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Quantitative and Qualitative Structure Activity Relationship Study for Development of the Pet- Inhibitory Activity of 3-Nitro-2,4,6-Trihydroxy Benzamides

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ABSTRACT

The aim in this paper of these work present two components analyses quantitative and qualitative which consisted in the development and evaluation of the first component quantitative and structure activity relationships (QSAR) for the prediction In fact, various compounds inhibiting photosynthesis constitute the largest class of commercial herbicides. All of those inhibitors, including ureas, triazines, bis carbamates and phenols, interrupt photosynthetic electron transport (PET) by binding to quinine-binding protein (D1-protein). Various physicochemical descriptors were used in multiple linear regressions method (MLR) to develop the theoretical models, than using a cross-validation with leave-one-out method to optimize the model as well as possible to fit with the biological data, the most common approach used to study. The second quality of the compound compared with criteria for their power, these rules Lu Propose the four basic characteristics that Lipinski has identified.

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Keywords: QSAR, Benzamides, Herbicidal activity, inhibiting Photosynthetic, Lipinski rules.

Introduction

Photosynthesis is an important target for herbicide action and photosynthetic electron transport (PET) is essential for photoresponse. Various compounds inhibiting photosynthesis constitute the best class of economic herbicides [1-3]. All of those inhibitors, including ureas, triazines, bis carbamates and phenols, interrupt photosynthetic electron transport (PET) by binding to quinine-binding protein (D1- protein) [3,4]. Certain commonly used herbicides are simazine, atrazine bromocil, a isocil, bipyridylium, diquat and paraquat [4]. A basic property of plants is ability to carry out photosynthesis and thus they provide organic carbon which forms the basis of food.

The photochemical reactions of photosynthesis proceed in the thylakoid membranes of the chloroplast and are mediated by the photosystems (PS), PSI and PSII catalyzing vectorial electron transport across the thylakoid membrane. Honda et al [5,6]. Reported a series of 3-nitro-2, 4, 6-trihydroxy benzamide as potent inhibitors of PET which were designed based on the structures of phloroglucinol derivatives like grandinol. The PET inhibitory activity was shown to depend on electronic parameters in the co-relation analysis.

Among the many, quantitative structure activity relationship (QSAR) has been a useful tool for drug design, particularly when the structure of target is unknown [7, 8]. The QSAR equations are evaluated on the basis of various statistical terms like correlation coefficient (r), standard error (s) and Fischer test (F- test). The regression models can then be used for prediction of new molecules [8]. In the present work, we performed QSAR analysis for the PET-inhibitory activity of 3-nitro-2,4 ,6-trihydroxy benzamides using various topological, structure dependent, thermodynamic and charge dependent descriptors. quality of the compound compared with criteria for their power, these rules Lu Propose the four basic characteristics that Lipinski has identified as being met by the majority of compounds taken orally according to a 2245 analysis of compounds based on World Drug Index data (WDI).

Materials and methods

Experimental details

The PET-inhibitory activity for a series of 3-nitro-2, 4,6-trihydroxy benzamide and thioamide derivatives containing20 compounds was subjected for QSAR analysis by multiple linear regression (MLR) technique. The literature values of the activity and the general structure of the compounds are given in Fig. 1 and Table-1. The PI50 data were used for QSAR analysis as a dependent parameter. Structures of compounds were built using 2D sketcher tool provided in the modeling environment of alchemy 2000 (Tripos, USA) software. The geometric optimization were performed using alchemy-2000 version of Sci QSAR 3.0 software (Tripos, USA) at a gradient of 1.0 KCal/Em with delta energy change of 0.001 Kcal/mL under tripos standard force field.

Descriptors generation

First, the twenty investigated molecules were preoptimized by means of the Molecular Mechanics Force Field (MM+) included in HyperChem version 8.03package [9,10]. After that, the resulted

minimized structures were further refined using the semi empirical PM3Hamiltonian implemented also in HyperChem. We chose gradient norm limit of0.01kcal/Å for the geometry optimization. PM3 optimized geometry was used to calculate a number of physicochemical descriptors: Surface area grid (SAG), molar volume (MV), molar weight (MW), partition coefficient octanol/ water (logP), hydration energy (HE), the molar refractivity (RF) and molar polarizability (Pol).Calculation of logP is carried out using atomic parameters derived by Viswanadhan and Coworkers [10,11]. Computation of molar refractivity was made via the same method as logP. Atomic contributions to the refractivity presented by Ghose and Crippen have been used in our study [11, 12].

Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bordet al [12, 13] using the atomic radii of Gavezotti [13,14]. Polarizability was estimated from additively scheme given by Miller with a 3% in precision for the calculation [14, 15], where different increments are associated with different atom types.

Results and discussion

Structure-Physicochemical Property Relationships

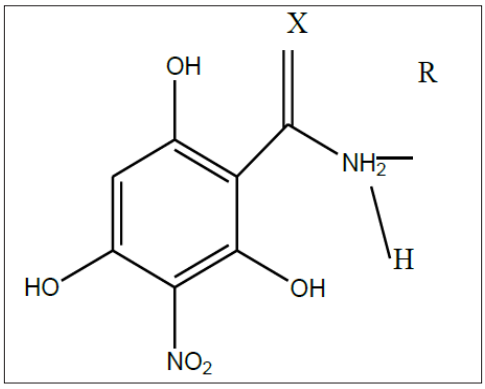


Figure 1: 3-Nitro-2,4,6-trihydroxy benzamides

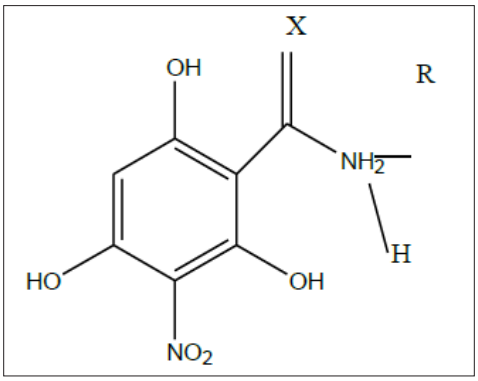
In the first step of our study, we have studied seven physical chemical proprieties of series of twenty which act as (Table.I).

Table 1: Chemical structures, physicochemical properties and experimental activities of 3-Nitro- 2,4 ,6-trihydroxy benzamides derivatives

COMP	X	R	PI50EXP[1]	MASS (amu)	S (m^2)	V(m^3)	HE(-)	LogP(-)
1	O	Ethyl	6,1	242,19	403,76	637,31	20,12	3,18
2	O	Propyl	6,0	256,22	426,36	683,99	19,23	2,72
3	O	Butyl	6,1	270,24	462,83	744,13	19,03	2,32
4	O	Pentyl	7,0	284,27	489,20	795,94	16,47	1,92
5	O	Hexyl	7,2	298,3	518,65	850,10	16,11	1,53
6	O	Heptyl	7,8	312,32	549,5	904,70	15,74	1,13
7	O	Octyl	8,1	326,35	586,59	960,04	17,58	0,73
8	O	Nonyl	8,3	326,39	620,95	1012,93	15,81	0,11
9	O	Decyl	8,4	354,4	645,35	1067,61	16,86	0,06
10	O	Phenyl	6,3	290,23	466,80	748,39	23,08	3,03
11	O	Benzyl	5,5	304,26	496,71	807,18	20,23	2,88
12	O	2Me-Phenyl	5,8	304,26	466,48	781,92	19,08	2,88
13	S	Ethyl	6,6	258,45	410,71	658,45	18,42	2,20
14	S	Butyl	7,0	286,3	471,5	765,96	17,24	1,34
15	S	Hexyl	7,9	314,36	532,99	873,61	16,49	0,54
16	S	Heptyl	8,4	328,38	562,84	927,55	16,13	0,15
17	S	Octyl	8,7	342,41	605,59	990,05	16,13	0,25
18	S	Nonyl	8,5	356,44	636,27	1044,27	18,14	0,64
19	S	Decyl	8,3	370,46	663,48	1098,16	17,76	1,04
20	S	Phenyl	7,0	306,29	471,64	771,06	20,58	1,91

Honda et al [5,6]. Reported a series of 3-nitro-2,4,6-trihydroxy benzamide as potent inhibitors of PET which were designed based on the structures of phloroglucinol derivatives like grandinol. The PET inhibitory activity was shown to depend on electronic parameters in the co-relation analysis. Development by application of various molecular modeling softwares. Among the many, quantitative structure activity relationship (QSAR) has been a useful tool for drug design, particularly when the structure of target is unknown [6,7]. The QSAR equations are evaluated on the basis of various statistical terms like correlation coefficient (r), standard error (s) and Fischer test (F-test). The regression models can then be used for prediction of new molecules [8]. In the present work, we performed QSAR analysis for the PET-inhibitory activity of 3-nitro-2,4,6-trihydroxy benzamides using various topological, structure dependent, thermodynamic and charge dependent descriptors.

The general structure of these compounds is as follows:



Since chemical structure was elucidated, the relationship between chemical structure and biological activity has intrigued scientists. It has been recognized that the investigate of QSARs may provide useful tools for obtaining information regarding the effects of chemicals on man and the environment. Initially developed to assess the value of drugs, QSARs are now proposed as a method to assess general toxicity. QSARs are based on the assumption that the structure of a molecule (its geometric, steric and electronic properties) contains the features responsible for its biological activity [15-17].

For example, biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response. When the information encoded in the molecular structure is expressed by molecular descriptors in the form of numbers, one can form a quantitative structure-activity relationship between the two.

By QSAR models, the biological activity of a new or untested chemical can be inferred from the molecular structure of similar compounds whose activities [16-18].

QSAR's most general mathematical form is:
Activity = f (physiochemical properties and/or structural properties)
It is therefore evident that the three key components required for the development of a QSAR model are:
•Some measure of the activity for a group of chemicals in a biological or environmental system
– Toxicological endpoint

•A description of the physicochemical properties and/or structure for this group of chemicals
– Molecular descriptors

•A form of statistical relationship to link activity and descriptors
In the second step of our study, 3-Nitro-2, 4, 6-trihydroxy benzamides derivatives were evaluated for their inhibitory activity. In order to determine the role of structural features, QSAR study was undertaken.
A set of 20 derivatives of 3-Nitro-2,4,6-trihydroxy benzamides were used for multi-linear regression model generation.

The different physicochemical descriptors calculated in the first step of our study were used as independent variables and were correlated with the 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 statistics19 Software [11]. The analysis of the matrix revealed five descriptors for the development of MLR models. The values of descriptors used in MLR analysis are presented in (Table I).

The correlation between the biological activities and descriptors expressed by the following relation:
(PIC50)pred= 6.729 – 0.603 logp - 0.073 ref + 0.249 pol (Eq. 1), [10,11]
N = 19 R= 0.968 ES = 0.287 F= 78.681
PRESS = 1.324 SSY= 20.850 $r^2cv = 0.937$ $r^2adj = 0.925$

Where n is the number of compounds, r is the correlation coefficient, F is the Fischer statistics and SE is the standard error of estimation. These statistical parameters indicate that our QSAR model allowed us to determine firmly the correlation between independent variables with the PET-inhibitory from r value and suggests its high predictive power from F value which found to be statistically significant at 95% level, since it is higher as compared to tabulated value. The negative coefficient of V and log P explain that any increase in the volume and Lipophilicity of the molecules cause a decrease in the biological activity. In other hand the increasing of the surface, refractivity and polarizability result increasing of the inhibitory. In order to test the validity of the predictive power of selected MLR model (Eq. 1), the leave-one out technique (LOO) was used.

The developed model was 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} and r^2_{cv}) and are represented in table II. PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. 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. Also, the value $r^2_{adj} = 0.925$ and $r^2_{cv} = 0.937$ allowed us to indicate firmly the correlation between different parameters; independent variables and specific activity of 3-nitro-2, 4, 6-trihydroxy benzamides.

Table 2: Cross-validation parameters [11]

Model	PRESS	SSY	PRESS/ SSY	S_{PRESS}	r^2cv	r^2_{adj}
1	1.324	20.850	0.0635	0.287	0.937	0.925

PRESS = 1.324 SSY= 20.850 $r^2cv = 0.937$ $r^2adj = 0.925$

However, the only way to estimate the true predictive power of developed model is to predict the by calculation of values of the investigated 1.3-Nitro-2,4,6-trihydroxy benzamides activities as predicted pIC_{50} using the QSAR model (eq.1). Figure.2 shows the plot of linear regression predicted versus experimental values of the biological activity of 1.3-Nitro-2,4,6-trihydroxy benzamides outlined above.

The plot show a good deal of correspondence with experimentally reported data having $R^2 = 0.968$.

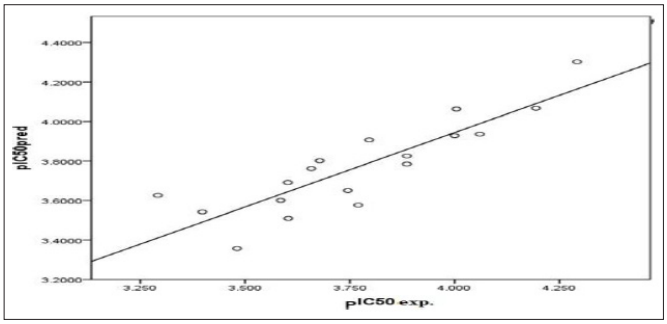


Figure 2: Predicted plots versus experimental observed specific the PET-inhibitory activity of 3-nitro-2, 4,6- trihydroxy benzamides [11].

To investigate the presence of a systematic error in developing the QSAR models, the residuals of predicted values of the biological activity were plotted against the experimental values, as shown in figure 3.

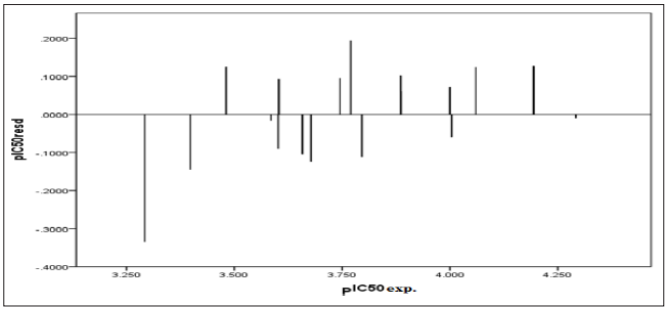


Figure 3: Plots of the residual values against the experimentally observed [11]

The propagation of the residuals on both sides of zero indicates that no systemic error exists, which mean that this model can be successfully applied to predict the specific activity of the PET-inhibitory by 3-Nitro-2, 4, 6-trihydroxy benzamides compounds [18-20].

QSAR Theoretical and Multi-Parameter Optimization (MPO) [20,21]

Allow these complex data that involve significant uncertainties levels be better used to quickly target the choice of compounds with a good balance of properties, but they all have their strengths and weaknesses. In research on the needs for an MPO method is ideal in drug discovery; there are factors that must be considered. The factors to be considered ideal for DFO Interpretability (interpretability): The criteria of the property and their impact on the priority of the compound should be easy to understand.

Rules of Thumb (Lipinski rules and Veber rules)

Rules of Thumb The most common approach used to study the quality of the compound compared with criteria for their power, these rules providing instructions regarding the characteristics of desirable compound (Lipinski, Veber, Lu, Johnson and other rules involving parameters such as proportion of SP3 carbon, the number of aromatic rings, etc.).Lu Propose the four basic characteristics that Lipinski has identified as being met by the majority of compounds taken orally according to a 2245 analysis of compounds based on World Drug Index data (WDI) .

Lipinski's ruleThe characteristics of Lipinski: are

1. Molecular Weight (MW) <500uma(Da)
2. Logarithm of the octanol / water partition coefficient (log P) <5
3. Number of Hydrogen Bond Donors (HBD) <5
4. Number of Hydrogen Bond Acceptors (HBA) <10

Molecular Weight (MW) Compounds which have molecular **weights <500 Da (u.m.a)** easily pass through cell membranes. The calculation of this parameter may be performed by several programs, such as:HyperChem, ChemAxon, Sybyl-X, etc. Logarithm of the octanol / water partition coefficient (log P) The **compounds which have log P <5** values are better solubilized in aqueous and lipid solutions.

Note: The calculation of this parameter is made by several software containing different Approximations such as: HyperChem (Log P comes by Ghose, Pritchett and Crippen). Discovery Studio (Log P comes by Ghose and Crippen).

Number of Hydrogen Bond Donors (HBD) and Acceptors (HBA)

The decrease of the hydrogen bonds promotes the passage of the aqueous phase to the lipid bilayer membrane for penetration by passive diffusion.The calculation of these 2 parameters is performed as follows:

The number of HBD is the sum of the atoms N and O.

The number of HBA is the sum of OH and NH groups to make our result Table N°III.

I in norm of Lipinski after the switching Lipinski rules of the standards are respected for (logP<5, HBA<10 and MW<500(u.m.a) for compound(19).After the rule of Lipinski candidates for the administration is orally and Compounds which have log P<5 values are better solubilizedin aqueous and lipid solutions, as shown in (Table.III).

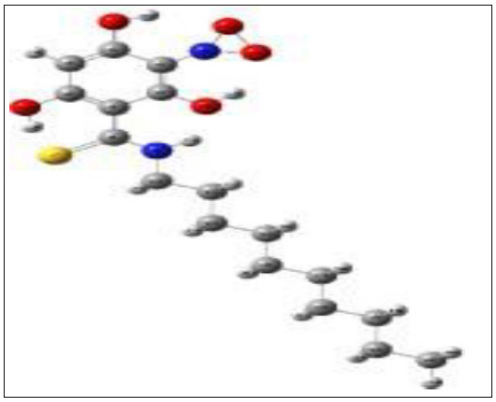
Table III: Lipinski rules of validation [21]

Compounds	Log P<5	MW<500Da(u.m.a)	HBD<5	HBA<10
1	/	/	x	/
2	/	/	X	/
3	/	/	X	/
4	/	/	X	/
5	/	/	X	/
6	/	/	X	/
7	/	/	X	/
8	/	/	X	/
9	/	/	X	/
10	/	/	X	/
11	/	/	X	/
12	/	/	X	/
13	/	/	X	/
14	/	/	X	/
15	/	/	X	/
16	/	/	X	/
17	/	/	X	/
18	/	/	X	/
19	/	x	X	/
20	/	/	X	/

(/) valid, (x) not valid

Our results show the rules of Lipinski candidate19, and for the administration is orally and compounds which have Log P<5

values are better solubilizedin aqueous and lipid solutions.



Candidat 19 by Gaussian 09

Conclusion

From the present investigation it can be concluded that the model was found to be more efficient to predict the specific activity of our studied. 3-Nitro-2, 4, 6-trihydroxy benzamides derivatives. In the present work, and by using this model, we have successfully determined quantitatively the necessary parameters needed to predict the studied activity. MLR regression analysis was used to develop the models and to predict biological activity from derived molecular descriptors belonging to 3-Nitro-2, 4, 6-trihydroxy benzamides series.

The developed QSAR model shows that hydrophilic and polar derivatives of 3-Nitro-2, 4,6-trihydroxy benzamides are a potential alternative to give a good inhibition activity as potent inhibitors of PET which were designed based on the structures of phloroglucinol derivatives like grandinol.

The PET inhibitory activity was shown to depend on electronic parameters in the relation analysis has developed important tools for drug development by application of various molecular modeling softwares. Among the many, quantitative structure activity relationship (QSAR) can be a useful tool for drug design, particularly when the structure of target is unknown,Through The PET inhibitory activity which can control the model activity, by decrease or increase descriptor

According to equation **PIC50) pred= 6.729 – 0.603 logp - 0.073 ref + 0.249 pol**.

On the other hand Our results show the rules of Lipinski candidate19,are selected and for the administration is orally and compounds which have Log P<5 values are better solubilizedin aqueous and lipid solutions.

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