Investigation of Anticancer Drug Activity 5-Fluorouracil and Some Analog Derivatives by QSAR: Theoretical Study

Razzaq Abd Al-Zahra Ibrahim Alamery1*, Falah Shareef Abed Suhail2 and Hussein Kadhem Al-Hakeim1

1Department of Chemistry, Faculty of Science, University of Kufa, Najaf, Iraq.
2Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Kufa, Najaf, Iraq.

Abstract. Theoretical measurements of pharmaceutical compound 5-fluorouracil (5-FU) drug and some analogue derivatives were achieved by DFT method with B3LYP/6–311G as a standard basis set. Series of 5-FU derivatives have a different activities (the minimum effective concentration; C), were studied depending on geometrical properties. Then, the straight line equations (Y = a X ± b) and square root of correlation factor (R²) can be extracted by plot of effective concentration logarithm [log (1/C)] for 5–FU derivatives versus each one of geometrical properties. This matter led to correct the geometrical properties of 5-FU derivatives and formulating of quantitative structure activity relationship (QSAR) by Hansch model. The final general mathematical equation of QSAR as a function of geometrical properties can be concluded by using wolfram alpha program, as empirical equation between theoretical activity and these properties of 5-FU derivatives. The empirical equation of QSAR was tested by substitution a theoretical values of geometrical properties to extract theoretical activity of 5-FU derivatives. A high correlation factor between theoretical and particular activities (R² = 0.9998) of derivatives made matter more acceptable to estimate the activity of new derivatives (synthesized or suggested). So, a new drugs of 5-FU derivatives as a pyrimidines were selected and the theoretical activities were calculated by QSAR–Hansch model as a function of the geometrical properties. The extracted results of a new derivatives shown how can the increase of minimum effective concentration in a new designed derivatives of 5-FU drug (as a starting martial).

Keywords. 5-FU and its derivatives; geometrical properties; QSAR; DFT; activity of new drug.

1. Introduction
Cancer is group of more than 100 different diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases [1]. It is now consider cause of mortality in Americans younger than age 85 years, so it can be classified as the imperator of diseases according to American Cancer Society. The four most common cancers are prostate, breast, lung, and colorectal cancer the most common cause of cancer-related deaths. In the United States is lung cancer, which
accounts for about 160,000 deaths each year. The four most common cancers are prostate, breast, lung
and colorectal cancer that related with death [2, 3].

Fluorouracil (5-FU) a pyrimidine analog has a stable fluorine atom in place of a hydrogen atom at
position five of the uracil ring (Figure 1). The fluorine atom interferes with the conversion of
deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential
precursors for DNA synthesis. Topically, 5-FU drug is employed primarily in treatment of slowly
growing solid tumors; it is also effective for the treatment of superficial basal cell carcinomas [4]. This
agent (trade names: Adrucil, Carac and Efudex) damages the cells during S phase (involved DNA
replication in cell cycle of human body) for at least about 18 to 20 h [5].

Quantitative structure activity relationship (QSAR) is statistical empirical model related with
quantitative description of chemical structure for molecules series proportion into their responses in the
experimental system [6]. In clinical biochemistry, the structure activity (as a response that equivalent to
effective activity concentration) is based on comparisons serial of different structures (derivatives) with
their activity. Therefore, the QSAR is consider a complementary approach of many trials to identify how
can changed the activity of molecules across a series of structures [7].

2. Experimental

2.1. Computational Methods

A series of 5-FU derivatives tested for chemotherapy activity were selected for the present study and the
program of Chemi Bio3D was adopted for molecular modeling studies. The molecules were generated
and energy minimization was carried out by using Molecular Modeling Program. All the calculations
were carried out by using GAMESS and Gaussian0321 quantum chemistry package, and density
functional theory (DFT) with a standard basis set of B3LYP/6-311G. After minimized energy, structural
properties (geometrical properties) were calculated for all studied molecules and the results are shown in
Tables 1.

2.2. Mathematical treatments

For each properties, select a sharing percent to the activity depending on slope (S) of properties linearity
behavior to activity (Tables 2, 3). The mathematical equations of QSAR were solved by using wolfram
alpha program, in order to set final activity equation as follow:

Activity = f(Physicochemical Properties and /or Structural Properties) + constant ……………… (1)
Activity = a₀ + a₁ d₁ + a₂ d₁² + a₃ d₂ + a₄ d₂² +………. ……………………………………….. (2)
Where; dᵢ: value of descriptor. aᵢ: calculated coefficient by the fitting data of regression analysis.

All the calculations were carried out by using computer Lenovo G220, has processor core i7 with
hard;1tera and RAM;8GB.

3. Result and Discussion

3.1. Optimization of 5-FU drug

Essentially, the optimized conditions of 5-FU drug as a main compound must be estimated for
subsequent studies (Figure 1). The length of bonds, angle of bonds and Mullikan charge of atoms were
selected as the some geometric parameters of 5-FU. Then, The optimum of geometric parameters were
measured by using the best method is density function theory (DFT; the method more acceptable with
the experimental results) and B3LYP/6-311G as a standard basis set.

| Pharmacokinetic data of 5-FU drug |
|----------------------------------|
| Formula                         | C₄H₃FN₂O₂       |
| Mol. Mass                       | 130.077 g/mol   |
Bioavailability 28 to 100%
Protein binding 8 to 12%
Metabolism Intracellular and hepatic
Half life 16 minute
Excretion Renal

Figure 1: The structural formula and Pharmacokinetic data of 5-FU drug [3,5].

Study of 5-FU drug derivatives
Series of 5-FU derivatives with different activities (the minimum effective concentration), were studied depending on the geometrical properties (as shown in Figure 2 and Table 1).

Table 1. The minimum effective concentration of 5–FU derivatives, bonds lengths (B.L) and bonds angles (B.A) by DFT [B3LYP/6-311G]

| No. | Compound   | B.L / Å  | B.A / Å  | Practical activity [9] Conc./mg (or; C) | Activity logarithm log (1/C) mg |
|-----|------------|----------|----------|----------------------------------------|----------------------------------|
| (1).| 5-FU drug  | 1.4254   | 121.8308 | 115.8485                               | 500 – 2.69897                    |
| (2).| Decitabine | 1.4704   | 118.6916 | 123.9517                               | 50 – 1.69897                     |
| (3).| 5-Azacytidine | 1.4729 | 119.0229 | 123.8640                               | 100 – 2.00000                    |
| (4).| Cytarbine  | 1.4552   | 119.2584 | 122.3733                               | 100 – 2.00000                    |
| (5).| Gencitabine | 1.4587 | 120.0855 | 122.5383                               | 200 – 2.30103                    |
| (6).| Floxuridine | 1.4370 | 122.7535 | 115.3307                               | 500 – 2.69897                    |
| (7).| Capecitabine | 1.4597 | 121.2026 | 120.8111                               | 250 – 2.39794                    |

Then, the plot of effective concentration logarithm for 5-FU derivatives [log (1/C)] versus each one of geometrical properties was achieved. The extracted results were represented by a straight line equation (Y = a X + b ) and square root of correlation factor as recorded in Table 2.
Table 2. The straight line equations (as linear regression); with correlation factor for geometrical properties of 5-FU derivatives.

| No. | Geometrical properties | R²  | Equation of straight line |
|-----|------------------------|-----|--------------------------|
| (1). | B.L : C(2)–N(3)       | 0.7312 | Y = 18.704 X – 29.456 |
| (2). | B.A : C(6)–N(1)–C(2)  | 0.9197 | Y = – 0.2334 X + 25.85 |
| (3). | B.A : C(5)–C(6)–N(1)  | 0.8256 | Y = 0.0945 X – 13.660 |

In each selected properties, there is sharing percent of activity depend on the slope (S) which represent a linearity behavior of properties to the activity. Therefore, the geometrical properties (Tables 1) must be corrected by a correct factor (S : slope of straight line for same property). This process is achieved of some 5–FU derivatives, and the obtained results were listed in Tables 3.

Table 3. The corrected bond length (B.L) and bond angles (B.A) by the slope of linear regression of some 5-FU derivatives.

| No. | The name of compound | B.L X Slope | B.A X Slope | log (1/C) |
|-----|----------------------|-------------|-------------|-----------|
| (1). | 5-FU drug            | C(2)–N(3)  | C(6)–N(1)–C(2) | mg       |
|      |                      | 26.6532    | – 28.4353  | 10.9476   | – 2.69897 |
| (2). | Decitabine            | 27.5023    | – 27.7026  | 11.7134   | – 1.69897 |
| (3). | Cytarbine             | 27.2180    | – 27.8349  | 11.5642   | – 2.00000 |
| (4). | Gemcitabine           | 27.2835    | – 28.0279  | 11.5798   | – 2.30103 |

Therefore, a general equation of QSAR (Eqn. 2) that expressed about the final activity equation of biological activity as a function of molecular descriptors can be extracted by Hansch model [10]. It can explained this equations by substitution the geometrical properties (d: descriptors; Table 3) in Eqn. 2, as shown in Table 4.

Table 4. The extracted QSAR equations by Hansch model according to geometrical properties of 5-FU derivatives.

| No. | The name of compound | log (1/C) | B.L X Slope | B.A X Slope |
|-----|----------------------|-----------|-------------|-------------|
| (1). | 5-FU drug            | – 2.69 = a₀ + a₁(26.65) – a₂(28.43) + a₃(10.94) |
| (2). | Decitabine            | – 1.69 = a₀ + a₁(27.50) – a₂(27.70) + a₃(11.71) |
| (3). | Cytarbine             | – 2.00 = a₀ + a₁(27.21) – a₂(27.83) + a₃(11.56) |
| (4). | Gemcitabine           | – 2.30 = a₀ + a₁(27.28) – a₂(28.02) + a₃(11.57) |

Then, the regression coefficient (aᵢ) can be calculated easily from these equations as follow;

\[ a₀ = 38.0521, a₁ = 0.993761, a₂ = 1.78501, a₃ = -1.52061 \]

Therefore, the final general equation of QASR as a function of geometrical properties can be concluded in the following formula;

\[ Y = a₀ ± a₁(Slope) d₁(B.L) ± a₂(Slope) d₂(B.A) ± a₃ (Slope) d₃(B.A) \] .............................. (3)

\[ \log 1/C = 38.0521 + 0.993761(18.704) d₁ + 1.78501 (– 0.2334) d₂ – 1.52061 (0.0945) d₃ \]

\[ \log 1/C = 38.0521 + 18.58 [C(2)–N(3)] – 0.416 [C(6)–N(1)–C(2)] – 0.143 [C(5)–C(6)–N(1)] \] .............................. (4)

The last relationship (Eqn. 4) between a theoretical activity and the geometrical properties of 5-FU derivatives represent the empirical formula of QSAR. To ensure, QSAR equation must be tested by substitution a calculated theoretical values of geometrical properties for 5-FU derivatives (Table 1).
Therefore, the calculated values of theoretical activity for 5-FU drug and some its derivatives were listed in Table 5 as follow:

| No. | The name of compound | \( \log(1/C) = 38.0521 + 18.58 (C_{(2)}-N_{(3)}) - 0.416 (C_{(6)\rightarrow N_{(1)}}-C_{(2)}) - 0.143 (C_{(5)\rightarrow C_{(6)\rightarrow N_{(1)}}}) \) | \( \log(1/C) \) |
|-----|----------------------|---------------------------------|-----------------|
| 1.  | 5-FU                 | \( \log(1/C) = 38.0521 + 18.58 (1.4254) - 0.416 (121.8308) \) | -2.7119 |
|     |                      | \( 0.143(115.8485) \)          | 515.1 |
| 2.  | Decitabine           | \( \log(1/C) = 38.0521 + 18.58 (1.4704) - 0.416 (118.6916) \) | -1.7286 |
|     |                      | \( 0.143(123.9517) \)          | 53.5  |
| 3.  | Cytarbine            | \( \log(1/C) = 38.0521 + 18.58 (1.4552) - 0.416 (119.2584) \) | -2.02116 |
|     |                      | \( 0.143(122.3733) \)          | 104.9 |
| 4.  | Gemcitabine          | \( \log(1/C) = 38.0521 + 18.58 (1.4587) - 0.416 (120.0855) \) | -2.3238 |
|     |                      | \( 0.143(122.5383) \)          | 210.7 |

Table 5. The theoretical activity according to QSAR – Hansch model as a function of geometrical properties for 5-FU derivatives.

Therefore, It can assess the quantity of correlation between a theoretical and practical activity of 5-FU derivatives (Tables 5 and 1), by the plot of values of theoretical versus practical activities (Figure 3) as follow:

Figure 3. The relation between practical and theoretical activity values (by the geometrical properties) for 5-FU derivatives [11].

Generally, it had been noted that geometrical properties given the most approach value of activity to the experimental (Figure 3; with high \( R^2 = 0.9998 \)). So that, QSAR equations (Eqns.3, 4) can be used to determine the activity of a new suggested compounds (as a new derivatives of 5-FU drug), according to geometrical properties.

3.2. Study of new 5-FU derivatives

By depending on a previous studies of 5-FU derivatives, the activity of new 5-FU derivatives (synthesized or suggested) can be estimated. So that, it can select new 5-FU derivatives to realize equations of QSAR, by depending on geometrical properties firstly in same a standard basis set (Table 6); as shown in the following Figure 4.
Figure 4. New drugs of 5-FU derivatives as a pyrimidines [12, 13].
(1). 5-[(fluorocyclopropyl) methyl]pyrimidine – 2,4 dione.
(2). 5-(fluoroethyl)-1-[4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-y] pyrimidine-2,4dione.
(3). 4-amino-1-[3,4-dihydroxy-5(hydroxymethyl)tetrahydrofuran][5fluoro-5,6dihydro-1,3,5triazin-2one.

Table 6. The bonds lengths (B.L) and bonds angles (B.A) of new 5-FU derivatives (as geometrical properties) by DFT(B3LYP/6–311G).

| No. | suggested compound (Abbreviated name) | B.L / Å | B.A / Å |
|-----|-------------------------------------|--------|--------|
|     | C(2)–N(3) N (1)–C(6)–C(5) C (2)–N(1)–C(6) |
| 1   | Fluorocyclopropyl                    | 1.4258 | 116.9901 121.7889 |
| 2   | Fluoroethyl                          | C(10)–N(11) C(13)–C(14)–N(9) C (14)–N(9)–C(10) |
|     | 1.4385                              | 122.3862 117.0552 |
| 3   | Fluoroamino                          | N(12)–C(11) N(10)–C(14)–N(17) C(11)–N(10)–C(14) |
|     | 1.45                                | 121.534 121.0147 |

The QSAR equations (Hansch model) of new 5-FU derivatives can be recorded (Table 7), for geometrical properties only by depend on the general QSAR equations (Eqns. 3, 4).

Table 7. The theoretical activity according to QSAR–Hansch model as a function of geometrical properties for new 5-FU derivatives.

| No. | Abbreviated name of a suggested compounds | Theoretical activity by geometrical properties | log (1/C) |
|-----|------------------------------------------|-----------------------------------------------|-----------|
|     |                                          | log1/C = 38.0521 + 18.58 (B.L / Å) – 0.416 | log1/C = 38.0521 + 18.58 (B.A / Å) – 0.143 |
| 1   | Fluorocyclopropyl                        | log1/C = 38.0521 + 18.58 (1.4258) – 0.416 | log1/C = 38.0521 + 18.58 (121.7889) – 0.143 |
|     |                                          | (116.9901) – 0.143(116.9901) | (116.9901) – 0.143(116.9901) |
|     |                                          | – 2.8503 | – 708.4 |
| 2   | Fluoroethyl                              | log1/C = 38.0521 + 18.58 (1.4385) – 0.416 | log1/C = 38.0521 + 18.58 (117.0552) – 0.143 |
|     |                                          | (122.3862) – 0.143(122.3862) | (122.3862) – 0.143(122.3862) |
|     |                                          | – 1.41676 | 26.1 |
| 3   | Fluoroamino                              | log1/C = 38.0521 + 18.58 (1.455) – 0.416 | log1/C = 38.0521 + 18.58 (121.0147) – 0.143 |
|     |                                          | (121.534) – 0.143(121.534) | (121.534) – 0.143(121.534) |
|     |                                          | – 2.6354 | 431.9 |

The graphical model of 3D-QSAR displays useful information in design of a new potential drugs. In addition, results of QSAR equations (Table 7) were afford the most important properties especially about the geometrical properties; and activities that equal to 5-FU derivatives. Firstly, a geometrical properties of suggested 5-FU derivatives must be checked; then complete achieving other properties (such physicochemical properties). Because the measurement of properties in theoretical quantum methods must be achieved gradually for a suggested new compounds.

Therefore, when synthesis or suggestion new 5-FU derivatives (as the anticancer drugs) some modifications must be applied on 5-FU molecule initially. In order to the increase of minimum effective concentration in the new designed derivatives of 5-FU drug (as a starting martial) [14, 15].
geometrical properties: the decrease of bond length $C(2)-C(3)$, then increasing of bonds angles $C(6)-N(1)-C(2)$ and $C(5)-C(6)-N(1)$; as shown in the following Figure 5.

![Chemical structure](image)

**Figure 5.** The most important geometrical properties in a starting material of 5-FU as antitumor drug.

4. Conclusion

Therefore, QSAR equations in turn is used to predict the activity of new analog derivatives. Since QSAR produces predictive models derived from application of statistical tools, which correlating with a biological activity included the desirable therapeutic effect with descriptors of molecular structure or properties. In general, the good quality of QSAR equation depends on many factors such as; quality of input data, selection of descriptors and a statistical methods for validation of model. Ultimately, QSAR would lead to robust equation and predictive models are capable of making accurate and reliable calculations for a new compounds.

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