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Synthesis and DFT-Based Quantitative Structure-Activity Relationships Study for Diphenyl Ethers Bactericide

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Density functional theory (DFT) and linear regression analysis method are used to investigate the quantitative structure-activity relationship (QSAR) of diphenyl ethers bactericide. It is found that there are good linear relationships between the experimental biological activity data [-log(1/MIC)] and the calculated energy gap of highest occupied molecular orbital and lowest unoccupied frontier orbital (ΔE_{gap}). The 2D-QSAR equations (R^2 = 0.87942) was established used -log(1/MIC) and ΔE_{gap} as factors. A validation set of 14 diphenyl ethers were selected and their activities were computed using the proposed QSAR model and three of them were synthesized and characterized. The correlation between the predicted and observed activities was excellent.

Key Words: Biological activities, Diphenyl ethers, QSAR, DFT, Synthesis.

INTRODUCTION

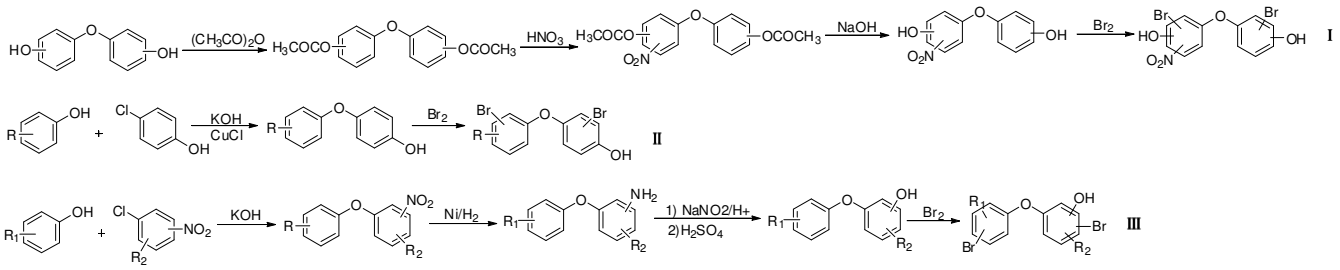
A kind of widely used organic compounds, halogenated hydroxy-diphenyl ethers possess good antibacterial activity and are applied in many fields as bactericide and germicide. A series of hydroxy diphenyl ethers compound were designed and synthesized by our research group *via* three different routes (**Scheme-I**)[1-5].

There are no report is available in literature before structure designed and synthesis work for the relationship between the structure and biological activity. Structure-activity relationship (QSAR) analysis show wide applications due to their well established predictive power[6]. Essentially, correlating the physico-chemical properties of a series of compounds with their respective biological activities is believed to provide a useful tool in designing new drugs[7,8].

In order to explore the relationship between structure and antibacterial activity of diphenyl ethers, density functional theory (DFT) and linear regression analysis method were used to construct the QSAR models of diphenyl ethers. Used the QSAR equation, the biological activity of new diphenyl ethers bactericide can be predicted. The predicted results provided an important reference for the future research work of designing and synthesis new derivative.

EXPERIMENTAL

Thin layer chromatography was performed with Qingdao Ocean silica gel GF_{254} and flash column chromatography was carried out with Qingdao Ocean gel 100-200 mes. Nuclear magnetic resonance (nmr) spectra were recorded on a Bruker DPX-300 FT NMR spectrometer at 300 MHz for ^1H and were referenced to tetramethylsilane (δ values are given in ppm and



Scheme-I: Synthesis route of the diphenyl ethers compound

J-values in Hz). Mass spectra were measured on a Varian CH-5 apparatus. IR spectra were measured on Nicolet380 and obtained using KBr plates.

4-(3-Bromo-5-hydroxyphenoxy)-3-nitrophenol (a_7): Potassium hydroxide (55 mmol) was added to a solution of the 1-chloro-4-methoxy-2-nitrobenzene (60 mmol) in DMF (65 mL) at room temperature. The mixture was stirred for 0.5 h and then 50 mmol of 5-bromobenzene-1,3-diol was added. The mixture was heated at reflux for 1 h under nitrogen. The cooled mixture was poured onto 250 mL water and the precipitate was collected by filtration, washed twice with 5 % aqueous NaOH and twice with H_2O to give crude 3-bromo-5-(4-methoxy-2-nitrophenoxy)phenol. The 3-bromo-5-(4-methoxy-2-nitrophenoxy)phenol and 80 mL of 48 % HBr were stirred in refluxing at 125 ºC for 24 h. After cooling, the mixture was neutralized with sodium hydroxide and was extracted several times with MTBE. The combined MTBE extract was washed twice with H_2O and dried over $MgSO_4$, filtration and evaporation of the solvent. The residue was subjected to column chromatography on silica gel (100-200 mesh) eluted with 35 % EtOA/chexanes to yield **a_7** as a yellow solid. Yield 29 %, ^{1}H NMR (300 MHz, $CDCl_3$): 7.91 (d, *J* = 3.0 Hz, 1H, ArH), 7.78 (dd, *J* = 9.0, 3.0 Hz, 1H, ArH), 7.30 (dd, *J* = 9.0, 3.0 Hz, 1H, ArH), 7.13 (d, *J* = 3.0 Hz, 1H, ArH), 7.00 (d, *J* = 9.0 Hz, 1H, ArH), 6.89 (d, *J* = 9.0 Hz, 1H, ArH), 6.41 (s, 1H, OH), 5.92 (s, 1H, OH), IR (KBr, ν_{max}, cm^{-1}): 3427, 1593, 1562, 1509, 1349, 1268, 1210, MS m/z: 326, 324.

2-(3-Bromo-5-hydroxyphenoxy)-3-nitrophenol (a_8): The above procedure was used to prepare **a_8** from 2-chloro-1-methoxy-3-nitrobenzene and 5-bromobenzene-1,3-diol. Yield 23 %, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.92 (d, *J* = 3.0 Hz, 1H, ArH), 7.76 (dd, *J* = 9.0, 3.0 Hz, 1H, ArH), 7.28 (d, *J* = 2.8 Hz, 1H, ArH), 7.12 (d, *J* = 9.0 Hz, 1H, ArH), 7.04 (dd, *J* = 9.0, 2.8 Hz, 1H, ArH), 6.78 (d, *J* = 9.0 Hz, 1H, ArH), 5.92 (s, 1H, OH), 5.51 (s, 1H, OH), IR (KBr, ν_{max}, cm^{-1}) ν: 3368, 1602, 1510, 1480, 1347, 1269, 1227, MS m/z: 326, 324.

2-(3-Bromo-5-hydroxyphenoxy)-6-nitrophenol (a_{15}): The procedure above was used to prepare **a_{15}** from 1-chloro-2-methoxy-3-nitrobenzene and 5-bromobenzene-1,3-diol. Yield 27 %, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.45 (d, *J* = 2.8 Hz, 1H, ArH), 7.15 (d, *J* = 2.8 Hz, 1H, ArH), 7.09 (dd, *J* = 8.8, 2.8 Hz, 1H, ArH), 7.06 (d, *J* = 8.8 Hz, 1H, ArH), 6.97 (d, *J* = 8.8 Hz, 1H, ArH), 6.86 (dd, *J* = 8.8, 2.8 Hz, 1H, ArH), 5.54 (s, 1H, OH), 5.34 (s, 1H, OH), IR (KBr, ν_{max}, cm^{-1}): 3385, 1596, 1529, 1495, 1324, 1258, 1219, MS m/z: 326, 324.

The minimum inhibitory concentrations (MIC) of hydroxy diphenyl ethers were determined by the agar dilution method used *Staphylococcus aureus* as testing bacteria[9]. Hydroxy diphenyl ethers were dissolved in 75 % of 2-methoxyethanol and agar plates were prepared that contained this biocide in dilutions ranging from 0-1024 μg/mL. Plates were inoculated to be absorbed into agar before incubation. Conditions of incubation were 35-37 ºC in air for 20 h. The MIC was defined as lowest concentration of antibiotic at which there is no visible growth of the organism.

RESULTS AND DISCUSSION

There are 24 diphenyl ethers (**Scheme-II**), which were synthesized by our research group, were used for constructing the 2D-QSAR models. The optimized molecular geometry of compound was computed first. All computations were carried out using the Gaussian 03[10] computer software package. The electronic descriptors were obtained from a single-point calculation at the B3LYP/6-311+g (d) level. The optimized geometrical parameters are given in Table-1.

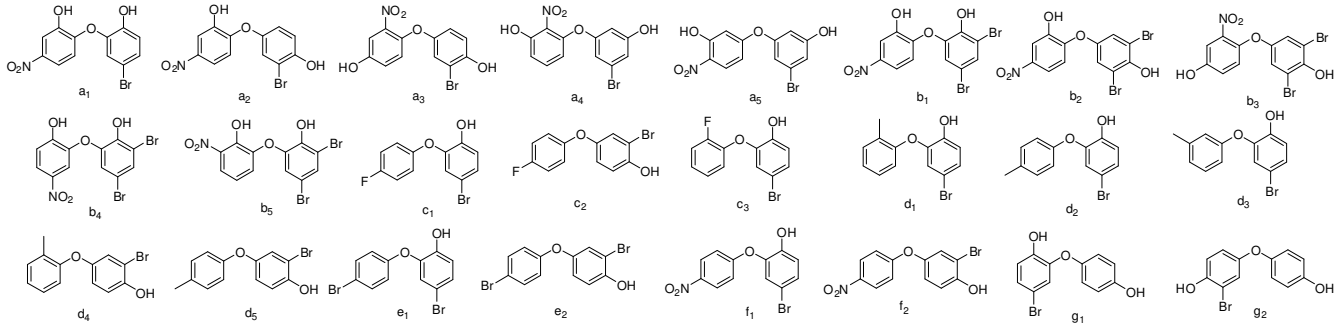
The frontier orbital theory states that the energy of the HOMO and LUMO are the important factors that determine the reactivity of a molecule. The chemicals which have greater ability to accept electron density through charge-transfer interaction should bind to the aryl hydrocarbon receptor with greater affinity than those with lower electron-acceptor properties[11,12]. This would suggest that these stronger electron acceptors should have a lower energy unoccupied frontier orbital (E_{LUMO}), lower energy for the occupied frontier orbital (E_{HOMO}) and a lower energy difference in these frontier orbitals (ΔE_{gap}), which can be related to molecular reactivity[13,14]. So the energy of geometry optimized diphenyl ethers was calculated and the HF, E_{HOMO}, E_{LUMO} and ΔE_{gap} Value were summarized in Table-2.

It was found that the MIC of diphenyl ethers compounds have a certain relation with theoretical data of the ΔE_{gap}, the antibacterial activity showed a downward trend with the increasing of ΔE_{gap} values. The present study presents a comprehensive QSAR analysis for diphenyl ethers as a bactericide drug. A multiple regression analysis was carried out and we arrived at the final QSAR equation. Thus, the QSAR equation can be written as:

$$-\log\left(\frac{1}{MIC}\right) = -1.6868 + 20.9237 \times \Delta E_{gap}$$

n = 24, R^2 = 0.877212, SD = 0.27871, F = 45.081, P < 0.0001.

The QSAR equations possess relatively high correlation coefficient R, low standard deviation SD and least number of

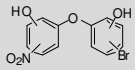
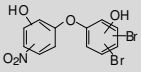
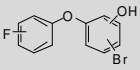
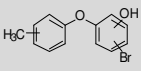
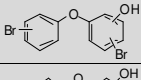
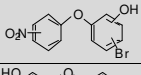
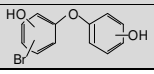


Scheme-II: Structure of the diphenyl ethers compound used for constructing the QSAR models

TABLE-1
OPTIMIZED GEOMETRICAL PARAMETERS OF DIPHENYL ETHERS FOR CONSTRUCTING THE QSAR MODELS

Compound	Ring A C-N	Ring A C-O	Ring A C-F	Ring A C-CH_3	Ring A C-Br	Ring A-O	O-Ring B	Ring B C-O	Ring B C-Br	Ring B C-Br	Dihedral angle
a1	1.47444	1.35859	–	–	–	1.36958	1.37974	1.36253	1.91772	–	28.20258
a2	1.47317	1.35727	–	–	–	1.37674	1.39386	1.35433	1.91854	–	69.08806
a3	1.47615	1.36382	–	–	–	1.36882	1.38846	1.35863	1.92239	–	27.14498
a4	1.47850	1.35656	–	–	–	1.36872	1.38455	1.36361	1.91602	–	33.30459
a5	1.44190	1.33620	–	–	–	1.36400	1.39117	1.36224	1.91365	–	80.35678
b3	1.47553	1.36308	–	–	–	1.37219	1.38283	1.35193	1.92049	1.90653	25.23897
b1	1.47531	1.35843	–	–	–	1.37154	1.37677	1.35097	1.91927	1.91505	27.33849
b2	1.47437	1.35707	–	–	–	1.37928	1.39116	1.34770	1.91806	1.90338	70.88311
b4	1.46776	1.35041	–	–	–	1.38618	1.38319	1.35044	1.91126	1.91660	71.56889
b5	1.45628	1.33326	–	–	–	1.37538	1.37562	1.35120	1.91946	1.91530	22.26875
c1	–	–	1.35880	–	–	1.38470	1.37686	1.36196	1.91661	–	73.18478
c2	–	–	1.35774	–	–	1.38171	1.38441	1.36218	1.90741	–	57.98806
c3	–	–	1.35004	–	–	1.37521	1.37831	1.36141	1.91638	–	18.90108
d1	–	–	–	1.50586	–	1.38882	1.37505	1.36224	1.91732	–	18.86771
d2	–	–	–	1.50599	–	1.38764	1.38254	1.36235	1.90896	–	21.92345
d3	–	–	–	1.50639	–	1.38562	1.38260	1.36269	1.90888	–	22.62333
d4	–	–	–	1.50968	–	1.38409	1.38231	1.36318	1.90827	–	29.94973
d5	–	–	–	1.50993	–	1.38596	1.37554	1.36186	1.91755	–	16.29069
e1	–	–	–	–	1.91897	1.38116	1.37819	1.36159	1.91640	–	110.16884
e2	–	–	–	–	1.91832	1.37825	1.38700	1.36122	1.90708	–	71.99985
f1	1.46887	–	–	–		1.36953	1.38323	1.36110	1.91466	–	77.43238
f2	1.46894	–	–	–		1.36716	1.39261	1.35933	1.90554	–	96.36661
g1	–	1.36475	–	–	1.91988	1.36941	1.39113	1.36907	–	–	95.96239
g2	–	1.36093	–	–	1.92445	1.37936	1.38932	1.36929	–	–	14.20552

TABLE-2
CALCULATED ENERGY VALUE AND THE OBSERVED ACTIVE VALUES OF DIPHENYL ETHERS

Structure	Compound	HF (Hartree)	E_{HOMO} (Hartree)	E_{LUMO} (Hartree)	ΔE_{gap} (Hartree)	ΔE_{gap} (kJ/mol)	MIC (μg/mL)	-log(1/MIC)
	a_3	-3467.2193396	-0.23103	-0.10894	0.12209	320.547295	8	0.90309
	a_1	-3467.2309972	-0.23548	-0.10855	0.12693	333.254715	12	1.07918
	a_2	-3467.2155827	-0.25149	-0.10095	0.15054	395.242770	16	1.20412
	a_5	-3467.2377244	-0.26035	-0.10952	0.15083	396.004165	24	1.38021
	a_4	-3467.2129707	-0.24809	-0.08627	0.16182	424.858410	64	1.80618
	b_5	-6040.7557998	-0.23975	-0.12345	0.11630	305.34570	2	0.30103
	b_3	-6040.7633589	-0.23793	-0.10724	0.13069	343.126595	20	1.30103
	b_1	-6040.7691917	-0.24294	-0.11171	0.13123	344.544365	20	1.30103
	b_2	-6040.7722341	-0.25574	-0.10269	0.15305	401.832775	64	1.80618
	b_4	-6040.7688792	-0.25542	-0.10019	0.15523	407.711595	128	2.10721
	c_1	-3286.6855684	-0.04206	-0.23500	0.19294	506.56397	200	2.30103
	c_2	-3286.6853119	-0.04616	-0.23120	0.18504	485.82252	128	2.10721
	c_3	-3286.6815839	-0.04069	-0.23699	0.19630	515.38565	280	2.44716
	d_1	-3226.7425413	-0.03691	-0.22905	0.19214	504.460023	400	2.60206
	d_2	-3226.7408792	-0.03080	-0.22339	0.19259	505.645045	386	2.58659
	d_3	-3226.7422464	-0.03962	-0.22671	0.18709	491.204795	380	2.57978
	d_4	-3226.7413883	-0.03908	-0.22323	0.18415	483.485825	360	2.55630
	d_5	-3226.7420546	-0.03687	-0.23010	0.19323	507.325365	400	2.60206
	e_1	-5760.960438	-0.04380	-0.23462	0.19082	500.99791	124	2.09342
	e_2	-5760.9601324	-0.04776	-0.23444	0.18668	490.12834	88	1.94448
	f_1	-3391.9840696	-0.09870	-0.25140	0.15270	400.91385	12	1.07918
	f_2	-3391.9835342	-0.10039	-0.25407	0.15368	403.48684	24	1.38021
	g_1	-3262.6567364	-0.03386	-0.22421	0.19035	499.763925	48	1.68124
	g_2	-3262.6618251	-0.03918	-0.22181	0.18263	479.495065	42	1.62325

variables. The high values of E_{HOMO} are likely to indicate a tendency of the molecule to donate electrons to appropriate acceptors and the lower value of E_{LUMO}, the more probable, it is the molecule would accept electrons[15]. So the values of the ΔE_{gap} show that higher efficiency can be related to a lower energy difference. A large ΔE_{gap} implies high stability for the molecule in the sense of its lower sensitivity in the biochemical processes.

Especially in the same series, where their have same substituent but different substitution position, a better linear

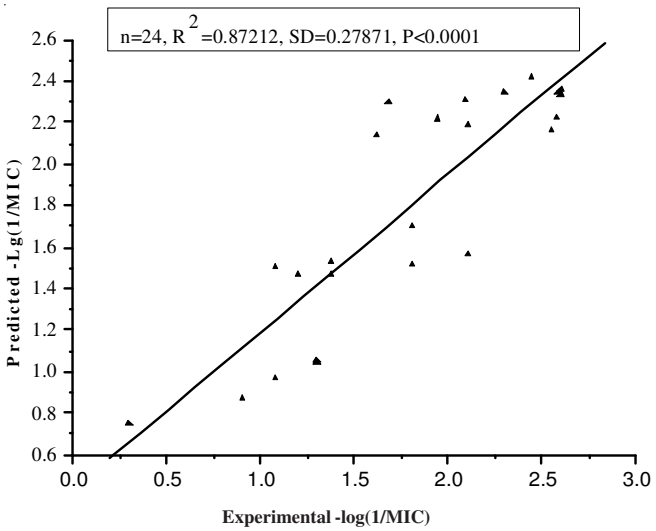


Fig. 1. Relationships between the -log(1/MIC) values from experiment and prediction based on QSAR equations

relationships were found (Figs. 1 and 2), such as $\mathbf{a_1}$-$\mathbf{a_5}$ the R^2 = 0.90115. The same regularity also showed in the series "b" (R^2 = 0.95704) and "d" (R^2 = 0.91897).

The QSAR models also show that the descriptors derived from DFT and linear regression analysis method can successfully be utilized to predict the antibacterial activity of the diphenyl ethers. A series of new diphenyl ethers $\mathbf{a_6}$-$\mathbf{a_{19}}$, which have same substituent but different substitution position, were designed and their structure showed in **Scheme-III**.

The geometry optimizations and energy calculations of new designed diphenyl ethers was done first. Used the QSAR equation, the biological activity of new diphenyl ethers bactericide were predicted and the result shown in Table-3. The calculated results show that $\mathbf{a_7}$, $\mathbf{a_6}$ and $\mathbf{a_{15}}$ (Table-3 entry 2, 3 and 10) have lower MIC, so they were chosen as a target for the research work of synthesis and antibacterial activity test. Dihydroxy nitro diphenyl ethers were prepared by williamson reaction and then demethoxylation by HBr to give three new diphenyl ethers (**Scheme-IV**).

The structures of the new targets were confirmed by ^{1}H NMR, IR and MS spectra. Their biological activity was tested by the agar dilution method also. To our interest, the MIC data of the $\mathbf{a_7}$, $\mathbf{a_6}$ and $\mathbf{a_{15}}$ are similar to predictive value (Table-3 entry 2, 3 and 10). Almost similar data of predicted and experimental biological activity fully proved the reliability and correctness of 2D-QASR equation. The antibacterial activities of the diphenyl ethers are highly dependent on the ΔE_{gap} of the drug as measured by the electronic descriptor, *i.e.*, ΔE_{gap} is an important stability index.

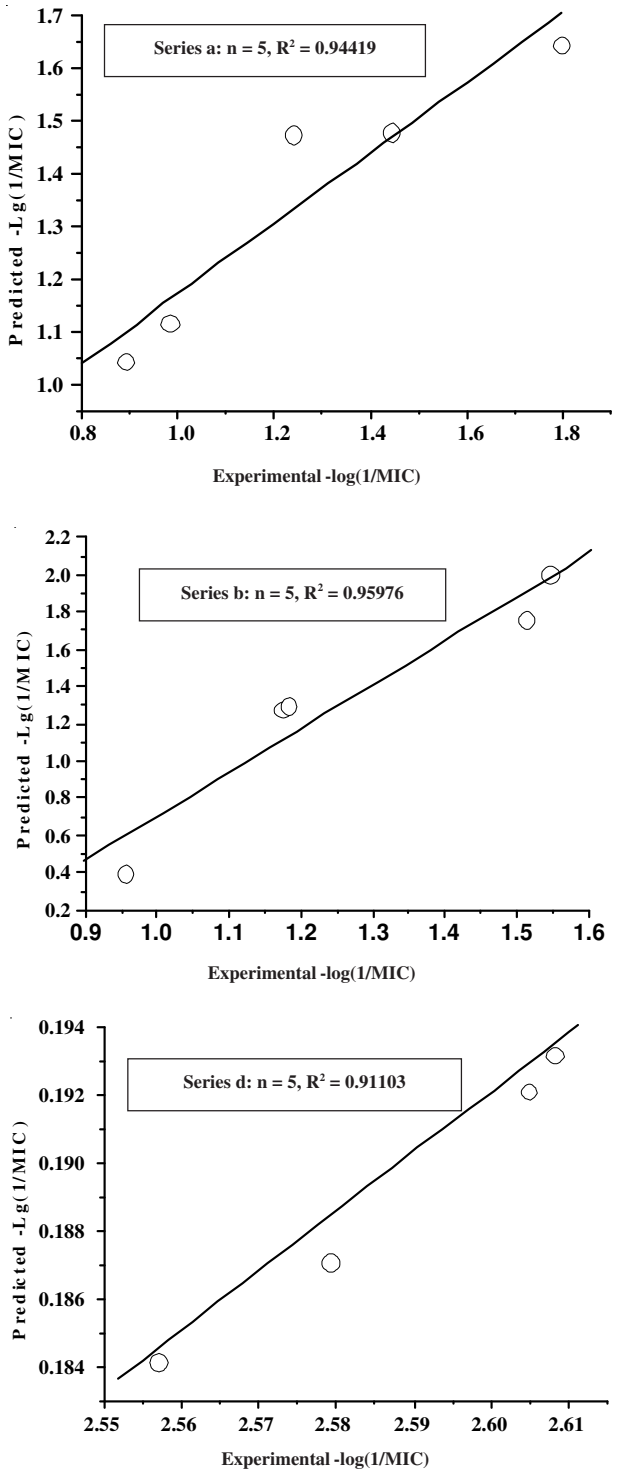
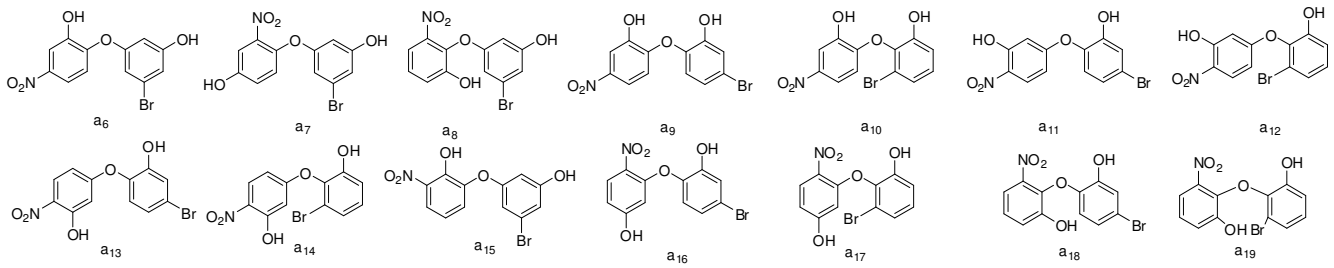


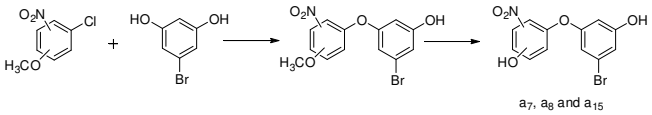
Fig. 2. Relationships between the -log(1/MIC) from experiment and prediction in same series based on QSAR equations



Scheme-III: Nnew designed diphenyl ethers compound

TABLE-3
CALCULATED ENERGY AND PREDICTED ANTIBACTERIAL ACTIVITY OF NEW DIPHENYL ETHERS

Compound	HF (Hartree)	E_{HOMO} (Hartree)	E_{LUMO} (Hartree)	ΔE_{gap} (Hartree)	Predicted activity -log(1/MIC)	Predicted MIC (μg/mL)	Expt. MIC (μg/mL)
$\mathbf{a_6}$	-3467.2300951	-0.10328	-0.25532	0.15204	1.4831	30	–
$\mathbf{a_7}$	-3467.2168032	-0.10557	-0.24608	0.14051	1.2417	17	16
$\mathbf{a_8}$	-3467.2141501	-0.10147	-0.24109	0.13962	1.2231	17	16
$\mathbf{a_9}$	-3467.2277055	-0.09814	-0.25054	0.15240	1.4906	31	–
$\mathbf{a_{10}}$	-3467.2252824	-0.09588	-0.24842	0.15254	1.4936	31	–
$\mathbf{a_{11}}$	-3467.2351969	-0.10731	-0.25602	0.14871	1.4134	26	–
$\mathbf{a_{12}}$	-3467.2317537	-0.10623	-0.2593	0.15307	1.5047	32	–
$\mathbf{a_{13}}$	-3467.2343426	-0.10829	-0.25624	0.14795	1.3975	25	–
$\mathbf{a_{14}}$	-3467.2325464	-0.10533	-0.25754	0.15221	1.4867	31	–
$\mathbf{a_{15}}$	-3467.2303465	-0.12215	-0.24557	0.12342	0.8839	8	8
$\mathbf{a_{16}}$	-3467.2170951	-0.08789	-0.24965	0.16176	1.6866	49	–
$\mathbf{a_{17}}$	-3467.2138073	-0.08533	-0.2525	0.16717	1.7999	63	–
$\mathbf{a_{18}}$	-3467.2078235	-0.09234	-0.23917	0.14683	1.3740	24	–
$\mathbf{a_{19}}$	-3467.2045143	-0.09193	-0.23835	0.14642	1.3654	23	–



Scheme-IV: Synthesis route of the new diphenyl ethers compound

Conclusion

In summary, the quantitative structure–activity relationships of diphenyl ethers derivatives have been studied. The quantum chemical parameters of diphenyl ethers were calculated at the B3LYP/6- 311G** level, based on which the QSAR model of -log(1/MIC) was proposed. The QSAR equation have better stability ability judging from the values of R^2 (0.877212), SD (0.27871), $p < 0.00010$ and F-value (45.081). Base on QSAR equation, the biological activity of series new designed diphenyl ethers were predicted. Three new diphenyl ethers, which were calculated to have better biological activity, were synthesized and characterized. The biological activity test results further confirm the reliability and good predictive ability of QSAR model.

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