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Quantitative Structure-Activity Relationship for Novel Benzenesulfonamides Derivatives as Prominent Inhibitors of Carbonic Anhydrase Isoforms Based on Cell Line Cytotoxic Screening Activity

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Abstract: Synthesis of new compounds and testing their biological activities were the major interest of drug development trends. Pyrrole and fused pyrrole rings have been reported as biologically active compounds, especially as anticancer. For producing new compounds containing benzenesulfonamide ring fragments with highly efficient antitumors, new postulation strategies should be performed to synthesize new structures with minimum side effects. The present study was evaluated to report the results of biological activity achieved from the design and synthesis of novel pyrrole, pyrrolo [2,3-d]pyrimidine, and fused pyrrolopyrimidine derivatives carrying benzenesulfonamide moiety using QSAR and regression analysis. Based up on physicochemical parameters of the studied benzenesulfonamide derivatives, six equations were performed using QSAR and regression analysis. These equations were used to calculate and postulate new benzenesulfonamide derivatives. The data showed that the calculated inhibition activities of derivatives containing benzenesulfonamide moiety against CA isoforms (hCA IX and hCA XII) were promising compared to those obtained experimentally. This, in turn, supports the use of QSAR to postulate new benzenesulfonamide compounds, which showed considerable inhibition activity against CA isoforms. The selected structures with various substituents can be directly characterized based on their molecular structure only. Consequently, the derived QSAR models will include information regarding the nature of the intermolecular forces involved in determining the biological activity of compounds by using the six new questions proposed by QSAR. The data concluded the importance of QSAR and regression equations in calculating the biological activity of previously reported benzenesulfonamide compounds and postulating new derivatives with pivotal antimicrobial validity.

Keywords: cytotoxic activity; sulfonamide; QSAR; carbonic anhydrase inhibitors.

1. Introduction

Several pyrroles, pyrimidines, and their fused derivatives were shown to have versatile biological activities, especially anticancer activity [1-5]. Sulfonamides are related to many drugs containing sulfonamide moiety (SO_2NH_2) in their structure. They comprise a potential

pharmaco-synthetic class of agents containing different biological activities, especially as antitumor [6,7], anti-carbonic anhydrase [8], antiviral [9], and anti-inflammatory [9,10].

Carbonic anhydrase (CA, EC 4.2.1.1) was shown to be overexpressed in human tumor cells. Only transmembrane tumor-associated CA isoforms (hCA IX and hCA XII) are over-expressed in several types of tumors [11,12].

Sulfonamide structures of aromatic/heterocyclic nature were potentially explored as CA inhibitors in the treatment/imaging of hypoxic tumors [13-15]. It was reported that many sulfonamide derivatives and 5, 7-diphenyl-pyrrolo [2, 3-d] pyrimidines were described as potent cytotoxic agents. They investigated their selective inhibition activity against CA hCA IX and hCA XII isoforms [16-18].

In cancer therapy, the major challenge for the wide use of chemotherapeutic agents is the lack of drug selectivity. Thus, this trend needs to synthesize new, safer, active antitumor agents with minimum side effects, such as therapeutic agents containing pyrimidines and pyridine moieties [19-20].

Computational approaches gained more interest in facilitating the selection and optimization of the synthesis and testing of new structures according to their physicochemical properties [21]. QSAR has been considered one of the most promising quantitative structure techniques, linking 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 [22]. So, QSAR models should be characterized by high efficiency, accuracy, and promising capability to speculate the required properties of a newly synthesized or a hypothetical molecule [23].

In light of the previous importance of QSAR analysis [22-24] and previous research work on the design and synthesis of sulfonamide compounds and measuring their biological activities as cytotoxic agents [23-29], the present study was evaluated to report the results of biological activity achieved from the design and synthesis of novel pyrrole, pyrrolo[2,3-d]pyrimidine and fused pyrrolopyrimidine derivatives carrying benzenesulfonamide moiety using QSAR and regression analysis.

2. Materials and Methods

This work is based on previous investigations of a series of novel pyrrolopyrimidines, derivatives bearing the biologically active benzene sulfonamide moiety. The synthesis, properties, and inhibitory potency of these derivatives against CA isoforms (hCA IX and hCA XII) and *in vitro* cytotoxic activity on human breast cancer cell line (MCF-7) were reported earlier by Ghorab *et al*. [30]. Thus, we selected 18 structures of previously synthesized pyrrole and pyrimidine derivatives carrying biologically active benzene sulfonamide moiety and tried to study the biological activity and structure relations and speculation of new derivatives with promising CA isoforms inhibition and cytotoxic activities 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 phthalazinedione compounds [31].

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 [32-34]. 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, the use of 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 which considered very 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, 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 [35].

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 [36,37].

3. Results and Discussion

Many sulfonamide-containing derivatives have been shown to exhibit various biological activities, especially anticancer activity. Therefore, these biological activities encourage more scientists to synthesize the sulfonamides containing important functional groups such as pyrazole, pyridine, and pyrimidine [19, 31-33]. Recently, Ghorab *et al*. [30] reported synthesizing a series of novel pyrroles, pyrimidines derivatives bearing the biologically active benzenesulfonamide moiety. All the synthesized compounds were tested for the *in vitro* inhibition activity of carbonic anhydrase against the human (h) isoforms hCA I, II, IX, and XII, and cytotoxic activity assays on human breast cancer cell line (MCF-7).

Hence we speculated new derivatives containing benzenesulfonamide moiety and derived carbonic anhydrase inhibition activity against the human (h) isoforms hCA I, II, IX, and XII for our speculated ones and compared the calculated activity with experimental activity previously reported [30] using QSAR and regression analysis.

In this study, QSAR equations have been elaborated using physicochemical parameters of benzenesulfonamide derivatives selected from the data previously reported by Ghorab *et al*. [30] as shown in Figure 1. This study used the predicted equations to speculate new benzenesulfonamide derivatives.

Using hyperchem and winks program for multi-regression statistical analysis at semi empirical theoretical method [31-36], more important physicochemical properties of

benzenesulfonamide derivatives were obtained, such as surface area, the surface grid, volume, hydration energy, log P, refractivity, polarizability, mass, total energy, bonding energy, isolated atomic energy, electronic energy, core-core interaction, the heat of formation, HOMO, LUMO, L-H, dx, and dy, and dz, as shown in Table 1.

The obtained physical parameters and the previously reported biological activities, such as inhibition rates against carbonic anhydrase isoforms and cytotoxic activity against human breast cancer cell line (MCF-7) [30], were fed again in hyperchem for multi-regression analysis. This results in the speculation of six equations capable of predicting the biological activity and carbonic anhydrase inhibition of the previously synthesized benzenesulfonamide derivatives, as shown in Table 2. The obtained equations focused on the most chief descriptors affecting the biological activity, showing clear variability among CA isoforms hCA I, II, IX, and XII.

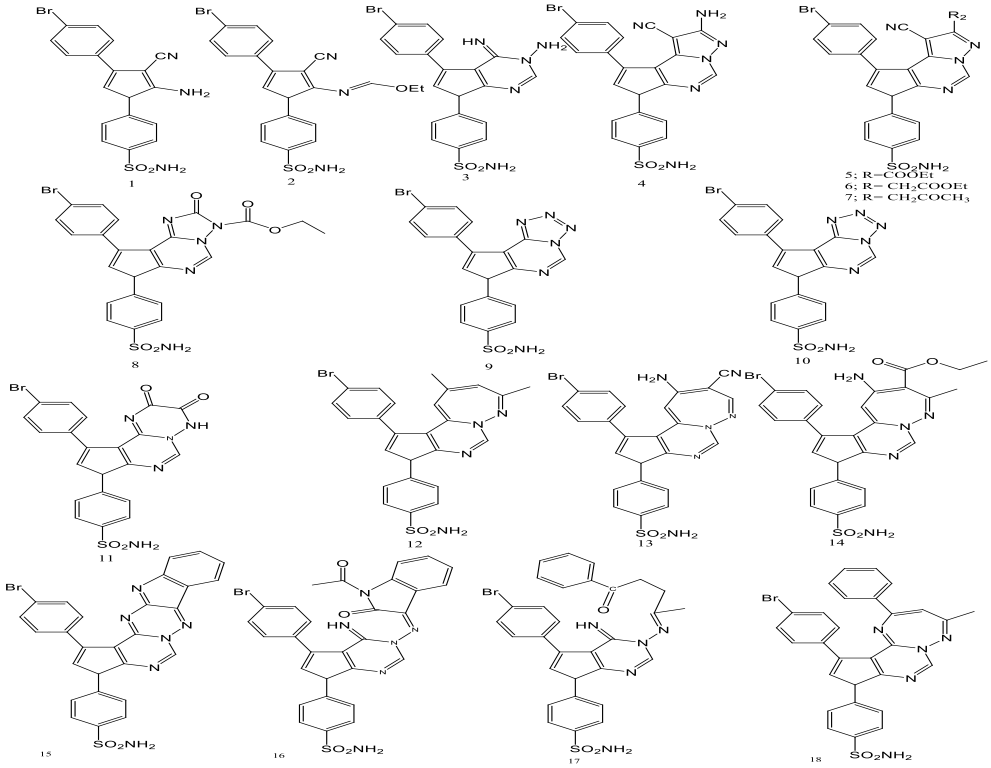

Figure 1. The chemical structure of 18 derivatives of benzenesulfonamide moiety derivatives selected from benzenesulfonamide compounds previously synthesized by Ghorab *et al.* [30].

The validity of the proposed equations was tested by theoretical calculation of activities of benzenesulfonamide derivatives and tabulated in comparison with those obtained from the work of Ghorab *et al*. [30], as shown in Table 3.

Table 1. Calculated equations to study inhibition activity of 18 benzene sulfonamide moiety derivatives against CA isoforms (hCA I, II, IX, and XII) using multi-regression analysis.

Eq.No.	Item	S A	S G	V	H E	Log P	Ref	Pol	Mass M	T E	B E	IAE	EE	CC I	HF	HOMO	LUMO	LUMO-HOMO	Dx	Dy	Dz	Absolute value
1	CA I	**-0.06**	**1.14**	**-0.06**	**-5.3**	**N1**	**-37.93**	**463.4**	**-53.0**	**385.31**	**0.77**	**-0.74**	**0.004**	**0.052**	**-0.431**	**-248.1**	**447**	-	-	-	-	**1538**
2	hCA II	-	-	-	-	-	-	**-45.0**	**7.8**	**-17.5**	**-0.051**	**0.042**	**-0.003**	**-0.036**	**0.093**	**1050.9**	**-936**	**-11**	**-3.8**	**-1.23**	**-13.2**	**-265**
3	hCA XII	**1.83**	**-0.83**	**-0.83**	**5.5**	-	**-12.54**	**-239**	**54**	**-240.43**	-	**0.61**	**-0.033**	**-0.034**	**0.89**	-	**280**	-	-	-	-	**-2492**
4	hCA I/XII	-	-	**0.52**	**-2.7**	**52.17**	**-45.73**	**542**	**-56**	**358.57**	**1.27**	**-0.70**	**0.051**	**0.006**	-	**-360.0**	**789**	-	-	-	-	**1047**
5	IC 25(µM)	-	-	-	-	-	-	-	-	**-0.055**	**0.0015**	**0.001**	**-0.001**	**0.005**	**-0.0001**	**1.476**	**-1.4**	**-1.51**	-	-	-	**0.1**
6	IC 50(µM)	**-0.04**	**0.01**	**-0.001**	**.039**	**0.1**	**0.1142**	**-0.28**	**0.003**	**-0.981**	**0.0034**	**0.002**	**-0.004**	**0.0017**	**-0.01**	**0.12**	-	-	-	-	-	**11.2**

Table 2. Calculated descriptors by HyperChem for 18 benzenesulfonamide moiety derivatives are presented in Figure 1 [30].

Compound No.	SA	SG	V	HE	Log P	Ref	Pol	M	T E	BE	I AE	EE	C-C I	H F	HOMO	LUMO	LUMO-HOMO	Dx	Dy	Dz
1	504.5	592.11	982.12	-16.11	-1.2	110	36	417.3	-161	-4178.5	-96577.1	568581.6	568581.6	68.2	-8.68	-1.31	7.37	3.12	-3.92	-2.5
2	633.9	724.31	1205.8	-15.6	-0.2	124.8	41.7	473.4	-188.3	-4849	-113276	-842975	724850.4	178.6	-9.1	-1.7	7.43	-3.91	-0.4	-3.0
3	546.95	637.4	1076.7	-22.8	-0.8	119.4	39.29	457.3	-180.3	-4440.3	-108699	-784797	671658	203.3	-9.0	-1.5	7.2	-1.6	0.8	-1.4
4	520.14	765.86	1300.45	-20.67	-1.13	141.21	47.91	513.12	-191.84	-5144.39	-115240	-907396	787011.2	227.12	-8.73	-1.71	-7.02	-3.88	3.42	-0.59
5	631.2	747.0	631.2	-12.2	-0.3	138.41	47.1	541.4	-224.8	-5584	-135474	-1085764	944707	71.6	-9.0	-1.5	-7.6	2.5	-2.5	-1.44
6	670.9	791.6	1354.3	-10.6	1.6	140.9	47.8	555.4	-230.5	-5857.5	-138785	-1133985	989342	72.3	-9.0	-1.31	-7.6	3.43	0.11	-1.8
7	596.4	757.9	1295.7	-11.8	1.01	136.11	46.0	541.1	-224.8	-5572.0	-135474	-1083540	942494	82.7	-9.0	-1.33	-7.62	2.9	-0.1	-1.9
8	633.3	748.4	1276.1	-12.34	-0.1	139.7	47.71	557.4	-236.53	-5664.1	-142763	-1167618	1019190	50.2	-9.1	-1.6	-7.5	1.59	-2.4	0.11
9	506.9	627.8	1056.0	-21.73	0.41	124.9	40.14	470.1	-187.43	-4516.4	-113104	-841988	724368.4	188.13	-9.13	-1.6	-7.6	1.61	-3.4	-2.8
10	534.9	672.3	1142.1	-14.3	-1.8	128.3	43.2	499.3	-202.6	-5048	-122086	-952103	824969	100.9	-8.73	-1.3	-7.4	3.5	-0.8	-2.3
11	557.3	713.3	1210.4	0.74	-1.7	128.7	43.3	513.3	-213.3	-4978	-128850	-977979	844152	126.7	-8.2	-1.2	-6.81	2.1	0.6	-2.3
12	588.5	719.8	1250.1	-10.32	-0.2	142.81	48.11	523.4	-207	-5660	-124206	-1043384	9135187	151	-8.3	-1.22	-7.1	5.41	2.1	-0.8
13	580.7	715.4	1239.6	-20.05	0.04	140.8	47.53	535.4	-215.4	-5455.1	-129704	-1063786	928627	202.24	-8.41	-1.5	-6.9	0.45	1.7	-0.8
14	651.9	828.8	1437.6	-19.7	-1.3	151.1	51.9	582.4	-243.3	-6182.4	-146502	-1233577	80892.4	83.4	-8.62	-0.99	-7.63	6.8	3.6	1.8
15	589.4	812.5	1394.2	-16.35	0.2	154.6	52.6	570.1	-226.9	-5940.0	-136444	-1140142	997758	340.01	-8.6	-1.13	-7.4	10.4	0.4	-0.3
16	748.6	962.9	1664.6	-12.03	-0.9	169.7	57.5	630.5	-261.8	-6661.7	-157647	-1326827	1162519	287.6	-8.8	-1.5	-7.3	6.5	2.7	1.2
17	634.7	795.8	1368.3	-14.9	0.5	158.91	53.41	575.4	-232.8	-6241.1	-139854	-1194975	1048880	141.8	-8.6	-1.11	-7.5	4.0	1.8	2.3
18	604.3	767.4	1317.3	-13.38	0.5	159	53.21	575.4	-232.5	-6240.7	-139854	-1199589	1053494	142.2	-8.6	-1.1	-7.5	4.1	2.1	1.6

Table 3. The biological activity (percentage inhibition of CA isoforms) of 18 derivatives containing benzenesulfonamide moiety as determined theoretically by predicted equations and experimentally as reported earlier [30].

Compound No.	% inhibition of human CA isoforms											
	Expert.						Cacul.					
	hCA I	hCA II	hCA IX	hCA XII	hCA I/XII	hCA II/XII	hCA I	hCA II	hCA IX	hCA XII	hCAI/XII	hCA II/XII
1	84.7	4.6	6.3	0.74	114.46	6.22	84.68	4.59	6.29	0.738	114.51	6.23
2	159.6	3.2	3.9	31.6	5.05	0.12	159.56	3.19	3.87	31.54	5.08	0.13
3	21.6	3.8	2.7	211	0.1	0.01	21.65	3.82	2.73	212.12	0.12	0.013
4	32.4	4.9	2.4	70.8	0.46	0.03	32.38	4.93	2.44	70.82	0.48	0.035
5	66	4.7	2.7	365	0.18	0.01	67	4.79	2.68	364.92	0.192	0.016
6	27.6	24.5	3	184	0.15	0.02	27.58	24.52	3.2	184.6	0.19	0.028
7	33.2	123.7	3.1	79.2	0.42	0.04	33.26	123.74	3.14	79.21	0.43	0.051
8	23.2	4.5	2.6	9.3	2.49	0.28	23.25	4.49	2.58	9.34	2.51	0.32
9	28.4	5.3	2.8	9.2	3.09	0.3	28.6	5.38	2.76	9.15	3.13	0.34
10	94.1	4.9	11.7	0.76	123.82	15.39	94.4	4.89	11.65	0.77	123.89	15.45
11	69.1	64.3	325	0.912	75.77	356.36	69.4	64.25	324.9	0.914	75.78	356.41
12	25.4	18.2	49.6	5.4	4.7	9.19	25.38	18.6	49.65	5.43	4.68	9.23
13	80.4	5.2	3.1	0.9	89.33	3.44	81.4	5.26	3.15	0.96	89.35	3.51
14	126	7.3	3	0.83	151.81	3.61	126.4	7.37	3.12	0.86	151.88	3.67
15	498	8.5	2.7	0.72	691.67	3.75	498.2	8.53	2.75	0.74	691.74	3.81
16	25.1	5.6	3.1	0.81	30.99	3.83	25.14	5.64	3.14	0.85	31.2	3.89
17	16.3	3.9	2.8	0.94	17.34	2.98	16.45	4.2	3.2	0.96	17.54	3.12
18	28.2	7.1	3.6	3.4	8.29	1.06	28.25	7.25	3.64	3.45	8.35	1.17

Table 4. Regression analysis reflects the validity of the proposed six equations.

	R-Square	Adjusted R-Square	F	p-value
CA I	0.9999	0.9983	625.24351	0.031
hCA II	1	1	-	-
hCA XII	0.9662	0.8851	11.909342	0.007
hCA XII	0.988	0.949	25.350688	0.003
25ul	1	1	-	-
IC50 (µM)	0.9968	0.9732	2.6302533	0.023

Table 5. The most important physicochemical descriptors of 18 derivatives containing benzenesulfonamide moiety affecting the % inhibition of CA isoforms indicated by p-value and t-value according to Hyperchem &Winks Program [26-30].

	Effective variable	**St. Erro**	**t-value**	**p-value**
CA In2	surface area (S A)	0.0196877	1.2648651	0.223
hCA II	Refractive (Ref)	0.0513935	2.2899051	0.035
hCA XII	Refractive (Ref)	0.1708568	2.1687545	0.045
hCA XII	Volume (V)	0.0301996	2.0504033	0.056
25ul	Total Energy T E	0.0000514	-29.52832	<.001
IC50 (µM)	surface area (SA)	0.001014	2.6302533	0.018

Table 6. Calculated physicochemical descriptors predicted from QSAR equations that could be used to speculate new chemical compounds containing benzenesulfonamide moiety.

Eq. No.	**Item**	**S A**	**S G**	**V**	**H E**	**Log P**	**Ref**	**Pol**	**M**	**T E**	**B E**	**IAE**	**EE**	**C-C-I**	**HF**	**HOMO**	**LUMO**	**LUMO-HOMO**	**Absolute value**
1	CA I	0.056	1.136	0.0583	-5.33	N1	-37.93	463.41	-53.1	385.32	0.7693	0.74	0.00037	0.00052	-0.431	-248.1	446.99	-	1537.6
2	hCA II	-	-	-	-	-	-	-45.03	7.8	-17.51	-0.051	0.042	-0.0000003	-0.00004	0.093	1051.0	-936.23	-1019.0	-265.3
3	hCA XII	1.83	-0.83	-0.83	5.5	-	-12.54	-238.94	53.7	-240.43	-	0.50	-0.000334	-0.00034	0.89	-	280.11	-	-2491.5
4	hCA I/XII	-	-	0.51	-2.7	52.2	-45.73	541.431	-55.78	358.57	1.286	-0.70	0.00061	0.0006	-	-360.12	788.7	-	1047.0
5	IC 25 (µM)	-	-	-	-	-	-	-	-	-0.055	0.00014	0.0001	-0.00007	0.0001	-0.00011	1.50	-1.43	-1.501	0.081
6	IC 50 (µM)	-0.0004	0.01	-0.001	.039	0.085	0.114	-0.28	0.0024	-0.981	0.0034	0.0015	-0.00035	0.0002	-0.010	1.1	-	-	11.24

Using regression analysis, the speculated equations showed higher validity, whereas R values were close to unity, and the obtained data of F and P-values supported the great proximity of calculated values to the experimentally measured biological activities of benzenesulfonamide derivatives as reported in Table 4, Table (5). These data gave us a promising stimulation to use these equations in postulating new derivatives of considerable CA inhibition and cytotoxic activity.

Also, the proposed equations reported that quantum chemical descriptors benzene-sulfonamide derivatives, such as surface area, refractivity, volume, and total energy, play a significant role in the biological activity of these compounds as anticancer and CA inhibitors (Table 5).

The data obtained indicated the validity of the proposed equations, which, in turn, displayed the importance of QSAR analysis to predict or speculate new compounds based on these equations, as shown in Table 6.

The synthesis of new benzenesulfonamide derivatives was recently described with their considerable carbonic anhydrase IX inhibitory affecting most cancer models [37-43]. Thus, the observed pharmacokinetic properties of our newly predicted compounds reproduced benzenesulfonamides [37-43], significantly revealing their favorable binding interactions for the active carbonic anhydrase inhibitors, confirming the proposed use of these speculated compounds as promising anticancer agents.

Finally, the postulated compounds in this study showed moderate to excellent CA inhibition and cytotoxicity activity compared to experimentally proposed activities, as reported by Ghorab *et al*. [30], Table 3.

4. Conclusions

In conclusion, the newly postulated QSAR equations can easily use to predicate new benzenesulfonamide moiety derivatives and help in the synthesis and investigation of the biological activity of these structures experimentally. Thus, our study might have potential interest for investigators attempting to find new prominent active compounds with potential anticancer and CA inhibition activities.

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Conflicts of Interest

The authors declare no conflict of interest.

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