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# Structure-Activity/Property Relationships and QSAR Modeling of Anti-amoebic activity of Citral Derived amides

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**ABSTRACT**

QSAR studies have been performed on eleven molecules of citral derived amides. A multiple linear regression (MLR) procedure was used to design the relationships between molecular descriptor and anti-amoebic activity of citral derived amides. The predictivity of the model was estimated by cross-validation with the leave-one-out method. Our results suggest a QSAR model based of the following descriptors: MW, Log P, HE, Pol, for the anti-amoebic activity. To confirm the predictive power of the models, an external set of molecules was used. High correlation between experimental and predicted activity values was observed, indicating the validation and the good quality of the derived QSAR models.
**Keywords:** Citral derived amides, SAR, QSAR, anti-amoebic activity, MLR.

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## INTRODUCTION

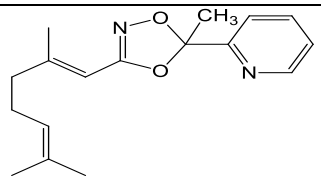
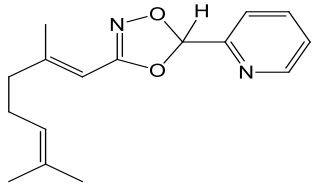
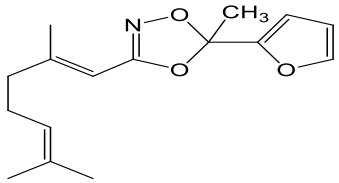
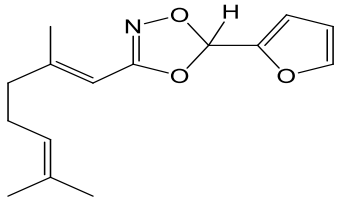
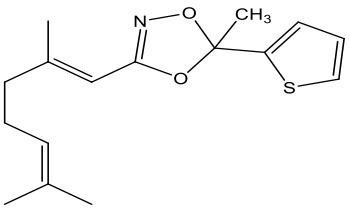
QSAR method, is a computational chemical technique is known to relate the biological activity of compounds with their molecular structure and has been extensively used as predicting tool in rational drug design [1].Quantitative structure/activity relationships (QSARs), as one of the most important areas in chemometrics, QSAR models are mathematical equations relating chemical structure to their biological activity. QSAR are attempts to correlate molecular structure, or properties derived from molecular structure with a particular kind of chemical or biochemical activity [2]. Multiple linear regression (MLR) is also a mathematical tool that quantifies the relationship between a dependent variable and one or more independent variables [3]. Citral derived amides, a potent efflux pump inhibitors against S. aureus 1199 and Nora overex pressing S. aureus 1199B, it was prepared from synthesis of alkenyl amides. Following our interest in this field, our present research aimed to describe the structure-property relationships study on citral derived amides and developed a QSAR model on these compounds with respect to their anti-amoebic activity.

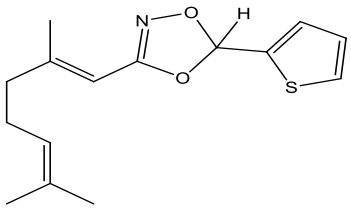
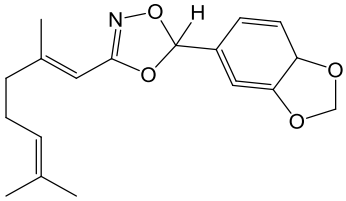
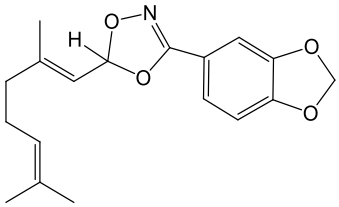
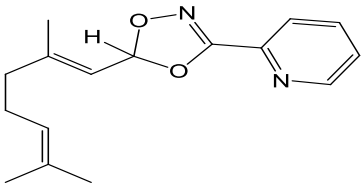
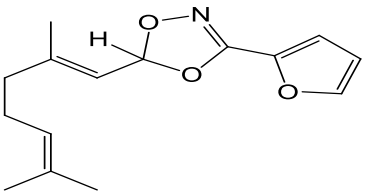
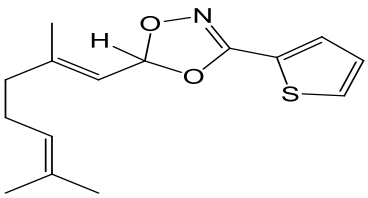
## EXPERIMENTAL

### Biological Data

The activity parameter used in this study is anti-amoebic activity. Interestingly, all these compounds were active and showed anti-amoebic activity with IC50 values, The half maximal inhibitory concentration ($IC_{50}$) is measured in µM by Wani et al. [4] (Table 1).

**Table 1: Chemical structures and experimental activity of the citral derived amides.**

| C. No | citral derived amides | PIC50 exp.[4] | PIC50 pred. | Residu |
|---|---|---|---|---|
| 1 |  | -0,352 | -0,363 | 0,011 |
| 2 |  | -0,474 | -0,387 | -0,086 |
| 3 |  | -0,305 | -0,346 | 0,041 |
| 4 |  | -0,383 | -0,377 | -0,005 |
| 5 |  | -0,478 | -0,450 | -0,027 |

| | | | | |
|---|---|---|---|---|
| 6 |  | -0,462 | -0,470 | 0,008 |
| 7 |  | -0,170 | -0,158 | -0,011 |
| 8 |  | -0,143 | -0,151 | 0,008 |
| 9 |  | -0,346 | -0,418 | 0,072 |
| 10 |  | -0,444 | -0,424 | -0,019 |
| 11 |  | -0,484 | -0,491 | 0,007 |

**Descriptors Generation**

Firstly, eleven investigated molecules were pre-optimized by means of the Molecular Mechanics Force Field (MM+) included in HyperChem version 8.03 package [5] . After that, the resulted minimized structures were further refined using the semi-empirical PM3 Hamiltonian implemented also in HyperChem. We chose a gradient norm limit of 0.01kcal/Å for the geometry optimization. Then, these citral derived amides were re-optimized by using Gaussian 09 program package [6], at the PM3, this theory was used to calculate a number of electronic descriptors: dipole moment (DM), energy of frontier orbital's, EHOMO and ELUMO.

The QSAR properties module from HyperChem 8.03 was used to calculate: molar polarizability (Pol), the molar refractivity (MR), partition coefficient octanol/water (log P), hydration energy (HE), molar volume (MV), Surface area grid (SAG) and molar weight (MW).

**Regression Analysis**

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows [7].

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## RESULTS AND DISCUSSION

### Structure Activity Relationships (SAR)

We have studied seven physical chemical proprieties of series of eleven citral derived amides, using HyperChem software. QSAR proprieties [8-13] such as van der Waals surface molecular volume, octanol-water partition coefficient (log P), molar refractivity (MR), polarizability (Pol), solvent-accessible, surface bounded molecular volume and molecular weight (M) were investigated.

**Table 2: Values of molecular descriptors used in the regression analysis.**

| C. No | $E_{HOMO}$ | $E_{LUMO}$ | Log P | HE | Pol | MR | MV | SAG | MW |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -0,339 | -0,010 | 5,40 | -3,01 | 32,79 | 83,96 | 924,89 | 557,68 | 286,37 |
| 2 | -0,339 | -0,012 | 4,78 | -4,20 | 30,96 | 78,94 | 880,39 | 533,59 | 272,35 |
| 3 | -0,342 | -0,010 | 3,50 | -4,05 | 30,66 | 79,88 | 889,58 | 539,30 | 275,35 |
| 4 | -0,344 | -0,013 | 2,88 | -5,37 | 28,83 | 74,86 | 843,13 | 519,05 | 261,32 |
| 5 | -0,343 | -0,015 | 3,84 | -3,06 | 33,03 | 86,33 | 916,16 | 552,87 | 291,41 |
| 6 | -0,343 | -0,019 | 3,22 | -4,23 | 31,19 | 81,31 | 866,10 | 525,58 | 277,38 |
| 7 | -0,336 | -0,014 | 4,91 | -7,67 | 34,00 | 87,27 | 956,30 | 576,41 | 315,37 |
| 8 | -0,337 | -0,025 | 5,03 | -7,77 | 34,00 | 87,35 | 922,02 | 541,59 | 315,37 |
| 9 | -0,345 | -0,031 | 4,90 | -5,07 | 30,96 | 79,02 | 879,44 | 529,50 | 272,35 |
| 10 | -0,341 | -0,021 | 3,91 | -8,43 | 28,83 | 73,77 | 842,11 | 515,03 | 261,32 |
| 11 | -0,347 | -0,037 | 4,26 | -6,78 | 31,19 | 80,22 | 864,53 | 519,05 | 277,38 |

Molecular polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties[14-18] and biological activities . The attractive part of the Van der Waals interaction is a good measure of the polarizability. Highly polarizable molecules can be expected to have strong attractions with other molecules. The polarizability of a molecule can also enhance aqueous solubility. The molar refractivity (MR) is important criterion to measure the steric factor. It is usually designated as a simple measure of the volume occupied either by an individual atom or a cluster (group) of atoms . Polarizability and molar refractivity relatively increase with the size and the molecular weight of the studied compounds [19-23] (Table 2). This result is in agreement with the formula of Lorentz-Lorenz which gives a relationship between polarizability, the molar refractivity and volume. This relationship shows that the polarizability and the molar refractivity increase with the volume and the molecular weight.

The presence of the hydrophobic groups in the structure of the citral derived amides induces a decrease of the hydratation energy, however, the presence of hydrophilic groups increases the hydratation energy (Table 2). The most important hydratation energy in the absolute value, (8,430kcal/mol) is that of the compound 10, but the lower one (3,010 kcal/mol) was performed for the compound 1 (Table 2). Indeed in the biological environment the polar molecules are surrounded by water molecules where the Hydrogen bonds can be established between the water molecule and the molecules under study. The first corresponds to the complex having strongest hydrogen bond. At least, these hydrated molecules are partially dehydrated before their interaction. These interactions of weak energy are generally reversible in particular between messengers and receivers. This property supports the compound 10 not only by fixing the receptors, but also activates it by playing the role of agonist. It has as a consequence a better distribution in fabrics .

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity. Hansch and Leo reasoned that highly lipophilic molecules will partition into the lipid interior of membranes and retained there. For good oral bioavailability, logP must be in the range (0 <logP< 3). For higher logP the drug has low solubility and for lower logP, the drug has difficulty to penetrate the lipid membranes . In opposition to hydratation energy, the presence of the hydrophobic groups in the structure of the citral derived amides induces an increase of the lipophilicity. Compound 4 presents the low coefficient of division (2,880). When the coefficient of division is rather low, it has as a consequence a better gastric tolerance. Compounds 1 which has higher value (5,400), has capacity to be dependent on plasmatic proteins.

**Quantitative Structure-Activity Relationships Studies**

Firstly, different substituted citral derived amides (Table 1) were evaluated for their anti-amoebic activity. The biological parameter (IC50) was introduced in this search and the results are illustrated in Table 1. In order to determine the role of structural features. A series of eleven citral derived amides was investigated by QSAR method.

These compounds were used for multilinear regression model generation. Different physicochemical descriptors such as steric, electronic and molecular structure were used as independent variables and were correlated with biological activity.

Developing a QSAR model requires a diverse set of data, and, thereby a large number of descriptors have to be considered. Descriptors are numerical values that encode different structural features of the molecules.

Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters. Pearson's correlation matrix has been performed on all descriptors by using SPSS Software. The analysis of the matrix revealed sixteen descriptors for the development of MLR model. The values of descriptors selected for MLR model are presented in Table 2.

The correlation between the biological activity (IC50) and descriptors expressed by the following relation:

PIC50 = 0.035+0.028 MW + 0.104 Log P + 0.050 HE -0.271 Pol.
*n = 11; r =* 0,943;s =0,052; F = 12,072; Q=18,135

The values of fraction variance may vary between 0 and 1. QSAR model having r2 > 0.6 will only be considered for validation. For example, the value r = 0,943and $r^2$ = 0.889 allowed us to indicate firmly the correlation between different parameters (independent variables) with anti-amoebic activity of the compounds.

The F-value has found to be statistically significant at 95 % level, since the calculated F value is higher as compared to tabulated value. The positive value of quality factor (Q) for this QSAR's model suggests its high predictive power and lack of over fitting.

In equation of PIC50, the positive coefficient of MW explains that any increase in molecular weight of the compounds causes a decrease in the biological activity.

In order to test the validity of the predictive power of selected MLR model (eq. PIC50), the leave-one-out technique (LOO technique) was used. The developed models were validated by calculation of the following statistical parameters: predicted residual sum of squares (PRESS), total sum of squares deviation (SSY) and cross-validated correlation coefficient ($r^2$adj) (Table 3).

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the model. Its value being less than SSY points out that model predicts better than chance and can be considered statically significant. The smaller PRESS value means the better of the model predictability. From the results depicted in Table 3, the model is statistically significant.

**Table 3: Cross-validation parameters.**

| Model | PRESS | SSY | PRESS/SSY | SPRESS | $r^2$ cv | $r^2$adj |
|---|---|---|---|---|---|---|
| PIC50 | 0.016 | 0.146 | 0.109 | 0.038 | 0,889 | 0,816 |

Also, for reasonable QSAR model (Fig 1, Fig 2 ), the PREES/SSY ratio should be lower than 0.4 . The data presented in Table 3 indicate that for the developed model this ratio is 0.109. Our result of $r^2$cv for this QSAR model has been to be 0,889. The high value of $r^2$cv and r2adj are essential criteria for the best qualification of the QSAR model (Fig 1, Fig 2 ).

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However, the only way to estimate the true predictive power of developed model is to predict the by calculation of PIC50 values of the investigated citral derived amides using this model (Table 1).

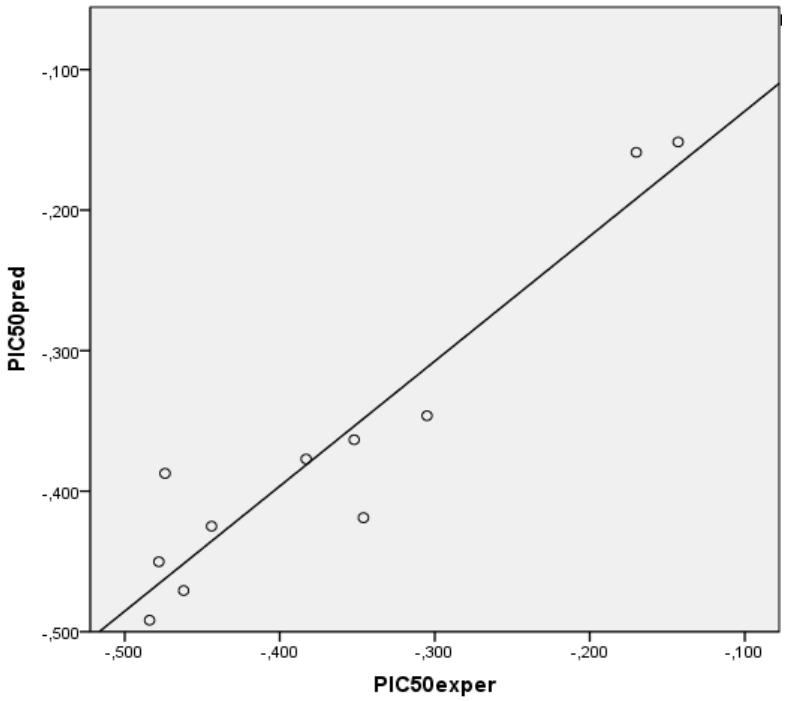


**Fig. 1 Predicted plot versus experimental observed anti-amoebic activity of citral derived amides.**

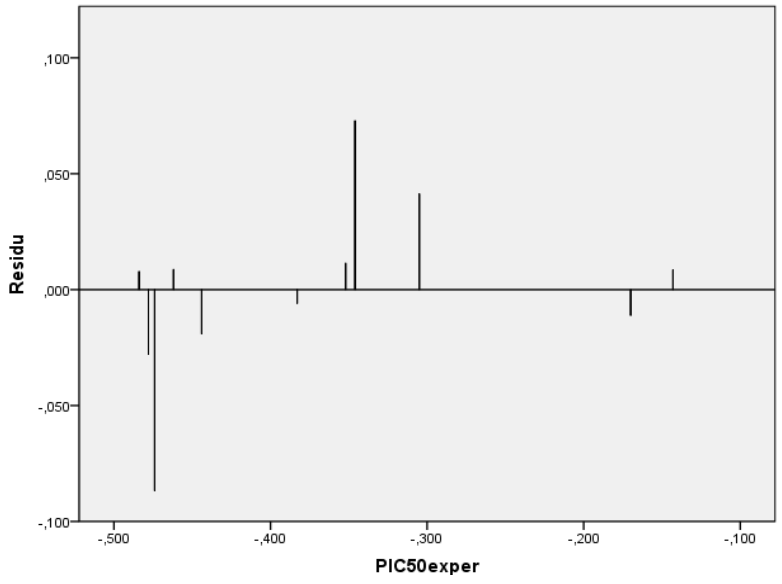


**Fig. 2: Plot of the residual values against the experimentally observed (PIC50).**

Figure 1 shows the plots of linear regression predicted versus experimental value of the biological activity of citral derived amides outlined above. The plots for this model show to be more convenient with $r^2$ = 0.889, It indicates that the model can be successfully applied to predict the anti-amoebic activity of these compounds.

## CONCLUSION

Based on the present investigation it can be concluded that the model " PIC50 = 0.035+0.028 MW + 0.104 Log P + 0.050 HE -0.271 Pol'' can be useful for predicting the activity of new citral derived amides prior to

their synthesis. LogP, HE, Pol, MW, are reliable descriptors for predicting activity. QSAR model indicates that these descriptors have significant relationships with observed bioactivity. We have observed a high relationship between experimental and predicted activity values, indicating the validation and the excellent quality of the derived QSAR model.

**REFERENCES**


[1] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J.J.P. Stewart, J. Am. Chem. Soc 1985; 107: 3902 .
[2] N. Melkemi, and S. Belaidi, J. Comput. Theor. Nanosci 2014;11:801.
[3] Z. Almi, S. Belaidi, N. Melkemi, S. Boughdiri, and L. Belkhiri, Quantum Matter 2015;4 :124.
[4] M. Y. Wani, F. Athar, A. Salauddin, S. M. Agarwal, A. Azam, I. Choi, and A. R. Bhat, Eur. J. Med. Chem 2011;46:4742.
[5] Hyperchem (Molecular Modeling System) Hypercube, Inc., 1115 NW, 4th Street, Gainesville, Fl 2007; 32601:Usa.
[6] Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.
[7] SPSS software packages, SPSS Inc., 444 North Michigan Avenue, Suite 3000, Chicago, Illinoi, 60611, USA
[8] G. L. Patrick, An Introduction to Médicinal Chemistry, Oxford University Press, Oxford, UK 1995;140.
[9] N. I. Zhokhova, I. I. Baskin, V. A. Palyulin, A. N. Zefirov, and N. S. Zefirov, Russ. Chem. B+ 2003 ;52:1061.
[10] Z. Almi , S. Belaidi, and L. Segueni, Rev. Theor. Sci 2015 ;3: 264.
[11] K. Dermeche, N. Tchouar, S. Belaidi, and T. Salah, J. Bionanosci. 2015; 9, in press
[12] E. H. Kerns, and L. Di, Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization, Academic Press, USA. 2008.
[13] S. Belaidi, A. Kerassa, T. Lanez, and M. Cinar, J. Comput. Theor. Nanosci 2015;12: 2127.
[14] V. N. Viswanadhan, A. K. Ghose, G. N. Revankar, and R. K. Robins, J. Chem. Inf. Comput. Sci 1989;29:163.
[15] T. Salah, S. Belaidi, N. Melkemi, and N. Tchouar, Rev. Theor. Sci 2015;3:355.
[16] S. Belaidi, H. Belaidi, and D. Bouzidi, J. Comput. Theor. Nanosci 2015;12: 1737.
[17] S. Belaidi, T. Salah, N. Melkemi, L. Sinha, and O. Prasad, J. Comput. Theor. Nanosci 2015;12 : 2421.
[18] D. Harkati, S. Belaidi, A. Kerassa, and N. Gherraf, Quantum Matter 2015; 4: 36.
[19] R. Mazri, S. Belaidi, A. Kerassa, and T. Lanez, International Letters of Chemistry, Physics and Astronomy 2014;14(2) :146.
[20] A. Kerassa, S. Belaidi, and T. Lanez, Quantum Matter 2015 ;4:45.
[21] A. Kerassa, S. Belaidi, D. Harkati, T. Lanez, O. Prasad, and L. Sinha, Rev. Theor. Sci 2015; 3 in press.
[22] S. Belaidi, Z. Almi, and D. Bouzidi, J. Comput. Theor. Nanosci 2014;11 :2481.
[23] S. Belaidi, R. Mazri, M. Mellaoui, A. Kerassa, and H. Belaidi, Res. J. Pharm., Biol. Chem. Sci 2014; 5: 811.