Article

The Impact of Physicochemical Descriptors on the Biological Activity of 5-Fluorouracil Analogs

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Abstract:

5-FU remains a key anticancer drug, especially for colon, breast, and other cancers. This study developed a QSAR model to predict the anticancer activity of seven 5-FU analogs. Physicochemical properties, calculated using ChemSW and GAMESS software, showed a strong correlation with experimental IC_{50} values (R^2), validating the model's predictive capability.

Introduction:

The anticancer medication 5-fluorouracil (5-FU) is still in use today. It has been used to treat breast cancer and other cancers, such as head and neck tumors and has been a key component in the treatment of colon cancer [1]. 5-FU is an analogue of uracil that has a fluorine atom at the C-5 position instead of a hydrogen atom. It is a heterocyclic aromatic organic chemical that resembles the pyrimidine molecules of DNA and RNA in structure [2].

A single crystal structure with four molecules in the asymmetric unit and a hydrogen-bonded sheet structure is the only one documented in the literature for pure 5-FU [3, 4]. 5-FU's structure causes it to disrupt the metabolism of nucleosides and can be integrated into DNA and RNA, which results in cytotoxicity and cell death [5, 6].

Despite its many benefits, drug resistance has significantly restricted its therapeutic usage during the past 50 years. 5-FU alone still only has an overall response rate of 10–

15% for advanced colorectal cancer [7], and when 5-FU is combined with other anti-tumor medications, response rates only increase to about 50% [8].

Thus, there is an urgent need for innovative therapeutic approaches and resistance reversal techniques. In the meanwhile, anticipating or overcoming tumor resistance to 5-FU requires an understanding of the mechanisms by which resistance develops. Thankfully, we have the opportunity to discover new genes that play important roles in drug resistance thanks to the advancement of microarray technology. We may now proceed to study the mechanism of these compounds, which may eventually help with clinical chemotherapy.

Quantitative Structure Activity Relation-ship: QSAR

Multiple regression analysis (MRA) is widely used in potency modeling because of its simplicity and interpretability. This method uses the equation.

$$Y = b + aX_1 + cX_2 + \ldots$$

To create a correlation between independent variables (molecular descriptors, X) and a dependent variable (biological activity, Y).

Since the seminal work of Corwin Hansch, who is regarded as the founder of contemporary QSAR modeling, the discipline of Quantitative Structure-Activity Relationship (QSAR) has undergone tremendous change machines that use vectors. The numerical values of the molecular descriptors used to categorize compounds into qualitative groups are referred to as "quantitative" in this context [9–12].

Material and methods:

1- Select compounds:

Seven 5-fluorouracil (5-FU) analogs, possessing established anticancer chemotherapeutic activity were selected for this study, this number enough to make [7x7] matrix of IC_{50} against best seven descriptors of higher regression coefficient. Their

known activities, quantified as [insert specific activity measurement, e.g., IC_{50} values against a specific cell line, or other relevant metric], are summarized in Table (1). These analogs were chosen due to their demonstrated potential as anticancer agents, making them suitable candidates for further investigation and analysis by Free-Wilson Analysis method's without statistics.

Table (1) presents the common and IUPAC names of the 5-FU analogs investigated, along with their corresponding IC_{50} values

No	Agent	IUPAC name	IC_{50} on MCF7 cell line
1	a	(RS)-5-Fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione	340 µM, [13]
2	b	5-fluoro-N-hexyl-2,4-dioxo-pyrimidine-1-carboxamide	1.82 µM,[14]
3	c	Pentyl [1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1H-pyrimidin-4-yl]carbamate.	235 µM, [15]
4	d	4-amino-1-[(2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one	3.37 µM, [16]
5	e	5-Fluoro-1-[4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1H-pyrimidine-2,4-dione	0.0692 µM, [17]
6	f	1-[4-Hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-(trifluoromethyl)-(1H,3H)-pyrimidine-2,4-dione	0.074 µM, [18]
7	g	1-[(2R,3R,4S,5R)-3,4-Dihydroxy-5-methyloxolan-2-yl]-5-fluoropyrimidine-2,4-dione	0.62 µM, [19]

2- Computational Methods:

Seven 5-fluorouracil (5-FU) analogs, selected for their promising activity, were subjected to detailed molecular modeling studies. Molecular structures were generated and optimized using ChemDraw Ultra 8 [20] and Chem3D Ultra 8 [21], respectively. Energy minimization was performed employing the MM2 force field, with all quantum chemical calculations executed using the General Atomic and Molecular Electronic

Structure System (GAMESS) software package [22-24]. Following geometry optimization, key physicochemical properties were calculated for each analog, and the results are presented in Table (2).

Table (2) presents the calculated molecular descriptors for the compounds included in the quantitative structure-activity relationship (QSAR) study

No.	Descriptor	Type
1	Energy gap = LUMO – HOMO	Electronic parameters
2	Ionization potential (I)= - HOMO	Electronic parameters
3	Electron Affinity (A) = -LUMO	Electronic parameters
4	Electro negativity (χ) =(I+A)/2	Electronic parameters
5	Electronic chemical potential (μ) = (HOMO+LUMO)/2	Electronic parameters
6	Global hardness (η) = (I-A)/2	Electronic parameters
7	Global softness (S) = 1/η	Electronic parameters
8	Electrophilicity (ω)= - χ^2/2(η	Electronic parameters
9	Log P	Physiochemical property
10	Log S	Physiochemical property
11	p Ka	Physiochemical property
12	Number of Hydrogen Bond Donors	Physiochemical property
13	Number of Hydrogen Bond Acceptors	Physiochemical property
14	Molecular Topology index	Molecular Topology
15	Dipole/Dipole	Molecular Topology
16	Polar Surface Area	Molecular Topology
17	Topological Diameter	Molecular Topology
18	Atomic bond length	Geometric parameter
19	Atomic bond angles	Geometric parameter
20	Atomic charges	Extended Huckel

Results and discussion:

Seven descriptors (Molecular energy cab, global hardness, log P, electrophilicity, polar surface area, Wiener index, and most negative charge atom) were selected from a set of twenty due to their strong regression coefficient with MCF-7 cell line activity.

Free-Wilson analysis [25] was employed, using calculated physicochemical, electronic, and topological descriptors [24]. The correlation between descriptor values and pIC50 was determined using simultaneous equations solved as a matrix within Microsoft Excel [26]. This process yielded seven correlation factors (a_n) for each descriptor relative to each IC_{50} value, ultimately generating a QSAR equation for each model, as follows:

Table (3) displays the coefficient values for the descriptors used in the model.

Coefficient	Value	Description
a_1	-649.365	Molecular energy cab (ΔE)
a_2	1299.362	Global hardness (η)
a_3	4.369335	Electrophilicity (ω)
a_4	0.589756	Log P
a_5	-0.01957	Polar S. A.
a_6	0.006695	Wiener Index
a_7	-2.38922	More -ve charge atom

$pIC_{50} = a_1\ \Delta E + a_2\ \eta + a_3\ \omega + a_4$ Log P + a_5 Polar S. A. + a_6 Wiener Index + a_7 More -ve charge atom.

pIC_{50} = -649.365 ΔE + 1299.362 η + 4.369335 ω + 0.589756 Log P - 0.01957 Polar S. A. + 0.006695 Wiener Index -2.38922 More -ve charge atom.

Table (4) practical and theoretical (calculated by QSAR equation) pIC_{50}

practical	-2.53	-0.26	-2.37	0.527	-1.16	-1.13	-0.21
theoretical	-2.53	-0.26	-2.37	0.527	-1.159	-1.13	-0.207

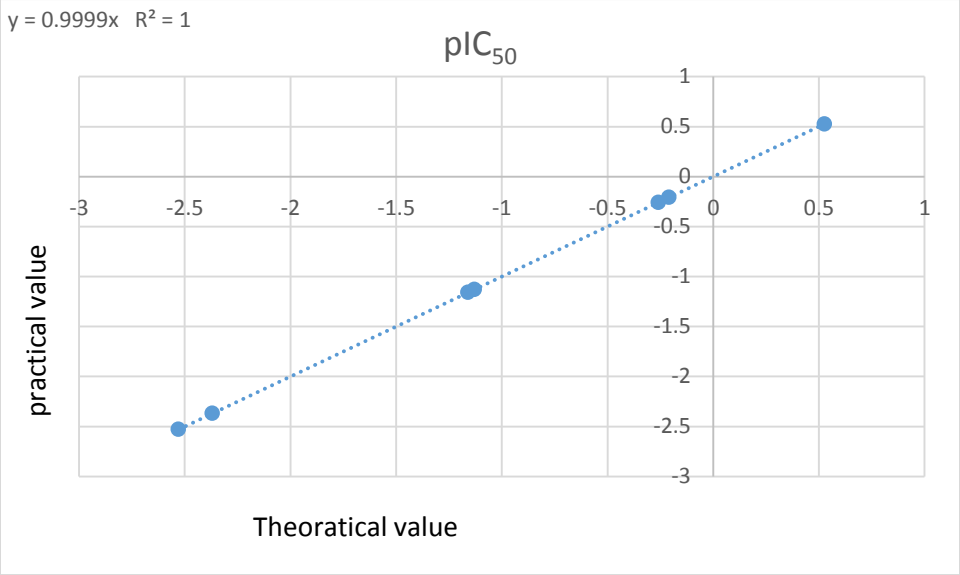

Figure (1) practical IC_{50} values of agents against theoretical values

Conclusion:

"In this study, we employed the Free-Wilson Analysis method which used on the impact of geometric parameters on activity [27] to develop Quantitative Structure-Activity Relationship (QSAR) equations for a series of compounds. The calculated IC50 values derived from these QSAR equations demonstrated a remarkable concordance with the experimentally determined IC_{50} values. This close agreement between calculated and practical IC_{50} values serves as a strong validation of the Free-Wilson Analysis method's efficacy in accurately predicting QSAR equations for the studied compounds."

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