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Prediction of New Phthalazine-1,4-Dione Derivatives with an Antibacterial Activity using Quantitative Structure Activity Relationship (2-D-QSAR)

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Abstract: Drug development trends focused on synthesizing new compounds and testing their biological activities. Nitrogen-containing heterocycles such as phthalazines are considered one of the most common moieties for reproducing new compounds with many biological activities. To produce new compounds containing phthalazine ring fragments with highly efficient antimicrobial activity, new postulation strategies should be performed to synthesize new structures with minimum side effects. So, the present study aimed to calculate the antimicrobial activity of previously published work that synthesized and investigated phthalazine 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. Based on the physicochemical parameters of the studied phthalazine derivatives, two equations were performed using QSAR and regression analysis. These equations were used to calculate and postulate new phthalazine derivatives. The data obtained showed that the calculated antibacterial activity of phthalazine derivatives was promising compared to those obtained experimentally. This supports the use of QSAR to postulate five new Phthalazine compounds, which showed remarkable antimicrobial growth inhibition activity. The data concluded the importance of QSAR and regression equations in calculating the biological activity of previously reported Phthalazine compounds and postulating new derivatives with pivotal antimicrobial validity.

Keywords: phthalazine; phthalazinedione; QSAR; antimicrobial activity.

1. Introduction

Recently, the demand for synthesizing newly activated antimicrobial agents increased with the evolution of microbial resistance against clinically used antimicrobial drugs [1,2]. One of which is the synthesis of new chemical structures with efficient antibacterial activity.

Thus, this trend needs synthesizing new, safer, more active antimicrobial agents with minimum side effects [3]. Computational approaches have gained more interest to facilitate the selection and optimization of the synthesis and testing of new structures according to their physicochemical properties [4]. QSAR is considered one of the most promising quantitative structure techniques linked to the biological activity of chemical derivatives with their

molecular structure. It depends on chemical compounds' geometric and chemical characteristics and their consistent relationships to the proposed biological activity.

Using QSAR, the theoretical speculation of new cheaper compounds with recommended biological activity depends mainly upon its physicochemical descriptors to achieve structure relationship modification analysis [5]. 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 [6-8].

Hetero cyclic compounds containing the phthalazine moiety are widely distributed and have important essentials to life as anti-diseases modulate due to their pharmacological and biological activities [9-13]. The phthalazine nucleus has pronounced several pharmacological applications, such as anti-inflammatory, anti-proliferative, and analgesic agents, due to its anticonvulsant, cardiotonic, and vasorelaxant activities [12-16].

However, many experimental trials were devoted to synthesizing structures containing phthalazine moiety. Still, an interesting challenge is trying to develop a new efficient methodology for synthesizing heterocyclic compounds containing phthalazine moiety [16-22].

In continuation of efforts to identify new candidates that may be of value in designing new, potent, selective, and less toxic antimicrobial agents, herein we applied the QSAR and regression analysis for the prediction of new heterocycles containing phthalazine moiety that could serve as models for the development of new antibacterial agents.

2. Materials and Methods

The present idea of this proposal depends mainly on a previously investigated series of novel phthalazinedione derivatives. The synthesis, properties, and in vitro antibacterial activities against gram-positive (*B. thuringiensis*) and negative (*E. coli*) bacterial strains of these derivatives were reported earlier [23]. Hence, the main target of our study is to reinvestigate the experimental antibacterial potency of their synthesized phthalazinedione derivatives, speculate new derivatives and derive their antibacterial 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 phthalazinedione compounds[24].

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 literature linked with the different models of QSAR analysis [25-29]. 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 MNDO methods were developed, which are simplified versions of Hartree-Fock theory and 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. In different models of QSAR analysis, AM1-SCF and developed MNDO methods along with PM3, AM1 was applied as the most reliable accurate methods of Hyperchem physicochemical analysis, and it recommended calculating the electronic properties, optimized geometries, total energy, and heat of formation [29-35].

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[36-38].

3. Results and Discussion

Phthalazine is an important heterocycle that is known to possess multiple biological activities such as antimicrobial, anticonvulsant, antifungal, anticancer, and anti-inflammatory activities [39-46]; most of these derivatives have found application in clinical medicine [47]. Moreover, in medicinal chemistry, versatile drug molecules are accessible starting from the corresponding phthalazinones derivatives [47-51].

Recently, phthalazine has emerged as an inexpensive and easily available target for synthesizing new phthalazine derivatives with promising antibacterial activity. Most of the newly synthesized phthalazine derivatives showed potent antibacterial activity against gram-positive and negative bacterial strains at different minimum inhibition concentrations (MIC) [23,49-51]. The development of new and efficient methodologies for the synthesis of such potentially bioactive phthalazine derivatives is important. Therefore, functionalization of the nucleus continues to be of synthetic interest. So, in the present work, we tried to study the synthesis and antibacterial activities of phthalazine derivatives previously reported by Khalil *et al*. [23], using QSAR and regression analysis as efficient methodologies to speculate new phthalazine derivatives with promising calculated antibacterial activities compared to those of their compounds.

In this study, QSAR equations have been elaborated using physicochemical parameters of 17- phthalazine derivatives selected from the data previously reported by Khalil *et al*. [23] (Figure 1); the predicted equations were used to speculate new phthalazine derivatives.

Using hyperchem and winks program for multi-regression statistical analysis, a semi-empirical theoretical method [24-38,50-51], more important physicochemical properties of phthalazine derivatives were obtained, such as the surface grid, hydration energy, Refractivity, Polarizability, the heat of formation, HOMO, LUMO, L-H, dmx, and dmz as shown in Table 1. The obtained physical parameters and the previously reported biological activities of phthalazine derivatives against bacterial infections [23] were fed again in hyperchem for multi-regression analysis. This results in the speculation of two equations capable of predicting the biological activity of the previously synthesized phthalazine derivatives against the infection

of gram-positive and negative bacteria, as shown in equations 1 and 2. The obtained equations focused on most chief descriptors affecting biological activity.

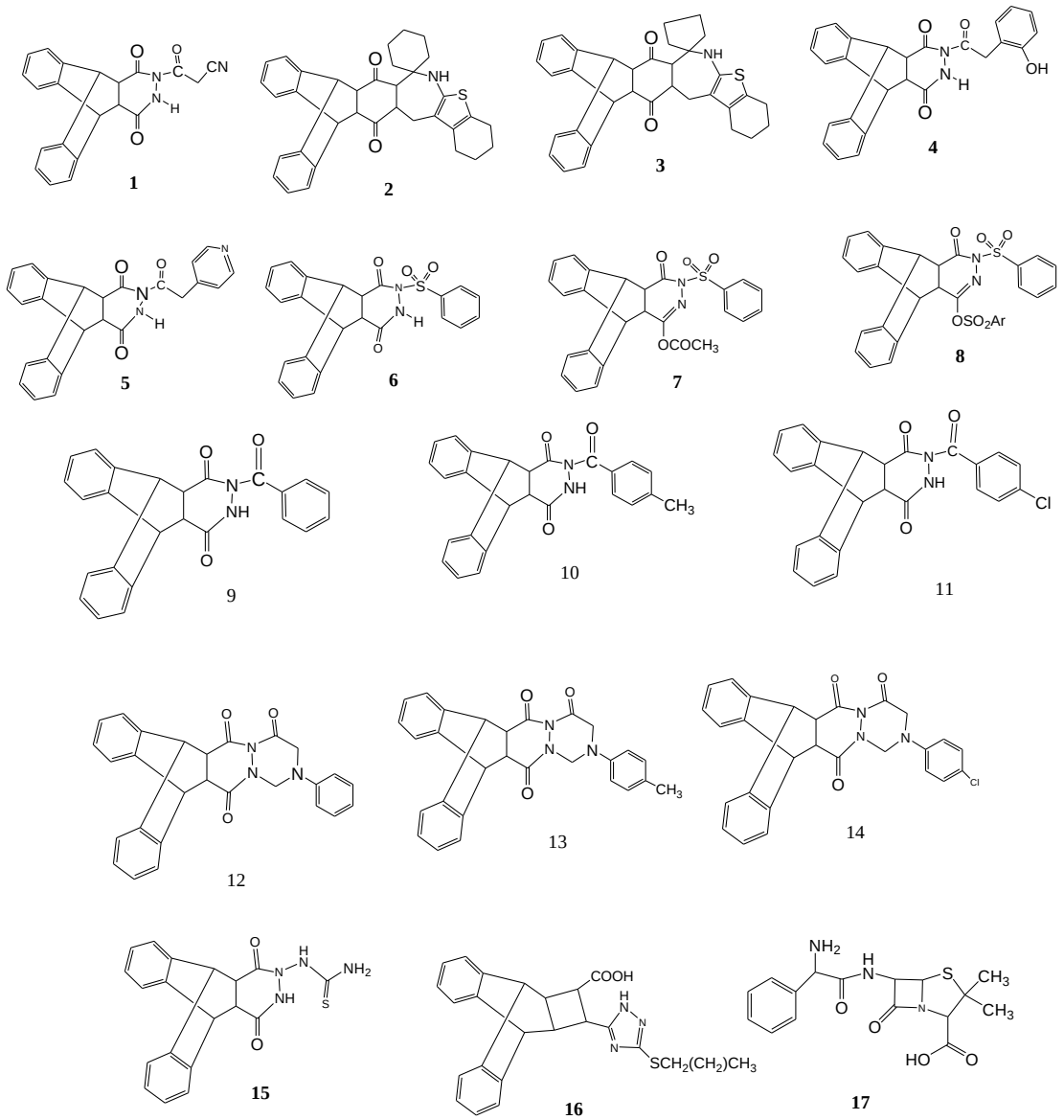


Figure 1. The chemical structure of 17 derivatives of phthalazine moiety was selected from phthalazine compounds previously synthesized by Khalil *et al*. [23].

Table 1. Calculated descriptors by HyperChem for 17 derivatives of phthalazine moiety were presented in Figure 1.

Surface grid	**Hydration**	**Refractivity**	**Polar**	**Heat of Formation**	**HOMO**	**LUMO**	**L-H**	**dmx**	**dmz**
602.1	-158.7	102.9	37.3	201.4	-7.65327	-0.94903	6.704239	4.025	-0.322
745.2	-3.03	162.4	60.1	70	-6.75602	-1.70842	5.047599	-0.702	3.198
721.9	-3.9	157.8	58.3	32.1	-8.62647	-0.33771	8.288759	-0.702	3.199
607.6	-6.6	126.7	45.2	69.9	-8.59096	-0.45075	8.14021	1.856	1.01
599.8	-8.2	123.2	44.5	81	-8.91573	-0.69053	8.225202	-0.306	0.882
616.1	-8.1	126.2	42.5	-17.3	-9.40109	-0.74187	8.659226	4.104	0.115
651.1	-6.1	135.9	46.3	-52.9	-8.98987	-0.39391	8.595967	1.881	5.869
689.5	-6	168.7	55.2	-55.3	-9.08481	-1.29381	7.790993	6.136	-0.594
608.3	-8.8	125.8	44.6	97.6	-8.35881	-0.32489	8.033927	0.518	1.34
636	-7.8	130.1	46.4	90.1	-8.27192	-0.31457	7.95735	0.868	1.45

Surface grid	Hydration	Refractivity	Polar	Heat of Formation	HOMO	LUMO	L-H	dmx	dmz
631.4	-8.5	130.5	46.5	90.9	-8.46471	-0.51586	7.948858	-0.756	0.778
731.1	-6.5	133.4	47.5	287.4	-9.45419	-2.50723	6.946961	-3.141	3.941
796	-4.8	137.7	49.3	282.7	-9.45426	-2.50223	6.952029	-3.129	3.904
746	-6.3	138.1	49.4	264.5	-9.61961	-2.69875	6.920859	-2.995	5.418
563.5	-19	107.7	39.4	90.3	-8.62222	-0.02372	8.598507	-0.865	-1.25
841.6	-12.7	138.4	51.5	85.1	-8.64325	-0.48212	8.161129	-0.673	2.573
719	4.9	91.5	34.5	74.4	-7.4712	-2.03005	5.441155	-14.238	1.076

LUMO: low unoccupied molecular orbital; HOMO: high occupied molecular orbital; H.E: hydration energy; dmx (dipole x): dipole moment in X direction.

Equation 1 and 2. Calculated equations to study the antibacterial activity of 17 derivatives of phthalazine moiety against gram-positive and negative bacterial strains using multi-regression analysis.

Equation 1:

$$\underline{\boldsymbol{Cal\ B.thuringiensis} = Sum(+0.0470099 surface - 0.0627378\ Hydration\ Energy + 0.839\ 8188\ Refractivity - 2.265476\ Polar - 0.0330409\ Heat\ of\ Formation + 44.455645\ HOMO - 44.95118\ LUMO + 44.112094(LU - HO) - 0.6551882\ dmz - 9.735559)}$$

Equation 2:

$$\underline{\boldsymbol{Cal\ E.coli} = \text{sum}\ (0.033196\ \text{surface grid} + 0.017114\ \text{Hydration} - 0.28633\ \text{Polar} - 0.02352\ \text{Heat of Formation} + 73.63007\ \text{HOMO} - 73.7996\ \text{LUMO} + 72.68784(\text{LU} - \text{HO}) + 0.486161\text{dmx} + 0.113375\ \text{dmz} + 18.38601)}$$

The validity of the proposed equations was tested by theoretical calculation of the activities of phthalazine derivatives against bacterial infection and by comparing the results with experimentally calculated data. Our speculated biological results were tabulated in comparison with those obtained from the work of Khalil *et al*. [23], as shown in Table 2. From the data obtained, it is easy to observe the great conformity between the experimental antibacterial data of Khalil *et al*. [23] and those obtained by our speculated equations.

Table 2. Antibacterial activity for 17 phthalazine derivatives against gram-positive and negative bacterial strains as determined theoretically by QSAR equations (1, 2) and experimentally, as reported earlier [23].

	B. thuringiensis		***E. coli***	
	Exper.	**Calc.**	**Exper.**	**Calc.**
1	22.00	22.16	16.00	16.00
2	21.00	20.42	20.00	19.77
3	18.00	19.05	17.00	17.10
4	17.00	17.70	15.00	17.28
5	16.00	15.89	17.00	15.83
6	27.00	27.33	22.00	20.91
7	26.00	25.64	21.00	21.43
8	40.00	39.86	22.00	22.46
9	18.00	17.32	16.00	16.25
10	16.00	18.29	18.00	17.10
11	20.00	18.74	17.00	16.07
12	17.00	16.24	16.00	14.98
13	18.00	18.89	16.00	16.76

	B. thuringiensis		***E. coli***	
	Exper.	**Calc.**	**Exper.**	**Calc.**
14	17.00	16.46	16.00	15.77
15	15.00	14.03	14.00	14.70
16	24.00	23.12	22.00	21.72
17	18.00	18.42	19.00	19.13

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 phthalazine derivatives as reported in Table 3, table 4, and figure 2 (A, B). These data gave us a promising stimulation to use these equations in postulating new phthalazine derivatives of considerable antibacterial activity.

Also, the proposed equations reported that the area of phthalazine derivatives plays a significant role in the biological activity of these compounds as antibacterial (Table 4). The data obtained indicated the validity of the proposed equations, which showed the importance of QSAR analysis in predicting or speculating new compounds based on these equations.

Table 3. Regression analysis reflects the validity of the proposed QSAR equations.

	F-Value	P-Value	**R**
Equation 1 at B.thuringiensis	36.649284	<.001	**0.9792**
Equation 2 at E.Coli	7.2643319	< 0.008	**0.0902**

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

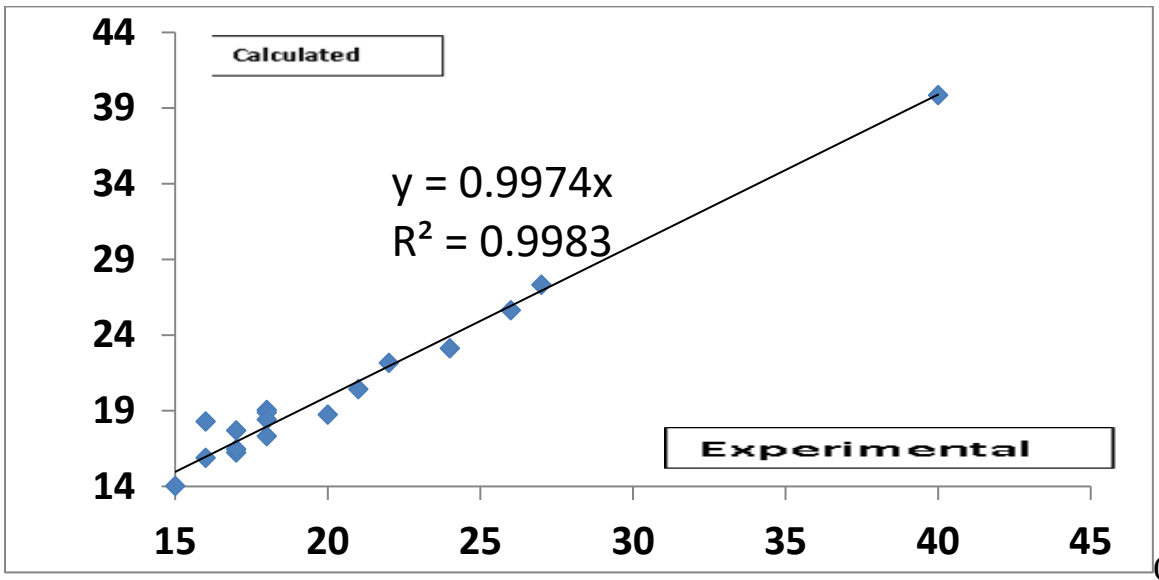
Table 4. The most important physicochemical descriptors affecting the % inh of *B.thuringiensis* & *E.Coli* indicated by p-value and t-value according to Hyperchem & Winks Program.

95% Confidence Using Interval At Our compounds

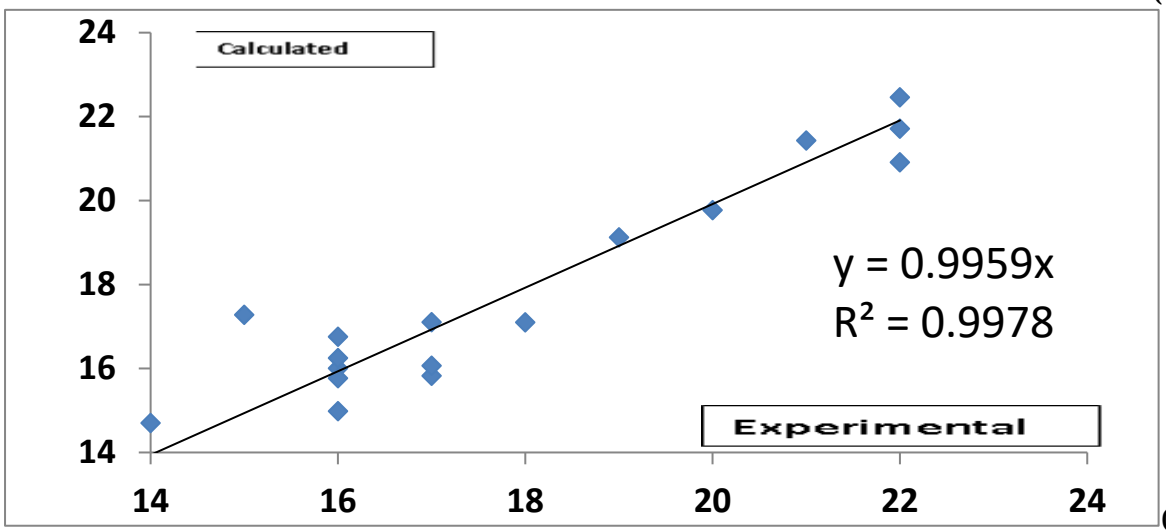
B. thuringiensis		***E. coli***	
AREA		AREA	
t-value	p-value	t-value	p-value
13.3856	<0.001	26.843323	<0.001

From the previous interpretations of phthalazine derivatives and postulated physicochemical parameters resulting from QSAR analysis, the physicochemical parameters of the newly postulated derivatives are examined and calculated as reported in Table 5.

Considering these data and applying our equations obtained from hyperchem, the biological activity of these compounds is calculated and illustrated (Table 6). The speculated derivatives depend on phthalazine moiety as a meaningful part of their structure, and the rest of their structures are completed by active sites complementing the best descriptors obtained from our hyperchem investigation, as shown in Figure 3. The postulated compounds showed moderate to excellent antibacterial activity against gram-positive and negative bacteria compared to the experimental antibacterial activity of phthalazine derivatives previously reported by Khalil *et al*. [23], as shown in Table 2.



(a)



(b)

Figure 2. Plot of experimental MIC values (% inhibition) vs calculated values postulated by QSAR equations for 17 phthalazine derivatives against gram bacterial strains; A) *B.thuringiensis* (Gram +Ve); B) *E.Coli* (Gram -Ve).

Table 5. Calculated physicochemical descriptors of newly speculated chemical compounds (5; structures) of phthalazine moiety.

	Surface grid	Hydration	Refractivity	Polar	Heat of Formation	HOMO	LUMO	L-H	dmx	dmz
Postulated1	691.0	-6.07	168.77	55.13	-28.64	-9.1271	-1.46887	7.65823	6.04	0.035
Postulated2	695.56	-6.00	168.73	55.04	-150.37	-9.1796	-1.5777	7.6019	4.881	1.208
Postulated3	702.96	-5.80	173.5	57.15	-62.155	-9.14203	-1.44610	7.69593	5.281	0.108
Postulated4	686.6	-6.03	169.13	55.11	-56.659	-9.1817	-1.285	7.8967	3.408	-1.299
Postulated5	712.5	-6.45	171.94	56.01	-44.231	-9.182	-1.2682	7.9138	2.928	-0.596

Table 6. Biological antibacterial activity of newly Postulated derivatives of phthalazine moiety using QSAR predictable Equations 1 and 2, and calculated physicochemical descriptors in Table 5.

Postulated derivatives	*B. thuringiensis*	*E. coli*
Postulated1	38.989871	22.0824
Postulated2	42.696959	24.7649
Postulated3	39.966553	22.2938
Postulated4	40.754916	20.9151
Postulated5	41.434355	21.045

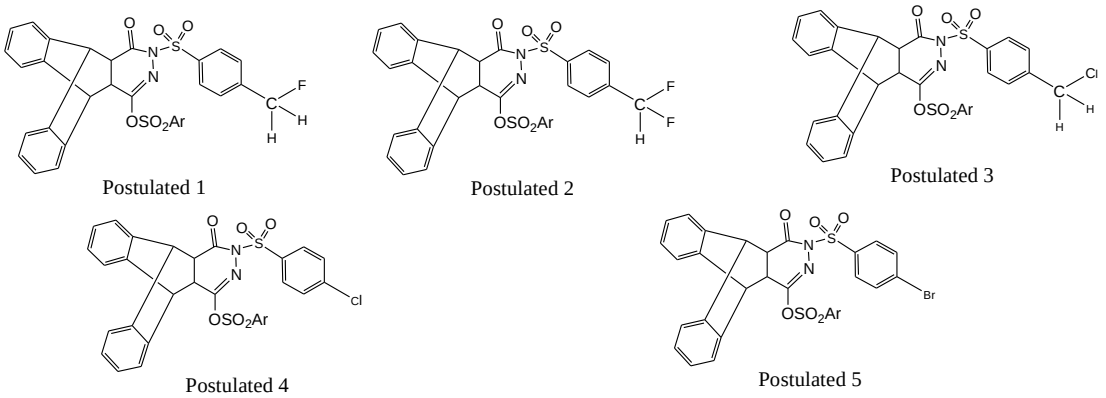


Figure 3. The chemical structure of newly postulated derivatives of phthalazine moiety using hyperchem programs.

4. Conclusions

In this study, a new phthalazine moiety derivative remains to be synthesized and investigated experimentally for its biological activity against gram-positive and negative bacteria. Finally, our data may exhibit a potential interest for investigators attempting to find new prominent active compounds with potential antibacterial activities.

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Conflicts of Interest

The authors declare no conflict of interest.

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