Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

QSAR of antioxidant activity of some novel sulfonamide derivatives

Shaymaa H Abdulrahman*[1], Rawya Z Al-khayat[2], Ali younis Alhamdany[2], and Wasan Kh. Ali[1]

[1]Department of Chemistry, College of Sciences, University of Mosul, Mosul, Iraq
[2]Department of Chemical and Oil Industries,Northern Technical University, Mosul Technical Institute, Mosul,Iraq

Abstract

Development in discovery new drugs as antioxidants is still take a large interest between the scientists because oxidative stress has been caused a wide range of diseases such as chronic obstructive pulmonary disease (COPD), atherosclerosis, cancer and Alzheimer disease. In this article, we have been chosen benzene sulphonamide derivatives which had been synthesized and evaluated as anti-oxidants for QSAR study. We made mathematical relationship between (AOs) and three descriptors log(ω) electrophilicity, SCF and Mol Refractivity (IC_{50} = - 6.38 - 9.26 log (ω)- 0.00173 SCF - 0.235 Mol Refractivity). By this equation, the values of experimental (IC_{50}) and estimated (IC_{50}) using the QSAR model have the convergence between the two values. By using QSAR model we predict new compounds have effectiveness as antioxidants. For example, **2g** and **2j** which have (calculated IC_{50} =0.33578 and 0.3412), respectively.

Keywords: QSAR, antioxidant activity, sulphonamide derivatives, molecular descriptors

1. Introduction

2. The microbial invasion can produce Reactive-Oxygen-Species (ROS)[1] Excess ROS can lead to oxidative stress. [2] Oxidative stress has been caused a wide range of diseases such as chronic obstructive pulmonary disease (COPD), atherosclerosis, cancer and Alzheimer disease. [3-5] Oxidative stress occurs due to an imbalance between production of oxidants and antioxidant defences and it damages biological systems. There are many mechanism explain oxidants contribute to cellular damage. [5, 6] So the scientists are trying to discover new antioxidants which are molecules that fight free radicals in the cell and minimise oxidative stress. [7] From these compound sulphonamide derivatives (SO2-NH-), which are very important class in drug. The different functional groups in these compounds are responsible for their activity. They are quite stable and well tolerated in humans beings.[8] sulphonamides are very important in several types of antibacterial,[9-11] hypoglycaemic,[12] diuretic,[13, 14] antibacterial,[15] anticarbonic anhydrase,[16] antithyroid in vitro and in vivo, anti-inflammatory,[17-19] anticancer,[20, 21] Anti HIV, [22] antioxidant,[23] anticonvulsant,[24] antitrypanosomal,[25] antitrypanosomal, [25] and antihypertensive.[26]

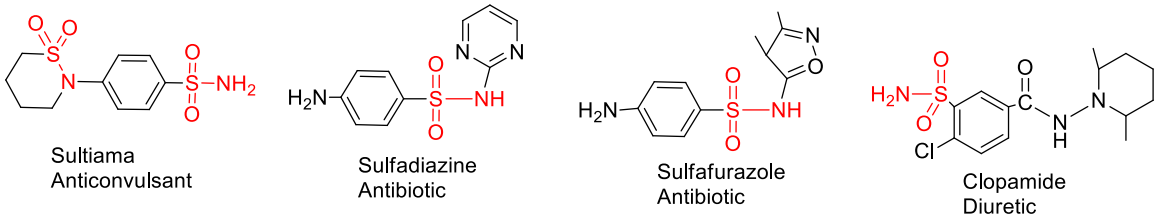


Figure 1: Examples of drugs synthesized from sulphonamides derivatives.

*Corresponding author e-mail: shaymaa.hashim@uomosul.edu.iq.; (Shaymaa H Abdulrahman).
Receive Date: 28 November 2021, **Revise Date:** 10 January 2022, **Accept Date:** 11 January 2022
DOI: 10.21608/EJCHEM.2022.108438.4957

Meanwhile, One of the most extensively utilized computational methods for designing pharmaceuticals and predicting pharmacological actions is quantitative structure activity relationships (QSARs).[27] (QSARs) are mathematical linear equations that aid in discovering and utilizing the relationship between molecular features and chemical, biological, toxicological, or other sorts of activities or attributes..[28] The target attribute of novel related compounds can be predicted using QSAR. As a result, strong and well-validated QSAR models can aid in the rational design of compounds with better activity, selectivity, safety, and/or physicochemical profile. [29, 30]

1- Computational methodology:

In this research, a data set of benzene sulphonamide derivatives which had been synthesized and evaluated as anti-oxidants has been selected for QSAR study.[31] In order to find factors that is directly related to their biological activity, through which mathematical models have been designed and the prediction of new compounds with biological effect.

In order to get on the best results of properties, one must follow the different steps in calculations including draw the structure of compounds. All molecules after built up by 2D Chemdraw then to ChemOffice Software were minimize their energy by using molecular mechanic MM2, then MMFF94. The reduction process is repeated until the root mean square (RMS) gradient value falls below 0.1 kcal/mol. Consequently, optimizations have been completed for those conformers through employing a semi-empirical method based on the Parameterized Model number3 (PM3). For optimization, the RHF wave function (restricted Hartree–Fock: closed shell) has been used until the root mean square (RMS) gradient was less than 0.01 kcal/mol.

Afterward, optimization structure and energy of the most stable conformer of the molecules, the next step was calculating of many of physical properties of compounds and also have been calculated the εHOMO, εLUMO, band gap Eg, hardness η, chemical potential μ, softness S, electronegativity χ, electrophilicity ω, and many descriptors.

Minitab release 14.1, was used for regression analysis of the calculated data. Firstly, a general correlation matrix that gathered all calculated properties has been done and that affected the biological activities properties. Really, such a matrix will be very useful in order to scrutinize if the existence of any combination between the calculated parameters with each other. Secondly, using this software, the varied combinations of descriptors were submitted to stepwise multiple linear regression analysis. The independent variables are individually added or eliminated from the model at each step of the regression based on the fisher ratio at the worth decided to enter and remove until the 'best' model is established in stepwise multiple linear regression analysis.

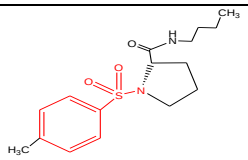
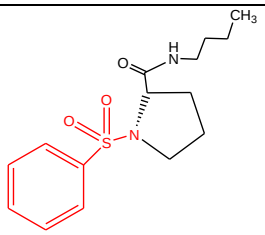
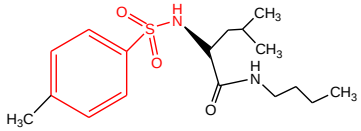
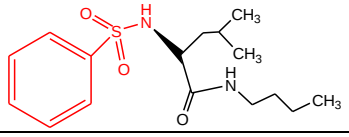
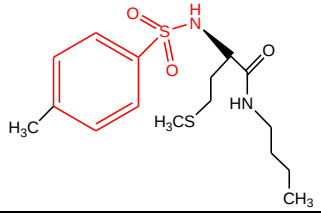
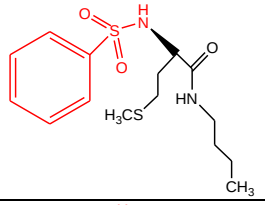
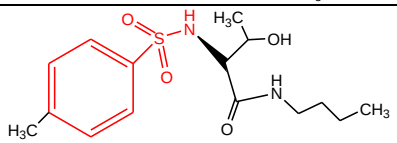
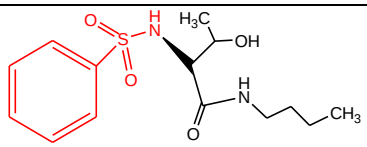
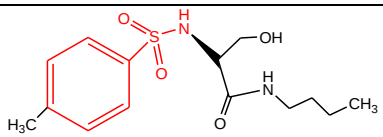
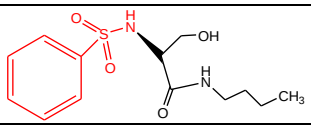
Thirdly, analysis of the results by using regression analysis based on the results of the stepwise to obtain the linear equation, and find the best models are summarized in statistical qualities of the models were reached by parameters like correlation coefficient (r), standard deviation SD, adjusted squared correlation coefficient (r2), and cross-validation (q^2). Another point is using the best subsets regression statistical method which is regarded as an effective method for identifying models that accomplish the goals with the fewest possible predictors Subset models can estimate regression coefficients and predict future responses with less variation than full models with all factors. Then, using the multiple regression analysis in order to find the relationship between activity and two descriptors or more. Finally, after regression analysis, the relationship between experimental and calculated bioactivity (Fitted values) has been drawn.

Multilinear regression statistical analysis was performed to develop the optimum QSAR equation for predicting (IC_{50}). The analysis was carried out utilising the backward technique in the Minitab programme. The original data for sulfonamide derivatives was optimized in this study by selecting the independent and dependent factors that impact the QSAR equation. The independent variable was (IC_{50}) data, and the independent variables were a mixture of electrophilicity (ω), The self-consistent field (SCF), and Mol Refractivity. The output data is subjected to multilinear regression analysis using statistical metrics such as the correlation coefficient r, r^2, standard deviation (SE), and cross validation (q^2). After considering the statistical data, the model is selected.

2- Results and Discussion:

Table 1, shown the chemical structures of benzene sulphonamide derivatives and experimental IC_{50} (mg/ml) as anti-oxidants.[31]

Table 2 shown the modelling for all the molecules and calculate descriptors using PM3 and HF 6-311 G (d,p) bases set calculations.

Comp. No.	Compounds structure	0.05 mg/mL (%)	0.10 mg/mL (%)	0.15 mg/mL (%)	0.20 mg/mL (%)	0.25 mg/mL (%)	IC_{50} (mg/mL)
1a		2.44	7.07	9.90	14.91	19.15	0.5358
1b		3.34	8.61	13.50	17.74	22.24	0.5080
1c		1.54	6.94	10.28	13.37	23.14	0.3799
1d		2.57	7.46	10.93	15.94	20.18	0.5294
1e		2.83	8.23	13.24	22.62	32.13	0.3287
1f		3.31	7.76	10.58	14.31	18.91	0.4779
1g		2.06	4.76	7.58	11.43	13.88	0.8475
1h		2.19	6.17	9.25	14.91	20.18	0.5250
1i		2.31	6.17	9.90	14.65	21.72	0.4653
1j		3.34	9.00	13.24	19.28	22.75	0.5826
	Vitamin C	**11.31**	**21.85**	**34.32**	**48.20**	**60.15**	**0.2090**

*Eze et al 2019: Table 1 the chemical structures and IC_{50} (mg/ml) for the studied compound

Table 2: The descriptors calculated for the studied compounds

Com. No. Descriptors	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j
HOMO (ev)	-0.33986	-0.33575	-0.33432	-0.33995	-0.33203	-0.33210	-0.33483	-0.33460	-0.33517	-0.33531
LUMO (ev)	-0.00316	-0.00276	-0.00309	-0.00268	-0.00352	-0.00355	-0.00244	-0.00318	-0.00370	-0.00370
GAP (ev)	0.30818	0.32969	0.32334	0.30331	0.28514	0.28549	0.30239	0.30142	0.30145	0.30161
Log P	2.363	1.876	3.321	2.834	2.421	1.934	1.551	1.063	1.232	0.745
Electrophilicity	0.11982	0.12403	0.14783	0.12289	0.10833	0.11337	0.10776	0.13559	0.10201	0.10393
Chemical pot.	-0.18577	-0.19251	-0.19265	-0.19934	-0.17777	-0.17829	-0.18641	-0.18893	-0.19944	-0.19508
Hardness	0.10905	0.10864845	0.10167	0.10665	0.10425 7	0.10427 45	0.10619 6	0.10571 2	0.10573 25	0.10580 5
Dipole (Debye)	6.7229	3.7273	3.2396	3.5368	5.4 07	5.0558	2.0854	4.6809	5.9402	4.3013
RMS (Kcal/Mol)	0.0016	0.0012	0.003	0.0022	0.001	0.0012	0.0011	0.0028	0.0017	0.0008
SCF (Kcal/Mol)	-111.96	-103.47	-128.07	-120	-115.05	-105.28	-155.83	-150.79	-154.04	-143.72
Connolly Acc. Area (A°2)	575.486	491.812	651.765	595.997	642.105	611.282	576.32	572.973	488.336	545.915
Connolly Molec. Area(A°2)	315.741	274.644	397.534	328.599	355.905	337.299	314.113	310.706	263.699	291.602
Connolly Sol.Excl.Vol.(A°3)	293.139	288.257	405.211	307.489	327.421	310.765	298.844	274.82	226.241	253.522
Ovality	1.47956	1.30147	1.55788	1.49152	1.54922	1.52023	1.45313	1.51996	1.46862	1.50532
Molar Refractivity (cm^3/mol)	8.7948	8.331	9.436	8.9722	9.7785	9.3147	8.6615	8.1977	8.1977	7.7339
Partition Coeff.	3.192	2.693	3.8992	3.4002	2.5902	2.0912	1.7704	1.2714	1.4614	0.9624
Molecular Volume (bohr**3/mol)	3186.29	2242.72	2794.24	3018.37	3053.77	3421.8	2724.23	2466.62	2630.06	2552.46
Entropy(Cal/Mol.K)	136.095	130.191	150.251	138.55	152.243	145.29	142.99	136.87	135.774	129.781
Therm. Energy (Kcal/Mol)	271.163	251.675	305.603	285.379	287.09	267.609	269.94	250.719	249.993	230.984
Zero-Point Energy(Kcal/Mol)	259.887	241.166	292.584	272.786	274.093	255.475	257.792	239.462	238.829	220.701
Balaban Index	363604	289534	664821	534783	674979	543607	537960	428009	443500	349452
Cluster Count	22	21	23	22	23	22	22	21	21	20
Mol.Top.	8340	7259	9733	8540	9629	8448	8372	7285	7539	6524

Index										
Pol.Sur.Area (A°^{2})	66.48	66.48	75.27	75.27	75.27	75.27	95.5	95.5	95.5	95.5
Shape Attribute	20.0455	19.0476	21.0435	20.0455	21.0435	20.0455	20.0455	19.0476	19.0476	18.05
Sum of degrees	46	44	46	44	46	44	44	42	42	40
Sum of Val. degrees	68.6667	66.6667	68.6667	66.6667	67.3333	65.3333	70.6667	68.6667	68.6667	66.6667
Topological Diameter (bonds)	13	12	13	12	13	12	13	12	13	12
Total Connect.	0.000709	0.000868	0.001002	0.001228	0.000868	0.001063	0.001418	0.001736	0.001736	0.002126
Wiener Index	1092	952	1272	1118	1292	1137	1125	982	1018	884

By using the Minitab and statistical methods to analysis and simulate of all descriptors with the (AO) activity. We conclude that cannot find mathematical relationship between all of them. So we carry out the filtering process for these descriptors by relied on the matrix result.

The correlation matrix shows the relationship between two variables and the best measure performs when the variables are connected in a linear fashion. Table 3 lists the descriptors after filtering and we obtain the mathematical relationship between (AOs) and three descriptors as shown in eq. (1):

$$\mathbf{IC_{50} = - 6.38 - 9.26 \log (\omega) - 0.00173\ SCF - 0.235\ Mol\ Refractivity} \quad \text{---------(1)}$$

n= 8 r^2 = 96.4 % q^2 = 93.6 % SE = 0.0396

The eq. (1) denotes the best QSAR model for sulfonamide derivatives. The predictive power of QSAR models is calculated by internal and external validate-using the methods of leave-one-out (LOO).

Statistical metrics of cross validation coefficients also validated the training and test sets' prediction capacity (q2). Three descriptors employed in the model have a strong link with (AO) bioactivity. (IC50). The result shows that (IC50) depends on these descriptors, so the (ω) is calculated from the orbitals energy using the eq. (2) below:

$$\omega = \mu^2 / 2\eta \quad \text{----------(2)}$$

Where μ is the chemical potential & it is calculating by eq. (3)

$$\mu = 0.5\ (\varepsilon_{HOMO} + \varepsilon_{LUMO}) \quad \text{----------(3)}$$

η is the Hardness that calculate by eq. (4)

$$\eta = 0.5\ (\varepsilon_{HOMO} - \varepsilon_{LUMO}) \quad \text{----------(4)}$$

From the model we can conclude that an electronic variable, (ω), SCF represents The self-consistent field approach for calculating a quantum many-body system's ground state wave function. As well as the Molar Refractivity, which is a measure of a compound's overall polarizability and is affected by temperature, pressure, and index of refraction. The Molar Refractivity is one of the most influenced attributes on the (IC50).

Table 4 indicates the values of experimental (IC50) and estimated (IC50) using the QSAR model. It shows the convergence between the two values and the presence of a slight difference that can be neglected.[32]

Table4. Shown the experimental (IC_{50}) and calculated (IC_{50})

Compound)	Experimental (IC_{50}) mg/mL	Calculated (IC_{50}) mg/mL	Residual error	[Residual error]^2
1a	0.5358	0.5598	-0.0240	0.0005760
1b	0.3799	0.3378	0.0421	0.0017724
1c	0.5294	0.5211	0.0083	0.0000689
1e	0.3287	0.3760	-0.0473	0.0022373
1f	0.4779	0.4495	0.0284	0.0008066
1g	0.8475	0.8396	0.0079	0.0000624
1i	0.4653	0.4911	-0.0258	0.0006656
1j	0.5826	0.5722	0.0104	0.0001082
PRESS			0.000787175	

By using QSAR model we can predict new compounds have effectiveness as antioxidants and apply all the steps of the theoretical calculation to calculate descriptors of the proposed model.[27] The new compounds are derived from compounds 1a-c and 1e by replacement CH3 in butyl group by NH2, OH or H to give compounds 2a-l respectively. Table 5From table 5, there is a difference in the values of the theoretical (IC50) between the compounds. This difference is due to the different electrophilicity values, SCF, and the mol refractivity.

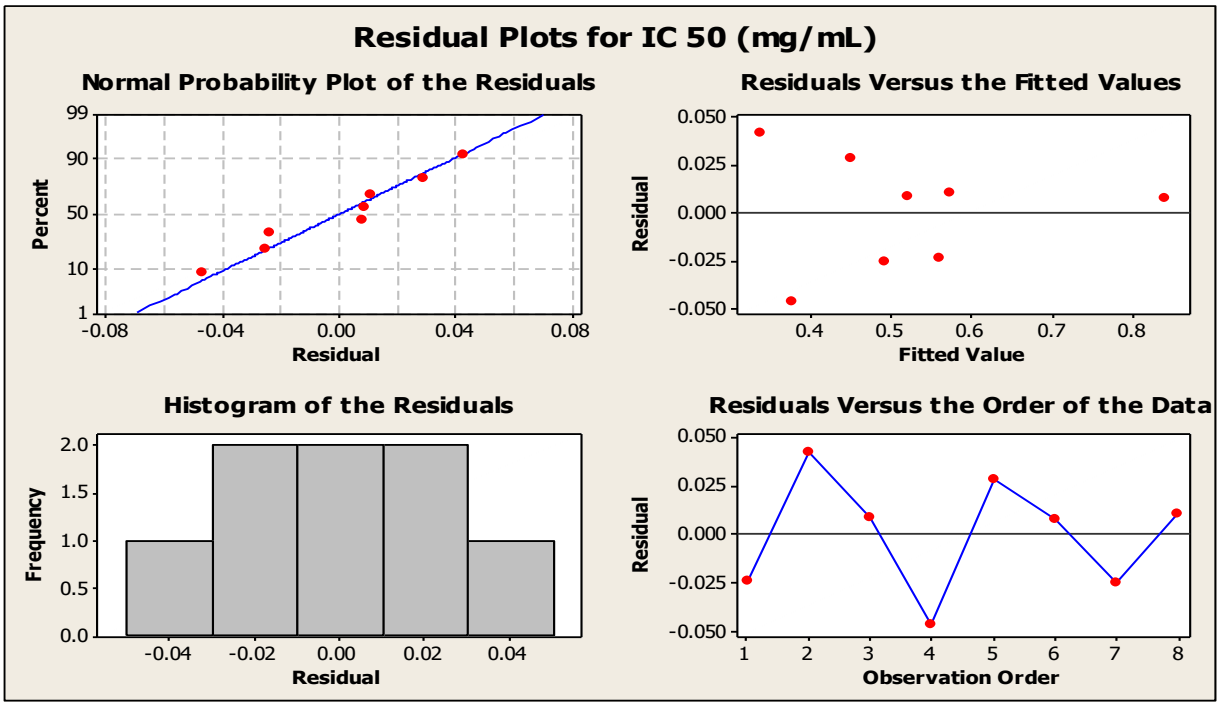
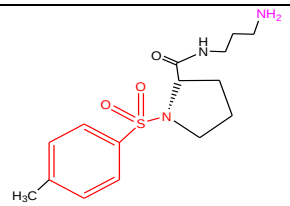
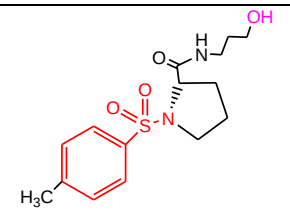
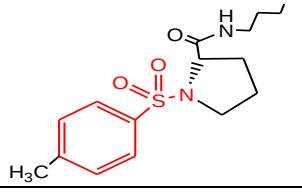
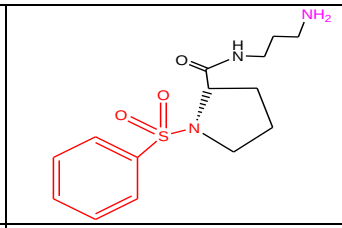
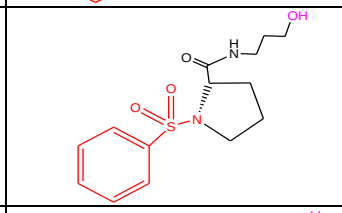
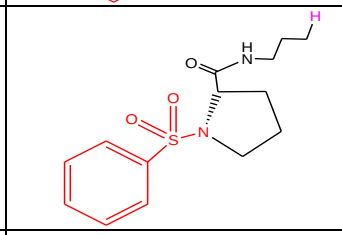
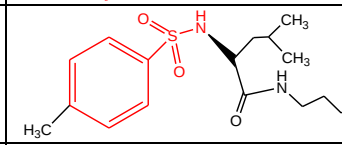
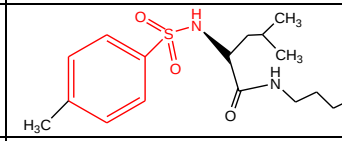
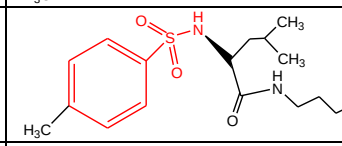
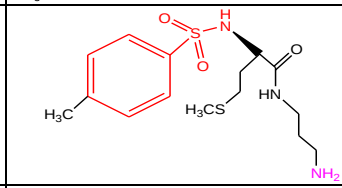
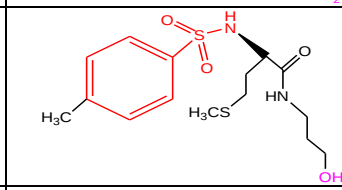
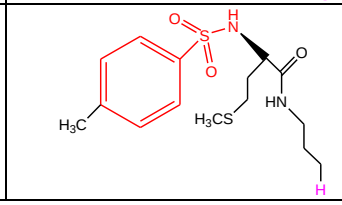


Fig (1): Residual plots for IC 50 (mg/mL)

The compounds 2g and 2j showed the lowest values of IC50 (calculated IC50 =0.33578 and 0.3412), respectively, which proves and confirms the success of the mathematical model, where the lower the value of (IC50) meaning the least amount of the compound gives the highest effectiveness. This activity may be due to the presence of the amine group as a compensator which has a medicinal character and biological activity. [33, 34] It is also possible to suggest many other compounds and calculate their effectiveness theoretically through the proposed model based on the available data.

Table 5: The predicted compounds and their important descriptors with calculated (IC_{50}) by the model of QSAR

NO.	COM.	ε_{HOMO}	ε_{LUMO}	Electro-philicity (ω)	Log(ω)	Mol.Ref	SCF	IC_{50}
2a		-0.36665	-0.085	0.181064	-0.74217	8.6997	-99.56	1.37972
2b		-0.3558	-0.02771	0.112073	-0.9505	8.4841	-145.15	0.67897
2c		-0.3558	-0.0273	0.111694	-0.95197	8.331	-106.72	0.66209

2d		-0.3565 8	-0.0255 2	0.11025 2	-0.9576 1	8.331	-89.79	0.6850 4
2e		-0.3579 4	-0.0282 3	0.11307 5	-0.9466 4	8.0203	-135.3 8	0.7352 8
2f		-0.3561 1	-0.0280 5	0.11246 3	-0.9489 9	7.8672	-96.86	0.7264 1
2g		-0.3451 8	-0.0329	0.11443 6	-0.9414 4	9.3409	-111.6 7	0.3357 8
2h		-0.3494 1	-0.0320 5	0.11462 7	-0.9407 1	9.1253	-157.4 7	0.4589 9
2i		-0.3478 6	-0.0321 1	0.11430 9	-0.9419 2	8.9722	-118.8 2	0.4392 7
2j		-0.3206 4	-0.0357 9	0.11149 9	-0.9527 3	9.6834	-100.8 9	0.3412
2k		-0.3215	-0.0361 2	0.11203 7	-0.9506 4	9.4678	-146.4 3	0.4513 2
2l		-0.3264 2	-0.0338 7	0.11092 9	-0.9549 6	9.3147	-108.9 2	0.4623 7

3- Conclusions

This study used a theoretical approach on a few molecular descriptors to create a model that might be used to link the structure of benzenesulfonamide derivatives as antioxidants to their biological activity. Internal and external validation using leave-one-out (LOO) approaches are used to determine the prediction potential of QSAR models. Statistical metrics of cross validation coefficients also validated the training and test sets' prediction capacity (q^2).

There is strong relationship between three descriptors which used in the model and (AO) bioactivity (IC_{50}). The result shows that (IC_{50}) depends on these descriptors. We used QSAR to predict new compounds have high effectiveness as antioxidants. QSAR model is robust, reliable and significant. QSAR model will be useful in medicinal chemists and pharmaceutical to design and synthesize novel antioxidants drugs.

4- Acknowledgments:

We would like to express our special and immense appreciation to the University of Mosul, College of Science, Dept. of Chemistry for his encouragement throughout this research.

5- References

[1] R. Spooner, Ö. Yilmaz, The role of reactive-oxygen-species in microbial persistence and inflammation, International journal of molecular sciences, 12 (2011) 334-352.

[2] M.L. Circu, T.Y. Aw, Reactive oxygen species, cellular redox systems, and apoptosis, Free Radical Biology and Medicine, 48 (2010) 749-762.

[3] G. Pizzino, N. Irrera, M. Cucinotta, G. Pallio, F. Mannino, V. Arcoraci, F. Squadrito, D. Altavilla, A. Bitto, Oxidative stress: harms and benefits for human health, Oxidative medicine and cellular longevity, 2017 (2017).

[4] I. Liguori, G. Russo, F. Curcio, G. Bulli, L. Aran, D. Della-Morte, G. Gargiulo, G. Testa, F. Cacciatore, D. Bonaduce, Oxidative stress, aging, and diseases, Clinical interventions in aging, 13 (2018) 757.

[5] H.J. Forman, H. Zhang, Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy, Nature Reviews Drug Discovery, (2021) 1-21.

[6] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, The international journal of biochemistry & cell biology, 39 (2007) 44-84.

[7] M.C. Santos, É.C. Gonçalves, Effect of different extracting solvents on antioxidant activity and phenolic compounds of a fruit and vegetable residue flour, Scientia agropecuaria, 7 (2016) 7-14.

[8] P. Shet, V. Vaidya, K. Mahadevan, M. Shivananda, S. Sreenivasa, G. Vijayakumar, Synthesis, Characterisation and antimicrobial Studies of novel Sulphonamides containing substituted naphthofuroyl group, Research Journal of Chemical Sciences, 3 (2013) 15-20.

[9] A. Ali, G.K.K. Reddy, H. Cao, S.G. Anjum, M.N. Nalam, C.A. Schiffer, T.M. Rana, Discovery of HIV-1 protease inhibitors with picomolar affinities incorporating N-aryl-oxazolidinone-5-carboxamides as novel P2 ligands, Journal of medicinal chemistry, 49 (2006) 7342-7356.

[10] A.J. McCarroll, T.D. Bradshaw, A.D. Westwell, C.S. Matthews, M.F. Stevens, Quinols As Novel Therapeutic Agents. 7. Synthesis of Antitumor 4-[1-(Arylsulfonyl-1 H-indol-2-yl)]-4-hydroxycyclohexa-2, 5-dien-1-ones by Sonogashira Reactions, Journal of medicinal chemistry, 50 (2007) 1707-1710.

[11] B.L. Wilkinson, L.F. Bornaghi, T.A. Houston, A. Innocenti, D. Vullo, C.T. Supuran, S.-A. Poulsen, Carbonic anhydrase inhibitors: inhibition of isozymes I, II, and IX with triazole-linked O-glycosides of benzene sulfonamides, Journal of medicinal chemistry, 50 (2007) 1651-1657.

[12] A.E. Boyd, Sulfonylurea receptors, ion channels, and fruit flies, Diabetes, 37 (1988) 847-850.

[13] C.T. Supuran, A. Scozzafava, Carbonic anhydrase inhibitors and their therapeutic potential, Expert Opinion on Therapeutic Patents, 10 (2000) 575-600.

[14] N. Hosseinzadeh, S. Seraj, M.E. Bakhshi-Dezffoli, M. Hasani, M. Khoshneviszadeh, S. Fallah-Bonekohal, M. Abdollahi, A. Foroumadi, A. Shafiee, Synthesis and antidiabetic evaluation of benzenesulfonamide derivatives, Iranian journal of pharmaceutical research: IJPR, 12 (2013) 325.

[15] S. Ali, A. Qasir, K. Saor, Synthesis of some sulfonamide derivatives with expected antibacterial activity, Iraqi J. Mark. Rec. Cons. Protection, 1 (2009) 85-93.

[16] D.J. Abraham, M. Myers, Burger's Medicinal Chemistry, Drug Discovery and Development, 8 Volume Set, John Wiley & Sons, 2021.

[17] A.A. Kadi, N.R. El-Brollosy, O.A. Al-Deeb, E.E. Habib, T.M. Ibrahim, A.A. El-Emam, Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1, 3, 4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1, 3, 4-thiadiazoles, European journal of medicinal chemistry, 42 (2007) 235-242.

[18] S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, A. Ranise, W. Filippelli, B. Rinaldi, A. Capuano, G. Falcone, New 1, 3, 4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities, Bioorganic & medicinal chemistry, 14 (2006) 1698-1705.

[19] T. Kushwaha, Synthesis of novel 2-benzylbenzo [d] thzole-6-sulfonamide derivatives as potential anti-inflammatory agent, J. Chem. Pharm. Sci, 7 (2014) 34-38.

[20] M.M. Ghorab, F.A. Ragab, H.I. Heiba, R.M. El-Hazek, Anticancer and radio-sensitizing

evaluation of some new thiazolopyrane and thiazolopyranopyrimidine derivatives bearing a sulfonamide moiety, European journal of medicinal chemistry, 46 (2011) 5120-5126.

[21] M.M. Ghorab, M.S. Bashandy, M.S. AL-SAID, Novel thiophene derivatives with sulfonamide, isoxazole, benzothiazole, quinoline and anthracene moieties as potential anticancer agents, Acta Pharmaceutica, 64 (2014) 419-431.

[22] N. Desai, A. Bhavsar, B. Baldaniya, Synthesis and antimicrobial activity of 5-imidazolinone derivatives, Indian journal of pharmaceutical sciences, 71 (2009) 90.

[23] M. Siddique, A.B. Saeed, S. Ahmad, N.A. Dogar, Synthesis and biological evaluation of hydrazide based sulfonamides, J Sci Innovative Res, 2 (2013) 627-633.

[24] N. Khan, L.K. Soni, A. Gupta, S. Wakode, R. Wagh, S. Kaskhedikar, QSAR analysis of N-Alkyl imidazole analogues as antibacterial agents, Indian journal of pharmaceutical sciences, 68 (2006).

[25] M.V. Papadopoulou, W.D. Bloomer, H.S. Rosenzweig, E. Chatelain, M. Kaiser, S.R. Wilkinson, C. McKenzie, J.-R. Ioset, Novel 3-nitro-1 H-1, 2, 4-triazole-based amides and sulfonamides as potential antitrypanosomal agents, Journal of medicinal chemistry, 55 (2012) 5554-5565.

[26] J.-P. Liou, K.-S. Hsu, C.-C. Kuo, C.-Y. Chang, J.-Y. Chang, A novel oral indoline-sulfonamide agent, N-[1-(4-methoxybenzenesulfonyl)-2, 3-dihydro-1H-indol-7-yl]-isonicotinamide (J30), exhibits potent activity against human cancer cells in vitro and in vivo through the disruption of microtubule, Journal of Pharmacology and Experimental Therapeutics, 323 (2007) 398-405.

[27] C. Hansch, A. Kurup, R. Garg, H. Gao, Chem-bioinformatics and QSAR: a review of QSAR lacking positive hydrophobic terms, Chemical Reviews, 101 (2001) 619-672.

[28] A. Golbraikh, X.S. Wang, H. Zhu, A. Tropsha, Predictive QSAR modeling: methods and applications in drug discovery and chemical risk assessment, Handbook of computational chemistry, (2012) 1309-1342.

[29] C. Nantasenamat, C. Isarankura-Na-Ayudhya, T. Naenna, V. Prachayasittikul, A practical overview of quantitative structure-activity relationship, (2009).

[30] A. Cherkasov, E.N. Muratov, D. Fourches, A. Varnek, I.I. Baskin, M. Cronin, J. Dearden, P. Gramatica, Y.C. Martin, R. Todeschini, QSAR modeling: where have you been? Where are you going to?, Journal of medicinal chemistry, 57 (2014) 4977-5010.

[31] F.U. Eze, U.C. Okoro, D.I. Ugwu, S.N. Okafor, Biological activity evaluation of some new benzenesulphonamide derivatives, Frontiers in chemistry, 7 (2019) 634.

[32] I. Rahmawati, H.W. Amini, R.F. Darmayanti, Molecular modelling of antioxidant agent by QSAR study of caffeic acid derivatives, in: IOP Conference Series: Materials Science and Engineering, IOP Publishing, 2020, pp. 012001.

[33] S.D. Roughley, A.M. Jordan, The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates, Journal of medicinal chemistry, 54 (2011) 3451-3479.

[34] H. Ismail, B. Mirza, I.-u. Haq, M. Shabbir, Z. Akhter, A. Basharat, Synthesis, characterization, and pharmacological evaluation of selected aromatic amines, Journal of Chemistry, 2015 (2015).