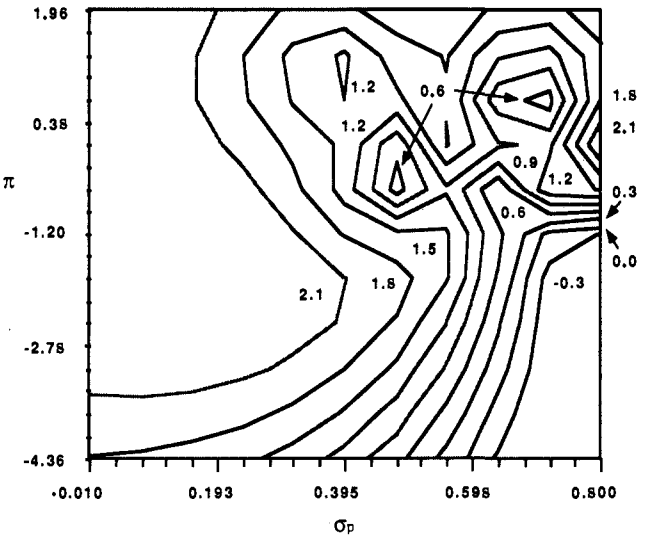


**Figure 4.** Contour surface showing the effect of lipophilicity and electron withdrawal of 3-X substituents on geometric mean MICs for compounds in sets A and B.

define the overall surface. The best mean MIC at this stage was 2.45 μg/mL.

The contour surface for compounds in sets A and B is shown in Figure 4. The five additional compounds have changed the shape of the hypersurface significantly. Although one minimum is still near the same location, a large new region of potentially better activity has opened up at high values of $\sigma_p$ and low values of $\pi$. That is, strongly electron-withdrawing and hydrophilic compounds would be worth exploring, and methyl sulfone was one of those suggested for synthesis. Also, methyl sulfone has a small MR value (low steric bulk), which at this stage appeared to be a minor contributor to increasing potency.

The substituents in set C are indeed primarily strongly electron-withdrawing and hydrophilic. Methyl sulfone is in this set. When the new data are combined with sets A and B, the data set yields a contour surface (Figure 5) in which a deep valley has opened up at high $\sigma_p$ and low $\pi$ ("southeast" corner). At the −0.3 contour surrounding this valley is $SO_2Me$ which yielded the best activity. At higher $\pi$ values are two shallower minima near the acetyl and

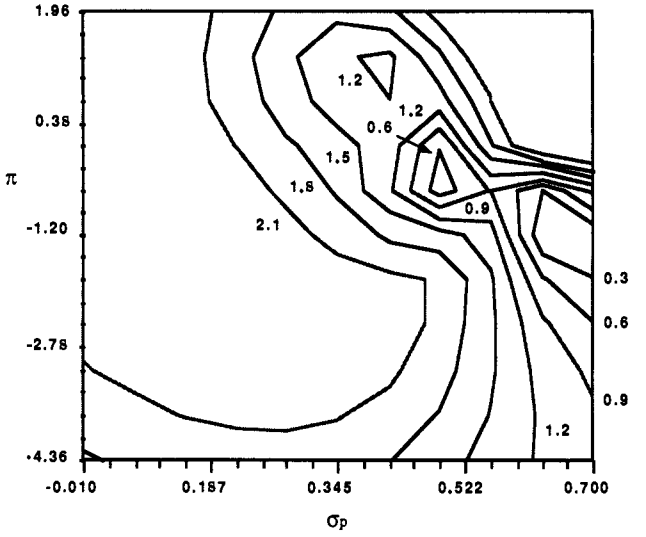


**Figure 5.** Contour surface showing the effect of lipophilicity and electron withdrawal of 3-X substituents on geometric mean MICs for compounds in sets A, B, and C.

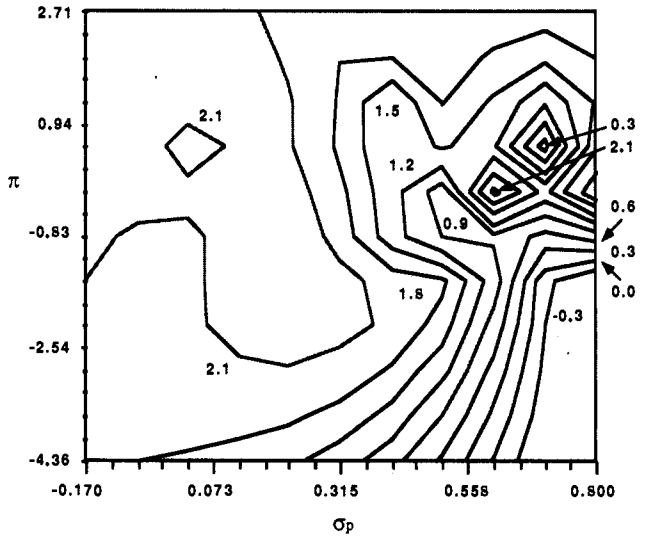


**Figure 6.** Contour surface showing the effect of lipophilicity and electron withdrawal of 3-X substituents on geometric mean MICs for compounds in sets A, B, C, and D.

phenyl sulfone substituents, respectively. Note also the peak at the right edge of the map arising from the unstable $COCF_3$ structure. From Figure 5, it can be concluded that the only region of parameter space still largely undefined is in the southeast corner corresponding to groups that are both highly electron-withdrawing and hydrophilic.

The nine compounds in set D do not meet these criteria but help define several other regions of parameter space. Figure 6 shows that the contours of the hypersurface have reshaped in the "northeast quadrant"; one of the shallow minima of Figure 5 has mostly disappeared, and a sharp peak has emerged in the vicinity of the diethyl phosphonate substituent. The best activity was still achieved with the methyl sulfone derivative, which was in set C. The southeast corner of the hypersurface is still ill-defined.

Finally, the two sulfone derivatives in set E were made. These are important because they define the contour surface at high $\sigma_p$ and low $\pi$. As seen in the topographical map of Figure 7, the compound with methyl sulfone ($\sigma_p$ = 0.72 and $\pi$ = −1.63) dwells in the deepest minima and is the most potent compound. Activity expressed by the

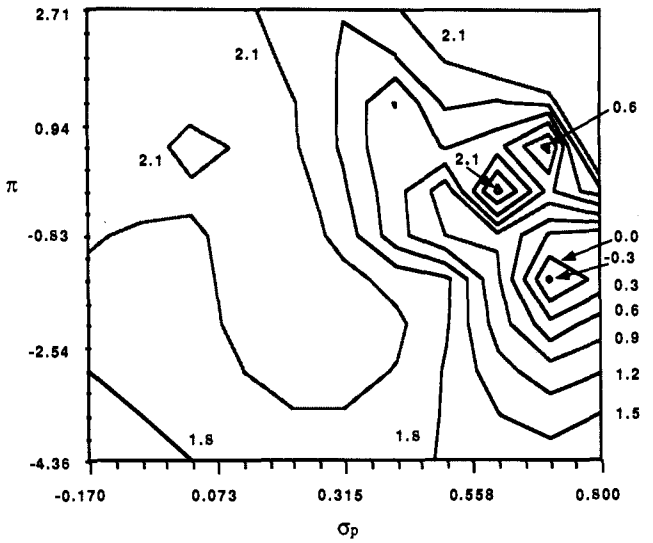


**Figure 7.** Contour surface showing the effect of lipophilicity and electron withdrawal of 3-X substituents on geometric mean MICs for compounds in sets A, B, C, D, and E.

mean MIC is below 0.4 μg/mL, which is 6-fold better than the best compound at the start of the analysis (set A). It can also be seen that the probability of finding compounds in this series with still better antibacterial activity is small if substituents were selected randomly. The requirements of being as electron-withdrawing and as hydrophilic as methyl sulfone dictate a very narrow region of parameter space.

## Discussion

At the start of this study it was not known for sure whether antibacterial activity would correlate with chemical reactivity of the lactam bond in the pyrazolidinone ring. And, if such a correlation did exist, it was not known if the optimum reactivity range would be higher or lower than for cephalosporins. We find that, analogous to what was previously discovered for the 3-substituent of cephalosporin antibiotics,[3,26,27] the substituent at the 3 position of the bicyclic pyrazolidinones is an important determinant of potency. The electronic properties of this group influence chemical reactivity, a fact that has been confirmed experimentally.[28] There are through-bond interactions between the lactam amide at the crucial 3 position. More electron-withdrawing groups increase reactivity of the lactam so that it can acylate the active site serine of penicillin-binding proteins more readily. We also find that for optimum inhibition of these cell wall proteins the electron-withdrawing power of the 3-substituent must be greater in the bicyclic pyrazolidinones than in cephalosporins.

Although separate from the HIP method, it may be of interest to some readers to see regression equations. Multiple linear regression on the data in Figure 7 and Table I shows that the Hammett $\sigma_p$ parameter is dominant. Thus, chemical reactivity is the main determinant differentiating members of the series. According to the $t$ ratio, $\pi$ is at the borderline of being significant. Other parameters, MR, $\sigma_p^2$, and $\pi^2$, were tried, but their contributions are not significant based on the $t$ ratio and probability of the null hypothesis, $p$. No derivatives were excluded in the following two equations.

$$\log \text{MIC} = (-2.15 \pm 0.36)\sigma_p + (2.27 \pm 0.17)$$

$$n = 36,\ r^2 = 0.51,\ \text{rms error} = 0.62,\ F = 34.96,\ p = 0.0001$$

$$\log \text{MIC} = (-2.01 \pm 0.36)\sigma_p + (0.16 \pm 0.08)\pi + (2.22 \pm 0.17)$$

$$n = 36,\ r^2 = 0.55,\ \text{rms error} = 0.60,\ F = 20.50,\ p = 0.0000$$

When examining the results of the regression analysis, it is useful to remember that the data set consists almost entirely of synthesizable compounds. Logic and experience indicate that there is an upper limit to the chemical reactivity that is allowable in stable compounds. The antibacterial activity will not keep increasing with reactivity indefinitely. The same is true for cephalosporins.[26,27]

The relationship between reactivity toward nucleophiles and antibacterial activity in the bicyclic pyrazolidinones is seen quite clearly in Figure 8. As usual with biological data, there is some noise, but almost all the points fit well within the 95% confidence limits. The outliers at the upper end of the $\sigma_p$ range occur because chemical stability, and hence biological activity, is lost above a "ragged edge" corresponding to a $\sigma_p$ value of 0.75–0.80. As the 3-R groups become more activating, the compounds are better able to bind covalently in the active site, but eventually excess reactivity is the molecule's undoing.

There are too few outliers to justify fitting a higher order curve, such as a quadratic equation, to the data set. When three outliers ($PO_3Et_2$, $COCF_3$, and $COCH_2F$) are removed, regression equations are obtained with even better statistics as expected. Based on the $t$ ratio, $\pi$ is more significant in these equations.

$$\log \text{MIC} = (-2.76 \pm 0.27)\sigma_p + (2.35 \pm 0.12)$$

$$n = 33,\ r^2 = 0.77,\ \text{rms error} = 0.43,\ F = 103.88,\ p = 0.0000$$

$$\log \text{MIC} = (-2.63 \pm 0.26)\sigma_p + (0.14 \pm 0.06)\pi + (2.30 \pm 0.11)$$

$$n = 33,\ r^2 = 0.81,\ \text{rms error} = 0.40,\ F = 63.90,\ p = 0.0000$$

Properties of the substituents other than inductive effect and lipophilicity play a minor role in determining antibacterial activity. Steric properties of the 3-substituent in the bicyclic pyrazolidinones do not appear to be critical even though this group is adjacent to the carboxyl group which is an essential part of the pharmacophore. The same situation is also observed for cephalosporins, where a wide latitude in 3-position side chains can be accommodated.[22,29] How the side chains are oriented and the mechanism of the acylation can be studied by further computations using, for instance, the geometries of the active site of two β-lactam-recognizing enzymes, a transpeptidase and a β-lactamase, that have been refined by recent molecular dynamics simulations.[30]

The results of medicinal chemistry on the bicyclic pyrazolidinones were dramatic. In a relatively short time, the spectrum and potency were improved from being modest for the earliest bicyclic pyrazolidinone (MICs in the range 8–128 μg/mL)[4] to that of third-generation cephalosporins for the methyl sulfone derivative. The

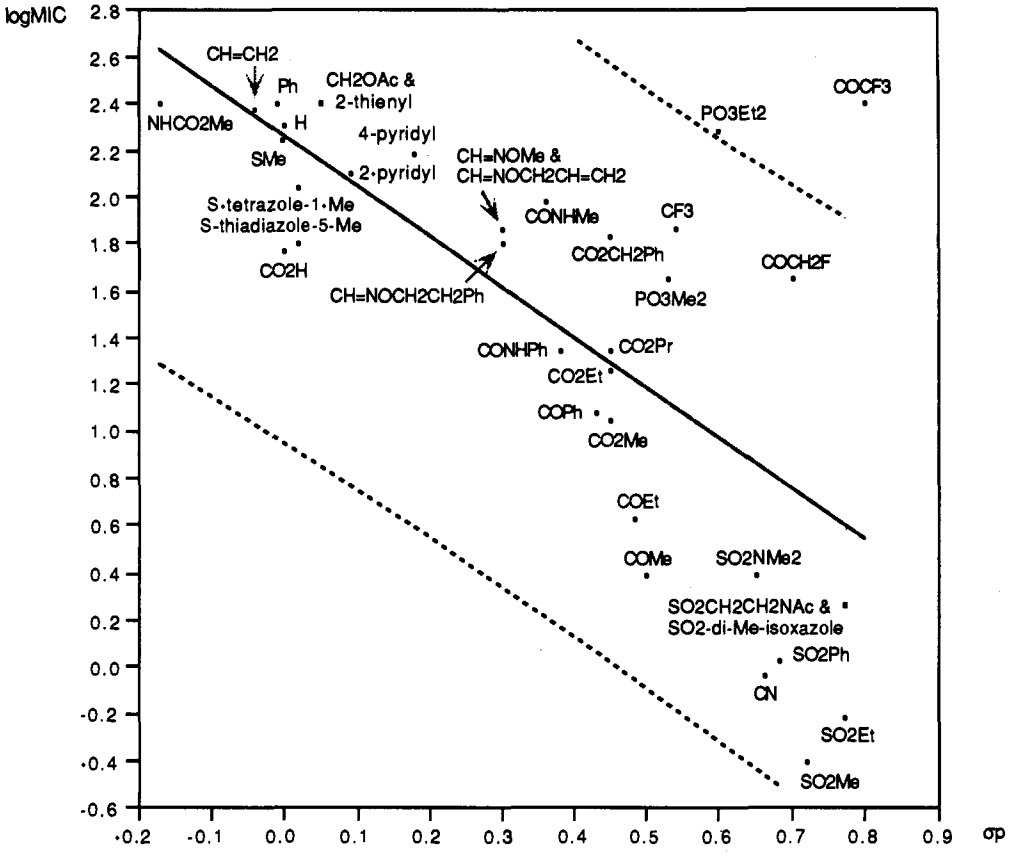


**Figure 8.** Antibacterial activity as a function of the electron-withdrawing effect of the substituent at the 3 position of bicyclic pyrazolidinones. The heavy line is the regression line fit to all 36 data points. The dashed lines delineate the 95% confidence limits.

pyrazolidinone ring system has the requisite reactivity, electronic, steric, and conformational properties to function as a bioisostere of a β-lactam ring. The importance of reactivity in determining relative antibacterial activity of a congeneric series is clear.

The hypersurface iterative projection method is aimed at analysis of multidimensional data. The dependence of a molecular property on two or more descriptors can be visualized. As mentioned above, SAS/GRAPH can produce scatter plots with up to six dimensions simultaneously. In cases where even more variables are under study, subsets of dimensions in parameter space would have to be examined. The method is best suited to studying substitutions at only one position at a time.

Most importantly, the method provides a way of rationally using existing data to decide what further information to acquire. Unlike some prior QSAR approaches which analyze static, e.g., published, data sets, the HIP method is intended to be used dynamically as an SAR is still developing. Although the primary purpose of the QSAR methods is to discover those structural variations that optimize a property—and the HIP method proved itself in this regard—a secondary purpose of QSAR methods is to determine when sufficient numbers of compounds have been synthesized so that the scientist can be confident in concluding that a struture–activity relationship has been taken as far as is worthwhile. The HIP method provides this information also.

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