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Quantitative Structure-Activity Relationship (QSAR) and Anticancer Evaluation of Certain Bisquinoline Derivatives Connected by 4-Oxy-3-Fluoroaniline

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Abstract: The development of new anti-cancer agents with excellent biological activities relay on using compounds containing Quinoline ring structures. Therefore, designing new molecule scaffolds with reduced side effects for targeting cancer is interesting. QSAR is considered one of the most strategies to postulate and design new structures containing quinoline rings with potential anti-cancer activity. So, this study was assessed to calculate the anti-tumor activity of previously published work that synthesized and investigated 4-Oxy-3-Fluoroaniline derivatives and postulate new structures with proposed biological activities based upon physicochemical parameters obtained from these derivatives using quantitative structure relationship activity (QSAR) without lab investigations. In this report, QSAR and regression analysis were used to predicate in vitro anti-tumor activities of these derivatives against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721, and compare the experimental anti-tumor activity of these molecules with those calculated using postulated equations performed by QSAR. The anti-tumor activity of newly postulated bisquinoline derivatives showed high efficacy with IC_{50} values in the single-digit nM range against cancer cell lines depending on the halogen-substituted phenyl ring. The data showed that QSAR and regression analysis significantly predicted the biological activity of the old and postulated four 4-Oxy-3-Fluoroaniline derivatives with promising anti-cancer validity.

Keywords: QSAR; Bisquinoline derivatives; cancer cell lines; anti-tumor activity.

1. Introduction

Cancer mortality was classified in most studies as the second leading cause, which increases the rate of death worldwide after cardiovascular diseases [1-3]; this may be due to the presence of drug resistance and high risks of the side effects of cancer therapeutics [4-6]. For this, new strategies were intensified searched that promote the synthesis of new safe, more efficient chemotherapeutic agents via identification, characterization, and development of new anti-cancer derivatives [6-8]. Most studies reported that quinoline structures were shown to

have a potential antibacterial [8] and anti-cancer activity [9-14]. The occurrence of the quinoline ring showed a pivotal role in developing new anti-cancer drugs via different modes of action, such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration, and modulation of nuclear receptor responsiveness [15-19]. More studies on cancer cell lines derived from all human organs support the biological activities of quinoline ring moieties that showed the diversity of poly-functionalized quinoline molecules in eradicating cancer cells [20-22]; in addition, other studies on plant-based anti-cancer quinolines showed that these structures exert their biological activity against cancer cell via DNA-quinoline ring binding power and iron chelation mechanisms [22-24].

The occurrence of the quinoline ring system in various natural products identified it as a prime candidate for developing newer and more potent anti-tumor molecules [25-27]. Although there is an acceptable number of anti-cancer drugs of plant origin, cancer medication is still in need of developing new anti-cancer drugs [25-28]. Thus, computational approaches gained the most interest to help select and optimize new compounds based on their physicochemical properties for synthesis and testing to increase their potency and minimize the risks of their side effects [29-31].

QSAR, considered one of the most promising quantitative structure techniques, links the biological activity of any such chemical derivatives with their molecular structure. It depends on chemical compounds' geometric and chemical characteristics and their consistent relationships to the proposed biological activity [32].

A mathematical model (QSAR) for drug designing is widely applied in many drug strategies targeting cancer, cell function abnormalities, and infectious and non-infectious human diseases [33-36]. It considers a good choice model for its cost reduction, minimal trial and error, its time-efficient nature [37].

Using QSAR, the theoretical speculation of new cheaper compounds with recommended biological activity has significantly appreciated many drug research types[33-38]. This predictable analysis depends mainly upon its physicochemical descriptors to achieve structure relationship modification analysis [38].

The biological activities of new anti-tumor compounds depend mainly upon their molecular structure [39,40]. The quinoline compounds have raised our interest in investigating their anti-tumor activities [41,42]. In this regard, we applied the QSAR and regression analysis to predict the anti-tumor activity of Bis-quinoline derivatives connected by 4-Oxy-3-Fluoroaniline that could serve as models for developing new anti-tumor drugs.

2. Materials and Methods

The postulated idea of the present work mainly depends on previous investigations of a series of novel bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety. The synthesis, properties, and in vitro anti-tumor activities against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721) of these derivatives were reported earlier [42-45]; the synthesis and study of anti-tumor activity of bisquinoline derivatives were supported with its wide range of biological activities as previously reported [42-45].

Li et al. [45] mentioned that most newly synthesized bisquinoline derivatives showed potent anti-tumor activity and high selectivity towards the H460 and MKN-45 cell lines at different IC50 values. Hence, the main target of our study is to reinvestigate the experimental anti-tumor activities of their synthesized bisquinoline derivatives, speculate new derivatives and derive their anti-tumor activities, and finally, compare the calculated activity of our

predicted compounds with the experimental activity for their compounds using QSAR and regression analysis.

2.1. Quantitative structure-activity relationship (QSAR).

Hyperchem version 8 programs using Austin Model 1(AM1) and the semi-empirical theoretical methods were used to calculate physicochemical descriptors of previously synthesized and newly speculated Bisquinoline derivatives [46-48].

2.2. Semi-empirical method.

The physicochemical parameters of studied phthalazinedione compounds were calculated using semi-empirical quantum mechanics, which is appreciated for all atoms in the periodic table as previously reported in the literature [44-46]. These calculations depend on solving the Schrödinger equation, with certain approximations using standard, non-optimized, and electron orbital basis functions to calculate the valence electrons atoms and molecules of targeted phthalazine compounds. However, using experimental biological activities of the previously studied compounds is very important to cancel or minimize errors resulting from approximations.

2.3. Austin Model 1(AM1).

All physicochemical calculations were performed using AM1-SCF and developed MNDO methods, simplified versions of Hartree-Fock theory useful for chemical compounds containing elements from long rows 1 and 2 of the periodic table except transition elements. Using biological activities resulting from experimental analysis of studied compounds as empirical corrections feed to empirical calculations to improve the performance of semi-empirical calculations. This method, along with PM3, and AM1, is the most reliable and accurate method of Hyperchem physicochemical analysis. It is recommended to calculate the electronic properties, optimized geometries, total energy, and heat of formation [49-51].

2.4. Statistical analysis.

The correlation between physicochemical descriptors and the biological activity of postulated and experimentally designed compounds was performed through multi-regression analysis using QSAR and the winks program [52,53].

3. Results and Discussion

Chemotherapy research focuses on developing new and safe cancer chemo-representative agents [54-61]. Previously, Quinoline derivatives have been recorded as active compounds with potential anti-tumor activities [62,63].

Our main target of this study is based on the newly synthesized bisquinoline derivatives, which showed a potent anti-tumor activity and high selectivity towards the H460 and MKN-45 cell lines at different IC50 values.

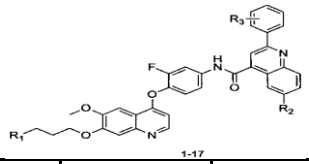
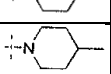
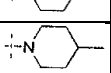
The cytotoxic activity of the examined bisquinoline derivatives was evaluated against the cancer cells lines H460 (human lung cancer), HT-29 (human colon cancer), MKN-45 (human gastric cancer), U87MG (human glioblastoma), and SMMC-7721 (human liver cancer)

by using an MTT assay. Using foretinib as the positive control, the results expressed as IC50 values are summarized in Table 1.

The IC50 values are the average of at least three independent experiments. All the target compounds showed moderate to excellent cytotoxic activity against the different cancer cells with potencies in the single-digit mM range, suggesting the replacement of the N-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide framework of foretinib with the 2-arylquinoline-4-carboxamide moiety maintained the potent cytotoxicity. Further analysis clearly revealed that different biological properties were observed when various R1 and R3 groups were introduced into the phenyl ring moiety.

The introduction of different R1 groups only slightly altered cytotoxicity, indicating that the R1 group contributed little to potency. However, substitution on the phenyl ring at position R3 displayed strong cytotoxicity against the cancer cells lines H460, HT-29, and MKN-45, which was confirmed by the potent cytotoxicity of compounds (1,6,7,8,12,16) with obvious improvement in anti-tumor activity as shown in Table 1.

Table 1. The biological activity (percentage inhibition of H460; HI-29, and MKN-45) for 17 derivatives of 4-oxy-3-fluoroaniline moiety

	 1-17			**IC_{50} (MMOL/L)**		
	R1	R2	R3	**H460**	**HI-29**	**MKN-45**
1		**H**	**3-Cl**	**0.01**	**0.06**	**0.01**
2		**H**	**3,4-$(Cl)_2$**	**0.82**	**1.21**	**0.73**
3		**H**	**H**	**0.19**	**1.52**	**0.09**
4		**H**	**4-OCH_3**	**0.75**	**3.19**	**0.16**
5		**H**	**3-OCH_3**	**0.56**	**3.05**	**0.11**
6		**H**	**3-Cl**	**0.08**	**1.08**	**0.04**
7		**H**	**4-CF_3**	**0.07**	**0.23**	**0.01**
8		**H**	**H**	**0.07**	**0.12**	**0.19**
9		**F**	**3-OCH_3**	**1**	**2.5**	**0.69**
10		**F**	**4-OCH_3**	**0.24**	**0.6**	**0.26**
11		**F**	**2,4-$(Cl)_2$**	**0.31**	**0.53**	**0.25**
12		**F**	**4-F**	**0.03**	**0.25**	**0.05**
13		**F**	**4-CH_3**	**0.44**	**0.39**	**0.32**
14		**F**	**4-CH_3**	**0.48**	**0.42**	**0.26**
15		**F**	**H**	**0.09**	**0.16**	**0.11**
16		**F**	**3-Cl**	**0.07**	**0.67**	**0.07**
17		**F**	**4-OCH_3**	**0.25**	**0.61**	**0.17**

The data presented indicate that the cytotoxicity for compound (1) is generally higher than that for the corresponding compounds, suggesting the introduction of the 3-coloro group to the 2-arylquinoline-4-carboxamide moiety is favorable for activity. In this study, by using QSAR and regression analysis, we tried to reinvestigate the experimental anti-tumor activities of their synthesized bisquinoline derivatives, speculate new derivatives, derive their anti-tumor activities and finally compare the calculated activity of our predicted compounds with the experimental activity for their compounds. As a result of the expense and difficulty of synthesizing bisquinoline derivatives for cancer treatment, QSAR equations and regression analysis using physicochemical parameters can help in this situation. The current study is based on the chemical structures of bisquinoline derivatives, as in Table 1. QSAR equations have been performed to predict new bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety with potential anti-tumor activity.

The physicochemical properties (descriptors) of the investigated chemical compounds are illustrated in Table 2 and Table 3. These descriptors include the area, volume, hydration energy, distribution coefficient, Refractivity, Polarizability, Mass, total energy, binding energy, isolated atomic energy, electronic energy, core-core interaction, and heat of formation. The descriptors were obtained from hyperchem at the semi-empirical theoretical method. Also, using the winks program and multi-regression statistical calculations, prolific descriptors are gained from the studied compounds. Then, after incorporation, the obtained descriptors, together with the biological activities previously measured (table 2&3).

Table 2. Calculated descriptors by HyperChem for 17 derivatives of 4-oxy-3-fluoroaniline moiety presented in table one.

	SURFACE AREA	VOLUME	HYDRATION ENERGY	LOGP (DISTRIBUTION-COEFFICIENT)	REFRACTIVITY	POLARIZABILITY∓
1	789.5	1784.3	-12.6	-2.24	207.7	72.6
2	822.5	1820.7	-12.4	-2.46	212.4	74.6
3	750.1	1718.4	-15.02	-3.08	199.9	69.5
4	806.3	1818.9	-16.5	-4.08	206.3	72
5	748.5	1817.9	-17.5	-4.08	206.3	72
6	784	1761.7	-14.7	-3.3	204.6	71.4
7	810.9	1806.5	-14.3	-2.51	205.1	71.1
8	783.8	1806.6	-12.3	-1.02	209.3	73.3
9	864.7	1855.8	-16.8	-3.61	209.5	73.1
10	829	1827.8	-14.4	-3.61	209.5	73.1
11	820.1	1828.8	-12	-3.06	212.5	74.5
12	777.9	1739.1	-14.5	-4.28	200.1	69.3
13	810.4	1786.1	-13.5	-3.53	204.3	71.3
14	843.6	1927.3	-11	-2.13	211.9	74.3
15	741.1	1727.3	-12.8	-3.01	198.5	68.8
16	780.5	1769.9	-12.5	-3.24	203.2	70.7
17	759	1847.7	-14.8	-4.01	204.9	71.3

Table 3. Calculated descriptors by HyperChem for 17 derivatives of 4-oxy-3-fluoroaniline moiety presented in table one.

	MASS	TOTAL ENERGY	BINDING ENERGY	ISOLATED ATOMIC ENERGY	ELECTRONIC ENERGY	CORE-CORE INTERACTION	HEAT OF FORMATION
1	677.2	-309	-9202	-185129	-1834397	1640065	-27
2	711.6	-322	-9185	-193449	-1892149	1689514	-34
3	644.7	-302	-9031	-180786	-1786970	1597153	-49
4	674.7	-319	-9336	-191388	-1904398	1703673	-19
5	674.7	-319.8	-9335.1	-191388	-1905231	1704508	-18.58
6	679.2	-315	-9013	-189107	-1849304	1651183	-55
7	712.7	-360	-9243	-216676	-2040312	1814393	-85
8	658.8	-303	-9603	-180646	-1869084	1678834	-26

	MASS	TOTAL ENERGY	BINDING ENERGY	ISOLATED ATOMIC ENERGY	ELECTRONIC ENERGY	CORE-CORE INTERACTION	HEAT OF FORMATION
9	690.8	-331.1	-9522.9	-198269	-1955389	1747597	-24.06
10	690.8	-331	-9601	-198269	-1974207	1766337	-102
11	729.6	-340	-9194	-204309	-1992193	1778689	-77
12	680.7	-337	-9054	-202505	-1921952	1710392	-139
13	676.7	-325	-9326	-194957	-1913179	1708895	-102
14	688.8	-324	-9575	-194291	-1971402	1767535	138
15	646.7	-307.9	-8857.8	-184356	-1788757	1595543	31.3
16	681.1	-321	-8841	-192676	-1851222	1649703	24
17	676.7	-325	-9159	-194957	-1904957	1700840	64

The multi-regression analysis by winks produced three equations that were used theoretically for calculating the compounds' biological activity (anti-tumor inhibition activity) depending on the chief descriptors affecting the biological activity of studied Bisquinoline derivatives. The postulated three equations are shown in Table 4. The obtained equations were used for calculating the ability of Bisquinoline derivatives connected by 4-Oxy-3-Fluoroaniline to act as anti-cancer agents. The degree of the validity of the three equations obtained from multi-regression statistical calculations was measured via different tools. One such is based on calculating the biological activity and applying our proposed equations.

Table 4. Calculated equations to study the anti-tumor activity of 17 derivatives of bisquinoline connected by 4-Oxy-3-Fluoroaniline using multi-regression analysis.

H460

=SUM(0.0050809* SURFACE AREA -0.0161233* VOLUME -0.4340501* LOGP-0.6297261* REFRACTIVITY +4.4364077* POLARIZABILITY -0.2500706* MASS+0.1508529* TOTAL ENERGY -0.1669597* BINDING ENERGY -0.1741498* ISOLATED ATOMIC ENERGY +0.1733749* ELECTRONIC ENERGY +0.1733602* CORE-CORE INTERACTION -11.70263) ……..EQUATION 1

HI-29

=SUM (0.0040845* SURFACE AREA -0.090489* VOLUME -0.6474557* HYDRATION ENERGY -0.8256246* LOGP -2.017293* REFRACTIVITY +6.1082263* POLARIZABILITY +0.2978874* BINDING ENERGY +0.3060386* ISOLATED ATOMIC ENERGY -0.3062737* ELECTRONIC ENERGY -0.306275* CORE-CORE INTERACTION +0.0432492* HEAT OF FORMATION +6.086928) ….. EQUATION 2

MKN-45

=SUM(0.00621* SURFACE AREA +0.007077* VOLUME +0.05503* HYDRATION ENERGY -0.14079* LOGP +2.641632* POLARIZABILITY -0.25079* MASS -0.20017* BINDING ENERGY -0.21041* ISOLATED ATOMIC ENERGY +0.209965* ELECTRONIC ENERGY +0.209954* CORE-CORE INTERACTION -0.01172* HEAT OF FORMATION -13.3204) ……..EQUATION 3

When the postulated data obtained in this study were matched with that obtained experimentally, as in Table (5) for comparison purposes. Reading such a table (5), one can easily notice the concordance between the results obtained experimentally and that calculated using our equations.

As shown from the results presented in Table 6 and figure 1(A, B, C), the R-value is close to unity, reflecting more validity of the proposed equations. By reading the F and P-values data in Table 5, one can touch the high proximity of calculated values to the experimentally measured biological activities.

Table 5. The biological activity (anti-tumor activity) for 17 derivatives of bisquinoline connected by 4-oxy-3-fluoroaniline moiety was determined theoretically (by equations; 1, 2,3) and experimentally, as reported earlier.

	H460		HI-29		MKN-45	
	EXPER.	CALCUL.	EXPER.	CALCUL.	EXPER.	CALCUL.
1	0.01	-0.0186	0.06	0.02595	0.01	0.09395
2	0.82	0.83659	1.21	1.1007	0.73	0.66156
3	0.19	0.0864	1.52	1.23093	0.09	0.01175
4	0.75	0.69939	3.19	3.02571	0.16	0.20885
5	0.56	0.52004	3.05	3.13895	0.11	0.05546
6	0.08	0.13273	1.08	1.33188	0.04	0.08932
7	0.07	0.05456	0.23	0.22991	0.01	0.07186

	H460		HI-29		MKN-45	
	EXPER.	CALCUL.	EXPER.	CALCUL.	EXPER.	CALCUL.
8	0.07	0.05141	0.12	0.13316	0.19	0.16388
9	1	0.92373	2.5	2.50623	0.69	0.69868
10	0.24	0.38005	0.6	0.69176	0.26	0.29006
11	0.31	0.27779	0.53	0.4348	0.25	0.29967
12	0.03	-0.0364	0.25	0.06599	0.05	0.01056
13	0.44	0.51205	0.39	0.5316	0.32	0.34059
14	0.48	0.46929	0.42	0.34409	0.26	0.18368
15	0.09	0.1889	0.16	0.24277	0.11	0.18435
16	0.07	0.06999	0.67	0.7716	0.07	0.06597
17	0.25	0.27796	0.61	0.56448	0.17	0.23223

Table 6. Regression analysis reflects the validity of the proposed three QSAR equations.

	F-VALUE	P-VALUE	R^2
EQUATION 1 H460	10.44	< 0.009	**0.96**
EQUATION 2 HI-29	20.8	< 0.002	**0.98**
EQUATION 3 MKN-45	**6.65**	**< 0.009**	**0.922**

Where F, P, and R are, respectively, the degree of freedom, the degree of significance, and the regression coefficient.

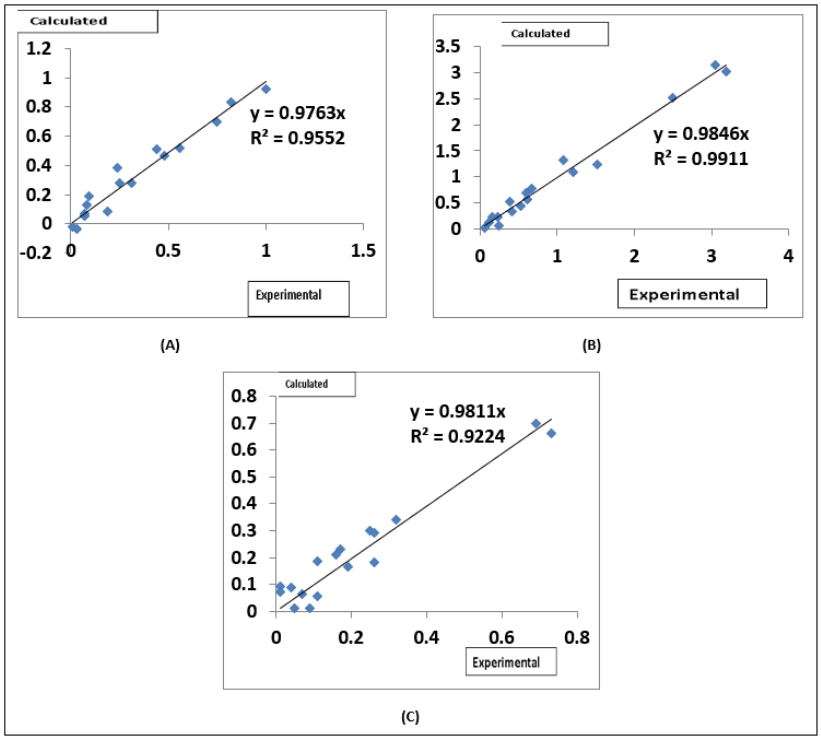


Figure 1. The plot of experimental IC_{50} values (50 % inhibition) vs. calculated values postulated by QSAR equations for 17 derivatives of bisquinoline connected by 4-oxy-3-fluoroaniline moiety against tumor cell lines; A) H460; B) HI-29; C) MKN-45.

Also, the proposed equations reported that the area of bisquinoline derivatives connected by a 4-oxy-3-fluoroaniline moiety plays a significant role in the biological activity of these compounds as anti-tumor, as illustrated in Table 7. The data obtained indicated the validity of the proposed equations, which displayed the importance of QSAR analysis to predict or speculate new compounds based on these equations.

Table 7. The most important physicochemical descriptors affecting the experimental biological parameters indicated by p-value and t-value according to Hyperchem &Winks Program.

95% CONFIDENCE USING H460		**95% CONFIDENCE USING HI-29**		**95% CONFIDENCE USING MKN-45**	
SURFACE AREA		Surface Area		**SURFACE AREA**	
T-VALUE	p-value	t-value	p-value	t-value	**P-VALUE**
4.52	**<0.001**	**3.98**	**<0.001**	**4.3**	**<0.001**

Because of the previous discussion and according to the facts obtained from applying for Hyperchem programs, the descriptors of the newly postulated structures are examined respectively in tables 8 and 9.

Taking into account these data and applying our newly calculated equations obtained from Hyperchem, we identified, calculated, and illustrated the biological activity of four new compounds, as shown in tables 8 and 9. These compounds are speculated, considering that they have 4-oxy-3-fluoroaniline moiety, and the rest of their structures are completed by active sites complementing the best descriptors obtained from our Hyperchem investigation.

In Table 10, the postulated compounds showed moderate to excellent cytotoxic activity against the different cancer cells with varying potencies. However, the cytotoxicity for compound (4) is generally higher than that for the corresponding compounds, suggesting that the introduction of chloro- and fluoro- groups to the 2-arylquinoline-4-carboxamide moiety is favorable for activity. Also, the postulated compound (4) showed higher cytotoxicity than compound (1), which was synthesized and investigated experimentally.

Thus the newly 4-oxy-3-fluoroaniline moiety derivatives remain to be synthesized and investigated experimentally for their cytotoxic activity against the cancer cell lines H460, HT-29, and MKN-45.

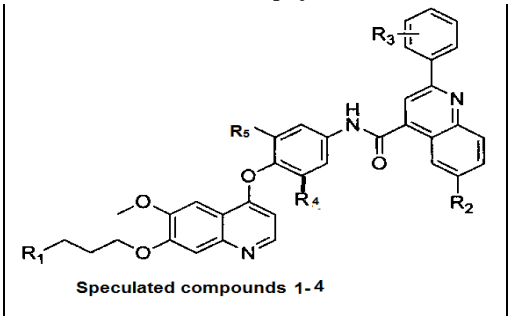
Table 8. Calculated physicochemical descriptors of four newly speculated chemical compounds.

POSTULATED COMPOUNDS	SURFACE AREA	VOLUME	HYDRATION ENERGY	LOGP (DISTRIBUTION-COEFFICIENT)	REFRACTIVITY	POLARIZABILITY
1	786.6	1779.6	-13.2	-1.64	207.54	72.75
2	782	1783.2	-12.26	-2.84	207.8	72.55
3	786.6	1779	-13.2	-1.64	207.54	72.75
4	747.5	1735.8	-12.52	-3.62	198.6	68.7

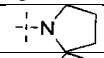
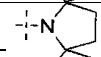
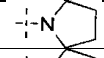
Table 9. Calculated physicochemical descriptors of four newly speculated chemical compounds.

POSTULATED COMPOUNDS	MASS	TOTAL ENERGY	BINDING ENERGY	ISOLATED ATOMIC ENERGY	ELECTRONIC ENERGY	CORE-CORE INTERACTION	HEAT OF FORMATION
1	659.19	-292.36	-9193.83	-174269.99	- 1742636.5	1559173	13.668
2	695.16	326.8	-9083.76	-195988.61	-1931304.4	1726232	57.318
3	659.18	-292.36	-9193.83	-174269.99	-1742636.5	1559173	13.668
4	664.7	-325.226	-8867.07	-195215.72	-1877021.1	1672938	-11.187

Table 10. The biological activity (anti-tumor activity) of 4 newly speculated derivatives containing 4-oxy-3 fluoroaniline moiety was determined theoretically by three predicted equations based on their calculated physicochemical descriptors.



Speculated compounds 1-4

	R_1	R_2	R_3	R_4	R_5	IC_{50}(µmol/L) H460	HI-29	MKN-45
1		**F**	**H**	**H**	**H**	0.561	0.511	0.707
2		**F**	**H**	**F**	**F**	99.441	4.647	-0.225
3		**F**	**3-Cl**	**H**	**H**	0.573	0.565	0.705
4		**F**	**3-Cl**	**F**	**F**	-0.091	-0.234	-0.0487

Finally, our data may be exhibited a potential interest for investigators attempting to find new prominent active compounds with potential anti-tumor activities.

4. Conclusions

In this study, four new bisquinoline derivatives were significantly postulated using QSAR and regression analysis. Moreover, anti-tumor activities of the new structures were predicted in vitro against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721) based upon their physicochemical parameters and without lab investigations

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Conflicts of Interest

The authors declare no conflict of interest.

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