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Determination of Physicochemical Descriptors of Some Penicillin Derivatives Based on Density Function Theory DFT: A QSAR Modelling Approach

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ABSTRACT :

In this study, a series of penicillin derivatives were systematically analyzed using quantitative structure–activity relationship (QSAR) methodologies to establish predictive models correlating molecular structure with biological activity. A diverse set of physicochemical descriptors was employed, including optimization energy, partition coefficient (log P), chemical hardness, total polarizability, global electrophilicity index, ionization energy, and electron affinity. Molecular geometries were fully optimized, and electronic properties were computed using Density Functional Theory (DFT) as implemented in the Gaussian software suite. Multiple linear regression (MLR) analysis was applied to develop a statistically robust QSAR model, yielding high regression coefficients and demonstrating strong predictive reliability. The model provides a theoretical framework for estimating the biological activity of newly synthesized penicillin analogues, facilitating rational drug design and accelerating the identification of potent antimicrobial agents.

KEYWORD: Computational Drug Design, Penicillin, QSAR, Gaussian, DFT, MLR

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Al-Qadisiyah Journal of Chemistry
Iraqi Academic Scientific Journals

INTRODUCTION :

Penicillin was the first antibiotic discovered due to accidental observation by the bacteriologist Alexander Fleming in 1929, noticing that the growing Penicilliumnotatum colonies impair the growth of Staphylococcus Aureus colonies in a lab setting. Penicillin used successfully used for the treatment of infections in 1941(Fig.1) [1,2].

Many Penicillin derivatives have been discovered since then; of these derivatives are Benzylpenicillin, Penicillin V, and others. Benzylpenicillin is a broad-spectrum antibiotic (suitable for destroying most Gram+ and some Gram-positive microorganisms). Because of being unstable in an acidic medium, the use of benzylpenicillin is limited to parenteral injection [2]. Penicillin V overcomes this instability, a natural penicillin derivative with a broad spectrum of activity. However, with less potency than benzylpenicillin, the acid stability makes it suitable for oral administration [3].

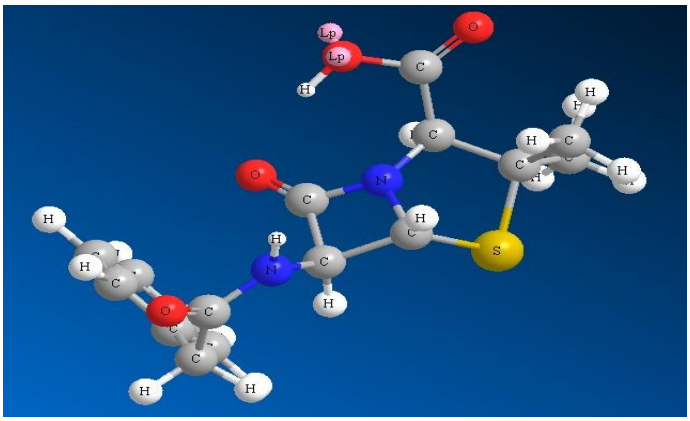

Fig.1 Geometric structure of Penicillin

Developing more semi-synthetic penicillins, such as aminopenicillins, ampicillin, and amoxicillin, to solve the bacterial resistance to natural Penicillin became critical [3]. Adding an amino group to the molecule of benzylpenicillin led to the production of

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Al-Qadisiyah Journal of Chemistry
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aminopenicillins, ampicillin, and amoxicillin, which are vastly effective against a broader range of bacteria than natural penicillins. [4]. These two approaches are effective against most aerobic Gram+ cocci and some Gram-negative organisms, including Salmonella, Shigella, and Escherichia coli [5].

These two derivatives inhibit the activity of β-lactamase, so they are often combined with β-lactamase inhibitors (egclavulanic acid)[6].

The ureidopenicillin group also includes carboxypenicillin derivatives (carbenicillin, ticarcillin) and mezlocillin (mezlocillin is also active against Pseudomonas aeruginosa).

It is a complex mechanism in which many proteins participate to orchestrate the different aspects of bacterial cell division. Of these crucial proteins are the penicillin-binding proteins (PBPs), membrane-bound large molecules participating in cell wall synthesis, which were discovered about 70 years ago and targeted successfully by β-lactam antibiotics such as penicillin [7,8,9,10].

The increasing bacterial resistance encouraged seeking new, more active derivatives of the existing antibiotics with fewer side effects and broader effectiveness. This paper aims to predict new penicillin derivatives with higher potency than the existing derivatives using the QSAR model.

METHODOLOGY

1. Data set:

Eight penicillin compounds have been selected in this study for QSAR model development. Table-1.

AL-QADISIYAH JOURNAL OF CHEMISTRY
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Al-Qadisiyah Journal of Chemistry
Iraqi Academic Scientific Journals

2. Descriptors calculation and molecular structure optimization:

The geometrical optimization of structures based on Gaussian 03 has been applied to all molecule structures at the DFT level. We used low-energy conformers from geometric optimization to extract quantum chemical descriptions from their output files.

Quantum chemical descriptions involve numerous physiological properties: heat of formation (which encompasses many physical properties), Gibbs free energy, partition coefficient, Mohr/Ampere, electric potential, chemical hardness, electrochemical potential, the electronegativity, world electrophilicity index (ω). In quantum chemistry, the lowest unoccupied molecular orbital energy (ELUMO) and the highest occupied molecular orbital energy (EHOMO) define different ways molecules interact.

Energy for HOMO and LUMO is correlated with the ionization potential and electron affinity, respectively. An important measure of stability is the HOMO-LUMO gap, or the energy variation between the HOMO and LUMO [12]. When the HOMO-LUMO gap is large, it makes the molecule stable in chemical reactions [13]. In addition to activation hardness, the HOMO–LUMO energy gap has also been used to calculate polarizability since polarizing molecules become more manageable when the energy gap decreases.

AL-QADISIYAH JOURNAL OF CHEMISTRY
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Al-Qadisiyah Journal of Chemistry
Iraqi Academic Scientific Journals

Table 1: "structure and activity(Log IC50) of Penicillincompounds "

No	abbreviation	Compound name	IUPAC name	Log IC50
1	**PN.1**	**Carbenicillin**	"(2S,5R,6R)-6-{[carboxy(phenyl)acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid"	**0.146**
2	**PN.2**	**Ticarcillin**	"(2S,5R,6R)-6-{[(2R)-2-carboxy-2-(3-thienyl)acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**0.079**
3	**PN.3**	**Piperacillin**	"(2S,5R,6R)-6-{[(2R)-2-[(4-ethyl-2,3-dioxo-piperazine-1-carbonyl)amino]-2-phenyl-acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.036**
4	**PN.4**	**Methicillin**	"(2S,5R,6R)-6-(2,6-dimethoxybenzamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.046**
5	**PN.5**	**Penicillin**	"(2S,5R,6R)-3,3-dimethyl-7-oxo-6-[(2-phenyl acetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.056**
6	**PN.6**	**Mezlocillin**	"(2S,5R,6R)-3,3-dimethyl-6-[[(2R)-2-[(3-methylsulfonyl-2-oxo-imidazolidine-1-carbonyl)amino]-2-phenyl-acetyl] amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.097**
7	**PN.7**	**Azlocillin**	"(2S,5R,6R)-3,3-dimethyl-7-oxo-6-{[(2R)-2-{[(2-oxoimidazolidin-1-yl)carbonyl]amino}-2-phenylacetyl]amino}-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.181**
8	**PN.8**	**Oxacillin**	"(2S,5R,6R)-3,3-dimethyl-6-[(5-methyl-3-phenyl-1,2-oxazole-4-carbonyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid"	**-0.222**

* IC50 values [10]

RESULTS AND DISCUSSIONS:

Calculating Penicillin's physical properties and derivatives will be necessary (table 2). In many studies of biological and pharmacological systems, P3LYP is used as a hybrid functional model [15,16].

AL-QADISIYAH JOURNAL OF CHEMISTRY
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Al-Qadisiyah Journal of Chemistry
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Table (2): physicochemical properties of Penicillin derivatives

Compound name	Balaban index	Partition coefficient	ω	χ	η	EA eV	IE eV	ΔE HOMO-LUMO eV
PN.1	595789	**1.437**	**-73.564**	**5.623**	**4.652**	**0.97**	**10.2**	**9.30**
PN.2	493252	**1.583**	**-65.855**	**5.302**	**4.684**	**0.61**	**9.98**	**9.36**
PN.3	367662	**1.696**	**-64.683**	**5.407**	**4.425**	**0.98**	**9.83**	**8.85**
PN.4	528366	**1.783**	**-57.488**	**5.157**	**4.322**	**0.83**	**9.48**	**8.64**
PN.5	354948	**1.897**	**-53.450**	**5.087**	**4.131**	**0.95**	**9.21**	**8.26**
PN.6	265944	**1.997**	**-48.936**	**4.960**	**3.977**	**0.98**	**8.93**	**7.95**
PN.7	199754	**1.993**	**-41.095**	**4.703**	**3.716**	**0.98**	**8.41**	**7.43**
PN.8	147383	**2.047**	**-38.493**	**4.549**	**3.719**	**0.83**	**8.26**	**7.43**

Compound name	Polar Surface Area A^{o2}	Mol Refractivity cm^3/mol	Log P	ΔG^{o}kJ/mol	Polar Surface Area A^{o2}	Mol Refractivity cm^3/mol	Log P	ΔH^{o} kJ/mol
PN.1	**104.3**	90.72	**1.13**	**-456.0**	**104.3**	90.72	**1.13**	**-880.4**
PN.2	**124.0**	**89.74**	**0.40**	**-396.8**	**124.0**	**89.74**	**0.40**	**-845.5**
PN.3	**156.4**	**97.15**	**0.71**	**-334.7**	**156.4**	**97.15**	**0.71**	**-643.1**
PN.4	**105.1**	**92.81**	**1.19**	**-258.9**	**105.1**	**92.81**	**1.19**	**-712.2**
PN.5	**116.7**	**89.43**	**1.75**	**-198.1**	**116.7**	**89.43**	**1.75**	**-604.2**
PN.6	**173.5**	**95.61**	**1.43**	**-150.2**	**173.5**	**95.61**	**1.43**	**-622.8**
PN.7	**148.1**	**111.5**	**0.74**	**95.42**	**148.1**	**111.5**	**0.74**	**-543.5**
PN.8	**163.3**	**101.2**	**2.317**	**49.38**	**163.3**	**101.2**	**2.317**	**-503.4**

Table (3): The relationship between the physicochemical properties and the log IC50 values of Penicillin derivatives

Physicochemical properties	R^2	Linear Regression
ΔG^{o}/KJ mol^{-1}	0.903	y = -1551.x - 286.0
Log P	0.259	y = -2.589x + 1.076
Mol Refractivity	0.546	y = -45.23x + 93.70
Polar Surface Area	0.447	y = -149.2x + 128.7

AL-QADISIYAH JOURNAL OF CHEMISTRY
VOL(1) , NO(2) , 2026
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Al-Qadisiyah Journal of Chemistry
Iraqi Academic Scientific Journals

ΔH°	0.932	y = -1070.x - 724.4
ΔE HOMO-LUMO /eV	0.909	y = 5.983x + 8.714
IE /eV	0.923	y = 5.741x + 9.597
EA/eV	0.051	y = -0.242x + 0.882
η /eV	0.909	y = 2.991x + 4.357
□ /eV	0.881	y = 2.749x + 5.240
ω	0.925	y = -97.34x - 60.45
Partition coefficient	0.905	y = -1.710x + 1.716
Balaban index	0.846	y = 1E+06x + 43149

Identification of all factors that affect the penicillin compound's activity is crucial. The partial correlation coefficient (PCC)is used to determine the importance of each predictor variable in expecting the dependent variable.

For each of the variables with the highest significant PCC, QSAR models are created. When all of the independent variables in the equation remain constant, the PCC for a variable is the correlation between the variable and the response.
Hansch's model was used to build a QSAR equation that connects a compound's activity to its physicochemical qualities using the properties of compounds with the highest correlation coefficient.
$y = a0 + a1D1 + a2D2 + \ldots\ldots\ldots\ldots aD$ (Hansch model) [17]

Where :

y: practical activity

a: regression coefficient

D: descriptors (b * property)

The following equation can be written as a general rule:

$$\mathbf{y = a0 + a1 \times Slope \times x1 \pm a2 \times Slope \times x2 \pm a3 \times Slope \times x3 \pm a4 \times Slope \times x4 \pm a5 \times Slope \times x5 \pm a6 \times Slope \times x6 \pm a7 \times Slope \times x7}$$

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Al-Qadisiyah Journal of Chemistry
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Where :

X_1= ΔG^o

X_2= ΔH^o

X_3= ΔE HOMO-LUMO

X_4= IE

X_5= η

X_6= **ω**

X_7= Partition coefficient

Select a sharing percent to the activity for each property based on the slope (S) of the properties linearity behavior to activity table-4

Table 4: "contribution of specified physicochemical properties with penicillin compounds' activity "

Property / Drug	ΔG^o *S	ΔH^o * S	ΔE HOMO-LUMO * S	IE *S	η *S	ω*S	Partition coefficient□□S□□
PN.1	707302.5	942092.	55.671	58.99	13.91	7160.79	-2.457
PN.2	615545.3	904727.	56.054	57.33	14.01	6410.41	-2.707
PN.3	519228.2	688181.	52.949	56.44	13.23	6296.32	-2.900
PN.4	401615.9	762150.	51.723	54.42	12.92	5595.96	-3.049
PN.5	307253.1	646568.	49.431	52.92	12.35	5202.83	-3.244
PN.6	232991.2	666406.	47.594	51.31	11.89	4763.45	-3.415
PN.7	-	581545	44.465	48.33	11.11	4000.24	-3.408
PN.8	-	538670.	44.507	47.47	11.12	3746.91	-3.500

Using Wolfram Mathematica 7.0, the regression coefficients of the activity equations were found by solving a set of mathematical equations [18].

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Al-Qadisiyah Journal of Chemistry
Iraqi Academic Scientific Journals

a0 =122.34 , a1 =-28.48 , a2 =0.79 , a3 = -67325 , a4 =16754 , a5 =-346924 , a6 =124783 and a_7= -293,14

Therefore, the final activity equation is:

$$Activity\ (Log\ IC50) = 122.34 - 28.48 \times \text{Slope} \times x1 + 0.79 \times \text{Slope} \times x2 - 67325 \times \text{Slope} \times x3 + 16754 \times \text{Slope} \times x4 - 346924 \times \text{Slope} \times x5 + 124783 \times \text{Slope} \times x6 - 293{,}14 \times \text{Slope} \times x7$$

With the help of computational chemistry, this equation can be used to suggest a new Penicillin derivative, which may prove to be a costly and time-consuming process due to methods for computationally suggesting new structures in the same way that was reported in our previous studies[19-22].

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CONFLICT OF INTEREST

There are no conflicts of interest.

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