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ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis and QSAR Study of Novel Oxadiazoles Having Antioxidant Activity

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ABSTRACT
Oxadiazole derivatives are an important class of heterocyclic compounds, reported to possess a wide spectrum of biological activities. Moreover, oxadiazole nucleus occupies a very important place in the field of antioxidant agents. The above observations prompted us to synthesize some novel oxadiazoles derivatives with various substitutions at along with heterocyclic rings in the same framework for synergistic action. We here in report the synthesis, antioxidant screening & QSAR studies of the new title compounds.Concentrated research on 2-[(substituted benzylidene) imino]-5-(4'-acetamidophenyl)-1,3,4 oxadiazole, 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole & were synthesized, screened for antioxidant activities & QSAR studies. All new entities have good yield & results. From antioxidant activity results, it was observed that the compounds with both electron donating and electron withdrawing groups on the aldehydic phenyl ring influenced the activity. Among all the compounds tested GS-8i-c, GS-8i-k, GS-9i-c, GS-9i-e and GS-9i-h showed the good % inhition and were found to be more significant compound among all the compounds tested. 2D & 3D-QSAR models with moderate to high predictive ability of oxadiazole derivatives were derived. The role of hydrophobicity as a 3D property was confirmed and also Electrostatic and Steric effects were found to contribute to antioxidant activity.
Key Words: Oxadiazole, antioxidant activity, 2D QSAR &3D QSAR.

INTRODUCTION

1,3,4-Oxadiazoles are a class of heterocyclic compounds which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities. Molecules containing a 1,3,4-oxadiazole core have been shown to have a broad range of important biological activities including anti-bacterial, anti-fungal, pesticidal, anti-mycobacterial, anti-inflammatory, anti-convulsant, insecticidal, anti-cancer, and anti-hypertensive properties.[1], [2] Among the 1,3,4-oxadiazoles, 2,5-unsymmetrical disubstituted derivatives have attracted considerable attention because of their biological and electrochemical properties.[3], [4] The widespread use of 1,3,4 -oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocycles. These molecules are also utilized as pharmacophores due to their favorable metabolic profile and ability to engage in hydrogen bonding.[5], [6], [7]

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. As a result, antioxidants are often reducing agents such as thiols, ascorbic acid or polyphenols.[8]

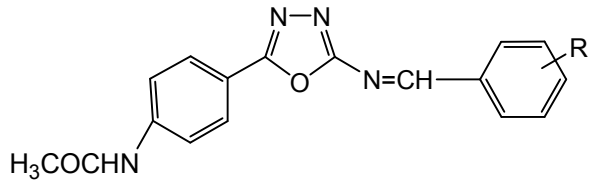
Majority of the diseases/disorders are mainly linked to oxidative stress due to free radicals. Antioxidant compounds like phenolic acids, polyphenols and flavonoids scavenge free radicals such as peroxide, hydroperoxide or lipid peroxyl and thus inhibit the oxidative mechanisms that lead to degenerative diseases. Considering the importance of this area, we have listed some important *in-vitro* models for evaluating antioxidant activity.[9]

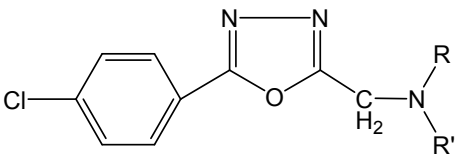
In simplest terms Quantitative Structure–Activity Relationship (QSAR) is a method for building computational or mathematical models which attempts to find a statistically significant correlation

between structure and function using a chemometric technique. In terms of drug design, structure were refer to the properties or descriptors of the molecules, their substituent's or interaction energy fields function corresponds to an experimental biological/biochemical endpoint like binding affinity, activity, toxicity or rate constants; While chemometric method include MLR, PLS, PCA, PCR, ANN, GA etc. The term 'quantitative structure–property relationship' (QSPR) is used when some property other than the biological activity is concerned. Various QSAR approaches have been developed gradually over more than a hundred years of time span and served as valuable predictive tools, particularly in the design of pharmaceuticals and agrochemicals.[10]

The methods have evolved from Hansch and Free-Wilson's one or two-dimensional linear free energy relationships via Crammer's three-dimensional QSAR to Hopfinger's fourth, Vedani's fifth and sixth dimensions. All one, two dimensional and related methods are commonly referred to as 'classical' QSAR methodologies. [11], [12] Every molecule included in the study binds to the same site of the same target receptor. However, the main difference between all these formalisms reside in the manner in which each one of them treats, represents structural properties of the molecules and extracts the quantitative relationships between the properties and activities. Due to the limited scope and space for this review, the author will focus only on the 3D-QSAR approaches in drug design. The antioxidant activity of this dataset is reported as IC_{50} values.

QSAR has shown that for hydrogen bond acceptors aromatic and hydrophobic are the important features for antioxidant activity. Antioxidant agents are becoming the area of choice for various researchers. We have taken QSAR studies of antioxidant drug to determine the activity which in turn depends further more on hydrophobic, steric or electrostatic parameters. We concentrated our research on synthesis, Antioxidant activity & 2D& 3D QSAR studies of 2-[(substituted benzylidene) imino]-5-(4'-acetamidophenyl)-1,3,4 oxadiazole, 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole.





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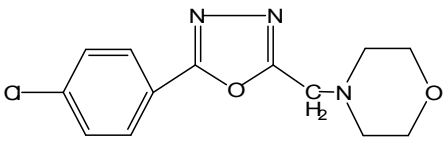
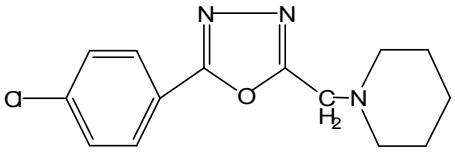




The newly synthesized compounds characterized by physical data, spectral analysis and were screened for their antioxidant activity for novel research.

MATERIAL AND METHODS

EXPERIMENTAL: SCHEME-I

4-Acetylaminophenyl hydrazide (GS-8):

A mixture of 4-carbethoxyacetanilide (20.7gm, 0.1 mole), hydrazine hydride (20 ml, 0.4 mole) and absolute alcohol (50 ml) was refluxed for 12 hr. Exess solvent was distilled off. The reaction mixture was cooled to 4-5^{o}C and solid crystals that separated were filtered, washed with cold water, dried and recrystallised from ethanol.

2-amino-5-(4'-acetamidophenyl)-1,3,4-oxadiazole (GS-8i):

A mixture of GS-8i (1.93gm,0.01 mol) and CNBr (1.58, 0.15 mol) in methanol(30ml) was refluxed for 3hr at 70^{o}C the reaction mixture was cooled and neutralized with $NaHCO_3$ and poured onto crushed ice. The solid product was isolated and recrystallised from DMF.[13]

General method for the syntheses of 2-[(substituted benzylidene) imino]-5-(p-acetamidophenyl)-1,3,4 oxadiazole GS-8i-(a-m):

A mixture of 2-amino-5-(p-acetamidophenyl)-1,3,4-oxadiazole(SSM-4) (0.01 mol), the required aryl aldehydes (0.01 mol) in isopropanol (30 ml) and catalytic amount
of glacial acetic acid (1ml) was subjected to reflux for 6 hr. The reaction mixture was cooled to room temperature. The solid separated was filtered, washed with isopropanol
and recrystallized with DMF: Water mixture(5:2) The new schiff bases formed were confirmed by MP, TLC, IR and representative compounds by NMR and Mass spectra.(*Table No-1:*) (*Fig. No.1)*

Fig. No.1 Scheme-I:2-[(substituted benzylidene) imino]-5-(p-acetamidophenyl)-1,3,4 oxadiazole GS-8i-(a-m)

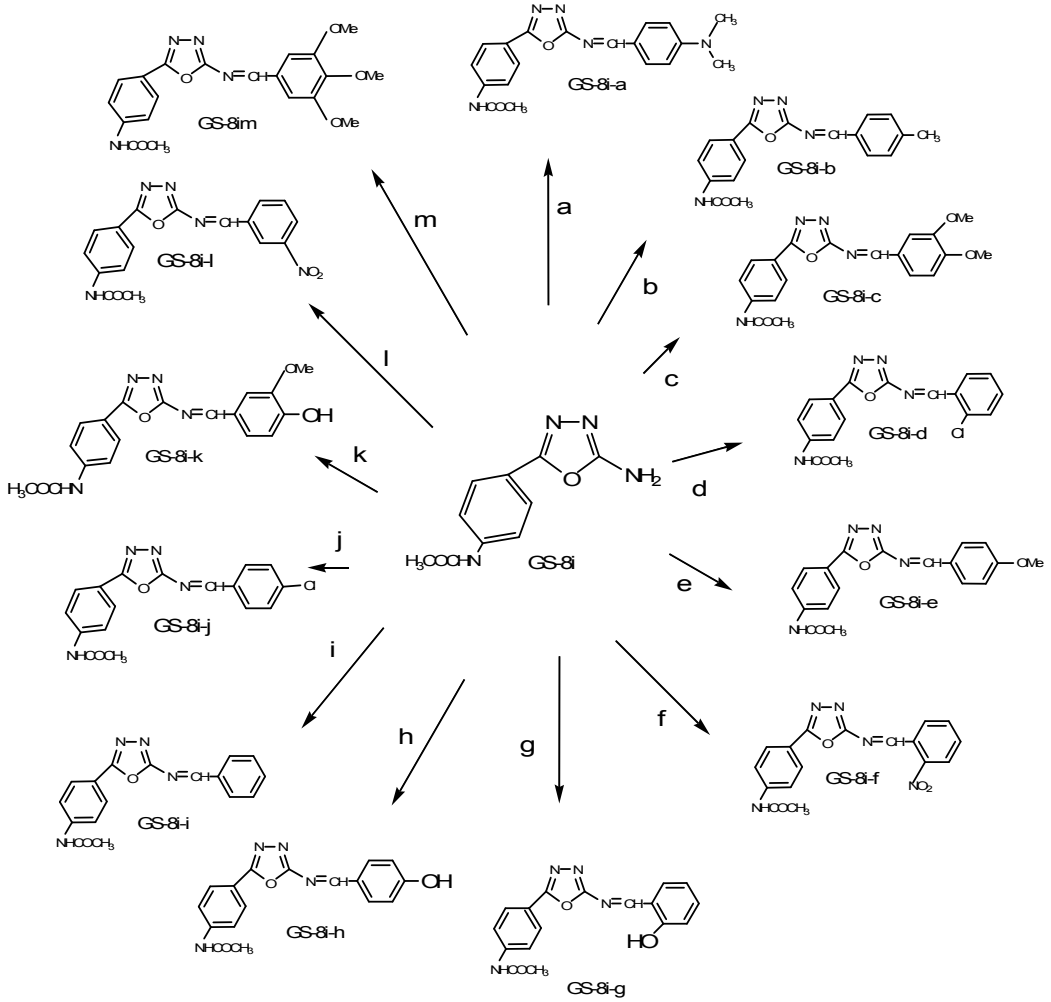


Table No-1: 2-[(substituted benzylidene) imino]-5-(p-acetamidophenyl)-1,3,4 oxadiazole

Comp. Code	R	Comp. Code	R
GS-8i-a	4-dimethylamino benzaldehyde	GS-8i-h	4-hydroxy benzaldehyde
GS-8i-b	4-methyl benzaldehyde	GS-8i-i	Benzaldehyde
GS-8i-c	3, 4-dimethoxy benzaldehyde	GS-8i-j	4-chloro benzaldehyde
GS-8i-d	2-chloro benzaldehyde	GS-8i-k	4-hydroxy-3-methoxy benzaldehyde
GS-8i-e	4-methoxy benzaldehyde	GS-8i-l	3-nitro benzaldehyde
GS-8i-f	2-nitro benzaldehyde	GS-8i-m	3, 4, 5-trimethoxy benzaldehyde
GS-8i-g	2-hydroxy benzaldehyde	-	--

EXPERIMENTAL: SCHEME-II

2-(chloromethyl)-5-(p-chlorophenyl)-1,3,4-oxadiazole (GS-9i):

The mixture of 4-Chlorophenylhydrazide (610 mg, 3.65 mmol), Chloroacetic acid (330 mg, 3.65 mmol) and Alumina (1.50 gm) were finely ground with a mortar and pestle. The mixture was taken in a conical flask, Phosphorous oxychloride (0.5 ml, 5.47 mmol) was added and heated in microwave oven at 1000 watt for 7 min. After completion of reaction, the mixture was cooled and poured into ice cold water. The precipitate was filtered and washed with 10% solution of $NaHCO_3$. Recrystallization was done by ethanol:water mixture (3:1). The same product was also obtained by conventional heating for 5-6 hours. The yield was better with microwave assisted method.

General method for the syntheses of 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole GS-9i-(a-i):

A mixture of 2-(chloromethyl)-5-(p-chlorophenyl)-1,3,4-oxadiazole (228 mg,1 mol) in dioxan (15 ml), triethylamine (0.2 ml,1.2 mol) and substituted primary and secondary amines (1.2 mol) was heated to reflux for 8 hours. Then the reaction mixture was cooled to room temperature and poured into ice water mixture and the excess amine was neutralized by dilute HCl (10%). The resultant precipitate thus

obtained was filtered, dried and recrystallised from Ethanol: Water mixture (3:1).[14], [15] *(Table No-2)(Fig no.2)*

Fig no.2 Scheme-II:2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole GS-9i-(a-i)

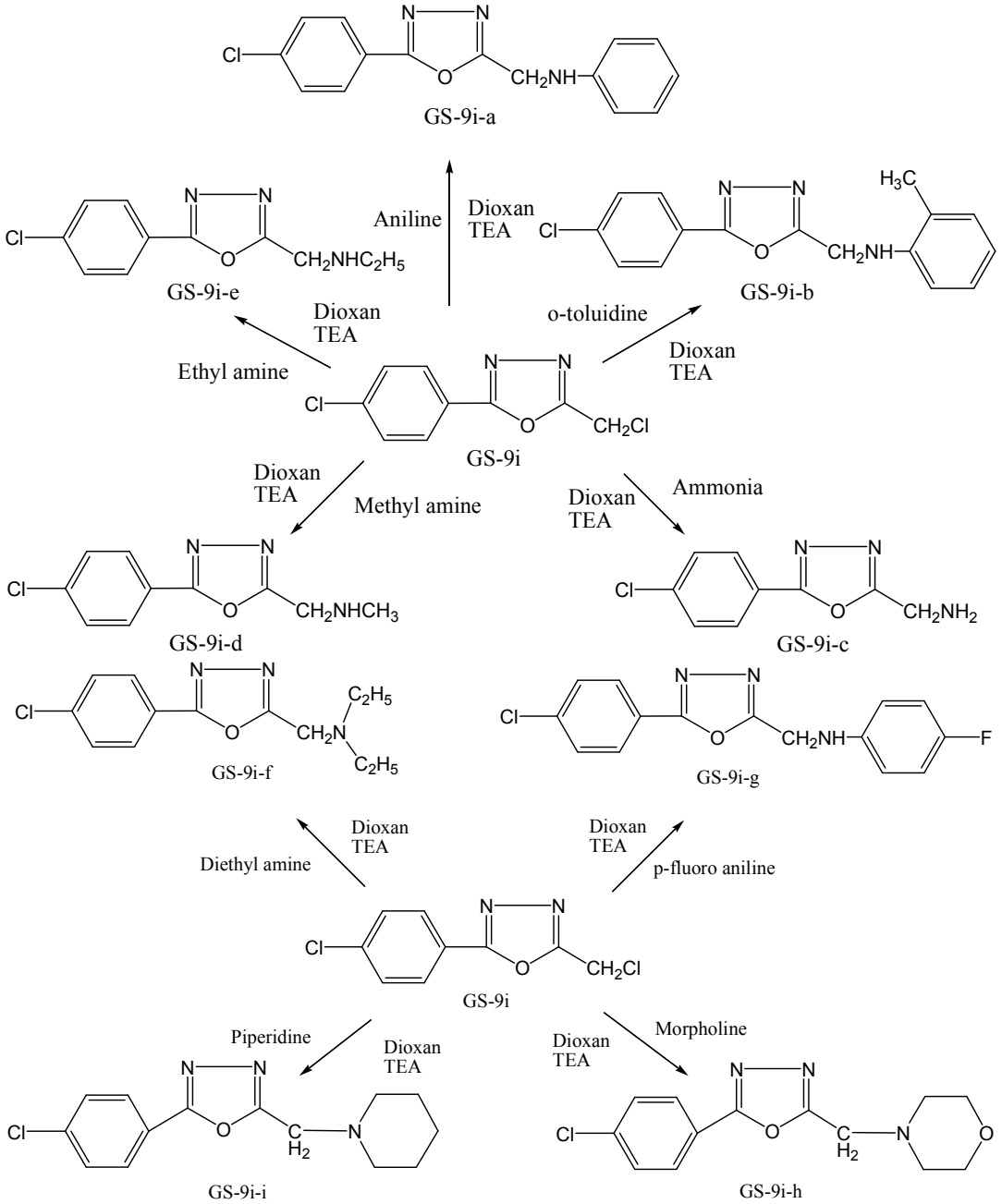


Table No-2: 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole

Compound Code	R	R'
GS-9i-a	H	Phenyl
GS-9i-b	H	2-methyl phenyl
GS-9i-c	H	H
GS-9i-d	H	Methyl
GS-9i-e	H	Ethyl
GS-9i-f	Ethyl	Ethyl
GS-9i-g	H	4-Fluoro phenyl
GS-9i-h	Morpholino	
GS-9i-i	Piperidino	

ANTIOXIDANT ACTIVITY

Screening of antioxidant activity:-

❖ To evaluate the antioxidant potential of all the compounds *in-vitro* free radical scavenging activity using Nitric oxide radical inhibition method:

Nitric oxide radical inhibition activity:

Nitric oxide radical inhibition can be estimated by the use of ***Griess Illosvoy reaction***. The procedure is based on the method, where sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide, which interacts with oxygen to produce nitrite ions that can be estimated using **Greiss reagent**. Scavengers of nitric oxide compete with oxygen leading to reduced production of nitrite ions.[16]

Procedure:

sodium nitroprusside (10 mM) in phosphate buffered saline was mixed with different concentrations (100-320 µg/mL) of synthesized compound were dissolved in DMSO and incubated at 25^0C for 150 min. The same reaction mixture without the synthesized compound but the equivalent amount of DMSO served as the control. After the incubation period, 0.5 ml of Griess reagent [1% sulfanilamide, 2% H_3PO_4 (*o*-phosphoric acid) and 0.1% naphthyl ethylenediamine] was added. The absorbance of the chromophore formed during the diazotization of nitrite with sulphanilamide and subsequent coupling with napthylethylenediamine was read at 546 nm. Inhibition of nitrite formation by the synthesized compound and the standard antioxidant ascorbic acid were calculated relative to the control. Inhibition data (percentage inhibition) were linearized against the concentrations of each synthesized compound and standard antioxidant (ascorbic acid). IC_{50} which is an inhibitory concentration of each synthesized compound required to reduce 50% of the nitric oxide formation was determined.[17]

$$\%\text{inhibition} = \frac{V_{control} - V_{sample}}{V_{control}} * 100$$

Where, V= absorbance

Preparation of Phosphate saline buffer Solution:

Dissolve 2.72 gms of potassium dihydrogen ortho phoaphate in 100 ml of distilled water. Dissolve 0.8 gms of NaOH in 100 ml of distilled water, pipette out 34.7 ml of NaOH solution mix with 50ml of potassium dihydrogen orthophosphate make upto 200 ml with distilled water.

Procedure for determining the IC_{50} value:

The percent inhibition values of oxidation were plotted against concentration and linear regression equation was obtained. IC_{50} values were obtained from the linear regression equation. By definition, IC_{50} which is an inhibitory concentration of each synthesized compound required to reduce 50% of the nitric oxide formation was determined.

%inhibition = (control-sample) / control×100.

y = mx+c.*(Table No-3)*

Table No 3- antioxidant activity data (Data represented as % Inhibition, IC_{50})

ANTIOXIDANT ACTIVITY

Sr. No	COMP. NO.	% OF INHIBITION				IC_{50}
		100	**200**	**300**	**Mean**	
1	GS-8i-a	50.2173913	61.12288136	73.28244275	61.54090514	99.94796184
2	GS-8i-b	51.63043478	62.5	78.73500545	64.28848008	94.58302583
3	GS-8i-c	60.54347826	73.09322034	84.95092694	72.86254185	12.66393443
4	GS-8i-d	50.76086957	61.44067797	75.13631407	62.44595387	97.85890074
5	GS-8i-e	49.67391304	62.5	69.68375136	60.61922147	93.91
6	GS-8i-f	57.2826087	74.15254237	82.76990185	71.40168431	32.0722135
7	GS-8i-g	56.73913043	59.95762712	75.13631407	63.94435721	48.40217391
8	GS-8i-h	49.23913043	62.28813559	79.38931298	63.63885967	109.4893899
9	GS-8i-i	50.2173913	61.97033898	69.57470011	60.5874768	90.59917355
10	GS-8i-j	48.58695652	58.26271186	75.13631407	60.66199415	119.7211756
11	GS-8i-k	57.2826087	69.17372881	78.40785169	68.28806307	26.8655303
12	GS-8i-l	42.17391304	65.99576271	75.35441658	61.17469744	132.6461724
13	GS-8i-m	39.7826087	60.16949153	64.99454744	54.98221589	160.4282316
14	GS-9i-a	59.56521739	64.40677966	87.78625954	70.58608553	54.11055989

15	GS-9i-b	48.04347826	61.01694915	68.37513631	59.14518791	109.9901672
16	GS-9i-c	58.26086957	67.26694915	79.17121047	68.23300973	25.59273423
17	GS-9i-d	58.58695652	68.43220339	84.40567067	70.47494353	41.39426801
18	GS-9i-e	52.60869565	55.19067797	58.77862595	55.52599986	20.90909091
19	GS-9i-f	50.76086957	63.77118644	72.62813522	62.38673041	86.74290942
20	GS-9i-g	52.7173913	65.99576271	74.70010905	64.47108769	68.35304823
21	GS-9i-h	58.36956522	73.09322034	81.67938931	71.04739162	19.41630901
22	GS-9i-i	47.5	68.8559322	77.31733915	64.55775712	161.1404435
23	Ascorbic acid	**58.91304**	**72.35169**	**83.31516**	**71.52663**	**23.56557±1.104*** **

Dose concentration: 100, 200, 300 µg/ml
Control : DMSO (Dimethyl sulfoxide)
Method : Nitric oxide scavenging method

2D and 3D QSAR

QSAR study involves data set consist of all synthetic derivatives having antioxidant activity. The antioxidant activity of this dataset is reported as IC_{50} values. The chemical structures were drawn in the 2D Draw App and converted to 3D, using V Life MDS 4.6 software (V Life sciences Pvt Ltd Pune). All structures were single point optimized using the MMFF94 force field and Gasteiger-Marsili charges, till gradient of 0.001kcal/A0 was reached. The optimized molecule should be aligned by template base alignment. The general structures and corresponding substitutions are included in table. Fig. No-3 & Fig. No-4

Fig. No-3:3D view of template based alignment of GS-8i-a to Gs-8i-m derivatives on the base template.

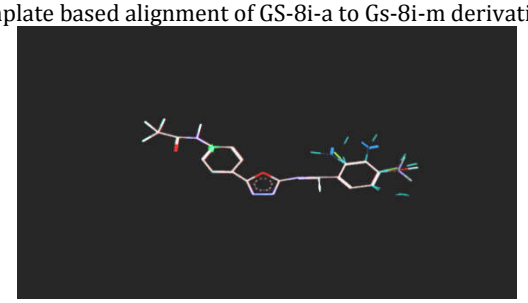
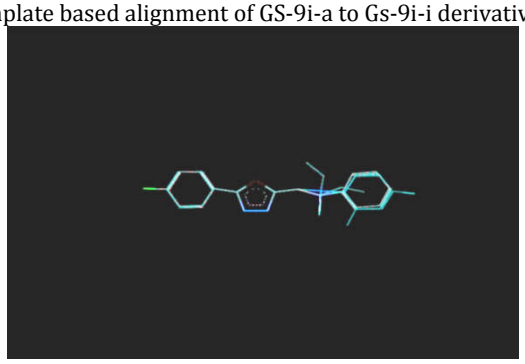


Fig No-4:3D view of template based alignment of GS-9i-a to Gs-9i-i derivatives on the base template.



Biological Activity Dataset for QSAR Analysis

The structures of all compounds were drawn in 2D Draw App (MDS 4.6 2010). The 2D structures were converted to 3D structures in MDS. Every compound was energy minimized and batch optimized by using Merck Molecular Force Field (MMFF) and charges. [18]

Molecular Modeling for 2D QSAR

Descriptor Calculation:

The Physicochemical Descriptor, Alignment Independent can be calculated by using descriptor calculation facility provided in MDS 4.6 Software. Near about several hundred of descriptors are calculated. The column containing zero value reading and invariability are removed by using 'remove invariable column tool'.

Variable Selection:

There are a hundreds of molecular descriptors available for building a QSAR model. Not all of the molecular descriptors are important in determining the biological activity. To find the optimal subset of the descriptors a variable selection method is required, which plays an important role in determining activity. The variable selection can be done by step wise forward-backward systemic variable selection method. The IC_{50} value is converted in to log value of IC_{50}; which can be used as dependent variable in QSAR analysis. Put all another descriptors as independent variable.[19, 20]

Statistical Methods:

A suitable statistical method coupled with a variable selection method allows analyses of this data in order to establish a QSAR model, with the subset of descriptors that are most statistically significant in determining the biological activity.

Preparation of training set and test set:

The data set can be divided in to two sets i.e. training set and test set. Optimized molecules should be aligned by template base alignment. The general structures and corresponding substitutions are included in Table.

Molecular Modeling for 3D-QSAR:

Preparation of Training Set and Test Set: for 3D QSAR data set can be divided in to training set and test set. The optimized molecule should be aligned by template base alignment. Descriptor calculation, variable selection and statistical methods are same as 2D QSAR of same molecule .

SPECTRAL DATA:

IR spectra (cm-2) were recorded in KBr on a Shimadzu FTIR-8700 spectrometer.1H NMR (ppm) in DMSO using TMS as reference on Bruker 400 AMX. Mass spectra of the compound coded MAI-2e was carried out.

GS-8i-a: IR (KBr) cm^{-1}1558.33 (N=CH); 1498.10 (Ar C=C); 2932.05 (Ali C-H); 3087.05 (Ar H); 1685.17 (C=O);1093.82 (C-O of oxadiazole); 1640.05 (C=N); 1124.08 (C-N) ;3447.76(NH str of amide); 1605.81 (Ar C-C); 869(Ar H bend); 1550.93 (NH bend).

^{1}H NMR (DMSO) 2.04 (s,3H, CH_3, at g) 3.1(s, 6H, N-$(CH_3)_2$ at e, e'); 6.7 (d, 2H, CH ArH at d, d'); 6.9 (d, 2H, CH, ArH, at a, a'); 7.4 (d, 2H, CH ArH at c, c'); 7.7 (d, 2H, CH ArH at b,b'); 8.5 (s, 1H, N=CH at h); 9.8 (s,1H, NH, at f).

GS-8i-b: IR (KBr) cm^{-1}1598.42 (N=CH); 1489.94 (Ar C=C); 3066.17(Ali C-H); 3163.8 (Ar H); 1686.77 (C=O); 1091.18 (C-O of oxadiazole); 1648.70 (C=N); 3463.65 (NH str of amide); 1510.99 (Ar C-C); 947.07(Ar H bend); 1554.23 (NH bend).

GS-8i-c: IR (KBr) cm^{-1}1586.97 (N=CH); 1458.12 (Ar C=C); 2989.57 (Ali C-H); 3163.57 (Ar H); 1684.01 (C=O); 1096.50 (C-O of oxadi azole); 1654.34 (C=N); 1247.59 (C-O of OCH_3); 3463 (NH str of amide) ;1558.39(Ar C-C); 831.36 (Ar H bend); 1550.59 (NH bend).

GS-8i-d: IR (KBr) cm^{-1}763.10 (C-Cl); 1594. 46 (N=CH); 1489.91 (Ar C=C); 2982.30 (Ali C-H); 3115.92 (Ar H); 1679.15(C=O); 1091.75 (C-O of oxadiazole); 1621.71(C=N); 3460.65(NH str of amide);1602.50 (Ar C-C); 905.46 (Ar H bend); 824.76 (C-N); 1563.07 (NH bend).

^{1}H NMR (DMSO) 2.06 (s,3H, CH_3 at f) ; 6.95 (d, 2H, CH, ArH at a, a'); 7.1 (t, 2H, CH, ArH at d,d'); 7.4 (d, 2H, CH, ArH at b ,b'); 7.7 (d, 2H, CH, ArH at c,c'); 8.6 (s, 1H, N=CH at g) ; 10.2 (s,1H, NH at e).

GS-8i-e: IR (KBr) cm^{-1}1582.92 (N=CH); 1438.24 (Ar C=C); 2972.91 (Ali C-H); 3020.75 (Ar H); 1689.22 (C=O); 1096.56 (C-O of oxadia zole); 1652.86 (C=N); 1253.17 (C-O of OCH_3 str); 3455.68 (NH str of amide); 1609.60 (Ar C-C str); 869 (Ar H bend); 1553.98 (NH bend).

GS-8i-f: IR (KBr) cm^{-1}1530.63, 1347.86 (N=O); 1583.54 (N=CH); 1412.44 (Ar C=C); 2992.15 (Ali C-H); 3145.41 (Ar H); 1681.54 (C=O); 1093.07 (C-O of oxadiazole); 1656.41 (C=N); 3465.42 (NH str of amide) 1605.17, (Ar C-C); 899.51 (Ar H bend); 1562.07 (NH bend).

GS-8i-g: IR (KBr) cm^{-1}3568.46 (O-H); 1592.31 (N=CH); 1488.88 (Ar C=C); 2908.66(Ali C-H); 3150.73 (Ar H); 1684.22 (C=O); 1095.82 (C-O of oxadiazole); 1622.60 (C=N); 3455.12(NH str of amide). 894.06 (Ar C-H bend); 1559. 30 (NH bend).

GS-8i-h: IR (KBr) cm^{-1}3595.12 (O-H); 1585.92 (N=CH); 1453.35 (Ar C=C); 2991.57(Ali C-H); 3157.57(Ar H); 1686.77 (C=O); 1093.60 (C-O of oxadiazole); 1625.75 (C=N); 3458.27 (NH str of amide). 1610.35 (Ar C-C); 867.80 (Ar H bend); 1550.23 (NH bend).

GS-8i-i: IR (KBr) cm^{-1}1596.07 (N=CH); 1442.50 (Ar C=C); 3016.12 (Ali C-H); 3163.86 (Ar H); 1686.77 (amide C=O); 1091.18 (C-O of oxadiazole); 1648.70(C=N); 3460.65 (NH str of amide). 1510.99 (Ar C-C); 890.30 (Ar H bend); 1565.42 (NH bend).

GS-8i-j: IR (KBr) cm^{-1}777.10 (C-Cl); 1595.56 (N=CH); 1489.91 (Ar C=C); 2987.42 (Ali C-H); 3159.46 (Ar H); 1682.62 (amide C=O); 1092.60 (C-O of oxadiazole); 1645.27 (C=N); 3464.09 (NH str of amide) 915.46 (Ar H bend); 1561.35 (NH bend).

GS-8i-k: IR (KBr) cm^{-1}3510.99 (O-H); 1579.89 (N=CH); 1483.78 (Ar C=C); 3074.19 (Ali C-H); 3197.67 (Ar H); 1688.28 (C=O); 1093.15 (C-O of oxadiazole); 1648.43 (C=N); 1259.54 (C-O of OCH_3); 3466.14 (NH str of amide) 1605.02 (Ar C-C); 901.45 (Ar H bend); 1550.75 (NH bend).
GS-8i-l: IR (KBr) cm^{-1}1536.65; 1351.08 (N=O); 1589.52 (N=CH); 1449.66 (Ar C=C); 2988.36(Ali C-H); 3107.36 (Ar H); 1678.23 (C=O); 1093.07 (C-O of oxadiazole); 1656.41 (C=N); 3455.42 (NH str of amide) 1607.19 (Ar C-C); 896.21(Ar H bend); 1598.96 (NH bend).
GS-8i-m: IR (KBr) cm^{-1}1583.73 (N=CH); 1454.16 (Ar C=C); 2981.66 (Ali C-H); 3151.96 (Ar H); 1684.01(C=O); 1089.18 (C-O of oxadiazole); 1654.34 (C=N); 1251.54 (C-O of OCH_3) 3455.68 (NH str of amide); 1604.55 (Ar C-C str); 896.30 (Ar H bend); 1569. 35 (NH bend).
GS-9i-a: IR (KBr) cm^{-1}3087.06 (Ar-CH); 2919.65 (Ali-CH); 1650 (C=N); 1602.36 (Ar C-C); 1500.10 (Ar C=C); 1251.46 (C-O of oxadiazole); 862.03 (Ar C-H bend); 1091.36 (Aryl C-Cl); 3208.06 (-NH-).
^{1}H NMR (DMSO) 6.43 (d,1H, Ar-CH, at a); 7.04 (t,1H, Ar-CH, at b); 6.58 (t, 1H, Ar-CH, at c); 7.04 (t,1H, Ar-CH, at d); 6.43 (d,1H, Ar-CH, at e); 4.01 (t,1H, NH, at f); 4.32 (d, 2H, CH_2 at g); 7.51 (d,1H, Ar-CH, at h); 7.85 (d, 1H, Ar-CH, at i); 7.85 (d,1H, Ar-CH, at j);
7.51 (d,1H, Ar-CH, at k).
GS-9i-b: IR (KBr) cm^{-1}3086.00 (Ar-CH); 3060.03 (Ali-CH); 1643.09 (C=N); 1506.51 (Ar C-C); 1495.92 (Ar C=C); 1258.17 (C-O of oxadiazole); 940.20 (Ar C-H bend); 1093.50 (Aryl C-Cl); 3162.06 (-NH-); 2958.96 (-CH stretch).
GS-9i-c: IR (KBr) cm^{-1}3163.66 (Ar-CH); 2969.81 (Ali-CH); 1653.09 (C=N); 1506.51 (Ar C-C); 1465.22 (Ar C=C); 1255.45 (C-O of oxadiazole); 841.89 (Ar C-H bend); 1095.25 (Aryl C-Cl); 1612.09 (-NH_2 bend); 3300.23 (-NH_2 stre).
GS-9i-d: IR (KBr) cm^{-1}3117.95 (Ar-CH); 2953.37 (Ali-CH); 1629.80 (C=N); 1605.51 (Ar C-C);1481.61 (Ar C=C); 1234.87 (C-O of oxadiazole); 878.93 (Ar C-H bend); 1093.41 (Aryl C-Cl); 3322.25 (-NH- stre).
GS-9i-e: IR (KBr) cm^{-1}3089.55 (Ar-CH); 2960.66 (Ali-CH); 1625.08(C=N); 1606.09 (Ar C-C); 1483.50 (Ar C=C); 1221.52 (C-O of oxadiazole); 864.94 (Ar C-H bend); 1093.23 (Aryl C-Cl); 3339.33 (-NH-); 1116.93 (Ali C-C).
GS-9i-f: IR (KBr) cm^{-1}3120.58 (Ar-CH); 2920.58 (Ali-CH); 1647.56 (C=N); 1605.44 (Ar C-C); 1412.26 (Ar C=C); 1221.10 (C-O of oxadiazole);
899.99 (Ar C-H bend); 1093.44 (Aryl C-Cl); 3087.49 (Ali-CH); 1165.56 (Ali C-C).
^{1}H NMR (DMSO) 2.40 (m,2H, CH_2, at a); 1.25 (t,3H,CH_3, at b); 1.25 (t,3H, CH_3, at c); 2.40 (m,2H, CH_2, at d); 3.62 (s,2H, CH_2, at e); 7.74 (d,1H, Ar-CH, at f); 7.49 (d, 1H, Ar-CH, at g); 7.49 (d,1H, Ar-CH, at h); 7.74 (d,1H, Ar-CH, at i).
GS-9i-g: IR (KBr) cm^{-1}3158.35 (Ar-CH); 2918.82 (Ali-CH); 1638.06 (C=N); 1610.48 (Ar C-C); 1488.32 (Ar C=C); 1217.06 (C-O of oxadiazole); 865.43 (Ar C-H bend); 1092.94 (Aryl C-Cl); 3462.06 (-NH Stre);1580 (-NH bend);1182.24 (C-F).
GS-9i-h: IR (KBr) cm^{-1}3167.94 (Ar-CH); 2918.41 (Ali-CH); 1644.33 (C=N); 1510.81 (Ar C-C); 1450.54 (Ar C=C); 1225.35 (C-O of oxadiazole);
890.97 (Ar C-H bend); 1093.06 (Aryl C-Cl); 1225.35 (Ar C-O).
^{1}H NMR (DMSO) 2.91 (t,2H, CH_2, at a); 3.25 (t,2H, CH_2, at b); 3.25 (t,2H, CH_2, at c); 2.91 (t,2H, CH_2, at d); 3.71 (s, 2H, CH_2, at e); 7.74 (d, 1H, Ar-CH at f); 7.49 (d,1H, Ar-CH, at g); 7.49 (d, 1H, Ar-CH, at h); 7.74 (d,1H, Ar-CH, at i).
GS-9i-i: IR (KBr) cm^{-1}3170.94 (Ar-CH); 2920.82 (Ali-CH); 1643.45 (C=N); 1603.30 (Ar C-C); 1447.09 (Ar C=C); 1225.08 (C-O of oxadiazole); 915.44 (Ar C-H bend); 1094.07 (Aryl C-Cl).

RESULTS AND DISCUSSION:

Based upon the literature survey, the present investigation was designed and extensive interest has been shown in Oxadiazoles containing compounds in search of potential drugs. Oxadiazole derivatives are known to exhibit an array of biological activities. In our laboratories we concentrated our research on 2-[(substituted benzylidene) imino]-5-(4'-acetamidophenyl)-1,3,4 oxadiazole, 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazole & were synthesized and screened for antioxidant activities. The newly synthesized compounds were characterized by physical data, spectral analysis and were screened for their antioxidant activity for novel research. The compounds of scheme-I & II were subjected to antioxidant activity which shown good novel result. The antioxidant activity was plotted against concentration and linear regression equation was obtained. IC_{50} values were obtained from the linear regression equation. By definition, IC_{50} is the concentration of the test compounds required which produces 50% inhibition.
%inhibition = (control-sample) / control×100.
y = mx+c.

Among all the compounds tested GS-8i-c, GS-8i-k, GS-9i-c, GS-9i-e and GS-9i-h showed the good % inhition and were found to be more significant compound among all the compounds tested and compounds GS-8i-f, GS-8i-g, GS-9i-a and GS-9i-d, were showed moderate % inhition and were found to be significant among all the tested compounds. Remaining compounds showing mild activity.

The derived models in 2D QSAR from multiple linear regression(MLR) with forward stepwise shows good correlation between biological activity and parameters Quadrupole2, MomInertiaX, ZcompDipole, QMDipoleY as the coefficient of determination, r^2 = 0.9660, r^2 = 0.758, capable of explaining 72% of variance in the observed activity values. All the descriptors contributed well for the generation of model. The low standard error of r^2 se = 0.0324, r^2 se = 0.0795 demonstrates accuracy of the model. The leave-one-out procedure was used for internal validation of the model. The model showed an internal predictive power cross validated r^2 (q^2 = 0.9262, q^2 = 0.6168) of 65% values reflect good internal predictive power of the model. In addition, the randomization test shows confidence of 99 % that the generated model is not random and hence it is chosen as the QSAR model. The F-test= 78.1905, 20.3746 shows the overall statistical significance level of 99 % of the model which means the probability of failure of the model is 1 in 10,000. The descriptors show positive correlation among the parameters selected for the derived QSAR model. The positive coefficients suggest that inclusion of such carbon atoms in the molecules lead to increased anrioxidant activity

Quadrupole2 descriptor signifies magnitude of first tensor of quadrupole moments. Its positive contribution in the QSAR model implies that will lead to increase potency. Its positive value suggests that increasing the number of such atom that increase the dipole moment will lead to better antioxidant potency. The MomInertiaX, ZcompDipole, QMDipoleY descriptor are type of dipole interaction and its contribution for the antioxidant activities indicate that optimum groups provide good antioxidant activity. Fig. No-5 & Fig. No-6, Table No- 4

The derived models in 3D QSAR from multiple linear regressions (MLR) with forward stepwise shows good correlation between biological activity and parameters. With coefficient of determination **r^2 = 0.6454, r^2 = 0.6921, r^2 = 0.8583, r^2 = 0.8723, r^2 = 0.9969, r^2= 0.9526, r^2=0.9665,** which is capable of explaining variance in the observed activity values. The model selection criterion is the value of q^2, the internal predictive ability of the model, and that of pred_r^2, the ability of the model to predict the activity of external test set. As the cross-validated correlation coefficient (q^2) is used as a measure of reliability of prediction, the correlation coefficient suggests that our model is reliable and accurate. The randomization tests suggest that the proposed QSAR model has a probability of less than 0.01 of being generated by chance. **E_77, E_287, E_143, S_490, E_277, H_66, H_194, H_334, S_142,, H_392, S_126, H_184, H_300, S_115, S_341, E_944, S_505, S_911, E_716, S_749, S_1124, E_529, E_944, E_539** are steric descriptors and electrostatic descriptors contributing to models. The q^2 value **obtained (q^2 = 0.2438, q^2 = 0.1129, q^2 = 0.5431, q^2 = 0.6551, q^2 = 0.9653, q^2 = 0.9262, q^2 = 0.9083, q^2 = 0.9278, q^2 = 0.6111)** are the indicative power of the models. Values of r^2, q^2, F test, r^2 se, q^2 se, pred_r^2, pred_r^2se prove that QSAR equation are obtained is statistically significant and shows that the predictive power of the model is 70% (internal validation) and 65 % (external validation). Steric descriptors indicate that steric potential is favorable for activity and less bulky substituent is preferred in that region. Steric and electrostatic field energy of interactions between probe (CH_3) and compounds at their corresponding spatial grid points show in 3D view. The contributions of steric and electrostatic fields indicate that both fields are more important. Fig. No-7 & Fig. No-8

Fig No-5: 3D View of aligned molecule and contribution of descriptors for GS-8i-a-m

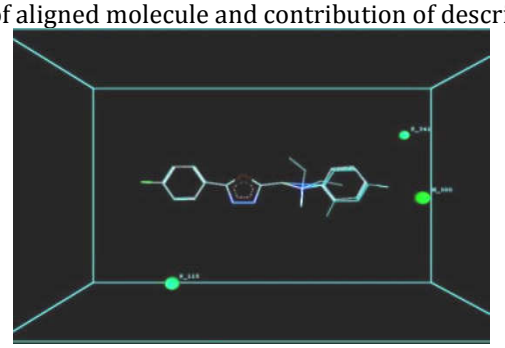


Fig No-6: 3D View of aligned molecule and contribution of descriptors for GS-9i-a-i

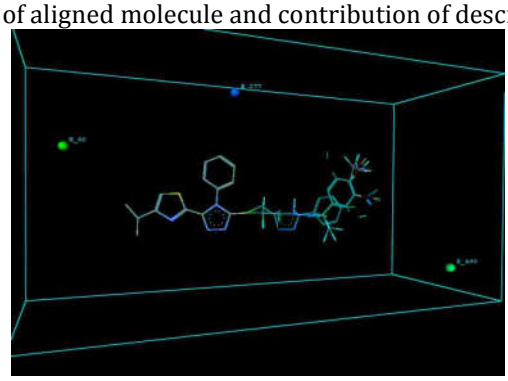


Fig No-7: Contribution charts of the descriptors for Gs-8i-a to GS-8i-m

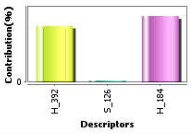
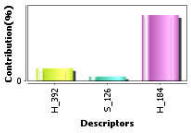
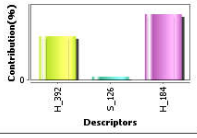
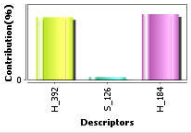
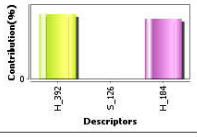
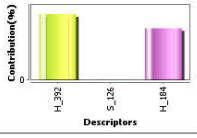
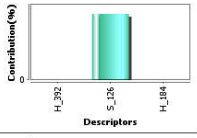
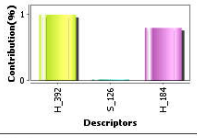
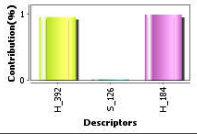
	Molecule	Graph	H_392	S_126	H_184
☑ 1	GS-8i-c.mol		0.349	-0.058	0.845
☑ 2	GS-8i-k.mol		0.313	-0.058	0.818
☑ 3	GS-8i-l.mol		0.331	-0.058	0.83
☑ 4	GS-8I-E.mol		0.352	-0.057	0.842
☑ 5	GS-8i-f.mol		0.338	-0.058	0.823
☑ 6	GS-8i-m.mol		0.36	-0.058	0.836
☑ 7	GS-8i-g.mol		0.308	-0.058	0.793
☑ 8	GS-8i-j.mol		0.439	-0.057	0.905
☑ 9	GS-8i-d.mol		0.435	-0.057	0.933

Fig No-8: Contribution charts of the descriptors for Gs-9i-a to GS-9i-i

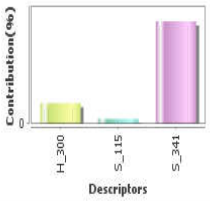
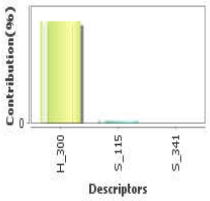
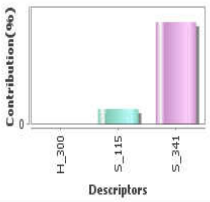
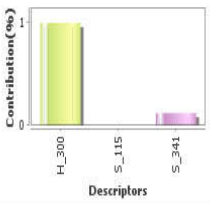
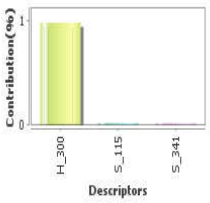
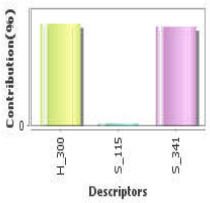
	Molecule	Graph	H_300	S_115	S_341
☑ 1	GS-9i-d.mol		0.143	-0.265	-0.01
☑ 2	GS-9i-i.mol		0.323	-0.271	-0.044
☑ 3	GS-9i-h.mol		0.069	-0.271	-0.04
☑ 4	GS-9i-b.mol		0.553	-0.275	-0.039
☑ 5	GS-9i-g.mol		0.542	-0.27	-0.044
☑ 6	GS-9i-f.mol		0.327	-0.272	-0.021

Table No- 4: 2D & 3D QSAR models & parameter of oxadiazoles derivatives

QSAR Methods	2D-QSAR (Parameters)				
	Sets	**Selected Descriptors**	**Coefficient**	**Constant**	**Statistics**
Multiple regressions Forward Method	Training Set Size = 16, Test Set Size = 4	Quadrupole2, MomInertiaX, ZcompDipole, QMDipoleY	0.0082(±0.0001), -0.0001(±0.0000), 0.0377(±0.0086), 0.0952(±0.0212)	0.8550	n = 16, Degree of freedom = 11, r2 = 0.9660, q2 = 0.9262, F test = 78.1905, r2 se = 0.0324, q2 se = 0.0478 pred_r2 = -3.5849, pred_r2se = 0.3011.
Principle Component Regression forward Method:	Training Set Size = 16, Test Set Size = 4	Quadrupole2, ZcompDipole	0.0057,-0.0110, 0.0253	1.6419	Optimum Components = 2, n = 16 Degree of freedom = 13, r2 = 0.7581, q2 = 0.6168 F test = 20.3746, r2 se = 0.0795, q2 se = 0.1001, pred_r2 = -1.1447, pred_r2se = 0.2059 (Fig 3 & 4)
QSAR	**3D-QSAR (Parameters)**				

Methods	Sets	Selected Descriptors	Coefficient	Constant	Statistics
Multiple Regression of GS-1a to Gs-1k	Training Set Size = 8 Test Set Size = 2	E_77 E_287 E_143	-0.1001(±0.0988) 0.0625(±0.0610) 0.0149(±0.0686)	1.7672	n = 8, Degree of freedom = 4, r^2 = 0.6454, q2 = 0.2438, F test = 2.4267, r2 se = 0.0876, q2 se = 0.1280 pred_r2 = 0.8224, pred_r2se = 0.0374.
Model-I	*Equation-1:* LOGMIC=-0.1001(±0.0988)E_77+0.0625(±0.0610) E_287+0.0149(±0.0686) E_143+1.7672				
Multiple Regression Of GS-2i-a to GS-4c	Training Set Size = 11 Test Set Size = 4	S_490 E_277 H_66	5.8796(±1.8229) -0.1240(±0.0095) -2.1572(±0.5447)	0.1876	n = 11, Degree of freedom = 7, r^2 = 0.6921, q^2 = 0.1129, F test = 5.2445, r2 se = 0.0720, q^2 se = 0.1222 pred_r^2 = -8.2972, pred_r2se = 0.1426.
Model -II	*Equation2:* LOGMIC=5.8796(±1.8229) S_-0.1240(±0.0095) E_277-2.1572(±0.5447) H_66+0.1876				
Multiple Regression Of GS-5i-a to Gs-7i-d	Training Set Size = 8 Test Set Size = 2	H_194 H_334 S_142	2.1151(±0.2924) 0.5661(±0.2117) -4.0070(±0.5939)	5.4060	n = 8, Degree of freedom = 4, r^2 = 0.8583, q^2 = 0.5431, F test = 8.0757, r^2 se = 0.0462, q^2 se = 0.0829 pred_r^2 = -78.9226, pred_r^2se = 0.1315.
Model-III	*Equation3:* LOGMIC=2.1151(±0.2924) H_194 0.5661(±0.2117) H_334-4.0070(±0.5939) S_142+5.4060				
Multiple Regression Of GS-8i-a to Gs-8i-m	Training Set Size = 9 Test Set Size = 2	H_392 S_126 H_184	5.9220(±0.0498) 154.3790(±37.0225) -6.1617(±0.0366)	10.2763	n = 9, Degree of freedom = 5, r^2 = 0.8723, q^2 = 0.6551, F test = 11.3871, r^2 se = 0.0431, q^2 se = 0.0708 pred_r^2 = -0.1064, pred_r^2se = 0.0639.
Model-IV	*Equation4:* LOGMIC=5.9220(±0.0498) H_392 +154.3790(±37.0225) S_126+ -6.1617(±0.0366) H_184+10.2763				
Multiple Regression Of GS-9i-a to Gs-9i-a	Training Set Size = 6 Test Set Size = 2	H_300 S_115 S_341	-0.5128(±0.0007) -7.1591(±1.5330) -7.3328(±0.1408)	-3.7375	n = 6, Degree of freedom = 2, r^2 = 0.9969, q^2 = 0.9653, F test = 217.13, r^2 se = 0.0099, q^2 se = 0.0333 pred_r^2 = -13.29, pred_r^2se = 0.1467.
Mode-V	*Equation5:* LOGMIC=-0.5128(±0.0007) H_300+-7.1591(±1.5330) S_115-7.3328(±0.1408) S_341-3.7375				
Principle Component Regression forward Method:	Training Set Size = 16, Test Set Size = 4	E_944, S_749, S_1124, E_529	-0.1071, 3.5072, -0.1799, 0.1171	0.7638	Optimum Components = 3, n = 16, Degree of freedom = 12, r2 = 0.9526, q2 = 0.9083, F test = 80.4572, r2 se = 0.0366, q2 se = 0.0509, pred_r2 = -2.7414, pred_r2se = 0.2720
Model-VI	***Equation-6:*** LOGMIC=0.1071E_944+3.5072S_749-0.1799 S_1124+0.1171E_529+0.7638(Eqn2)				
Partial Least Square Regression forward Method	Training Set Size = 16, Test Set Size = 4	E_944, S_749, S_1124, E_539	:-0.0972, 3.6200, -0.2435, 0.2332	0.7655	Optimum Components = 3 n = 16 Degree of freedom = 12, r2= 0.9665, q2 = 0.9278, F test = 115.4957, r2se= 0.0308, q2 se = 0.0452 pred_r2 = -3.2191, pred_r2se = 0.2889
Model-VII	*Equation-7:* LOGMIC=0.0972E_944+3.6200S_749-.2435S_1124+0.2332E_539+0.7655 (Eqn 3)				

CONCLUSION

In Scheme I & II synthesized of 2-[(substituted benzylidene) imino]-5-(p-acetamidophenyl)-1,3,4 oxadiazole GS-8i-(a-m), 2-(ω-chloro substituted amino)-5-(p-chlorophenyl)-1,3,4-oxadiazoles GS-9i(a-i) The formation and purity of all the new compounds were studied and confirmed by melting point, TLC, IR, ^{1}H NMR, Mass spectra, UV spectra of all the compounds showing good yield & result. The antioxidant screening was carried out for the new compounds reported in all scheme by Nitric oxide scavenging method at a concentration of 100, 200, 300 µg/0.1ml using DMSO as solvent. The % inhibition IC_{50} was measured. And reported in the corresponding table with best result. In conclusion, from antioxidant results of compounds the aldehydic phenyl ring containing electron donating groups had shown more promising result. Among all the compounds tested with 2'-hydroxy and 4' -hydroxy substituent at R was found to be most significant with 3'-nitro and 4' substituent also showed more significant.

In QSAR studies Equation 1 explains ~97 % (**r^2 = 0.6454**) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2se) predictive ability of ~92 % and ~28% respectively. The equation 2 explains ~95 %(**r^2 = 0.6921**) of the total variance in the training set as well assist has internal (q^2) and external (pred_r2se) predictive ability of~90 % and ~27% respectively. Equation 3 explains ~96% (**r^2 = 0.8583)** of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2se) predictive ability of ~92 % and ~28% respectively. Forward method, the descriptor range is,

H_66, H_194, H_334, H_392, H_184, H_300, H_298 0.4491 to 0.4518, that means Positive range of hydrophobic descriptor indicates that positive hydrophobic potential is favorable for increase in the antioxidant activity, hence a less bulky substituent group is Preferred in that region. 2D & 3D-QSAR models with moderate to high predictive ability of oxadiazole derivatives were derived. The role of hydrophobicity as a 3D property was confirmed and also Electrostatic and Steric effects were found to contribute to antioxidant activity. The obtained models may help design of new active thiazole as antioxidant activity.

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