QSAR studies of 2-substituted 2,3-dihydro-1h-naphtho[1,8-de]-1,3,2-diazaphosphorine 2-oxides and sulphides

A. Sirisha Madhuritha, B. Ashok Kumar, T. Parthasarathy*, V. Uma†

Department of Chemistry, Nizam College, Basheerbagh, Osmania University, Hyderabad 500001, India

Received 15 July 2003; accepted 6 July 2004

Abstract: A quantitative structure activity relationship (QSAR) study of 2-substituted 2,3-dihydro-1H-naphtho[1,8,de]-1,3,2-diazaphosphorine 2-oxides and sulphides (DND), examines the extent of the contribution by various physicochemical parameters with respect to their antimicrobial activity. Simple bivariant regression analysis, based on the least squares method, is applied in order to predict models. The predicted models reveal that the steric factor, MR, is the major contributor influencing antimicrobial activity. Bulky groups at the C-19 (C=O group) position positively influence the potency of the compounds.

Keywords: QSAR, Regression analysis, 2-Substituted 2,3-Dihydro-1H-Naphtho[1,8-de]-1,3,2-Diazaphosphorine 2-Oxides/Sulphides

1 Introduction

Organophosphorus compounds have acquired a place of importance as potent antibacterial, antitumour, and chemotherapeutic agents and also as pesticides. The presence of nitrogen in these compounds promotes antitumour activity [1-3], whereas carbamate moieties are responsible for antitumour activity [4] as well as bactericidal activity [5,6]. These compounds also exhibit pesticidal activity [7]. The N-phosphorylated nitrogen mustard compounds possess anticancer activity [8-11], and substituted ureas of type RR'P(O)NHCONR"R" exhibit pesticidal activity [12-14]. Belonging to this class of com-
pounds, 2 – substituted 2,3 – dihydro - 1H- naphtho [1,8-de]-1,2-diazaphosphorine 2-oxides and sulphides (DND) (presented in Fig. 1) have been recently synthesized and evaluated by Venugopal et al [15] and are expected to possess a broad spectrum of activities and less toxicity. The present communication is an attempt to explore the Quantitative Structure Activity Relationship (QSAR) of a series of DND compounds. It is aimed at explaining the observed variation in biological activity as a function of various physicochemical parameters and at predicting the best lead compounds for providing insight into substitutional and configurational requirements for optimum receptor fit, leading to the development of the best pharmacological activity.

![Structure of 2-substituted 2,3-dihydro-1H-naphtho-[1,8-de]-1,3,2-diazaphosphorine 2-oxides and sulphides.](image)

**Fig. 1** Structure of 2-substituted 2,3-dihydro-1H-naphtho-[1,8-de]-1,3,2-diazaphosphorine 2-oxides and sulphides.

2 Experimental methods

2.1 Computational method

A series of 12 compounds of DND (a-l), previously tested for antimicrobial activity (Table 1), were modeled using Molecular Modeling Pro from WindowChemsoftware Inc.[16]. Molecules were built, followed by geometrical optimization, energy minimization, and calculation of physicochemical parameters (chemical descriptors), such as MR (a steric parameter), QlogP (a hydrophobicity parameter) [17] and σ* (an electronic parameter) [18] using Physical Properties Pro. The results were analyzed using SPSS software, version 10.0, in order to generate the equation with the best fit correlation.

3 Chemical descriptors

3.0.1 Lipophilicity parameter (QlogP)

The lipophilicity factor P is the most used property where P is defined by 1-octanol/water partition coefficient. All the QlogP values were calculated as per Bodor and Buchwald
Table 1 Activities and physicochemical parameter data for 2-substituted 2,3-dihydro-1H-naphtho-[1,8-de]-1,3,2-Diazaphosphorine-2oxides and sulphides.

| S no | Comp no | Substituent (R) | Log1/IC$_{50}$ | $\sigma^*$ | MR | QlogP | MR$^2$ | Calculated Activity |
|------|---------|----------------|----------------|----------|-----|-------|--------|---------------------|
| 1    | a       | OCH$_3$        | 1.9445         | 1.859    | 70.479 | 1.1018 | 4967.32 | 1.9289             |
| 2    | b       | OCH$_2$CH$_3$  | 1.9445         | 1.784    | 75.227 | 1.5839 | 5659.13 | 1.9760             |
| 3    | c       | OCH$_2$CH$_2$Cl | 1.9823         | 1.868    | 79.823 | 0.5404 | 6371.63 | 2.0116             |
| 4    | d       | OCH(CH$_3$)$_2$ | 2.0171         | 1.709    | 79.645 | 0.6205 | 6343.39 | 2.0104             |
| 5    | e       | OCH$_3$CH(CH$_3$)$_2$ | 1.9823 | 1.628 | 84.223 | 1.1071 | 7093.55 | 2.0365             |
| 6    | f       | 0C$_6$H$_{11}$ | 2.0493         | 1.814    | 94.671 | 1.9161 | 8962.60 | 2.0597             |
| 7    | g       | OCH$_2$C$_6$H$_5$ | 2.0792 | 1.928 | 98.526 | 2.4407 | 9707.43 | 2.0554             |
| 8    | h       | SCH$_2$CH$_2$CH$_3$ | 2.1073 | 2.274 | 87.545 | 1.2002 | 7664.11 | 2.0494             |
| 9    | i       | SCH$_2$CH$_2$CH$_2$CH$_3$ | 2.1073 | 2.274 | 92.146 | 1.6842 | 8490.87 | 2.0587             |
| 10   | j       | NHC$_6$H$_5$   | 2.0792         | 2.555    | 97.662 | 0.8572 | 9537.85 | 2.0570             |
| 11   | k       | NHC$_6$H$_4$CH$_3$ | 1.9445 | 2.555 | 101.944 | 1.3278 | 10392.6 | 2.0459             |
| 12   | l       | NHC$_6$H$_4$Br | 2.0493         | 2.555    | 105.196 | 1.4983 | 11066.2 | 2.0318             |

3.0.2 Electronic parameter ($\sigma^*$)

It is an electronic substituent descriptor reflecting the electron donating or accepting properties of a substituent.

3.0.3 Steric factor (molar refractivity, MR)

This parameter gives a measure of the steric factors and bulkiness of the given base molecule with various substituents. It is the molar volume corrected by the refractive index and represents size and polarisability of a fragment of molecule.

Molar refractivity is given by:

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

where $n$ is the refractive index, $MW$ is the molecular weight, and $d$ is the compound density.

3.1 QSAR studies

In order to establish a relationship between chemical structure and antimicrobial activity, the antimicrobial activity, measured in the form of inhibition concentration (IC) using Aspergillus niger [15], was transformed to Log1/IC$_{50}$ and was used as the dependent variable. Various physicochemical parameters were used as independent, or predictor variables, and quantitative structure activity relationships in terms of the correlation...
between Log1/IC$_{50}$ and the physicochemical parameter was derived. The data obtained were analyzed statistically using multiple, nonlinear regression through the origin and by fitting it in the equation, which consisted of various combinations of parameters.

$$\text{Log1/IC}_{50} = \sum a_i X_i$$  \hspace{1cm} (1)

where $a_i$ – regression co-efficient and $X_i$ – independent parameter.

Acceptability of the equation was judged examining significance of regression constant by t-test. Prediction models were identified using maximum 1R2improvement method and considering statistical parameters viz $^2\text{SEE}$, $^3\text{F}$ and $^4\text{df}$.

The final equation (2) thus obtained is used in the prediction of the probable lead compound.

$$\text{Activity} = 0.043(0.001)MR - 0.000231(0.000)MR^2$$ \hspace{1cm} (2)

$N = 12$, $R = 1.000$, $R^2 = 1.000$, $SEE = 0.049$, $F = 10104.564$,

where R denotes regression constant, $\text{SEE}$ – Standard error estimate, $\text{F}$ – $\text{F}$ ratio and $\text{df}$ – degrees of freedom respectively.

### 4 Results and discussion

The correlation matrix generated using SPSS software, version 10.0, for all 12 of the DND compounds with Log1/IC$_{50}$ as the predicted value and MR, QlogP and $\sigma^*$ as predictor values is presented in Table 2. The activity (Log1/IC$_{50}$) correlates well with MR and $\sigma^*$. Hence, the multiple nonlinear regression technique through the origin is applied using these parameters. The model equations generated by this technique are tabulated in Table 3. Equation A, obtained with single parameter MR, shows a good $R^2$ value of 0.988, an F Ratio of 938.682, and an SEE value of 0.22, indicating that the data points fit well in the equation. Equation B, generated using $\sigma^*$ alone, shows low $R^2$ and F Ratio values of 0.977 and 477.02, respectively, and a high SEE value of 0.31, indicating the equation is statistically insignificant. Moreover, the correlation matrix also suggests significant correlation between MR and QlogP, and between QlogP and $\sigma^*$. In order to understand the influence of the hydrophobic effect on both electronic and steric parameters, equations C and D (Table 3) were generated using a combination of MR and QlogP, and QlogP and $\sigma^*$, respectively. The modeled equations are statistically insignificant due to large errors (above 50 %) with QlogP in both the equations, indicating that its contribution is statistically insignificant. Equation E (Table 3), obtained using a combination of MR and MR$^2$, shows a high regression value of $R = 1.000$ and $R^2 = 1.000$, and an excellent F Ratio = 10952.66 with a negligible SEE value of 0.04, indicating that almost all data points fit well in this regression model. The statistical significance of this equation is greater than 90 %. Cross validation of the data using a stepwise regression gives the same equation. Hence, considering the high $R^2$ value and the low SEE value, equation E is projected as the best regression model, revealing that the steric bulk factor is a major
contributing factor of the activity of the DND variants. The equation exhibits a quadratic relationship of activity with MR, represented graphically in Figure 2.

Upon differentiating the equation to zero, an optimum value of MR=93.5 is obtained for the maximum activity.

Therefore, we conclude that bulky groups enhance the pharmacological activity of the drug until an optimum MR value of 93.5 is achieved. Further increases in the bulkiness beyond the optimum value leads to a decrease in the pharmacological activity and drug receptor interaction of the lead compound. The best pharmacophore for the DND series is a compound with an MR value between 93 and 95.

| Equations                  | Log1/IC\textsubscript{50} | MR  | \sigma* | QlogP |
|----------------------------|-----------------------------|-----|---------|-------|
| Log1/IC\textsubscript{50}  | 1.000                       | 0.502| 0.461   | 0.260 |
| Pearson Correlation\textsuperscript{a} |                     |     |         |       |
| N\textsuperscript{b}       | 12                          | 12  | 12      | 12    |
| MR                         | 0.502                       | 1.000| 0.718   | 0.441 |
| Pearson Correlation        |                             |     |         |       |
| N                          | 12                          | 12  | 12      | 12    |
| \sigma*                    | 0.461                       | 0.718| 1.000   | 0.037 |
| Pearson Correlation        |                             |     |         |       |
| N                          | 12                          | 12  | 12      | 12    |
| QlogP                      | 0.260                       | 0.441| 0.037   | 1.000 |
| Pearson Correlation        |                             |     |         |       |
| N                          | 12                          | 12  | 12      | 12    |

\textsuperscript{a} Pearson Correlation: A measure of linear association between two variables. Values of the correlation coefficient range from –1 to 1. The sign of the coefficient indicates the direction of the relationship, and its absolute value indicates the strength, the larger absolute values indicating stronger relationships.

\textsuperscript{b} N – number of data points.

**Table 2** Correlation matrix for the 2-substituted 2,3-dihydro-1H-naphtho-[1,8-de]-1,3,2-diazaphosphorine 2-oxides and sulphides.

| Eq | Equations                                      | N\textsuperscript{a} | R\textsuperscript{b} | R\textsuperscript{2} | SEE\textsuperscript{c} | F Ratio\textsuperscript{d} |
|----|-----------------------------------------------|-----------------------|----------------------|----------------------|------------------------|--------------------------|
| A. | \text{Act} = 0.022(0.001)MR                    | 12                    | 0.994                | 0.988                | 0.226                  | 938.682                  |
| B. | \text{Act} = 0.949(0.043) \sigma\textsuperscript{e} | 12                    | 0.989                | 0.977                | 0.315                  | 477.040                  |
| C. | \text{Act} = 0.211(0.158) QlogP + 0.818(0.107) \sigma\textsuperscript{e} | 12                    | 0.990                | 0.981                | 0.305                  | 256.128                  |
| D. | \text{Act} = 0.023(0.002)MR – 0.0613(0.143)QlogP | 12                    | 0.994                | 0.989                | 0.235                  | 434.575                  |
| E. | \text{Act} = 0.043(0.001)MR – 0.000231(0.000)MR\textsuperscript{2} | 12                    | 1.000                | 1.000                | 0.049                  | 10104.564                |

\textsuperscript{a} N – number of data points

\textsuperscript{b} R – regression coefficient

\textsuperscript{c} SEE – standard error estimate

\textsuperscript{d} F – F ratio.

**Table 3** Model equations generated for 2-substituted –2,3-dihydro-1H-naphtho-[1,8-de]-1,3,2-diazaphosphorine 2-oxides and sulphides.
Fig. 2 Graphical representation of quadratic relationship between MR (Table 1) and calculated activity (from modeled equation-5) of 2-substituted 1,3-dihydro-1H-naphtho-[1,8-de]-1,3-diazaphosphrine-2-oxides and sulphides.

Acknowledgment

The authors (SM & AB) convey thanks to the Head of the Department of Chemistry, Nizam College, Osmania University for the computational lab facilities.

References

[1] O.M. Freidman, E. Boger, V. Gublianskar and H. Sommer: “Synthesis of N-Phosphorylated Derivatives of Nitrogen Mustards with latent cytotoxicity”, *Journal of Medicinal Chemistry*, Vol. 6, (1963), pp. 50.

[2] H. Zimmer and A. Sill: “Potential Anticancer Agents (iv) Heterocyclic Phospharamide Nitrogen-Mustards”, *Arzneimittel Forschung Drug Research (Progressive Drug Research)*, Vol. 5, (1964), pp. 150.

[3] H. Arnold and F. Bourseaux: “Synthesis Und Abbau Cytoststisch Wirksamer Cyclischer N-phosphamidester des Bis-(ß-Chloräthyl)-Amins”, *Angewante Chemie*, Vol. 70, (1958), pp. 539.

[4] R.I. Zhadanov, W.A. Buina, N.A. Kapitnova and I.A. Nuretdinov: “Biologically Active Stable Radicals XV: Spin-labeled Alkyl Carbamate-N-Phosphorl Acid Aziridides”, *Synthesis*, Vol. 1, (1979), pp. 269.
[5] C. Fest and K.J. Schmidt: "Reactivity, Synthesis, Mode of action, Toxicology", In: The Chemistry of Organophosphorus Pesticides, Springer Verlag, New York, 1973, pp. 12.

[6] M.S. Bhatia and P. Jit: “Phosphorous-Containing Heterocycles as Fungicides: Synthesis of 2,2′-Dyphenylene Chlorophosphonate and 2,2-Diphenylene Chlorothiophosphonate”, Experientia, Vol. 32, (1976), pp. 1111.

[7] R. Ismail: “Benzacondensed 1,3,2 Dioxaphosphacycloalkanes”, German patents, 1 543 539, (1975).

[8] A.V. Kirsanov: “Chlorides of Isocynatophosphoric Acid”, Zhur Obshchei Khim, Vol. 24, (1954), pp. 1033.

[9] A.V. Kirsanov and I.N. Zhmurova: “Reaction of Phosphorus Pentachloride with Amides of Phosphoric Acid”, Zhur Obshchei Khim, Vol. 28, (1958), pp. 2478.

[10] A.V. Kirsanov and M.S. Marenets: “Esters of Urethanphosphoric Acids”, Zhur Obshchei Khim, Vol. 29, (1959), pp. 2256.

[11] H. Arnold, F. Bourseaux and N. Brock: “Chemotherapeutic Action of a Cyclic Nitrogen Mustard Phosphamide Ester (B 518-ASTA) in Experimental Tumours of the Rat”, Nature, Vol. 181, (1958), pp. 931.

[12] S.M. Ludeman and G. Zon: “Synthesis and antitumour Activity of Cyclophosphomide Analogs. 1. Benzo Annulated Cyclophosphamide and Related Systems”, Journal of Medicinal Chemistry, Vol. 18, (1975), pp. 251.

[13] C.M. Thompson, J.A. Frick and D.L.C. Green: “Synthesis, Configuration and Chemical Shift Correlations of Chiral 1,3,2-Oxazophospholidin-2-one Derived from l-Serine”, Journal of Organic Chemistry, Vol. 55, (1990), pp. 111.

[14] R. Martino, V. Gillard, M.M. Martino, U. Neimayer and J. Phol: “Chemical Stability and Fate of the Cytostatic Drug Ifosfamide and its N-Dechloroethylated Metabolites in Acidic Aqueous Solutions”, Journal of Medicinal Chemistry, Vol. 42, (1999), pp. 2542.

[15] M. Venugopal, C. Devendranath Reddy and M. Bavaji: “Synthesis and Antimicrobial activity of “2-Substituted-2,3-Dihydro-1H-Naptho-[1,8-de]-1,3,2-Diazaphosphorine 2-Oxides/Sulphides”, Indian Journal of Chemistry, Vol. 40B, (2001), pp. 822–827.

[16] ChemSW, Inc: MolecularModelingPro, version 3.24, 420F Executive Ct.North, Fairfield, CA 94585; http://www.Chemsw.com.

[17] N. Bodor and P. Buchwald: “Molecular size Based Approach to Estimate Partition properties of Organic Solute”, Journal of Physical Chemistry.B, Vol. 101, (1997), pp. 3404–3412.

[18] C. Hansch and A.J. Leo: Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and sons, New York, 1979, pp. 55.