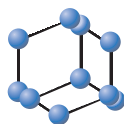


RESEARCH ARTICLE

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Application of Topological Descriptors in QSAR Modeling: Substituted Hydrazones Used As a Model System



Vesna Dimova^{1,*} and Mirjana Stojan Jankulovska²

¹Department of Organic Chemistry, Faculty of Technology and Metallurgy, Ss Cyril and Methodius University, Ruger Boskovic 16, 1000 Skopje, Republic of Macedonia; ²Faculty of Agricultural Sciences and Food, Ss. Cyril and Methodius University, Blvd. Aleksandar Makedonski bb, 1000 Skopje, Republic of Macedonia

Abstract: Background: QSAR study of *p*-substituted aromatic hydrazones was performed to estimate the quantitative effects of selected topological descriptors on their antimicrobial activity. None of the hydrazones inhibited the growth of the *Aspergillus spp.*, while the data obtained with regard to the antifungal activity of the compounds against *Candida utilis* were insufficient to develop reliable statistical QSAR models. Therefore, the investigation was focused on developing QSAR models for predicting the antibacterial activity of the compounds against *Bacillus subtilis*.

Methods: A set of substituted hydrazones were tested for their *in vitro* growth inhibitory activity against *Candida utilis*, *Bacillus subtilis* and *Aspergillus niger* and the diameter of the inhibition zone (mm) was measured. The inhibitory activity data, determined in $\mu\text{g/mL}$, were transformed to the negative logarithms of molar MICs (\log_1/C_{MIC}). Using MarvinSketch software package, 28 topological descriptors were calculated. Statistical parameters, such as R^2 , Sd, F-test, R^2_{adj} , Q , S_{PRESS} , PSE and Q^2 , were used to test the quality of the developed two-, three-, four-parametric and higher QSAR models.

Results and Conclusion: Statistical evaluation of the data used to test the quality of the obtained QSAR models indicated that the two-parametric model involving the descriptors Atom Count (AC) and Maximal Projection Area (MAPA) was statistically significant when all the statistical parameters were summarized. The two parameters, AC and MAPA, had opposite input in modeling the antimicrobial activity of the selected hydrazones against *Bacillus subtilis*.

Keywords: QSAR, hydrazones, antimicrobial activity, topological descriptors, MAPA, AC.

1. INTRODUCTION

Quantitative structure - activity/property relationship (QSAR/QSPR) models attempt to investigate the relationship between a selected type of descriptors, defining the unique properties of a set of organic compounds, and their biological activity or chemical property. The correlation and prediction of physical, chemical and biological activity/property based on the molecular structure are very significant and still unsolved problem in various chemistry fields (computational, theoretical, environmental) and in life sciences as well [1].

The most significant step in QSAR/QSPR is the numerical transformation of the chemical structures of organic molecules. Accurately transferring the chemical

formula/ molecular graph into a numerical form has been a major task in QSAR/QSPR researches [2].

Many numerical molecular descriptors are available in chemistry: physical-chemical, topological, 3D descriptors and quantum chemical descriptors.

Numerous chemists prefer to use topological indices as molecular descriptors to evaluate toxicity, and predict biological activity [2]. These indices offer an easy way for measuring molecular shape, symmetry, branching, size and complexity.

The second step in the QSAR/QSPR approach is to find a mathematical relationship between the properties of compounds and the descriptors derived from their structures [3], expressed mathematically as [4]:

$$R(A/P) = f(\text{Information of molecular structure/property}) \\ = f(\text{molecular descriptors})$$

where $R(A/P)$ denotes the response of activity/property, which is essentially the measured value of a biological activity/property. Information regarding the boiling point,

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*Address correspondence to this author at the Department of Organic Chemistry, Faculty of Technology and Metallurgy, Ss Cyril and Methodius University, P.O. Box: 1000, Skopje, Republic of Macedonia; Tel/Fax: +389-2-3088-260, +389-2-3065-389; E-mail: vdimova@tmf.ukim.edu.mk

density, refractive index, heat of formation, chromatographic retention time, and octanol-water partition coefficient can also be used as an activity/property of a molecule. The model function, $f(x)$, can be linear or non-linear, depending on different complexity of the data. Once a statistically reliable model is established, the property of an unknown or new compound can be easily estimated.

A topological index is a real number related to a graph (G) [5]. In 1947, chemist Harold Wiener developed the Wiener index (most widely known topological descriptor) to determine the physical properties of alkanes). The hyper-Wiener index was introduced in 1993 by Milan Randić. Klein *et al.* [6], in 1995, generalized by Randić's definition for all connected graphs as a generalization of the Wiener index. The Szeged index [7] is a topological index closely related to the Wiener index.

When applied to chemical graphs, the indices mentioned above have many chemical applications and are related to the physico-chemical properties of many complex organic compounds.

Hydrazones, as a significant set of organic compounds, find enormous application in many scientific areas. This class of compounds possesses a broad spectrum of biological activity and it has been confirmed that the changes in this activity depend on the substituent presence/absence in the molecule [8]. In medicine, hydrazones are used due to their antimicrobial, antitumoral, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, anti-schistosomiasis and antiviral activities [9], by virtue of the azomethine proton (-NHN=CH-) in the hydrazone structure. The broad palette of the useful medical properties of hydrazones has attracted extensive scientific interest in their synthesis [10].

Some of the hydrazones are used as chelating agents; hydrazone complexes with transition metals are used in a wide range of fields, including the analytical, clinical and biological ones [11]. It has been confirmed that hydrazones and their metal complexes exhibit a number physiological and pharmacological activities [12], and thus they are used as herbicides, insecticides, and plant growth stimulants [13]. Some quinoline-substituted hydrazone derivatives have been evaluated as DNA gyrase inhibitors [14]. Hydrazone derivatives also have industrial application, being used as polymer stabilizers, polymerization initiators, plasticizers and antioxidants [15].

Taking into consideration the above-mentioned hydrazone applications, some *p*-substituted aromatic hydrazones have been synthesized and characterized [16].

The aim of this paper was to find the mathematical equations relating the chemical structure of the investigated hydrazones to a variety of their properties by using topological indices (essentially, numerical molecular descriptors associated with their molecular structure).

When a correlation between the hydrazone structure and its activity/property is found, any substituted hydrazone derivatives (including those not yet synthesized) can be readily screened on the computer in order to select the compound with the desired activity/properties. This allows

selecting the most promising hydrazone derivatives to synthesize and test in the laboratory.

2. MATERIALS AND METHODS

2.1. Structure of *p*-Substituted Aromatic Hydrazones (H₁-H₁₅)

A series of 15 previously reported [16] *p*-substituted aromatic hydrazones were used for this study. The structures of the investigated compounds are presented in Table 1.

2.2. Antibacterial Investigation

All *p*-substituted hydrazones were tested for their *in vitro* growth inhibitory activity against *Candida utilis*, *Bacillus subtilis* and *Aspergillus niger*, using the filter paper disc method. Stock solutions of the compounds were prepared in DMSO, as inert medium, with the following concentrations: 1, 5 and 10 mg/mL DMSO. There was no inhibitory activity in the control disc (the disk impregnated with DMSO only, without any test compound). The diameter of the inhibition zone (mm) was measured and the inhibitory activity data, determined in µg/mL, were transformed to the negative logarithms of molar MICs (\log_1/C_{MIC}), (Table 1). Every test was done in triplicate to confirm the findings.

2.3. Descriptor Calculation and Selection

The 2D structures of all the compounds were drawn and their topological descriptors were calculated using MarvinSketch software package [17]. Since not all the descriptors calculated were relevant to the property considered, only the descriptors with adequate values were chosen for analysis. The calculated topological descriptors (abbreviation and meaning) are presented in Table 2.

2.4. Statistical Analysis

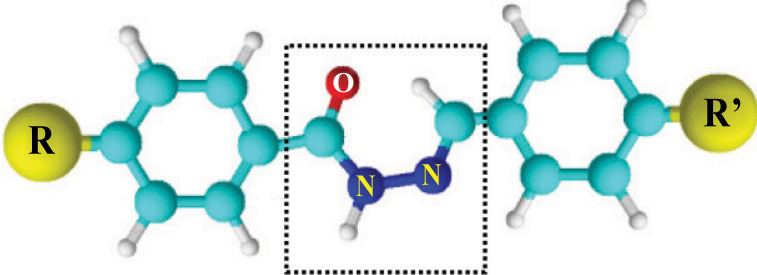
Statistica software package [18] was used for the statistical evaluation of the data. The quality of the regression models was tested by the following statistical parameters: Correlation coefficient (R^2), Standard deviation of the estimate (Sd), Fisher test for significance of the equation (F-test), Adjusted R^2 (R^2_{adj}), Quality factor (Q), Uncertainty of Prediction (S_{PRESS}), Predictive Square Error (PSE) and Cross-validation squared correlation coefficient (Q^2).

3. RESULTS AND DISCUSSION

The process of QSAR model building starts with the analysis of the results gathered from the antimicrobial investigation against *Candida utilis*, *Bacillus subtilis* and *Aspergillus niger*. The results indicated that none of the investigated compounds inhibited the growth of the *Aspergillus spp.*, while the data for the antifungal activity of the compounds relative to *Candida utilis* were insufficient to develop statistically reliable QSAR models (Table 1).

In the next step, the investigation was focused on developing QSAR models for evaluating the antibacterial activity of the compounds against *Bacillus subtilis*, using a set of selected descriptors. Experimentally obtained inhibitory activity data were first transformed to the negative

Table 1. Structure, experimental obtained zone of inhibition [mm] and calculated $\log 1/C_{MIC}$ values of investigated *p*-substituted hydrazones (H_1 - H_{15}) against *Bacillus subtilis*, *Candida utilis* and *Aspergillus niger**.

| Compounds | R | R' | | | | |
|--------------------------|------------------|------------------|--|------------------------------------|--|--|
| H ₁ | H | H |  | | | |
| H ₂ | CH ₃ | H | | | | |
| H ₃ | OCH ₃ | H | | | | |
| H ₄ | Cl | H | | | | |
| H ₅ | OH | H | | | | |
| H ₆ | H | OCH ₃ | | | | |
| H ₇ | CH ₃ | OCH ₃ | | | | |
| H ₈ | OCH ₃ | OCH ₃ | | | | |
| H ₉ | Cl | OCH ₃ | | | | |
| H ₁₀ | OH | OCH ₃ | | | | |
| H ₁₁ | H | NO ₂ | | | | |
| H ₁₂ | CH ₃ | NO ₂ | | | | |
| H ₁₃ | OCH ₃ | NO ₂ | | | | |
| H ₁₄ | Cl | NO ₂ | | | | |
| H ₁₅ | OH | NO ₂ | | | | |
| <i>Bacillus Subtilis</i> | | | | | | |
| Compounds | 1 mg/mL | 5 mg/mL | 10 mg/mL | Log ₁ /C _{MIC} | | |
| H ₁ | 11.0 | 10.3 | 9.0 | 5.3500 | | |
| H ₂ | 9.3 | 11.0 | 12.0 | 5.3766 | | |
| H ₃ | 11.0 | 10.0 | 13.0 | 5.4048 | | |
| H ₄ | 10.3 | 11.6 | 13.3 | 5.4116 | | |
| H ₅ | 9.6 | 9.0 | 8.3 | 5.3802 | | |
| H ₆ | 9.3 | 14.3 | 9.7 | 5.4048 | | |
| H ₇ | 9.5 | 9.7 | 11.7 | 5.4280 | | |
| H ₈ | 9.3 | 9.0 | 12.3 | 5.4533 | | |
| H ₉ | 8.7 | 10.5 | 13.1 | 5.4594 | | |
| H ₁₀ | 9.0 | 10.2 | 9.2 | 5.4149 | | |
| H ₁₁ | 11.2 | 12.0 | 10.7 | 5.4297 | | |
| H ₁₂ | 12.0 | 10.8 | 11.0 | 5.4517 | | |
| H ₁₃ | 11.5 | 11.0 | 10.3 | 5.4756 | | |
| H ₁₄ | 10.3 | 10.0 | 11.0 | 5.4814 | | |
| H ₁₅ | 10.7 | 11.0 | 10.3 | 5.4548 | | |

(Table 1) contd...

| <i>Candida Utilis</i> | | | | |
|-----------------------|---------|---------|----------|-----------------------|
| Compounds | 1 mg/mL | 5 mg/mL | 10 mg/mL | Log1/c _{MIC} |
| H ₁ | - | 8.0 | 9.6 | 4.6510 |
| H ₂ | - | - | 8.0 | 4.3765 |
| H ₃ | - | 7.0 | 8.0 | 4.7059 |
| H ₄ | 7.0 | 9.0 | 15.0 | 5.4116 |
| H ₅ | 7.6 | 7.6 | 13.6 | 5.3802 |
| H ₆ | 7.0 | - | - | 5.4048 |
| H ₇ | 7.5 | - | - | 5.4280 |
| H ₈ | - | - | 13.0 | 4.4533 |
| H ₉ | - | - | 5.0 | 4.4594 |
| H ₁₀ | - | 7.0 | 6.33 | 4.7160 |
| H ₁₁ | - | - | - | - |
| H ₁₂ | - | - | - | - |
| H ₁₃ | - | - | - | - |
| H ₁₄ | - | - | - | - |
| H ₁₅ | - | - | - | - |

*None of investigated compounds do not inhibit the growth of the *Aspergillus spp.* after applying the filter paper disc method; zone of inhibition = 0.

Table 2. Calculated values for selected topological descriptors.

| - | AAC | ABC | AC | BC | CAC | CBC | RBC | PI | X | J | H | WW | Sz | W |
|-----------------|-----|-----|----|----|-----|-----|-----|----|-------|------|-------|------|------|------|
| H ₁ | 5 | 6 | 29 | 30 | 5 | 6 | 3 | 44 | 8.36 | 1.57 | 48.49 | 2179 | 866 | 614 |
| H ₂ | 6 | 7 | 32 | 33 | 6 | 7 | 3 | 48 | 8.75 | 1.49 | 52.78 | 2694 | 1027 | 724 |
| H ₃ | 7 | 8 | 33 | 34 | 7 | 8 | 4 | 50 | 9.29 | 1.42 | 56.86 | 3337 | 1206 | 852 |
| H ₄ | 6 | 7 | 29 | 30 | 6 | 7 | 3 | 48 | 8.75 | 1.49 | 52.78 | 2694 | 1027 | 724 |
| H ₅ | 6 | 7 | 30 | 31 | 6 | 7 | 3 | 48 | 8.75 | 1.49 | 52.78 | 2694 | 1027 | 724 |
| H ₆ | 7 | 8 | 33 | 34 | 7 | 8 | 4 | 50 | 9.29 | 1.40 | 56.76 | 3388 | 1212 | 858 |
| H ₇ | 8 | 9 | 36 | 37 | 8 | 9 | 4 | 54 | 9.69 | 1.56 | 61.20 | 4099 | 1412 | 995 |
| H ₈ | 9 | 10 | 37 | 38 | 9 | 10 | 5 | 56 | 10.22 | 1.49 | 65.42 | 4967 | 1632 | 1152 |
| H ₉ | 8 | 9 | 33 | 34 | 8 | 9 | 4 | 54 | 9.69 | 1.56 | 61.20 | 4099 | 1412 | 995 |
| H ₁₀ | 8 | 9 | 34 | 35 | 8 | 9 | 4 | 54 | 9.69 | 1.56 | 61.20 | 4099 | 1412 | 995 |
| H ₁₁ | 8 | 9 | 31 | 32 | 8 | 9 | 4 | 54 | 9.66 | 1.57 | 61.30 | 4061 | 1396 | 991 |
| H ₁₂ | 9 | 10 | 34 | 35 | 9 | 10 | 4 | 58 | 10.06 | 1.50 | 65.81 | 4877 | 1616 | 1142 |
| H ₁₃ | 10 | 11 | 35 | 36 | 10 | 11 | 5 | 60 | 10.60 | 1.43 | 70.10 | 5865 | 1857 | 1314 |
| H ₁₄ | 9 | 10 | 31 | 32 | 9 | 10 | 4 | 58 | 10.06 | 1.50 | 65.81 | 4877 | 1616 | 1142 |
| H ₁₅ | 9 | 10 | 32 | 33 | 9 | 10 | 4 | 58 | 10.06 | 1.50 | 65.81 | 4877 | 1616 | 1142 |

(Table 2) contd....

| - | Wp | DE | MM | MIPA | MAPA | MIPR | MAPR | LPMA | LPMI | VWV | PSA | MSA | Log P | R |
|-----------------|----|-------|--------|-------|-------|------|------|------|-------|--------|--------|--------|-------|-------|
| H ₁ | 20 | 40.73 | 138.78 | 32.11 | 79.03 | 4.26 | 7.76 | 5.37 | 15.19 | 205.35 | 41.46 | 318.91 | 2.963 | 68.24 |
| H ₂ | 22 | 44.61 | 146.63 | 27.77 | 83.80 | 3.78 | 8.25 | 5.99 | 16.65 | 222.13 | 41.46 | 351.08 | 3.477 | 73.28 |
| H ₃ | 24 | 46.62 | 142.78 | 32.29 | 85.30 | 3.90 | 8.73 | 5.68 | 17.28 | 231.48 | 50.69 | 367.10 | 2.805 | 74.70 |
| H ₄ | 22 | 41.08 | 136.77 | 27.92 | 83.35 | 4.01 | 8.36 | 5.34 | 16.59 | 219.09 | 41.46 | 334.93 | 3.567 | 73.04 |
| H ₅ | 22 | 39.93 | 124.52 | 29.79 | 81.19 | 3.91 | 8.14 | 5.24 | 16.11 | 213.85 | 61.69 | 329.53 | 2.660 | 70.22 |
| H ₆ | 24 | 46.71 | 142.73 | 30.78 | 87.82 | 4.23 | 8.87 | 5.64 | 17.73 | 231.55 | 50.69 | 367.26 | 2.805 | 74.70 |
| H ₇ | 26 | 50.70 | 151.39 | 31.33 | 93.02 | 3.80 | 9.38 | 6.22 | 18.79 | 248.37 | 50.69 | 399.77 | 3.319 | 79.74 |
| H ₈ | 28 | 52.56 | 147.93 | 32.89 | 94.01 | 3.91 | 9.86 | 5.79 | 19.46 | 257.64 | 59.92 | 415.70 | 2.648 | 81.16 |
| H ₉ | 26 | 46.90 | 140.78 | 27.83 | 92.73 | 3.72 | 9.51 | 5.11 | 18.95 | 245.30 | 50.6 | 383.4 | 3.410 | 79.50 |
| H ₁₀ | 26 | 48.97 | 136.28 | 31.83 | 90.00 | 3.63 | 9.19 | 6.37 | 18.35 | 239.96 | 70.92 | 378.69 | 2.502 | 76.68 |
| H ₁₁ | 26 | 47.24 | 183.85 | 31.37 | 87.91 | 3.79 | 8.53 | 4.83 | 16.95 | 228.20 | 84.60 | 356.76 | 2.903 | 74.56 |
| H ₁₂ | 28 | 50.80 | 191.94 | 27.07 | 91.82 | 3.78 | 8.96 | 6.50 | 18.02 | 245.08 | 84.60 | 389.13 | 3.417 | 79.60 |
| H ₁₃ | 30 | 53.31 | 188.19 | 35.83 | 95.82 | 4.29 | 9.51 | 6.58 | 18.87 | 254.35 | 93.83 | 405.26 | 2.745 | 81.02 |
| H ₁₄ | 28 | 47.55 | 181.17 | 27.76 | 92.39 | 3.92 | 9.10 | 5.64 | 18.19 | 242.17 | 84.60 | 373.18 | 3.507 | 79.36 |
| H ₁₅ | 28 | 46.89 | 169.96 | 31.43 | 90.49 | 4.13 | 8.86 | 5.41 | 17.63 | 236.96 | 104.83 | 368.07 | 2.600 | 76.54 |

Abbreviations: Aliphatic atom count (AAC); Aliphatic bond count (ABC); Atom count (AC); Bond count (BC); Chain atom count (CAC); Chain bond count (CBC); Ring bond count (RBC); Platt index (PI); Randic index (X); Balaban index (J); Harary index (H); Hyper Wiener index (WW); Szeged index (Sz); Wiener index (W); Wiener polarity (Wp); Dreiding energy (DE); MMFF94 energy (MM); Minimal projection area (MIPA); Maximal projection area (MAPA); Minimal projection radius (MIPR); Maximal projection radius (MAPR); Length perpendicular to the max area (LPMA); Length perpendicular to the min area (LPMI); van der Waals volume (VWV); Polar Surface Area (2D)(PSA); Molecular Surface Area (3D)(MSA); Octanol/water partition coefficient (logP) and Refractivity (R).

logarithms of molar MICs ($\log 1/C_{MIC} = \log 1/C$), (Table 1), which were used as a dependent variable in the QSAR study.

In our previous investigation, QSAR analysis of a selected series of hydrazones, tested for their growth inhibitory activity against *Bacillus subtilis* was performed, using physicochemical descriptors, such as molar refraction, molar volume, parachor, index of refraction, surface tension, density and polarizability [19].

Therefore, in the present study, the selected topological descriptors (Table 2) were used as independent variables in correlation with antibacterial activity ($\log 1/C_{MIC} = \log 1/C_{MICobs}$).

3.1. Two, Three, Four Parametric and Higher Models

Several two-, three-, four-parametric and higher models that were statistically found to be optimum have been selected for further discussion.

- The Best Two-Parametric Models

In bivariate correlation analysis, applying the stepwise multiple linear regression method, 6 QSAR models were obtained (**Models 1-6**). The selection was based on the preliminary statistical quality of the models (R ; Sd; F-test; R^2_{adj} ; p-level). Preliminary regression analysis indicated that, out of the 28 descriptors used, AAC, ABC, AC, CBC, X, H, MAPA and logP, in combination with each other, play a dominating role in modeling the activity (**Models 1-6**).

Model 1

$$\log 1/C = 5.1573 \pm 0.03 + 0.0255 \pm 0.00 \text{ AAC} + 0.0239 \pm 0.00 \log P$$

$$R^2 = 0.9246 \text{ Sd} = 0.0113 \text{ Ftest} = 73.5661 \text{ } R^2_{adj} = 0.9120 \text{ } p < 0.0001.$$

Model 2

$$\log 1/C = 5.1318 \pm 0.03 + 0.0256 \pm 0.00 \text{ ABC} + 0.0238 \pm 0.00 \log P.$$

$$R^2 = 0.9246 \text{ Sd} = 0.0114 \text{ Ftest} = 73.5661 \text{ } R^2_{adj} = 0.9121 \text{ } p < 0.0001.$$

Model 3

$$\log 1/C = 4.8172 \pm 0.05 - 0.0091 \pm 0.00 \text{ AC} + 0.0102 \pm 0.00 \text{ MAPA}.$$

$$R^2 = 0.9444 \text{ Sd} = 0.0097 \text{ Ftest} = 101.9875 \text{ } R^2_{adj} = 0.9352 \text{ } p < 0.0001.$$

Model 4

$$\log 1/C = 5.1318 \pm 0.03 + 0.0255 \pm 0.00 \text{ CBC} + 0.0240 \pm 0.00 \log P.$$

$$R^2 = 0.9246 \text{ Sd} = 0.0113 \text{ Ftest} = 73.5661 \text{ } R^2_{adj} = 0.912 \text{ } p < 0.0001.$$

Model 5

$$\log I/C = 4.7971 \pm 0.06 + 0.0573 \pm 0.00X + 0.0272 \pm 0.01 \log P.$$

$$R^2 = 0.9211 \quad Sd = 0.0116 \quad F_{test} = 70.0121 \quad R^2_{adj} = 0.9079 \quad p < 0.0001.$$

Model 6

$$\log I/C = 5.0021 \pm 0.04 + 0.0059 \pm 0.00 H + 0.0231 \pm 0.01 \log P.$$

$$R^2 = 0.9231 \quad Sd = 0.0114 \quad F_{test} = 72.0451 \quad R^2_{adj} = 0.9103 \quad p < 0.0001.$$

According to preliminary statistical results, it could be concluded that excellent correlation ($R^2 = 0.9444$; $Sd = 0.0097$) was obtained when AC and MAPA were used in bivariate correlation. The correlation is expressed by **Model 3**.

- The Best Three-Parametric Models

No significant improvement in the quality of the models was achieved by adding one more parameter (**Models 7-9**). In all the cases, R^2 is above 0.92.

Model 7

$$\log I/C = 5.1675 \pm 0.15 + 0.0268 \pm 0.02 AAC - 3.970E-4 \pm 0.01 PI + 0.0242 \pm 0.01 \log P.$$

$$R^2 = 0.9246 \quad Sd = 0.0118 \quad F_{test} = 44.9778 \quad R^2_{adj} = 0.9070 \quad p < 0.0001.$$

Model 8

$$\log I/C = 5.2081 \pm 0.09 + 0.0258 \pm 0.00 AAC - 0.0012 \pm 0.00 MIPA + 0.0182 \pm 0.01 \log P.$$

$$R^2 = 0.9269 \quad Sd = 0.0116 \quad F_{test} = 46.5364 \quad R^2_{adj} = 0.9070 \quad p < 0.0001.$$

Model 9

$$\log I/C = 5.1632 \pm 0.12 + 0.0259 \pm 0.01 AAC - 1.017E-4 \pm 0.00 MAPA + 0.024 \pm 0.01 \log P.$$

$$R^2 = 0.9245 \quad Sd = 0.0118 \quad F_{test} = 44.9685 \quad R^2_{adj} = 0.9400 \quad p < 0.0001.$$

Model 8 was the best three-parametric model with: $R^2 = 0.9269$ and $Sd = 0.0116$.

- The Best Four-Parametric Model

In the case of tetravariate combinations, the best statistics was achieved by the model based on the descriptors MAPA, LPMA, PSA and logP (**Model 10**):

Model 10

$$\log I/C = 4.8573 \pm 0.06 + 0.0062 \pm 0.00 MAPA - 0.0152 \pm 0.01 LPMA + 6.024E-4 \pm 0.00 PSA + 0.0209 \pm 0.01 \log P.$$

$$R^2 = 0.9424 \quad Sd = 0.0108 \quad F_{test} = 40.9195 \quad R^2_{adj} = 0.9424 \quad p < 0.0001.$$

The positive coefficient of MAPA, PSA and log P indicates that the activity is continually enhanced with the increase in the magnitude of those descriptors.

- The Best Five-Parametric Model

Similar statistics were obtained with the addition of another descriptor. The attained model is presented below:

Model 11

$$\log I/C = 4.7993 \pm 0.10 + 0.0064 \pm 0.00 MAPA + 0.0115 \pm 0.01 MIPR - 0.0153 \pm 0.00 LPMA + 5.831E-4 \pm 0.00 PSA + 0.0222 \pm 0.01 \log P$$

$$R^2 = 0.9458 \quad Sd = 0.0111 \quad F_{test} = 31.4230 \quad R^2_{adj} = 0.9157 \quad p < 0.0001$$

- Higher Parametric Models

Considering the achieved satisfactory results, further regression analysis was not needed. However, hoping for further improvement, we carried out higher-parametric regression analysis. When MIPA (six- and seven-parametric) and J (seven-parametric) were added to equation 11, there was a slight improvement in the statistics (**models 12 and 13**):

- Six-Parametric Model

Model 12

$$\log I/C = 4.8153 \pm 0.11 - 0.0013 \pm 0.00 MIPA + 0.0066 \pm 0.00 MAPA + 0.0169 \pm 0.02 MIPR - 0.0146 \pm 0.01 LPMA + 5.482E-4 \pm 0.00 PSA + 0.0162 \pm 0.02 \log P$$

$$R^2 = 0.9475 \quad Sd = 0.0116 \quad F_{test} = 24.0409 \quad R^2_{adj} = 0.9008 \quad p < 0.0001$$

- Seven-Parametric Model

Model 13

$$\log I/C = 5.0190 \pm 0.17 - 0.1010 \pm 0.07 J + 1.128E-4 \pm 0.00 MIPA + 0.0063 \pm 0.00 MAPA - 0.0025 \pm 0.02 MIPR - 0.0181 \pm 0.01 LPMA + 6.202E-4 \pm 0.00 PSA + 0.0240 \pm 0.02 \log P$$

$$R^2 = 0.9598 \quad Sd = 0.0108 \quad F_{test} = 23.8947 \quad R^2_{adj} = 0.9197 \quad p < 0.0001$$

3.2. Variance Inflation Factor (VIF)

The variance inflation factor (VIF), as a measure of multicollinearity [20], was calculated for each of the parameters involved in the two- and three-variable models (**Models 3 and 8** chosen as models with the best preliminary statistical values) and higher-variable models (**models 10, 11, 12 and 13**).

The VIF is defined as:

$$VIF = 1/(1 - R_i^2)$$

where R_i is the multiple correlation coefficient of the i -th independent variable on all of the other independent variables [20].

For large data sets, a VIF of 10 or higher (no upper limit is defined) indicates a collinearity problem. For small data sets, as in our case, even VIFs of 5 or higher (here, no upper limit is defined either) can indicate collinearity [20]. The variables with high VIF values are candidates for being left out from the model.

The VIF values for **Models 3, 8, 10, 11, 12 and 13** are presented in Table 3.

Table 3. Calculated VIF values for models: 3, 8, 10, 11, 12 and 13.

| Models | | | | | |
|----------------|------|----------------|------|-------|------|
| 3 ^a | | 8 ^a | | 10 | |
| Desc. | VIF | Desc. | VIF | Desc. | VIF |
| AC | 4.61 | AAC | 1.08 | MAPA | 1.85 |
| MAPA | 4.61 | MIPA | 2.47 | LPMA | 1.29 |
| - | - | logP | 2.35 | PSA | 1.68 |
| - | - | - | - | logP | 1.16 |
| Models | | | | | |
| 11 | | 12 | | 13 | |
| Desc. | VIF | Desc. | VIF | Desc. | VIF |
| MAPA | 1.94 | MIPA | 4.15 | J | 1.70 |
| MIPR | 1.12 | MAPA | 2.37 | MIPA | 4.80 |
| LPMA | 1.29 | MIPR | 1.65 | MAPA | 2.49 |
| PSA | 1.71 | LPMA | 1.35 | MIPR | 2.53 |
| logP | 1.21 | PSA | 1.93 | LPMA | 1.54 |
| - | - | logP | 3.44 | PSA | 2.06 |
| - | - | - | - | logP | 3.93 |

^a Models 3 and 8 chosen as models with best preliminary statistical values.

Table 4. Correlation $\log 1/C_{MICpred} = a \log 1/C_{MICobs} + b$ and predictive correlation coefficient (R_{pre}) for models: 3, 8, 10, 11, 12 and 13.

| Models | | | | | | |
|-------------|----------------|----------------|-------|-------|-------|-------|
| - | 3 ^a | 8 ^a | 10 | 11 | 12 | 13 |
| <i>a</i> | 0.943 | 0.925 | 0.938 | 0.950 | 0.952 | 0.963 |
| <i>b</i> | 0.305 | 0.402 | 0.332 | 0.271 | 0.263 | 0.198 |
| R_{pre}^2 | 0.944 | 0.927 | 0.942 | 0.945 | 0.947 | 0.959 |

^a Models 3 and 8 chosen as models with best preliminary statistical values.

As can be seen from the results, no parameters exhibited VIF values much higher than 5, meaning that those models were accurately selected and free from defects caused by collinearity.

Also, the data on the antimicrobial activity against *B. subtilis*, as predicted by **Models 3, 8, 10, 11, 12 and 13** ($\log 1/C_{MICpred}$), were compared with the corresponding $\log 1/C_{MICobs}$ values reported in Table 1. Subsequently, it was found that, within experimental error, the values agreed well. We evaluated the predictive correlation coefficients (R_{pre}) to examine the relative potential of the selected models. The R_{pre} values achieved were up to 0.9, for all the models. The predictive correlation coefficient (R_{pre}) and the correlation $\log 1/C_{pred} = a \log 1/C_{obs} + b$ are presented in Table 4.

3.3. Occurrence of Collinearity

At this stage of investigation, the occurrence of collinearity in the proposed models should be examined by: (a) correlation matrix and (b) calculation of additional statistical parameters, such as: PRESS/SSY, Q^2 , PSE, SPRESS and Q .

(a) **Correlation matrix** The data presented in Table 5 reveal high collinearity among most of the descriptors ($R > 0.8$), indicating that these parameters could not be combined to get multiple linear regression (MLR) models. In case of their combination, the model may be defective because of collinearity.

Table 5. Correlation matrix.

| - | AAC | ABC | AC | BC | CAC | CBC | RBC | PI | X | J | H | WW | Sz | W |
|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| AAC | 1.00 | - | - | - | - | - | - | - | - | - | - | - | - | - |
| ABC | 1.00 | 1.00 | - | - | - | - | - | - | - | - | - | - | - | - |
| AC | 0.66 | 0.66 | 1.00 | - | - | - | - | - | - | - | - | - | - | - |
| BC | 0.66 | 0.66 | 1.00 | 1.00 | - | - | - | - | - | - | - | - | - | - |
| CAC | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | - | - | - | - | - | - | - | - | - |
| CBC | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | 1.00 | - | - | - | - | - | - | - | - |
| RBC | 0.87 | 0.87 | 0.81 | 0.81 | 0.87 | 0.87 | 1.00 | - | - | - | - | - | - | - |
| PI | 0.99 | 0.99 | 0.59 | 0.59 | 0.99 | 0.99 | 0.80 | 1.00 | - | - | - | - | - | - |
| X | 1.00 | 1.00 | 0.70 | 0.70 | 1.00 | 1.00 | 0.91 | 0.98 | 1.00 | - | - | - | - | - |
| J | -0.10 | -0.10 | -0.15 | -0.15 | -0.10 | -0.10 | -0.24 | -0.06 | -0.12 | 1.00 | - | - | - | - |
| H | 1.00 | 1.00 | 0.65 | 0.65 | 1.00 | 1.00 | 0.86 | 0.99 | 1.00 | -0.10 | 1.00 | - | - | - |
| WW | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | 1.00 | 0.88 | 0.98 | 0.99 | -0.11 | 1.00 | 1.00 | - | - |
| Sz | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | 1.00 | 0.88 | 0.99 | 1.00 | -0.10 | 1.00 | 1.00 | 1.00 | - |
| W | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | 1.00 | 0.88 | 0.99 | 1.00 | -0.11 | 1.00 | 1.00 | 1.00 | 1.00 |
| Wp | 1.00 | 1.00 | 0.66 | 0.66 | 1.00 | 1.00 | 0.87 | 0.99 | 1.00 | -0.10 | 1.00 | 1.00 | 1.00 | 1.00 |
| DE | 0.88 | 0.88 | 0.90 | 0.90 | 0.88 | 0.88 | 0.91 | 0.83 | 0.90 | -0.12 | 0.87 | 0.88 | 0.88 | 0.88 |
| MM | 0.73 | 0.73 | 0.22 | 0.22 | 0.73 | 0.73 | 0.51 | 0.76 | 0.70 | -0.05 | 0.74 | 0.74 | 0.73 | 0.74 |
| MIPA | 0.26 | 0.26 | 0.39 | 0.39 | 0.26 | 0.26 | 0.55 | 0.17 | 0.31 | -0.19 | 0.26 | 0.31 | 0.29 | 0.29 |
| MAPA | 0.94 | 0.94 | 0.78 | 0.78 | 0.94 | 0.94 | 0.88 | 0.92 | 0.95 | -0.04 | 0.94 | 0.93 | 0.94 | 0.94 |
| MIPR | -0.07 | -0.07 | -0.22 | -0.22 | -0.07 | -0.07 | 0.06 | -0.11 | -0.06 | -0.49 | -0.07 | -0.01 | -0.03 | -0.03 |
| MAPR | 0.83 | 0.83 | 0.86 | 0.86 | 0.83 | 0.83 | 0.88 | 0.77 | 0.85 | -0.08 | 0.81 | 0.81 | 0.82 | 0.82 |
| LPMA | 0.42 | 0.42 | 0.64 | 0.64 | 0.42 | 0.42 | 0.39 | 0.41 | 0.43 | -0.24 | 0.42 | 0.44 | 0.44 | 0.44 |
| LPMI | 0.83 | 0.83 | 0.86 | 0.86 | 0.83 | 0.83 | 0.85 | 0.79 | 0.85 | -0.09 | 0.82 | 0.81 | 0.82 | 0.82 |
| VWV | 0.90 | 0.90 | 0.87 | 0.87 | 0.90 | 0.90 | 0.90 | 0.86 | 0.92 | -0.11 | 0.89 | 0.89 | 0.90 | 0.90 |
| PSA | 0.78 | 0.78 | 0.18 | 0.18 | 0.78 | 0.78 | 0.52 | 0.82 | 0.75 | -0.03 | 0.79 | 0.78 | 0.78 | 0.78 |
| MSA | 0.85 | 0.85 | 0.94 | 0.94 | 0.85 | 0.85 | 0.90 | 0.80 | 0.88 | -0.13 | 0.84 | 0.84 | 0.85 | 0.85 |
| logP | -0.15 | -0.15 | -0.23 | -0.23 | -0.15 | -0.15 | -0.36 | -0.08 | -0.18 | 0.18 | -0.14 | -0.16 | -0.15 | -0.16 |
| R | 0.90 | 0.90 | 0.80 | 0.80 | 0.90 | 0.90 | 0.84 | 0.88 | 0.91 | -0.08 | 0.90 | 0.89 | 0.90 | 0.90 |
| - | Wp | DE | MM | MIPA | MAPA | MIPR | MAPR | LPMA | LPMI | VWV | PSA | MSA | log P | R |
| Wp | 1.00 | - | - | - | - | - | - | - | - | - | - | - | - | - |
| DE | 0.88 | 1.00 | - | - | - | - | - | - | - | - | - | - | - | - |
| MM | 0.73 | 0.59 | 1.00 | - | - | - | - | - | - | - | - | - | - | - |
| MIPA | 0.26 | 0.39 | 0.07 | 1.00 | - | - | - | - | - | - | - | - | - | - |
| MAPA | 0.94 | 0.92 | 0.58 | 0.21 | 1.00 | - | - | - | - | - | - | - | - | - |
| MIPR | -0.07 | -0.14 | 0.10 | 0.47 | -0.16 | 1.00 | - | - | - | - | - | - | - | - |

(Table 5) contd....

| - | Wp | DE | MM | MIPA | MAPA | MIPR | MAPR | LPMA | LPMI | VWV | PSA | MSA | Log P | R |
|------|-------|-------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| MAPR | 0.83 | 0.87 | 0.30 | 0.26 | 0.94 | -0.21 | 1.00 | - | - | - | - | - | - | - |
| LPMA | 0.42 | 0.63 | 0.28 | 0.22 | 0.46 | -0.05 | 0.42 | 1.00 | - | - | - | - | - | - |
| LPMI | 0.83 | 0.88 | 0.32 | 0.19 | 0.95 | -0.26 | 0.99 | 0.46 | 1.00 | - | - | - | - | - |
| VWV | 0.90 | 0.94 | 0.48 | 0.24 | 0.98 | -0.20 | 0.97 | 0.52 | 0.98 | 1.00 | - | - | - | - |
| PSA | 0.78 | 0.48 | 0.78 | 0.23 | 0.55 | 0.10 | 0.32 | 0.18 | 0.33 | 0.44 | 1.00 | - | - | - |
| MSA | 0.85 | 0.96 | 0.43 | 0.30 | 0.94 | -0.19 | 0.96 | 0.58 | 0.96 | 0.99 | 0.37 | 1.00 | - | - |
| logP | -0.15 | -0.15 | 0.15 | -0.76 | -0.01 | -0.26 | -0.10 | -0.02 | -0.05 | -0.06 | -0.32 | -0.10 | 1.00 | - |
| R | 0.90 | 0.91 | 0.54 | 0.11 | 0.98 | -0.23 | 0.95 | 0.50 | 0.96 | 0.99 | 0.45 | 0.95 | 0.10 | 1.00 |

Table 6. Cross-validation parameters (Q^2 , PRESS/SSY; S_{PRESS} , PSE and Q) and t-values and p values for selected variables for models: 3, 8, 10, 11, 12 and 13.

| A. Cross-validation parameters: Q , PRESS/SSY, S_{PRESS} , PSE and Q^2 | | | | | | |
|--|----------------|----------------|--------------|---------|--------------|---------|
| - | Models | | | | | |
| - | 3 ^a | 8 ^a | 10 | 11 | 12 | 13 |
| Q | 100.1858 | 83.0007 | 89.8864 | 87.6146 | 83.9135 | 90.7124 |
| PRESS/SSY | 0.0564 | 0.0736 | 0.0656 | 0.0649 | 0.0579 | 0.0473 |
| S_{PRESS} | 0.0098 | 0.0088 | 0.0116 | 0.0121 | 0.0122 | 0.0118 |
| PSE | 0.0088 | 0.0256 | 0.0094 | 0.0094 | 0.0089 | 0.0080 |
| Q^2 | 0.9436 | 0.9264 | 0.9344 | 0.9351 | 0.9421 | 0.9527 |
| B. T-values and p-values for selected variables ^{b,c} | | | | | | |
| Models | | | | | | |
| 3 ^a | | 8 ^a | | 10 | | |
| Desc. | t / p values | Desc. | t / p values | Desc. | t / p values | |
| AC | -5.174 / 0.000 | AAC | 11.554/0.000 | MAPA | 7.981/0.000 | |
| MAPA | 12.332 / 0.000 | MIPA | -0.597/0.562 | LPMA | -2.423/0.035 | |
| - | - | logP | 1.460/0.172 | PSA | 3.355/0.007 | |
| - | - | - | - | logP | 2.552/0.020 | |
| Models | | | | | | |
| 11 | | 12 | | 13 | | |
| Desc. | t / p values | Desc. | t / p values | Desc. | t / p values | |
| MAPA | 7.793/0.000 | MIPA | -0.498/0.630 | J | -1.468/0.185 | |
| MIPR | 0.751/0.471 | MAPA | 6.958/0.000 | MIPA | 0.043/0.960 | |
| LPMA | -2.395/0.041 | MIPR | 0.875/0.407 | MAPA | 6.93/0.000 | |
| PSA | 3.146/0.012 | LPMA | -2.132/0.060 | MIPR | -0.112/0.913 | |
| logP | 2.592/0.028 | PSA | 2.662/0.028 | LPMA | -2.651/0.032 | |
| - | - | logP | 1.074/0.313 | PSA | 3.123/0.017 | |
| - | - | - | - | logP | 1.596/0.154 | |

^a Models 3 and 8 chosen as models with best preliminary statistical values;

^b Critical t-values: (0.05, 12) = 2.178; (0.05, 11) = 2.201; (0.05, 10) = 2.228; (0.05, 9) = 2.262; (0.05, 8) = 2.306; (0.05, 7) = 2.365;

^c Critical F values: (0.05, 2, 12) = 3.89; (0.05, 3, 11) = 3.59; (0.05, 4, 10) = 3.48; (0.05, 5, 9) = 3.48; (0.05, 6, 8) = 3.58; (0.05, 7, 7) = 3.79.

From the above-mentioned considerations related to the data presented in Table 5, the models with high collinearity among the descriptors ($R > 0.8$) were excluded from further analysis.

The descriptors used in the selected **Models 3, 8, 10, 11, 12** and **13** are poorly correlated. Taking into consideration the above-mentioned preliminary conclusions of the statistical evaluation regarding the quality of the selected models (R , R^2_{adj} , F , S_d , p), **Models 3, 8, 10, 11, 12** and **13** can be used as relatively statistically significant.

(b) Statistical evaluation. The predictivity of the obtained **Models 3, 8, 10, 11, 12** and **13** was measured by several cross-validation parameters: Q , PRESS/SSY, S_{PRESS} , PSE and Q^2 (Table 6A).

On the basis of the Q parameter, the selected models can be ranked (from the best to the worst) in the following order: $3 > 13 > 10 > 11 > 12 > 8$ (Table 6A). Nevertheless, the Q factor ranking was not sufficient, since the parameters in the quality factor definition ($Q = R/S_d$) [21] were not in any way connected to the prediction power of the model.

The next step of statistical evaluation consisted in ranking the models according to PRESS/SSY, S_{PRESS} , PSE and Q^2 statistical parameters, which are related to the prediction power (goodness of prediction) of the models

Models with PRESS/SSY < 0.4 [20, 22], as in this case, PRESS/SSY ranges between 0.0473 - 0.0736, are considered reliable QSAR models (Table 6A). Good S_{PRESS} and PSE values were obtained for all the selected models (S_{PRESS} and $PSE < 0.02$ and 0.03 , respectively), confirming the assumption that those models can be used as a tool for predicting the inhibition of *B. subtilis* [23].

For a statistically reliable model, the cross-validation squared correlation coefficient values (Q^2) should be > 0.6 [20], and the difference between R^2 and Q^2 should not exceed 0.3 [24]. According to all additional statistical parameters, **Models 3** and **13** can be distinguished as the models generating the best prediction results among all.

In **model 3**, the t-value for the independent variables (AC and MAPA) was -5.174 for AC and 12.332 for MAPA, with the corresponding p-value = 0, indicating that they were statistically significant at 95% or higher confidence level (Critical $t_{(0.05,12)} = 2.178$; Critical $F_{(0.05,2,12)} = 3.89$) (Table 6B).

Meanwhile, in **Model 13**, there were some descriptors with an unsatisfactory t-value for the independent variables; t-value for BI = -1.468; MIPA = 0.043; MIPR = -0.112 and $\log P = 1.596$ (Critical $t_{(0.05,7)} = 2.365$; Critical $F_{(0.05,7,7)} = 3.79$) (Table 6B).

Due to this fact, **Model 3** can be selected as the best describing model, in which the parameters have opposite input in modeling the antimicrobial activity of the selected hydrazones against *Bacillus subtilis* (AC-negative; MAPA-positive). The slightly higher influence associated with the Maximal Projection Area (MAPA) coefficient (52.85 %), compared to the other descriptor coefficient (AC = 47.15%), indicates the positive role of MAPA in predicting biological activity.

In this model, the coefficients of AC and MAPA were higher than their standard deviation, which is another confirmation for the statistical significance of **Model 3**.

CONCLUSION

A series of *p*-substituted aromatic hydrazones have been synthesized and evaluated for their *in vitro* antimicrobial activity against *Candida utilis*, *Bacillus subtilis* and *Aspergillus niger*. None of the hydrazones inhibited the growth of the *Aspergillus spp.*, while the data regarding the antifungal activity of the compounds relative to *Candida utilis* were insufficient to develop statistically reliable QSAR models. Therefore, the QSAR study was performed to estimate the quantitative effects of the selected set of topological descriptors of hydrazone derivatives on their antimicrobial activity against *Bacillus subtilis*. The selected topological descriptors were calculated for each molecule and several two-, three-, four-parameter and higher mathematical models were selected for further discussion. The statistical significance of each model was measured by Q , PRESS/SSY, S_{PRESS} , PSE and Q^2 . Statistical evaluation of the data used to test the quality of the obtained models indicated that **Model 3** (a two-parametric model) was statistically significant when all the parameters were summarized. The two parameters involved in the best statistical model (**Model 3**), AC (atom count) and MAPA (maximal projection area), have opposite input in modeling the biological activity of the selected hydrazones.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available in the Faculty of Technology and Metallurgy, Ss Cyril and Methodius University, Skopje, Republic of Macedonia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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