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SYNTHESIS AND QSAR STUDY OF NOVEL THIAZOLE MOIETIES HAVING ANTIOXIDANT ACTIVITY

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ABSTRACT: Thiazoles derivatives are an important class of heterocyclic compounds, reported to possess a wide spectrum of biological activities. Moreover, thiazole nucleus occupies a very important place in the field of antioxidant agents. The above observations prompted us to synthesize some novel thiazole 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 N-((Substituted) benzylidene)-4-(4-chlorophenyl) thiazole-2-carbohydrazides GS-5i-(a-k) & were synthesized, screened for antioxidant activities & QSAR studies. All new entities have good yield and 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-5i-b, GS-5i-d, GS-5i-e, GS-5i-h & GS-5i-i showed the good % inhibition and were found to be more significant compound among all the compounds tested. Compounds GS-5i-j were showed moderate % inhibition and were found to be significant among all the tested compounds. 2D & 3D-QSAR models with moderate to high predictive ability of thiazole 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.

INTRODUCTION: Thiazoles are a class of organic compounds related to azoles. It is a 5-membered ring, in which two of the vertices of the ring are nitrogen and sulfur, and the other three are carbons. Moreover, among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process and this ring structure is found in several marketed drugs.

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For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids. Aminothiazoles are known to be ligands of oestrogen receptorsas well as a novel class of adenosine receptor antagonists. Fanetizole, a derivative of 2-aminothiazole is an anti-inflammatory agent [1, 2].

A tetrahydrothiazole also appears in the skeleton of penicillin which is one of the first and still most important of the broad spectrum antibiotics. Thiazolamines are key intermediates for synthesizing many pharmaceuticals. Some thiazolidones are valuable medicines [3]. It is obvious that compounds with the thiazole ring have

potential biological activity. We also know that some Schiff bases are effective antitumor and antibiotic drugs [4, 5].

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 acidor polyphenols [6].

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 [7, 8]. Considering the importance of this area, we have listed some important *in-vitro* models for evaluating antioxidant activity [9, 10].

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 [11]. 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*. [12] 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 [13].

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. 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 N-((Substituted) benzylidene)- 4- (4- chlorophenyl) thiazole- 2- carbohydrazides GS-5i-(a-k).

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

EXPERIMENTAL:

P-Chloro Phenacyl Bromide: To a mixture of bromine (0.1 M) and acetic acid (15 ml) was added drop wise to the solution of P-Chloro acetophenone (0.1M) in acetic acid (20 ml) was stirred at 0-10 ºC for 1 h. It was further stirred for 2 h at room temperature then poured onto crushed ice. The solid was separated and filtered, washed with water and dried under vaccum. The crude P-Chloro phenacyl bromide was purified by recrystalization twice with methanol to obtain colourless crystals.

P-Methoxy Phenacyl Bromide: To a mixture of 4-Methoxy acetophenone (0.1M) and hot chloroform (20 ml) Bromine was added drop wise for 30 min with stirring. The solution mixture was stirred for additional 2 h, washed with water dried over

anhydrous sodium sulphate. The solvent was distilled off under vaccum and the crude product obtained was recrystallized from methanol.

P-Nitro Phenacyl Bromide: To a mixture of P-Nitro acetophenone (0.1M) in chloroform (50 ml) and anhydrous aluminium chloride (200 mg) was added to a solution of Bromine (0.1 M) in chloroform (20 ml) drop wise at 40-45 ºC for 1hr. The solvent was removed under reduced pressure; the residual solid was filtered and recrystallized from methanol.

Ethyl 4- (4- substituted phenyl) thiazole- 2-carboxylate GS (5): A mixture of ethyl thiooxamate (1 equivalent weight) substituted phenacyl bromides (1.1 equivalent weight) and ethanol 10 - 15 ml were taken, in a round bottom flask and the mixture was refluxed for 2 h, the ethanol was distilled off under vaccum and it was neutralized with sodium bi carbonate. The mixture was extracted with ethyl acetate, it was wash with water. The solvent was removed under vaccum. The crude product obtained was recrystallized from ethanol.

General method for the syntheses of N-(Substituted benzylidene)- 4- (4- Substituted-phenyl) thiazole-2-carbohydrazides): A mixture of the starting compound (0.005 Mol) and the required aryl aldehydes (0.005 Mol) in isopropyl alcohol (10 ml) and catalytic amount of glacial acetic acid (2 ml) was subjected to Microwave irradiation for 2 - 4 min. Then cooled to room temperature. The solid separated was filtered, washed with isopropyl alcohol and recrystallized with following mentioned solvents.

TABLE 1: N-(SUBSTITUTED BENZYLIDENE)-4-(4- SUBSTITUTED PHENYL) THIAZOLE-2-CARBOHYDRAZIDES)

Substitution		Sample code	Solvents used for recrystallization
R	R_1		
4'-Chloro	4'-Dimethylamino	GS-5i-a	Acetonitrile
4'-Chloro	4'-Hydroxy-3-methoxy	GS-5i-b	Acetonitrile
4'-Chloro	2'-Nitro	GS-5i-c	Acetonitrile
4'-Chloro	3',4',5'-Trimethoxy	GS-5i-d	Acetonitrile
4'-Chloro	4-methoxy	GS-5i-e	Acetonitrile
4'-Chloro	4-methyl	GS-5i-f	Acetonitrile
4'-Chloro	2-hydroxy	GS-5i-g	Acetonitrile
4'-Chloro	4-chloro	GS-5i-h	Acetonitrile
4'-Chloro	4-hydroxy	GS-5i-i	Acetonitrile
4'-Chloro	3-nitro	GS-5i-j	Acetonitrile
4'-Chloro	3,4-dimethoxy	GS-5i-k	Acetonitrile

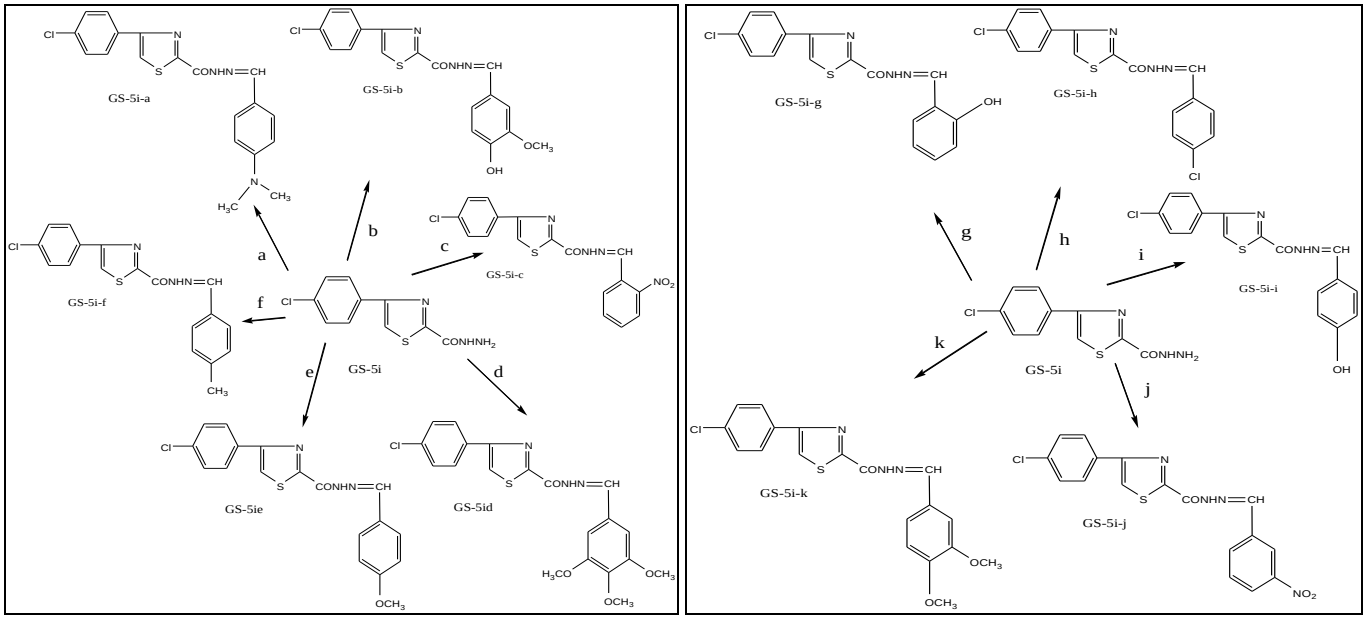


FIG. 1: SCHEME- N- (SUBSTITUTED BENZYLIDENE)- 4- (4- SUBSTITUTED PHENYL) THIAZOLE- 2-CARBOHYDRAZIDES) GS-5I(A-K)

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 [14].

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 ºC 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 ethylene-diamine] 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].

Where, V= absorbance

Preparation of Phosphate Saline Buffer Solution: Dissolve 2.72 g of potassium dihydrogen ortho phoaphate in 100 ml of distilled water. Dissolve 0.8 g of NaOH in 100 ml of distilled water, pipette out 34.7 ml of NaOH solution mix with 50 ml of potassium dihydrogen orthophos-phate make upto 200 ml with distilled water [15, 16].

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.

$$\% \text{ inhibition} = (\text{control-sample}) / \text{control} \times 100.$$

$$y = mx + c.$$

IC_{50} Antioxidant Activity:

TABLE 2: ANTIOXIDANT ACTIVITY DATA (DATA REPRESENTED AS % INHIBITION, IC_{50})

S. no.	Comp. no.	% of inhibition				IC_{50}
		100	200	300	Mean	
1	GS-5i-a	43.15217391	64.61864407	76.22682661	61.3325482	131.4510278
2	GS-5i-b	58.15217391	69.49152542	78.73500545	68.7929016	17.39552964
3	GS-5i-c	47.5	65.6779661	75.46346783	62.88047798	107.8898426
4	GS-5i-d	57.5	70.97457627	78.40785169	68.96080932	18.63157895
5	GS-5i-e	58.26086957	71.39830508	79.38931298	69.68282921	13.80952381
6	GS-5i-f	45.86956522	60.38135593	81.67938931	62.64343682	129.4413408
7	GS-5i-g	50.43478261	71.9279661	82.00654308	68.12309726	85.66878981
8	GS-5i-h	57.93478261	71.9279661	79.28026172	69.71433681	15.47169811
9	GS-5i-i	58.26086957	70.97457627	79.28026172	69.50523585	14.47619048
10	GS-5i-j	55.97826087	66.73728814	79.49836423	67.40463775	52.30769231
11	GS-5i-K	46.63043478	60.38135593	77.75354417	61.58844496	126.0645161
12	GS-5i-l	51.63043478	58.79237288	71.10141767	60.50807511	92.02258727
13	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 0.001 kcal/A0 was reached. The optimized molecule should be aligned by template base alignment. The general structures and corresponding substitutions are included in table.

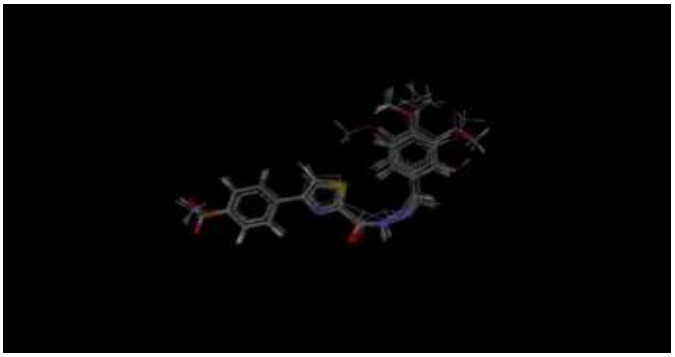


FIG. 2: 3D VIEW OF TEMPLATE BASED ALIGNMENT OF GS-5I-A TO GS-5I-K DERIVATIVES ON THE BASE TEMPLATE

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 [17, 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-5i-a: IR (Kbr) cm^{-1} 3375(NH), 2926(ArC-H), 2900(CH_3), 1743(C=O), 1663(N=CH), 1600 & 1513(Ar-C=C), 831(C-N), 817(C-S), 764(C-Cl).

1H NMR (DMSO) 3.02(s, 6H, 2CH3 at h & i); 6.73(d, 2H, Ar-H at g & g'); 7.28(d,2H, Ar-H at a & a'); 7.45(d, 2H, Ar-H at f & f'); 7.69(d, 2H, Ar-H at b & b'); 7.95(s, 1H, Thiazole-H at c); 8.20(s, 1H, -N=CH at e); 10.08(s, 1H, NH at d).

GS-5i-b: IR (KBr) cm^{-1} 3441(NH), 3249(OH), 3110(Ar-CH), 2936(CH_3), 1696(C=O), 1606 (N=CH), 1514(Ar-C=C), 865(C-N), 834(C-S), 760(C-Cl).

GS-5i-c: IR (KBr) cm^{-1} 3493(NH), 3103(ArC-H), 1735(C=O), 1688(N=CH), 1525(Ar-C=C), 1442 (NO_2), 834(C-N), 781(C-S), 744(C-Cl).

GS-5i-d: IR (KBr) cm^{-1} 3517(NH), 3102(ArC-H), 2931(CH_3), 1694(C=O), 1626(N=CH), 1544(Ar-C=C), 1329(C-O), 872(C-N), 835(C-S), 767(C-Cl).

GS-5i-e: IR (KBr) cm^{-1} 3447(NH), 3141(ArC-H), 2931(CH_3), 1701(C=O), 1638(N=CH), 1521(Ar-C=C), 1435(NO_2), 831(C-N), 750(C-S), 689(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 N-((Substituted) benzylidene)- 4- (4- chlorophenyl) thiazole-2-carbohydrazides GS-5i-(a-k) and 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 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.

$$\% \text{ inhibition} = (\text{control-sample}) / \text{control} \times 100$$

$$y = mx + c.$$

Among all the compounds tested GS-5i-b, GS-5i-d, GS-5i-e, GS-5i-h and GS-5i-i, showed the good % inhibition and were found to be more significant compound among all the compounds tested and compounds GS-5i-j were showed moderate % inhibition 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 Quadrupole 2, Mom Inertia X, Zcomp Dipole, QM Dipole Y as the coefficient of determination, $r^2 = 0.9110$, $r^2 = 0.7891$ capable of explaining 75% 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 = 0.0245, r^2 se = 0.0765 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 = 0.8596, q2 =0.6258) of 70% 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= 71.1005, 25.4589 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 [19, 20].

Quadrupole 2 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, Zcomp Dipole, QM Dipole Y descriptor are type of dipole interaction and its contribution for the antioxidant activities indicate that optimum groups provide good antioxidant activity.

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 $r^2 = 0.8583$ 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. H_194,

H_334, S_142 are steric descriptors and electrostatic descriptors contributing to models. The q^2 value obtained (q^2 = 0.5431) 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^2 se 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 [21, 22].

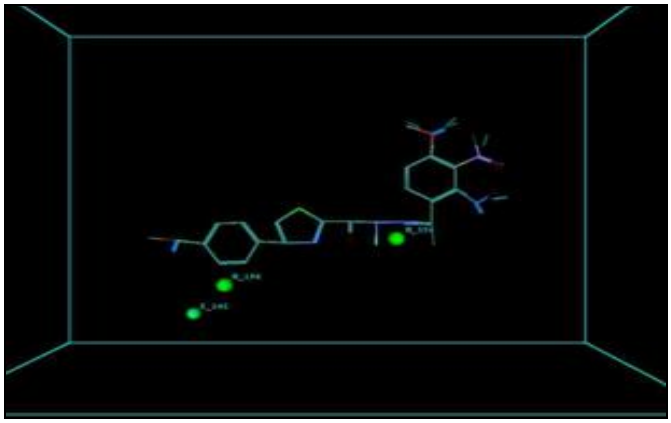
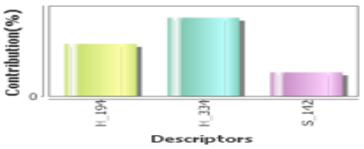
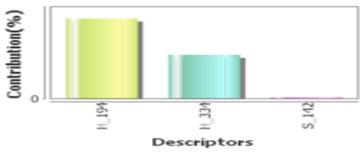
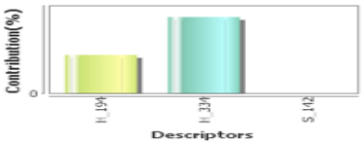
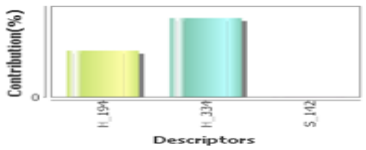
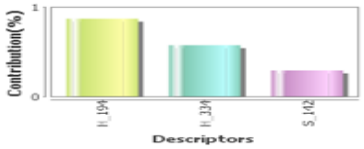
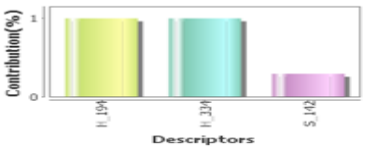
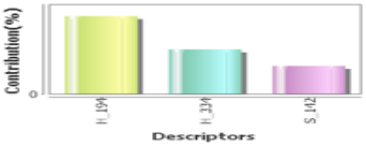


FIG. 3: 3D VIEW OF ALIGNED MOLECULE AND CONTRIBUTION OF DESCRIPTORS FOR GS-5I-A-K

TABLE 3: 2D & 3D QSAR MODELS & PARAMETER OF N-(SUBSTITUTED BENZYLIDENE)-4-(4-SUBSTITUTED PHENYL) THIAZOLE-2-CARBOHYDRAZIDES)

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, r^2 = 0.9110, q^2 = 0.8596, F test = 71.1005, r^2 se = 0.0245, q^2 se = 0.0189 pred_r^2 = -3.5849, pred_r^2se = 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, r^2 = 0.7891, q^2 = 0.6258 F test = 25.4589, r^2 se = 0.0765, q^2 se = 0.1001, pred_r^2 = -1.1447, pred_r^2se = 0.2059 (Fig 3 & 4)
QSAR Methods	**3D-QSAR (Parameters)**				
	Sets	**Selected Descriptors**	**Coefficient**	**Constant**	**Statistics**
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	Equation 3: LOGMIC=2.1151(±0.2924) H_194 0.5661(±0.2117) H_334-4.0070(±0.5939) S_142+5.4060				

S. no.	Molecules	Graph	H_194	H_334	S_142
1	GS-6i-b.mol		0.831	0.567	-0.378
2	GS-7i-d.mol		0.779	0.473	-0.423
3	GS-7i-a.mol		0.77	0.467	-0.423

4	GS-7i-b.mol		0.808	0.55	-0.423
5	GS-7i-c.mol		0.832	0.583	-0.423
6	GS-5i-a.mol		0.995	0.631	-0.298
7	GS-5i-e.mol		1.028	0.75	-0.299
8	GS-5i-c.mol		0.981	0.6	-0.298

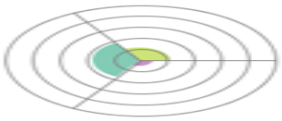
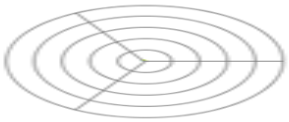
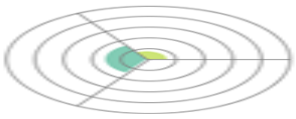
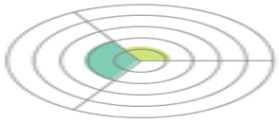
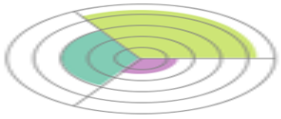
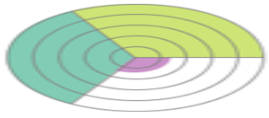
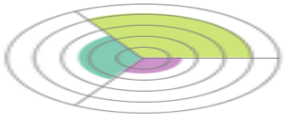
S. no.	Molecules	Graph	H_194	H_334	S_142
1	GS-6i-b.mol		0.831	0.567	-0.378
2	GS-7i-d.mol		0.779	0.473	-0.423
3	GS-7i-a.mol		0.77	0.467	-0.423
4	GS-7i-b.mol		0.808	0.55	-0.423
5	GS-7i-c.mol		0.832	0.583	-0.423
6	GS-5i-a.mol		0.995	0.631	-0.298
7	GS-5i-e.mol		1.028	0.75	-0.299
8	GS-5i-c.mol		0.981	0.6	-0.298

FIG. 4: CONTRIBUTION CHARTS OF THE DESCRIPTORS FOR GS-5I-A TO GS-5I-K

CONCLUSION: In Scheme I and II synthesized of N-(Substituted benzylidene)-4-(4- Substituted phenyl) thiazole- 2- carbohydrazides) GS-5i(a-k). 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 and 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 / 0.1 ml 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 ~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 ~90 % and ~25% respectively. Forward method, the descriptor range is, H_194, H_334, S_142 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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REFERENCES:

1. Rahul R, Kumar RJ and Saravanan J: Synthesis and *in-vitro* antioxidant activity of novel 1, 3, 4-oxadiazole-2-thione. J of Inno in pharma and Bio Sci. 2016; 3: 114-22.
2. Jaishree V, Ramdas N, Sachin J and Ramesh B: *In vitro* antioxidant properties of new thiazole derivatives. I of Saudi Chem Soc. 2012; 16: 371-76.
3. Cristian D, Codrut A, Parashiveccu, Ioana D and Lavinia: Convenient preparation of unsymmetrical 2, 5-disubstituted 1, 3, 4-oxadiazoles promoted by Dess–Martin reagent. Tetrahedron Lett. 2009; 50: 1886-88.
4. Hiroyuki W, Masahiro O, Ryoichi I, Mamoru H and Hideo S: Synthesis of radioiodinated 2, 5-diphenyl-1, 3, 4-oxadiazoles. Bioorg Med Chem Lett. 2009; 17: 6402-06.
5. Neithnaddka P, Venugopala K and Sheena S: Synthesis of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted-phenyl)-[1, 3, 4] oxadiazole. Eur J of Med Chem. 2009; 44: 4522-27.
6. Shahnaz R and Somaye G: A mild and facile method for one pot synthesis of 2, 5-di-substituted 1, 3, 4-oxadiazoles at room temperature. Chinese Chem Lett. 2008; 19: 639-42.
7. Laddi U, Desai S, Bennur R and Bennur S: synthesis of 1, 3, 4-oxadiazoles as antimicrobial agents. Ind J Heterocyclic Chem. 2002; 11: 319-22.
8. Clara C, Massimo B, Donatella B, Marta G and Alberto G: Use of the furoxan (1, 2, 5-oxadiazole 2-oxide) system in the design of new NO-donor antioxidant hybrids. ARKIVOC 2006; 7: 301-9.
9. Bertrand C, Stéphanie R, Jacques C and Gérald G: New Synthesis of Pyrazolyl-1, 3, 4-Oxadiazole and 1, 3, 4-Oxadiazoline Derivatives. Letters in Org Chem. 2005; 2: 599-601.
10. Rostamizadeh S and Ghasem H: Microwave assisted syntheses of 2, 5-disubstituted 1, 3, 4-oxadiazoles. Tetrahedron Letters 2004; 45: 8753-56.
11. Rakesh R, Prabhakar Y, Shirodkar and Vilasrao J: Synthesis and Anticancer Evaluation of some Newer 2, 5-Disubstituted-1, 3, 4-Oxadiazole. Analogues Letters in Drug Design & Discovery 2008; 5: 364-8.
12. Ying Q, Zhifeng Lu, Changgui Lu, Zhiming C and Yiping C: Synthesis and two-photon absorption properties of 2,5-bis[4-(2-arylvinyl)phenyl]-1, 3, 4-oxadiazoles. Dyes and Pigments. 2007; 75: 641-46.
13. Regression and Linear Models, RB. Darlington, New York, USA: McGraw-Hil; 1990.
14. Shen M, Xiao Y, Golbraikh A, Gombar VK and Tropsha A: Development and validation of k-nearest-neighbor QSPR models of metabolic stability of drug candidates J Med Chem 2003; 46: 3013.
15. Ajmani S, Jadhav K and Kulkarni SA: Three-dimensional QSAR using the k-nearest neighbor method and its interpretation. J Chem Inf Model 2006; 46: 24-31.
16. Feng S, Chunmei L, Ming X and Kangjie M: Green chemoselective synthesis of thiazolo [3, 2-a] pyridine derivatives and evaluation of their antioxidant and cytotoxic activities. Bioorg. Med. Chem. Lett. 2009; 19: 5565-68.
17. Harish K, Sadique A, Suroor A and Mohd A: Synthesis of 1, 3, 4-oxadiazole, thiadiazole and 1, 2, 4-triazole derivatives of biphenyl-4-yloxy acetic acid and their preliminary evaluation of biological properties. Eur J Med Chem. 2008: 1-11.

18. Kumar S, Kumar D, Singh N and Vasisht BD: *In vitro* free radicals scavenging and antioxidant activity of *Moringa oleifera* pods. J herbal med. toxicol. 2007; 1(2): 17-22.
19. Moni R, Rumana J, Mynol V and Israt J: *In vitro* nitric oxide scavenging activity of ethanol leaf extracts of Four Bangladeshi Medicinal Plants. Stamford J of Phar Sciences 2008; 1: 57-62.
20. Mukesh CS and Kohli DV: Insight into the structural requirement of aryltriazolinone derivatives as angiotensin II AT1 receptor: 2D and 3D-QSAR k-Nearest Neighbor Molecular Field Analysis approach. Medicinal Chemistry Research 2012; 21(10): 2837-53.
21. Saitoh M, Kunitomo J, Kimura E, Hayase Y and Kobayashi H: Design, synthesis and structure-activity relationships of 1, 3, 4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase-3b. Bioorganic & Medicinal Chemistry 2009; 17: 2017-1029.
22. Mahmud T, Muhammad C, Khalid M, Mubeen R and Atta R: Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2, 5-disubstituted-1, 3, 4-oxadiazole analogues. Bioorg & Med Chem Lett 2005; 13: 3385-95.

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