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3D-QSAR study, synthesis and biological evaluation of *p*-hydroxy benzohydrazide derivatives as antimicrobial agents

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ABSTRACT

Series of compounds N'-[(3-Substituted alkyl/aryl)-4-(substituted aryl)-1,3-thiazol-2-ylidene]-4-hydroxybenzohydrazide ***(10-37)*** *were designed via 3D-QSAR studies. These compounds were synthesized by reacting compounds* ***(3-9)*** *with various substituted phenacyl bromides in presence of sodium acetate. Good yield of compounds (10-37) were obtained by established reaction. Structure of newly synthesized compounds were evaluated on the basis of spectral data. These compounds* ***(10-37)*** *were tested in vitro against species of gram-positive bacteria, Staphylococcus aureus (ATCC 3750) and Bacillus subtilis (ATCC 6633), and gram-negative bacteria, Salmonella typhi (NCTC 786) and Escherchia coli (ATCC 25922). The minimum inhibitory concentration (MIC) was determined by the tube dilution technique using modified Muller-Hinton agar culture medium. Among the compounds tested, the compound* ***(23)*** *N'-[4-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3H)-ylidene]-4-hydroxybenzohydrazide had shown highest antimicrobial activity against gram-positive and gram-negative organisms while other compounds* ***(19)*** *N'-[3-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1,3-thiazol-2(3H)-ylidene]-4-hydroxybenzohydrazide,* ***(16)*** *N'-[4-(2-chloro-4-methylphenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]-4-hydroxybenzohydrazide and* ***(25)*** *N'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3H)-ylidene]-4-hydroxybenzohydrazide, also showed good antimicrobial activity against gram-positive and gram-negative organisms. The results of antimicrobial activity were compared with standard antibiotics (ampicillin, penicillin-G, chloramphenicol).*

Key words: *p*-Hydroxybenzohydrazide; 3-D QSAR; Antimicrobial; ampicillin; penicillin-G; chloramphenicol.

INTRODUCTION

Bacterial resistance to clinically important antibacterial agents represents a crucial and worldwide health care problem.[1] The emerging and spread of resistance among bacteria to a wide variety of structurally unrelated antibacterial agents has become a serious public health concern.[2] The seriousness of antibiotic resistance lies in the fact that today bacterial strains not only are resistance to commonly available antibiotics but also many have acquired augmented virulence.[3,4] Therefore new strategies are needed to overcome resistance pathogens and to avoid the increasing prevalence of multi drug resistance (MDR) bacteria.[5] Increasing drug resistance among Gram-positive bacteria is a significant health problem because these organisms are responsible for nearly one-third of all community-acquired infections.[6] Among the multi drug resistance bacteria methicillin resistance *Staphylococcus aureus* (MRSA) is a major course of health care associated with infections.[7] In spite of the

availability of potent MRSA drugs (viz., Vacomycin, Linezoline, Daptomycin) for management of infections; there is continuing increase in the morbidity and mortality rates, which necessities continuing research and discovery of new more effective compounds.[8] In the recent past, we have identified 4-hydroxy-N-[1,3-thiazole-2(3H)-ylidene] benzohyrazide series and as a good scaffold to achieve better MRSA agents.[9] Subsequently work continued in the class and here we report the synthesis, antibacterial and 3D QSAR study of *N*'-[4-(substituted phenyl)-3-(4-substituted phenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide.

MATERIALS AND METHODS

Instrumentation and Chemicals:

All the chemicals were of Alfa Aesar (UK), E. Merck laboratory grade. The percentage yields are based upon the products obtained after purification through crystallization. The melting points of compounds were determined in open capillary method and were uncorrected. The melting points are mentioned and are in centigrade. Silica gel G plates (activated at 1100, 30 min) were used for thin layer chromatography and were developed in iodine vapor chamber. The R_f value is reported for better comparable solvent system. The IR spectra of synthesized compounds were recorded using KBr pellets on FTIR-8400 S, Shimadzu Marce and are in cm^{-1}. The ^1H NMR spectra ($CDCl_3$) were recorded on BRUKER AVANCE II 400 NMR Spectrometer (chemical shift in δ ppm) and Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC DART-MS spectrometer.

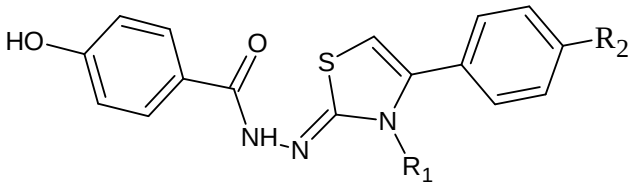
Antibacterial Activity:

The inoculum was prepared with fresh cultures of bacterial strains, cultured on plate count agar (PCA-merck, Germany) for 18 h at 35 °C. The minimal inhibitory concentration, MIC, was determined by the broth twofold macro dilution method in Tryptic Soy Broth (TSB-Difco Laboratories, Detroit, USA), using the serial dilution tests in two sequential steps against standard (ATCC 25923) and multi drug-resistant (3SP/R33) *S. aureus* strains. Initially, stock solutions were prepared in dimethylsulfoxide (DMSO-Merck, Germany) and then diluted in culture medium, TSB. The tubes were inoculated with a standardized number of microorganisms and incubated at 35 °C for 18 h, after which the tubes were examined for visible signs of bacterial growth.[10-12] MIC was defined as the lowest concentration of a compound that completely inhibited the bacterial growth. All experiments were performed in quadruplicate.[13-14]

3D-QSAR Analysis:

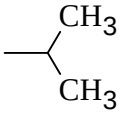
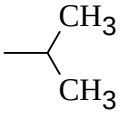
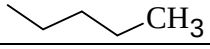
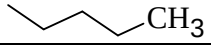
Data set and biological activity:

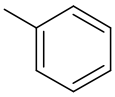
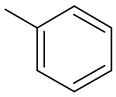
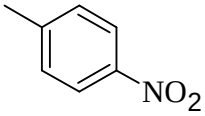
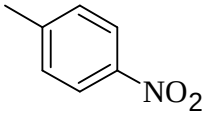
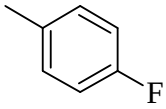
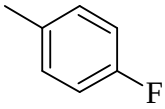
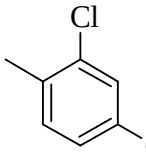
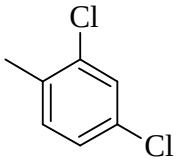
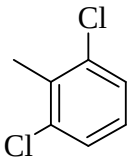
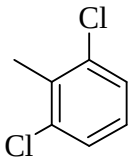
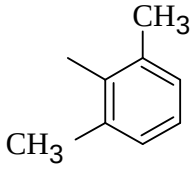
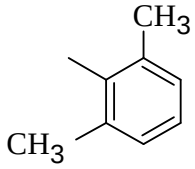
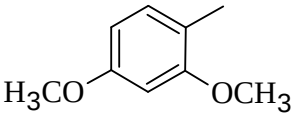
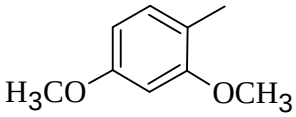
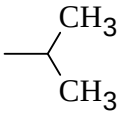
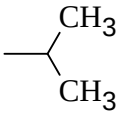
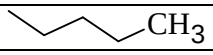
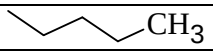
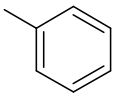
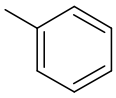
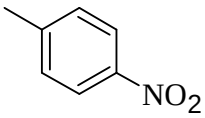
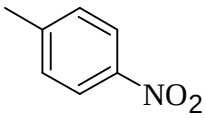
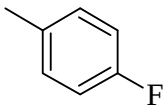
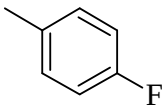
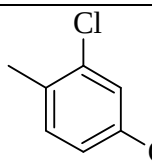
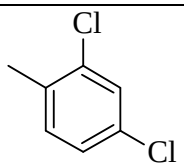
A set of 54 molecules (Table 1) was used for the generation of 3D-QSAR model.[15] The data set was divided into a training set and test set based on the Tanimoto similarity coefficient. All the biological activity data were converted to negative logarithmic molar concentration of MIC values [pMIC= -log (MIC in μmol)] and used for 3D-QSAR studies.

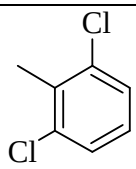
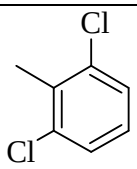
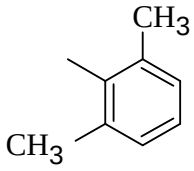
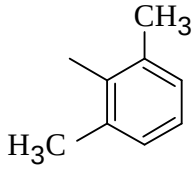
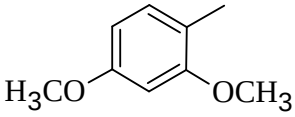
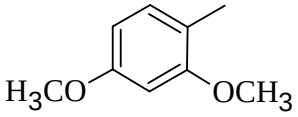
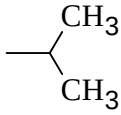
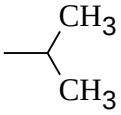
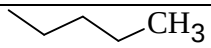
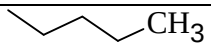
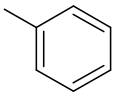
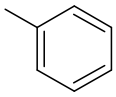
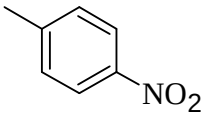
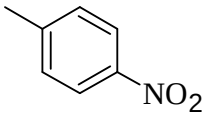
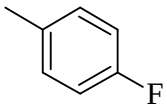
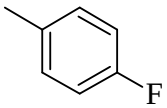
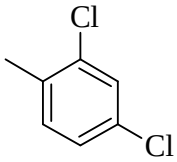
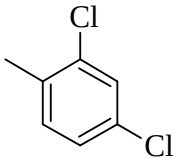
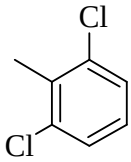
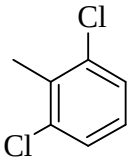
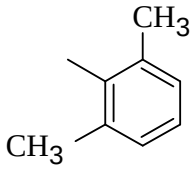
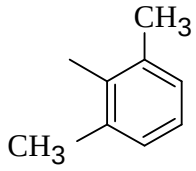
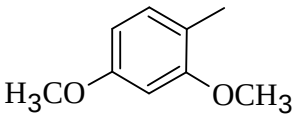
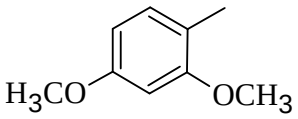


***N*'-[4-(substituted phenyl)-3-(4-substituted phenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide**

Table 1 Compds (I.a-VI.i) and their antimicrobial activity

Compd	R_1	R_2	*p*IC_{50}	Compd	R_1	R_2	*p*IC_{50}
I.a		H	4.31	IV.a		CH_3	4.43
I.b		H	3.83	IV.b		CH_3	4.58

I.c		H	3.75	IV.c		CH_3	4.52
I.d		H	3.99	IV.d		CH_3	4.28
I.e		H	4.00	IV.e		CH_3	4.17
I,f		H	3.95	IV.f		CH_3	4.40
I.g		H	3.98	IV.g		CH_3	5.96
I.h		H	4.11	IV.h		CH_3	4.85
I.i		H	3.72	IV.i		CH_3	4.25
II.a		Cl	4.19	V.a		OH	4.46
II.b		Cl	4.44	V.b		OH	4.32
II.c		Cl	4.31	V.c		OH	4.12
II.d		Cl	4.23	V.d		OH	4.32
II.e		Cl	3.98	V.e		OH	4.55
II.f		Cl	4.23	V.f		OH	5.22

II.g		Cl	4.79	V.g		OH	4.72
II.h		Cl	4.60	V.h		OH	4.62
II.i		Cl	5.24	V.i		OH	4.87
III.a		Br	4.02	VI.a		OCH_3	4.37
III.b		Br	4.79	VI.b		OCH_3	4.79
III.c		Br	4.60	VI.c		OCH_3	5.12
III.d		Br	4.79	VI.d		OCH_3	4.14
III.e		Br	3.99	VI.e		OCH_3	4.74
III.f		Br	4.74	VI.f		OCH_3	4.72
III.g		Br	5.45	VI.g		OCH_3	4.88
III.h		Br	4.44	VI.h		OCH_3	4.40
III.i		Br	4.03	VI.i		OCH_3	4.16

3D-QSAR methodology:

All molecular modeling and 3D-QSAR studies were performed using VlifeMDS QSAR plus software on a DELL computer with Core2Duo processor and windows XP operating system. The structures and inhibitory activity pMIC of *N*'-[4-(substituted phenyl)-3-(4-substituted phenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide derivatives used in the present QSAR studies is depicted in Table 1 . Electrostatic, steric and hydrophobic field descriptors were calculated with cutoffs of 10.0 kcal/mol for electrostatic and 30.0 kcal/mol for steric, and charge type was selected as by Gasteiger-Marsili. The data set of 20 compounds were divided into training and test set using random selection method with 80% as training and 20% as test set compounds and various methodologies were applied to the descriptors generated over the grid. The linear and non-linear regression analysis methods available in VLifeMDS QSAR Plus were employed in deducing the 3D-QSAR models.[16] The detailed protocol for molecular modeling and QSAR analyses is described elsewhere. The 3D pharmacophore features were generated using MolSign module of VLife with aligned compound.[17]

RESULTS AND DISCUSSION

3D-QSAR studies:

The results were in terms of r^2, q^2 and pred_r^2 values. The QSAR models having significant values were selected for the design of compds. The standard model was explained in Table 2.

The results of QSAR were found in terms of r^2, q^2, predicted r^2 values and the QSAR models having significant values were selected for the design of compounds.

Table 2 Comparative results of QSAR method for antimicrobial activity

Method	r^2	q^2	f-test	Pred r^2	Pred r^2 se
FB_MLR	0.9258	0.6564	37.4354	0.8292	0.1522
FB_PLS	0.9258	0.6556	47.3887	0.8301	0.1518
FB_PCR	**0.9079**	**0.7819**	**37.4813**	**0.9050**	**0.1135**
SA_kNN_1	-	0.3931	-	0.7819	0.1720
SA_kNN_2	-	0.3389	-	0.9555	0.0777

Figure 1 Distribution of points of PCR method for antimicrobial activity

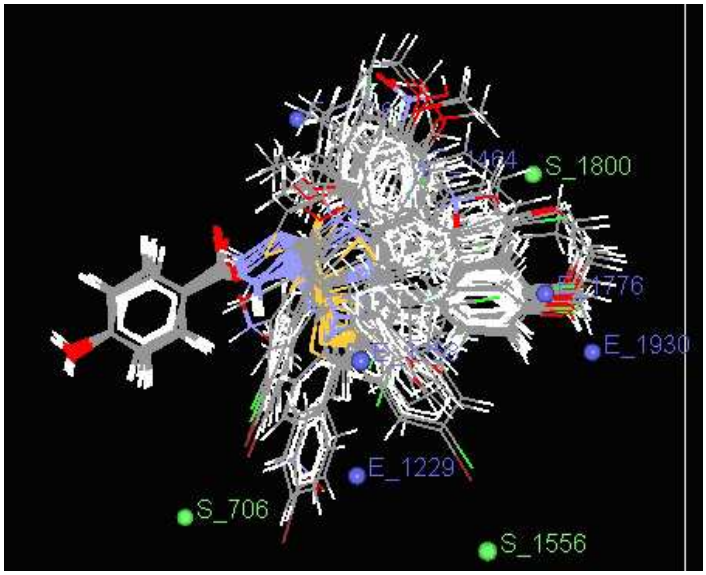


Figure 23D-Plot of compound (35) with grid points

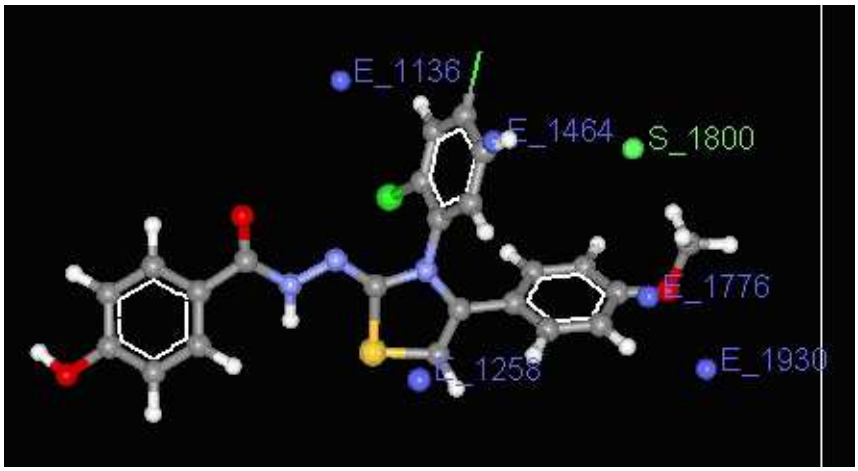


Figure 3 Contribution chart of PCR method for antimicrobial activity

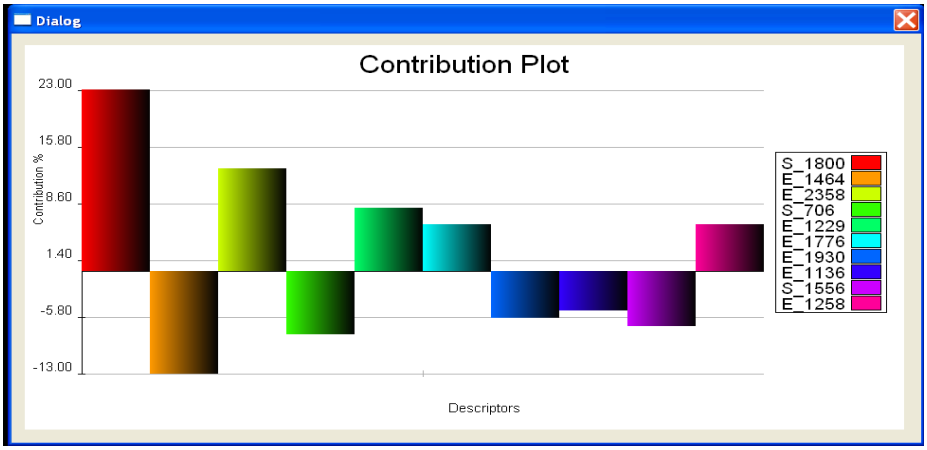
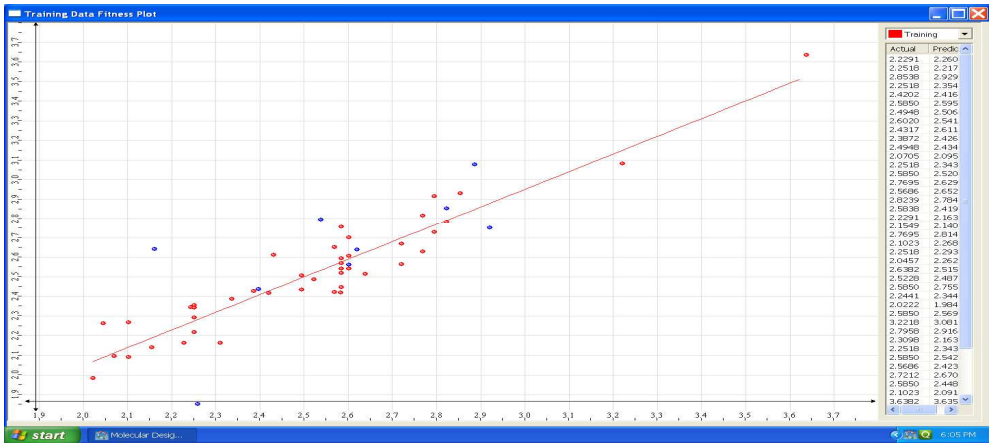


Figure 4 Fitness plot for antimicrobial activity by PCR method

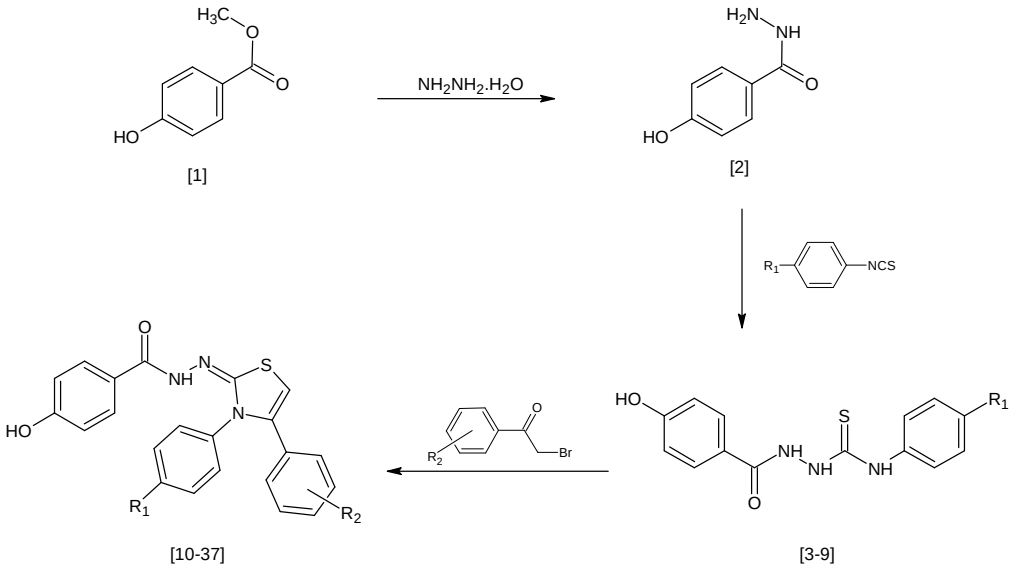


From the study of all these methods (table 2), the values of pred r^2, q^2, r^2 and pred r^2se were found significant as compare to FB_MLR, FB_PLS, SA_kNN_1, SA_kNN_2. So, in consideration of this principle component regression method showed the best results. Distribution of points were shone in figure 1, 2 and contribution, fitness plot in figure 3 and figure 4 respectively.

The descriptors that got selected in a given model were the field points either of steric or electrostatic nature at different locations in a common grid around set of molecules. For utilizing these descriptors for new ligand design, the field values were considered at different grid points of compounds cluster having most active compd.[18] The extreme of field values of compounds in the cluster of most active compounds decided the range of field values which was recommended for new compound design.

Chemistry:

The present study describes the synthesis and antibacterial activity of some *N*'-[4-(substituted phenyl)-3-(4-substituted phenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxy-benzohydrazide derivatives and development of 3D-QSARs using the generated data. A series of 28 new derivatives (compounds 10–37) were synthesized in satisfactory yields (67–94%) as illustrated in Scheme 1 and their structures were characterized by spectral data. The IR spectrum (compounds 10–37) showed the stretching bands in the region of 1400-1460 cm^{-1} (C-O stretching and O-H deformation) also N–H and N-N stretching bands in the region of 3360–3298 and 1650–1600 cm^{-1}, respectively. In their ^1H NMR spectrum these derivatives exhibited the characteristic signals of thiazoline ring as singlet in the regions δ 5.47–5.82 ppm. However, all the other protons were resolved in appropriate regions confirming the assigned structures.



Scheme 1: General scheme for the synthesis of compounds (10-37)

Table 3 Substitutions of compds (10-37)

Compd No.	R_1	R_2	Compd No.	R_1	R_2
10	H	2-Cl	24	NO_2	2-Cl, 4-CH_3
11	H	2-Cl,4-Cl	25	NO_2	2-Cl, 4-OH
12	H	2-Cl, 4-CH_3	26	CH_3	2-Cl
13	H	2-Cl, 4-OH	27	CH_3	2-Cl,4-Cl
14	F	2-Cl	28	CH_3	2-Cl, 4-CH_3
15	F	2-Cl,4-Cl	29	CH_3	2-Cl, 4-OH
16	F	2-Cl, 4-CH_3	30	OH	2-Cl
17	F	2-Cl, 4-OH	31	OH	2-Cl,4-Cl
18	Cl	2-Cl	32	OH	2-Cl, 4-CH_3
19	Cl	2-Cl,4-Cl	33	OH	2-Cl, 4-OH
20	Cl	2-Cl, 4-CH_3	34	OCH_3	2-Cl
21	Cl	2-Cl, 4-OH	35	OCH_3	2-Cl,4-Cl
22	NO_2	2-Cl	36	OCH_3	2-Cl, 4-CH_3
23	NO_2	2-Cl,4-Cl	37	OCH_3	2-Cl, 4-OH

Synthesis:

Procedure for synthesis of compd (2)

The mixture of **(1)** (1 g, 0.01 mol) and hydrazine hydrate 99% (30mL, 6 mol) was refluxed for 20 h. The reaction mixture was cooled at 4-5^0. The solid of (2) were filtered and washed with cold water. The product **(2)** was dried and recrystallized from ethanol.

Generalised procedure for Synthesis of *N*-(4-substituted phenyl)-2-[(4-hydroxyphenyl) carbonyl] hydrazinecarbothioamide (3-9)

To the solution of compound **(2)** (1 g, 0.01 mol) in ethanol (190 mL), 4-substituted isothiocyanatobenzene (1 g, 0.01 mol) was added. The reaction mixture was refluxed for 20 h.Excess solvent was removed under vacuum upto 10 mL. The residue **(3-9)** was washed with diethyl ether and recrystallized using methanol.

Generalised procedure for Synthesis of *N*'-[4-(substituted phenyl)-3-(4-substituted phenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (10-37)

The mixture of **(3-9)** (1g, 0.01 mol) with substituted phenacyl bromide (0.58g, 0.01 mol) and sodium acetate (4.82g, 0.2 mol) in ethanol (50 mL) was refluxed for 10 h. The mixture was cooled and diluted with enough water to developed turbidity. It was left overnight to obtain the product. The product **(10-37)** was filtered, dried and recrystallized using aqueous methanol (99%).

***N*'-[4-(2-chlorophenyl)-3-phenyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (10)**

Yield: 0.84 g (90.10%). mp 164–168˚ (methanol), R_f: 0.78 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 6.46-7.61 (m, 13H, Ar-H), 4.87 (s, H, Ar-OH), 5.65 (s, H, C-H ethylene); EI-MS (m/z, 100%): 422.89[M+1] (100%).; Anal calculated for $C_{22}H_{16}ClN_3O_2S$ (421.8): C, 62.63; H, 3.82; N, 9.96. Found: C, 62.69; H, 3.87; N, 9.91.

***N*'-[4-(2,4-dichlorophenyl)-3-phenyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (11)**

Yield: 0.63 g (64.10%). mp 270–274˚ (methanol), R_f: 0.76 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.61 (s, H, C-H ethylene), 6.42-7.65 (m, 12H, Ar-H), 4.95 (s, H, CONH), 5.21 (s, H, Ar-OH); EI-MS (m/z, 100%): 457.34 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}Cl_2N_3O_2S$ (456.3): C, 57.90; H, 3.31; N, 9.21. Found: C, 58.06; H, 3.33; N, 9.27.

***N*'-[4-(2-chloro-4-methylphenyl)-3-phenyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (12)**

Yield: 0.54 g (93.10%). mp 230–234˚ (methanol), R_f: 76 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching); ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.56 (s, 3H, C-H methyl), 5.41 (s, H, C-H ethylene), 6.55-7.73 (m, 12H, Ar-H), 4.77 (s, H, Ar-OH); EI-MS (m/z, 100%): 436.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_2S$ (435.9): C, 63.37; H, 4.16; N, 9.64. Found: C, 63.35; H, 4.14; N, 9.66.

***N*'-[4-(2-chloro-4-hydroxyphenyl)-3-phenyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (13)**

Yield: 0.74 g (75.10%). mp 216–218˚ (methanol), R_f: 0.71 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1421 (C-O stretching and O-H deformation), 1725 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching); ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.17 (s, 2H, Ar-OH), 5.72 (s, H, C-H ethylene), 6.63-7.58 (m, 12H, Ar-H); EI-MS (m/z, 100%): 438.89 [M+1] (100%).; Anal Calculated for $C_{22}H_{16}ClN_3O_3S$ (437.8): C, 60.34; H, 3.68; N, 9.60. Found: C, 60.36; H, 3.66; N, 9.63.

***N*'-[4-(2-chlorophenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (14)**

Yield: 0.45 g (70.10%). mp 80–82˚ (methanol), R_f: 0.48 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 1050 (C-F)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 4.76 (s, H, Ar-OH), 5.71 (s, H, C-H ethylene), 7.06 (s, H, CONH); EI-MS (m/z, 100%): 440.88 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}ClFN_3O_2S$ (439.8): C, 60.07; H, 3.44; N, 9.55. Found: C, 60.15; H, 3.47; N, 9.58.

_N_'-[4-(2,4-dichlorophenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (15)
Yield: 0.98 g (90.20%). mp 230–234˚ (methanol), R_f: 0.53 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 1050 (C-F)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.13 (s, H, Ar-OH), 5.67 (s, H, C-H ethylene), 6.42-7.79 (m, 11H, Ar-H); EI-MS (m/z, 100%): 475.33 [M+1] (100%).; Anal Calculated for $C_{22}H_{14}Cl_2FN_3O_2S$ (474.3): C, 55.71; H, 2.97; N, 8.86. Found: C, 55.67; H, 2.90; N, 8.88.

_N_'-[4-(2-chloro-4-methylphenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (16)
Yield: 1.54 g (87.10%). mp 116–120˚ (methanol), R_f: 0.44 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl) stretching, 1050 (C-F) stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.53 (s, 3H, C-H methyl), 5.17 (s, H, Ar-OH), 6.38-7.89 (m, 11H, Ar-H); EI-MS (m/z, 100%): 454.91 [M+1] (100%).; Anal Calculated for $C_{23}H_{17}ClFN_3O_2S$ (453.9): C, 60.86; H, 3.77; N, 9.26. Found: C, 60.75; H, 3.63; N, 9.19.

_N_'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (17)
Yield: 1.23 g (85.10%). mp above 300˚ (methanol), R_f: 0.84 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching, 1050 (C-F)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.11 (s, H, Ar-OH), 5.65 (s, H, C-H ethylene), 6.37-7.84 (m, 11H, Ar-H); EI-MS (m/z, 100%): 456.88 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}ClFN_3O_3S$ (455.8): C, 57.96; H, 3.32; N, 9.22. Found: C, 57.87; H, 3.27; N, 9.18.

_N_'-[4-(2-chlorophenyl)-3-(4-chlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (18)
Yield: 0.86 g (80.10%). mp 290–292˚ (methanol), R_f: 0.59 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.61 (s, H, C-H ethylene), 4.97 (s, H, Ar-OH), 6.40-7.90 (m, 12H, Ar-H); EI-MS (m/z, 100%): 457.34 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}Cl_2N_3O_2S$ (456.3): C, 57.90; H, 3.31; N, 9.21. Found: C, 57.84; H, 3.26; N, 9.16.

_N_'-[3-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (19)
Yield: 0.85 g (73.10%). mp 126–128˚ (methanol), R_f: 0.63 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.08 (s, H, Ar-OH), 5.72 (s, H, C-H ethylene), 6.38-7.88 (m, 11H, Ar-H); EI-MS (m/z, 100%): 491.78 [M+1] (100%).; Anal Calculated for $C_{22}H_{14}Cl_3N_3O_2S$ (490.8): C, 53.84; H,2.88; N, 8.56. Found: C, 53.76; H,2.82; N, 8.51.

_N_'-[4-(2-chloro-4-methylphenyl)-3-(4-chlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (20)
Yield: 1.12 g (70.10%). mp 180–184˚ (methanol), R_f: 0.65 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 760 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.48 (s, 3H, C-H methyl), 5.04 (s, H, Ar-OH), 5.61 (s, H, C-H ethylene), 6.42-7.88 (m, 11H, Ar-H); EI-MS (m/z, 100%): 471.37 [M+1] (100%).; Anal Calculated for $C_{23}H_{17}Cl_2N_3O_2S$ (470.3): C, 58.73; H, 3.64; N, 8.93. Found: C, 58.69; H, 3.57; N, 8.88.

_N_'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-chlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (21)
Yield: 1.04 g (93.10%). mp 150–152˚ (methanol), R_f: 0.76 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 760 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 4.97 (s, 2H, Ar-OH), 6.44-7.82 (m, 11H, Ar-H), 5.62 (s, H, C-H ethylene); EI-MS (m/z, 100%): 473.34 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}Cl_2N_3O_3S$ (472.3): C, 55.94; H, 3.20; N, 8.90. Found: C, 55.87; H, 3.12; N, 8.82.

_N_'-[4-(2-chlorophenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (22)
Yield: 1.23 g (85.10%). mp above 300˚ (methanol), R_f: 0.84 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching,1525 (N-O) stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.0 (s, H, Ar-OH), 5.66 (s, H, C-H

ethylene), 6.75-7.82 (m, 12H, Ar-H); EI-MS (m/z, 100%): 467.87 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}ClN_4O_4S$ (466.9): C, 56.59; H, 3.24; N, 12.00. Found: C, 56.65; H, 3.19; N, 12.07.

***N*'-[4-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (23)**
Yield: 0.82 g (76.20%). mp 276–278˚ (methanol), R_f: 0.61 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching, 1525 (N-O) stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 4.94 (s, H, Ar-OH), 5.59 (s, H, C-H ethylene), 6.81-7.93 (m, 11H, Ar-H); EI-MS (m/z, 100%): 502.34 [M+1] (100%).; Anal Calculated for $C_{22}H_{14}Cl_2N_4O_4S$ (501.3): C, 52.71; H, 2.81; N, 11.18. Found: C, 52.67; H, 2.76; N, 11.22.

***N*'-[4-(2-chloro-4-methylphenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (24)**
Yield: 1.12 g (91.10%). mp 290–292˚ (methanol), R_f: 0.78 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 1525(N-O)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.48 (s, 3H, C-H methyl), 5.18 (s, H, Ar-OH), 5.71 (s, H, C-H ethylene), 6.73-7.81 (m, 11H, Ar-H); EI-MS (m/z, 100%): 481.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{17}ClN_4O_4S$ (480.9): C, 57.44; H, 3.56; N, 11.65. Found: C, 57.46; H, 3.49; N, 11.58.

***N*'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-nitrophenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (25)**
Yield: 0.92 g (78.10%). mp 178–182˚ (methanol), R_f: 0.82 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.18 (s, H, Ar-OH), 5.70 (s, H, C-H ethylene), 6.68-7.82 (m, 11H, Ar-H); EI-MS (m/z, 100%): 483.89 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}ClN_4O_5S$ (482.9): C, 54.72; H, 3.13; N, 11.60. Found: C, 54.67; H, 3.18; N, 11.63.

***N*'-[4-(2-chlorophenyl)-3-(4-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (26)**
Yield: 0.69 g (90.10%). mp 236–238˚ (methanol), R_f: 0.96 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1444 (C-O stretching and O-H deformation), 1637 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.47 (s, 3H, C-H methyl), 4.91 (s, H, Ar-OH), 5.63 (s, H, C-H ethylene), 6.42-7.73 (m, 12H, Ar-H); EI-MS (m/z, 100%): 436.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_2S$ (435.9): C, 63.37; H, 4.16; N, 9.64. Found: C, 63.33; H, 4.11; N, 9.61.

***N*'-[4-(2,4-dichlorophenyl)-3-(4-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (27)**
Yield: 0.94 g (89.10%). mp 154–156˚ (methanol), R_f: 0.84 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.52 (s, 3H, C-H methyl), 5.13 (s, H, Ar-OH), 5.58 (s, H, C-H ethylene), 6.41-7.53 (m, 12H, Ar-H); EI-MS (m/z, 100%): 471.37 [M+1] (100%).; Anal Calculated for $C_{23}H_{17}Cl_2N_3O_2S$ (470.4): C, 58.73; H, 3.64; N, 8.93. Found: C, 58.67; H, 3.59; N, 8.88.

***N*'-[4-(2-chloro-4-methylphenyl)-3-(4-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (28)**
Yield: 0.92 g (78.10%). mp 178–182˚ (methanol), R_f: 0.82 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.48 (s, 6H, C-H methyl), 4.97 (s, H, Ar-OH), 5.56 (s, H, C-H ethylene), 6.37-7.62 (m, 12H, Ar-H); EI-MS (m/z, 100%): 450.95 [M+1] (100%).; Anal Calculated for $C_{24}H_{20}ClN_3O_2S$ (449.9): C, 64.06; H, 4.48; N, 9.34. Found: C, 64.11; H, 4.37; N, 9.33.

***N*'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-methylphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (29)**
Yield: 0.89 g (69.10%). mp 260–264˚ (methanol), R_f: 0.62 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.48 (s, 3H, C-H methyl), 5.05 (s, H, Ar-OH), 5.66 (s, H, C-H ethylene), 6.47-7.76 (m, 12H, Ar-H); EI-MS (m/z, 100%): 452.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_3S$ (451.9): C, 61.13; H, 4.01; N, 9.30. Found: C, 61.06; H, 4.11; N, 9.33.

_N_'-[4-(2-chlorophenyl)-3-(4-hydroxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (30)
Yield: 0.84 g (90.10%). mp 164–168˚ (methanol), R_f: 0.78 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.17 (s, 2H, Ar-OH), 5.52 (s, H, C-H ethylene), 6.29-7.70 (m, 12H, Ar-H); EI-MS (m/z, 100%): 438.89 [M+1] (100%).; Anal Calculated for $C_{22}H_{16}ClN_3O_3S$ (437.9): C, 60.34; H, 3.68; N, 9.60. Found: C, 60.27; H, 3.61; N, 9.63.

_N_'-[4-(2,4-dichlorophenyl)-3-(4-hydroxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (31)
Yield: 0.96 g (80.50%). mp 250–254˚ (methanol), R_f: 0.74 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching); ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.08 (s, 2H, Ar-OH), 5.61 (s, H, C-H ethylene), 6.32-7.75 (m, 11H, Ar-H); EI-MS (m/z, 100%): 473.34 [M+1] (100%).; Anal Calculated for $C_{22}H_{15}Cl_2N_3O_3S$ (472.3): C, 55.94; H, 3.20; N, 8.90. Found: C, 55.87; H, 3.15; N, 8.93.

_N_'-[4-(2-chloro-4-methylphenyl)-3-(4-hydroxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (32)
Yield: 0.94 g (89.10%). mp 154–156˚ (methanol), R_f: 0.84 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.35 (s, 3H, C-H methyl), 5.11 (s, 2H, Ar-OH), 5.58 (s, H, C-H ethylene), 6.29-7.78 (m, 11H, Ar-H); EI-MS (m/z, 100%): 452.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_3S$ (451.9): C, 61.13; H, 4.01; N, 9.30. Found: C, 61.16; H, 4.12; N, 9.26.

_N_'-[4-(2-chloro-4-hydroxyphenyl)-3-(4-hydroxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (33)
Yield: 1.12 g (91.10%). mp 290–292˚ (methanol), R_f: 0.78 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching); ^{1}H-NMR (300MHz, DMSO-d_6: δ 5.15 (s, 3H, Ar-OH), 5.56 (s, H, C-H ethylene), 6.24-7.72 (m, 11H, Ar-H); EI-MS (m/z, 100%): 454.89 [M+1] (100%).; Anal Calculated for $C_{22}H_{16}ClN_3O_4S$ (453.9): C, 58.21; H, 3.55; N, 9.26. Found: C, 58.26; H, 3.48; N, 9.19.

_N_'-[4-(2-chlorophenyl)-3-(4-methoxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (34)
Yield: 0.78 g (75.20%). mp 220–222˚ (methanol), R_f: 0.54 (acetonitrile : methanol :: 7:); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 3.72 (s, 3H, C-H methyl), 5.12 (s, H, Ar-OH), 5.64 (s, H, C-H ethylene), 6.34-7.91 (m, 12H, Ar-H); EI-MS (m/z, 100%): 452.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_3S$ (451.9): C, 61.13; H, 4.01; N, 9.30. Found: C, 61.17; H, 4.06; N, 9.27.

_N_'-[4-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (35)
Yield: 1.21g (93.10%). mp 238–240˚ (methanol), R_f: 0.76 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 745 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 3.74 (s, 3H, C-H methyl), 5.02 (s, H, Ar-OH), 5.60 (s, H, C-H ethylene), 6.33-7.94 (m, 11H, Ar-H); EI-MS (m/z, 100%): 487.37 [M+1] (100%).; Anal Calculated for $C_{23}H_{17}Cl_2N_3O_3S$ (486.4): C, 56.80; H, 3.52; N, 8.64. Found: C, 56.84; H, 3.47; N, 8.59.

_N_'-[4-(2-chloro-4-methylphenyl)-3-(4-methoxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (36)
Yield: 0.81 g (75.10%). mp 210–212˚ (methanol), R_f: 0.63 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 775 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 2.36 (s, 3H, C-H methyl), 3.72 (s, 3H, C-H methyl), 5.08 (s, H, Ar-OH), 5.58 (s, H, C-H ethylene), 6.37-7.90 (m, 11H, Ar-H); EI-MS (m/z, 100%): 466.95 [M+1] (100%).; Anal Calculated for $C_{24}H_{20}ClN_3O_3S$ (465.9): C, 61.86; H, 4.33; N, 9.02. Found: C, 61.81; H, 4.36; N, 9.11.

_N'_-[4-(2-chloro-4-hydroxyphenyl)-3-(4-methoxyphenyl)-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxybenzohydrazide (37)

Yield: 1.12 g (70.10%). mp 180–184˚ (methanol), R_f: 0.65 (acetonitrile : methanol :: 7: 3); IR (KBr): cm^{-1} 1413 (C-O stretching and O-H deformation), 1728 (C=O stretching), 3350 (N-H stretching), 1615 (N-N stretching), 760 (C-Cl)stretching; ^{1}H-NMR (300MHz, DMSO-d_6: δ 3.75 (s, 3H, C-H methyl), 5.11 (s, 2H, Ar-OH), 5.62 (s, H, C-H ethylene), 6.41-7.92 (m, 11H, Ar-H); EI-MS (m/z, 100%): 468.92 [M+1] (100%).; Anal Calculated for $C_{23}H_{18}ClN_3O_4S$ (467.9): C, 59.04; H, 3.88; N, 8.98. Found: C, 59.11; H, 3.84; N, 8.89.

Antibacterial Activity:

The test compds were subjected *in vitro* screening by the tube dilution technique against various species of gram-positive and gram-negative bacteria viz. *S. aureus B. subtillus* and *E. coli* and *S. typhi* using Muller-Hinton broth (Himedia) as the culture medium. Muller Hinton broth (sterilized) was dispensed in each test tube (150 x 20 mm). The stock solution was sterilized by passing through polycarbonate sterile membrane (Nuclepore) filters (0.2 mm). Further, the serial dilution of test compds were carried out and the following concentration were used as 250, 125, 62, 32, 16, 8, 4 and 1 µg/mL. Similarly, the diluation were prepared for standard drugs. The test compds at various concentrations were added to culture medium in a sterilized test tube and different bacterial strains were inoculated at 10^6 bacilli/mL concentration. The tubes were incubated at 37° for 24 h.[19] The presence or absence of growth of the test organisms was examined. The experiments were performed in triplicate. The lowest concentration which showed no visible growth was taken as an end point (MIC). The results are summarized in Table. Antimycobacterial results are also given with these results for comparison.[20-21] The MIC values were compared with the standard antibiotics (ampicillin, penicillin-G and chloramphenicol).

Table 4 *In vitro* antimicrobial activity data of tested compounds (10-37)

Compd No.[a]	MIC[b] (µg/mL)			
	Gram positive organism		Gram negative organism	
	S. aureus	*B.subtilis*	*E.coli*	*S.typhi*
Std[1]	12.5	2.6	25	12.5
Std[2]	0.01	0.09	0.015	0.016
Std[3]	5	7	6	7
10	19	25	36	9.7
11	23	18	04	10.2
12	28	64	37	10.7
13	95	56	26	9.4
14	76	35	25	6.3
15	19	18	09	7.5
16	16	14	10	8.9
17	26	48	39	6.5
18	19	21	18	10
19	13	15	14	5.7
20	36	84	56	8.9
21	85	54	25	10.2
22	57	49	26	9.2
23	11	13	06	3.1
24	25	27	16	7.6
25	12	19	08	11.4
26	35	36	57	10.8
27	17	32	19	4.0
28	21	29	24	12.4
29	25	23	69	10.4
30	65	45	47	10.4
31	48	63	47	9.6
32	38	39	25	5.8
33	18	15	26	7.6
34	42	78	49	8.7
35	19	13	09	6.6
36	14	17	13	8.7
37	16	21	39	11.6

a = DMSO has no antibacterial activity at the concentration used to dissolve the compds, b = MIC in µg/mL, S. aureus= Staphylococcus aureus, B. subtilis = Bacillus subtilis, E. coli = Escherichia coli, S. typhi = Salmonella typhi, Std[1]: Ampicililin, Std[2]: Penicilin-G,Std[3]: Chloramphenicol.

CONCLUSION

3D-QSAR studies indicate that the antimicrobial activity might have increased by placing electron withdrawing groups like flurophenyl /dichlorophenyl on position 3 and 4 of thiazoline ring. Moreover, phenyl/ substituted phenyl groups on position 3 and 4 of thiazoline could be retained as analysis exhibited significant influence of aromatic moieties. To improve the activity of the said compounds, methyl and hydroxyl group were placed along with the chloro substitution. This attempt was made to check the possible hydrogen binding with receptor and increase hydrophobic volume in that region. Depending upon the QSAR results newer compounds were designed and compounds (10-37) were finalised for the synthesis and antimicrobial activity.

The compds, (10-37) exhibits the antimicrobial significant activity as expected. The compound (23) had shown highest antimicrobial activity against gram-positive and gram-negative organism while other compds (19), (16) and (25) also showed good antimicrobial activity. The activity was compared with ampicillin penicillin G, and chloramphenicol as standard drug.

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