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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antimicrobial evaluation of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazides and QSAR studies

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Abstract A series of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazides (**1**–**20**) was synthesized and tested for in vitro antimicrobial activity against *S. aureus, B. subtilis*, *E. coli, C. albicans* and *A. niger*. The results of antimicrobial studies indicated that 3-phenylacrylic acid-(3-hydroxybenzylidene)-hydrazide, **16**, was the most effective as it showed both bactericidal and fungicidal properties and other compounds possessed bacteriostatic/fungistatic activity. The multi-target QSAR model demonstrated that the topological parameter, Balaban topological index (*J*) is effective in describing the antimicrobial activity of synthesized substituted hydrazides.

Keywords Hydrazides derivatives · Antimicrobial · QSAR · MBC · MFC

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Introduction

Almost all the major classes of antibiotics have encountered resistance in clinical applications. The emergence of bacterial resistance to β-lactam antibiotics, macroliodes, quinolones and vancomycin is becoming a major worldwide health problem (Metwally *et al.*, 2006). The increasing incidence of bacterial resistance to established antibiotic classes is driving researchers to search for newer antibacterial agents (Tanitame *et al.*, 2004).

Hydrazones are well known class of compounds, possess various activities like antimicrobial (Vittorio *et al.*, 1995), antimycobacterial (Nayyar *et al.*, 2007), antitumour (Sztanke *et al.*, 2007), anti-inflammatory (Kalsi *et al.*, 1990), trypanocidal (Leite *et al.*, 2006), anti-HIV (Al-Mawsawi *et al.*, 2007), antimalarial (Gemma *et al.*, 2006) and antidiabetic activities (Smalley *et al.*, 2006).

During the last 20 years quantitative structure activity relationship (QSAR) models have gained an extensive recognition in physical, organic, analytical, pharmaceutical and medicinal chemistry. The success of the QSAR approach can be explained by the insight offered based on the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them among the homologous series (Ivanciuc *et al.*, 2002).

Inspired by the above facts and in continuation of our work in describing biological activity and QSAR study (Kumar *et al.*, 2008, 2009; Narasimhan *et al.*, 2003, 2004, 2006a, b, 2007a, b, c, d), we hereby report the synthesis, antimicrobial evaluation and QSAR studies of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazides.

Experimental

Melting points were determined in open capillary tubes using Sonar melting point apparatus and are uncorrected. Reaction progress was monitored by thin layer chromatography on silica gel sheets (Merck silica gel G) and purity of compound was ascertained by single spot TLC. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Avance II 400 NMR spectrometer using appropriate deuterated solvents and are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (internal standard). Infrared (IR) spectra were recorded on Perkin Elmer FTIR spectrometer using KBr pellets.

General procedure for synthesis of esters

The mixture of corresponding acid (0.08 mol) and ethanol (0.74 mol) was heated under reflux in the presence of sulphuric acid till the completion of reaction. When the reaction completed, the mixture was added to 200 ml ice-water and the produced ester was extracted with ether (50 ml). The ether layer was separated and after evaporation yielded the related ethyl esters.

General procedure for synthesis of acid hydrazides

The ethanolic solution of ester (0.01 mol) and hydrazine hydrate (99%) (0.015 mol) was refluxed for 5 h. The reaction mixture was then cooled, filtered and the precipitated solid was washed with water, dried and recrystallized in ethanol.

General procedure for synthesis of hydrazones (**1**–**20**)

A solution of 0.01 mol of acid hydrazide and appropriate aldehyde (0.01 mol) in ethanol was heated under reflux for 4–5 h. The precipitates obtained was filtered off, washed with water and recrystallized with ethanol.

*Compound **1***

Mp (°C) 79–83; Yield—63.20%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.85–0.89 (t, 3H, terminal CH_3 of CH_2CH_3), 1.25–1.38 (m, 16H, C_4–C_{10} of lauric acid), 2.72–2.76 (t, 2H, CH_2 of CH_2CONH), 8.06 (s, 1H, N=CH), 2.49–2.53(s, 3H, CH_3 of S-CH_3), 1.68–1.76 (m, 2H terminal CH_2 of CH_2CH_2CONH), 7.22–7.58 (m, 4H, ArH), 9.80 (s, 1H, NH). IR (KBr pellets) cm^{-1}: 3193.09 (NH str., amide), 3037.25 (CH str., aromatic), 2955.23 (CH str., aliphatic), 1737.98 (C=O str.), 720.45 (C–S str.).

*Compound **3***

Mp (°C) 103–107; Yield—43.10%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.86–0.89 (t, 3H, CH_3 of CH_2CH_3), 1.23–1.28 (m, 24H, C_4–C_{15} of palmitic acid), 7.59 (s, 1H, N=CH), 1.59–1.63 (m, 2H, terminal CH_2 of CH_2CH_2CONH), 2.26–2.30 (t, 2H, CH_2 of CH_2CONH), 2.48–2.53 (s, 3H, CH_3 of S-CH_3), 7.81–8.27 (m, 4H, ArH), 9.91–9.92 (s, 1H, NH). IR (KBr pellets) cm^{-1}: 3235.57 (NH str., amide), 3043.10 (CH str., aromatic), 2925.96 (CH str., aliphatic), 1702.40 (C=O str.), 720.01 (C–S str.).

*Compound **11***

Mp (°C) 87–91; Yield—69.40%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.77–0.80 (t, 3H, terminal CH_3), 7.76 (s, 1H, N=CH), 1.17–1.22 (m, 14H, C_4–C_{10} of lauric acid), 1.26–1.30 (m, 2H, CH_2 of CH_2CH_3), 1.56–1.64 (m, 2H, terminal CH_2 of CH_2CH_2CONH), 2.60–2.63 (t, 2H, CH_2 of CH_2CONH), 2.84 (s, 1H, OH), 6.99–7.17 (m, 4H, ArH), 10.42 (s, 1H, NH). IR (KBr pellets) cm^{-1}: 3307.46 (NH str., amide), 3040.15 (CH str., aromatic), 2916.47 (CH str., aliphatic), 1706.26 (C=O str.).

*Compound **12***

Mp (°C) 90–94; Yield—65.02%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.91–0.94 (t, 3H, terminal CH_3), 1.26–1.36 (m, 20H, CH_2 of $CH_3(CH_2)_{10}$), 2.73–2.76 (t, 2H, CH_2CONH), 1.70–1.71 (m, 2H terminal CH_2 of CH_2CH_2CONH), 6.88–7.25 (m, 4H, ArH), 10.69 (s, 1H, NH), 8.59 (s, 1H, N=CH). IR (KBr pellets) cm^{-1}: 3193.09 (NH str., amide), 3037.25 (CH str., aromatic), 2958.79 (CH str., aliphatic), 1731.82 (C=O str.).

*Compound **13***

Mp (°C) 107–111; Yield—52.01%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 0.85–0.89 (t, 3H, terminal CH_3), 1.22–1.27 (m, 24H, C_4–C_{15} of palmitic acid), 1.57–1.67 (m, 2H terminal CH_2 of CH_2CH_2CONH), 2.25–2.29 (t, 2H, CH_2 of CH_2CONH), 7.10–7.37 (m, 4H, ArH), 7.5 (s, 1H, N=CH), 9.91 (s, 1H, NH). IR (KBr pellets) cm^{-1}: 3301.83 (NH str., amide), 3043.10 (CH str., aromatic), 2925.96 (CH str., aliphatic), 1739.70 (C=O str.).

*Compound **20***

Mp (°C) 270–274; Yield—71.10%; ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.32–7.56 (m, 4H, ArH of ArOH), 9.12–9.26 (s, 3H, ArH of $Ar(NO_2)_2$), 8.06 (s, 1H, N=CH), 9.9 (s, 1H, NH). IR (KBr pellets) cm^{-1}: 3334.69 (NH str., amide),

3095.76 (CH str., aromatic), 2988.94 (CH str., aliphatic), 1725.14 (C=O str.), 1343 cm^{-1} (symmetric NO_2 stretching), 1538 cm^{-1} (asymmetric NO_2 stretching).

Evaluation of antimicrobial activity

Determination of MIC

The antimicrobial activity was performed against Gram-positive bacteria: *S. aureus MTCC 2901, B. sublitis MTCC 2063*, Gram-negative bacterium: *E. coli MTCC 1652* and fungal strains: *C. albicans MTCC 227* and *A. niger MTCC 8189* by tube dilution method (Cappucino and Sherman, 1999). Dilutions of test and standard compounds [ciprofloxacin (antibacterial) and fluconazole (antifungal)] were prepared in double strength nutrient broth—I.P. (bacteria) and Sabouraud dextrose broth—I.P (fungi) (Pharmacopoeia of India, 2007). The samples were incubated at 37°C for 24 h (bacteria), at 25°C for 7 days (*A. niger*) and at 37°C for 48 h (*C. albicans*), respectively, and the results (Table 2) were recorded in terms of MIC (the lowest concentration of test substance which inhibited the growth of microorganisms).

Determination of MBC/MFC

The minimum bactericidal concentration (MBC) and fungicidal concentration (MFC) were determined by subculturing 100 µl of culture from each tube that remained clear in the MIC determination into fresh medium. MBC and MFC values represent the lowest concentration of compound that produces a 99.9% end point reduction (Rodriguez-Arguelles *et al.*, 2005).

QSAR studies

In an attempt to determine the role of structural features which appears to influence the observed activity of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazide derivatives (**1**–**20**), QSAR studies were undertaken using linear free energy relationship (LFER) model of Hansch and Fujita (1964). The pMIC value of the biological activity data was used as dependent variable in QSAR study. These were correlated with different molecular descriptors like log of octanol–water partition coefficient (log *P*), molar refractivity (MR), Kier's molecular connectivity ($^0\chi^v$), shape (κ_1, $\kappa\alpha_1$) topological indices, Randic topological index (*R*), Balaban topological index (*J*), Total energy (T_e), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ), electronic energy (Ele.E) and nuclear energy (Nu.E) (Hansch *et al.*, 1973; Kier and Hall, 1976; Randic, 1975, 1993; Balaban, 1982; Wiener, 1947).

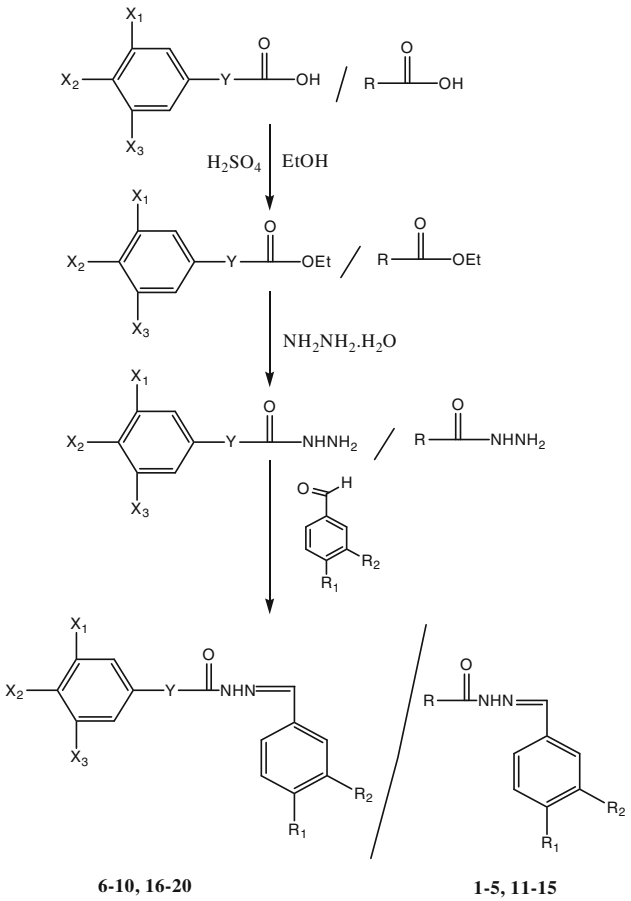
The structure of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazides was optimized by energy minimization. The physicochemical properties of each molecule was calculated in TSAR 3.3 software (TSAR 3D for Windows, Version 3.3, 2000) for the geometrically optimized structures and the values of selected descriptors are presented in Table 4. Further, the regression analysis was performed using the SPSS software package (SPSS for windows, version 10.05, 1999). The predictive powers of the equations were validated by leave one out (LOO) cross-validation method (Schaper, 1999), where a model is built with $N - 1$ compounds and *N*th compound is predicted. Each compound is left out of the model derivation and predicted in turn.

Results and discussion

Chemistry

The synthesis of target compounds was carried out as outlined in Scheme 1. The ethyl esters of different carboxylic acids were prepared by their reaction with ethanol in the presence of sulphuric acid. The ethyl ester (0.01 mol) on reaction with hydrazine hydrate (0.015 mol) yielded the corresponding hydrazides which on treatment with corresponding aromatic aldehydes resulted the acid hydrazones (**1**–**20**). The products so obtained were purified by recrystallization from ethanol. The target compounds were obtained in appreciable yield and their physicochemical characteristics are presented in Table 1.

The structures of the synthesized compounds (**1**–**20**) were ascertained on the basis of their consistent IR and NMR spectral characteristics. The presence of C=O functional group was marked by the appearance of stretching band around 1700 cm^{-1}, which is a characteristic of amide linkage. The appearance of stretching band around 3200 cm^{-1} indicates the presence of NH linkage in the synthesized hydrazide derivatives. The presence of peaks slightly above and below 3000 cm^{-1} indicates the presence of aromatic and aliphatic portion in synthesized compounds, respectively. The aromatic nitro stretching around 1343 cm^{-1} (symmetric NO_2 stretching) and 1538 cm^{-1} (asymmetric NO_2 stretching) depicts the presence of nitro functional group in compound **20**. The appearance of stretching band around 720 cm^{-1} indicates the presence of C–S linkage in the synthesized hydrazide derivatives (compounds **1** and **3**). The appearance of singlet around δ 7–8 ppm of N=CH indicated the formation of title compounds. The appearance of singlet signal ranging from δ 9.8 to 10.69 in synthesized compounds confirms the presence of NH of hydrazide. The display of singlet signal in



Comp.	R	R_1	R_2	Y	X_1	X_2	X_3
1	$CH_3(CH_2)_9CH_2$-	H	SCH_3	-	-	-	-
2	$CH_3(CH_2)_{11}CH_2$-	H	SCH_3	-	-	-	-
3	$CH_3(CH_2)_{13}CH_2$-	H	SCH_3	-	-	-	-
4	$CH_3(CH_2)_{15}CH_2$-	H	SCH_3	-	-	-	-
5	$CH_3(CH{=}CH)_2$-	H	SCH_3	-	-	-	-
6	-	H	SCH_3	CH=CH	H	H	H
7	-	H	SCH_3	-	CH_3	H	H
8	-	H	SCH_3	-	H	CH_3	H
9	-	H	SCH_3	-	OCH_3	OCH_3	H
10	-	H	SCH_3	-	NO_2	H	NO_2
11	$CH_3(CH_2)_9CH_2$-	OH	H	-	-	-	-
12	$CH_3(CH_2)_{11}CH_2$-	OH	H	-	-	-	-
13	$CH_3(CH_2)_{13}CH_2$-	OH	H	-	-	-	-
14	$CH_3(CH_2)_{15}CH_2$-	OH	H	-	-	-	-
15	$CH_3(CH{=}CH)_2$-	OH	H	-	-	-	-
16	-	OH	H	CH=CH	H	H	H
17	-	OH	H	-	CH_3	H	H
18	-	OH	H	-	H	CH_3	H
19	-	OH	H	-	OCH_3	OCH_3	H
20	-	OH	H	-	NO_2	H	NO_2

Scheme 1 Synthetic route followed to obtain target compounds from aliphatic acids

the range of δ 2.48–2.53 in compounds **1** and **3** reveals the presence of thiomethyl group. The appearance of multiplet signal in the range of δ 9.12–9.26 (compound **20**) reveals the presence of proton of aromatic nucleus containing of NO_2 group.

Table 1 Physicochemical characteristics of substituted benzylidene hydrazides

Comp.	M. formula	M. wt.	M.p./B.p.$^+$ (°C)	R_f value	% Yield
1	$C_{20}H_{32}N_2OS$	348	79–83	0.65	63.20
2	$C_{22}H_{36}N_2OS$	376	97–101	0.57	58.20
3	$C_{24}H_{40}N_2OS$	404	103–107	0.78	43.10
4	$C_{26}H_{44}N_2OS$	432	129–133	0.82	62.08
5	$C_{14}H_{16}N_2OS$	260	127–131$^+$	0.61[a]	72.08
6	$C_{17}H_{16}N_2OS$	296	Semisolid	0.44[a]	70.20
7	$C_{16}H_{16}N_2OS$	284	143–147	0.75[a]	39.80
8	$C_{16}H_{16}N_2OS$	284	150–154	0.63[a]	52.20
9	$C_{17}H_{18}N_2O_3S$	330	198–202$^+$	0.89[a]	60.10
10	$C_{15}H_{12}N_4O_5S$	360	249–253	0.82	77.70
11	$C_{19}H_{30}N_2O_2$	318	87–91	0.86	69.40
12	$C_{21}H_{34}N_2O_2$	346	90–94	0.66	65.02
13	$C_{23}H_{38}N_2O_2$	374	107–111	0.82	52.01
14	$C_{25}H_{42}N_2O_2$	402	113–117	0.68	76.60
15	$C_{13}H_{14}N_2O_2$	230	121–125	0.59[a]	71.80
16	$C_{16}H_{14}N_2O_2$	266	Semisolid	0.62[a]	65.70
17	$C_{15}H_{14}N_2O_2$	254	157–161	0.59[a]	39.01
18	$C_{15}H_{14}N_2O_2$	254	187–191	0.73[a]	45.30
19	$C_{16}H_{16}N_2O_4$	300	213–217	0.62[a]	63.20
20	$C_{14}H_{10}N_4O_6$	330	270–274	0.72[a]	71.10

Mobile phase—toluene:chloroform (7:3)

[a] Ethyl acetate:hexane (6:4)

Antimicrobial activity

For antifungal activity against *A. niger* compounds **10**, **16**, **19** and **20** were found to be highly active having high pMIC value of 2.06, 1.93, 1.98 and 2.02 (Table 2), respectively, as compared to other synthesized derivatives. Further, in case of *C. albicans* compounds **8**, **16** and **19** have shown good antifungal potential at pMIC values of 1.96, 1.93 and 1.98 (Table 2), respectively.

In case of *B. subtilis* compounds **2**, **3**, **10** and **12** have shown marked antibacterial capability at pMIC value greater than 2.03 as compared to other synthesized substituted benzylidene hydrazide derivatives. For antibacterial activity against *S. aureus* compounds **18** and **19** have shown better antibacterial potential as compared to other synthesized derivatives. Compounds **3**, **8**, **10** and **18** have shown appreciable antibacterial activity against *E. coli* with pMIC value of 1.81 1.96, 2.06 and 1.77 (Table 2), respectively. In general, synthesized benzylidene hydrazide derivatives have shown higher antifungal and antibacterial potential against *A. niger* and *B. subtilis*, respectively.

Table 2 Antimicrobial activity (μM/ml) of substituted benzylidene hydrazides

Comp.	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{am}$	$pMIC_{b}$	$pMIC_{f}$
1	1.30	1.45	1.30	1.66	1.25	1.39	1.35	1.46
2	0.58	2.08	1.48	0.58	1.70	1.28	1.38	1.14
3	1.21	2.11	1.81	0.61	0.61	1.27	1.71	0.61
4	0.94	0.64	1.65	0.70	0.70	0.93	1.08	0.70
5	1.02	0.72	1.32	1.32	1.32	1.14	1.02	1.32
6	1.68	1.68	1.68	1.37	1.37	1.56	1.68	1.37
7	1.55	1.06	1.66	1.67	1.70	1.53	1.42	1.69
8	1.66	1.96	1.96	1.96	1.66	1.84	1.86	1.81
9	1.72	1.42	1.70	1.42	1.59	1.57	1.61	1.51
10	1.46	2.06	2.06	0.86	2.06	1.70	1.86	1.46
11	0.98	0.80	0.98	1.10	1.71	1.11	0.92	1.41
12	0.94	2.04	0.94	0.54	1.20	1.13	1.31	0.87
13	0.99	1.78	1.13	0.57	1.20	1.13	1.30	0.89
14	1.10	1.51	1.30	0.60	1.51	1.20	1.30	1.06
15	0.96	1.27	1.27	1.41	1.27	1.24	1.17	1.34
16	1.70	1.93	1.32	1.93	1.93	1.76	1.65	1.93
17	1.31	1.31	1.77	1.31	1.31	1.40	1.46	1.31
18	1.91	1.91	1.77	1.31	1.61	1.70	1.86	1.46
19	1.98	1.38	1.38	1.98	1.98	1.74	1.58	1.98
20	1.12	1.42	1.42	1.42	2.02	1.48	1.32	1.72
S.D.	0.14	0.29	0.26	0.23	0.28	0.17	0.18	0.20
Std.	2.61[a]	2.61[a]	2.61[a]	2.64[b]	2.64[b]	2.62	2.61	2.64

S.D. standard deviation

[a] Ciprofloxacin

[b] Fluconazole

In general, the results of MBC/MFC (Table 3) revealed that the synthesized compounds were bacteriostatic and fungistatic in action as their MBC and MFC values were threefold higher than their MIC values (a drug is considered to be bacteriostatic/fungistatic when its MBC and MFC values are threefold higher than its MIC value) (Rodriguez-Arguelles *et al.*, 2005). Particularly compounds **9** and **16** were bactericidal for *S. aureus*, compounds **16** and **18** were bactericidal against *B. subtilis*, compounds **4**, **10** and **16** were bactericidal for *E. coli* and compounds **16**, **19** and **20** were found to fungicidal in case of *A. niger*. Compound **16** was found to be active fungicidal agent against *C. albicans*. 3-Phenylacrylic acid-(3-hydroxybenzylidene)-hydrazide, **16**, was found to be bactericidal as well as fungicidal.

Development of one-target QSAR model

In this work, a data set of 20 benzylidene hydrazide derivatives was used for linear regression model generation. The values of selected descriptors are presented in Table 4. The correlation matrix constructed for antibacterial activity against *E. coli* is presented in Table 5. The high interrelationship was observed between $\kappa\alpha_3$ and κ_3 ($r = 0.999$), and low interrelationship was observed between HOMO and J ($r = -0.008$) (Table 5).

The correlation of calculated molecular descriptors with antimicrobial activity is presented in Table 6 which depicted the importance of valence third order molecular connectivity index ($^3\chi^v$, $r = 0.825$) in describing the antimicrobial activity of benzylidene hydrazides against *E. coli*.

ot-QSAR model for antibacterial activity against E. coli

$$pMIC_{ec} = 1.859\,^3\chi^v + 0.725 \quad (1)$$

when $n = 20$, $r = 0.825$, $q^2 = 0.589$, $s = 0.180$, $F = 38.36$; where, n number of data points, r correlation coefficient, q^2 cross-validated r^2 obtained by leave one out methods, s standard error of the estimate and F Fischer statistics.

The topological index, $^3\chi^v$, signifies the degree of branching, connectivity of atoms and the unsaturation in the molecule which accounts for variation in activity (Wiener, 1947). The positive coefficient of $^3\chi^v$ in Eq. 1 indicates that there is a positive correlation between the

Table 3 MBC/MFC values of substituted benzylidene hydrazides

Comp.	MBC/MFC (μM/ml)				
	S. aureus	*B. subtilis*	*E. coli*	*C. albicans*	*A. niger*
1	>0.142	>0.142	>0.142	>0.142	0.071
2	>0.132	0.033	>0.132	>0.132	>0.132
3	>0.122	0.061	0.061	>0.122	>0.122
4	>0.115	>0.115	0.028	>0.115	0.115
5	0.192	>0.192	>0.192	>0.192	0.096
6	>0.168	>0.168	0.168	0.084	>0.168
7	>0.176	>0.176	0.176	0.176	0.088
8	>0.176	0.044	0.088	0.088	0.088
9	0.037	>0.151	>0.151	>0.151	>0.151
10	0.069	0.069	0.008	>0.138	0.069
11	>0.157	0.157	0.157	0.157	0.078
12	>0.144	0.144	>0.144	>0.144	>0.144
13	>0.133	0.133	>0.133	>0.133	>0.133
14	>0.124	0.124	>0.124	>0.124	>0.124
15	>0.217	0.217	>0.217	0.217	0.217
16	0.046	0.046	0.046	0.093	0.093
17	>0.196	>0.196	0.098	0.098	0.098
18	0.098	0.012	0.098	0.098	>0.196
19	0.083	>0.166	>0.166	0.083	0.041
20	>0.151	>0.151	>0.151	>0.151	0.037
Std.	0.019	0.019	0.019	0.040	0.040

Table 4 Values of selected descriptors used in the regression analysis

Comp.	log *P*	$^{3}\chi$	$^{3}\chi^{v}$	κ_1	κ_2	κ_3	$\kappa\alpha_1$	$\kappa\alpha_2$	*J*	HOMO
1	5.798	0.697	0.384	22.042	15.270	12.086	21.313	14.599	1.801	−8.007
2	6.591	0.697	0.384	24.039	17.123	13.786	23.310	16.444	1.774	−8.007
3	7.384	0.697	0.384	26.036	18.993	15.519	25.307	18.308	1.750	−8.007
4	8.176	0.697	0.384	28.033	20.878	17.280	27.304	20.188	1.729	−8.143
5	3.240	0.697	0.370	16.056	9.868	7.259	14.810	8.785	1.897	−7.958
6	3.924	0.901	0.467	17.355	9.904	6.743	15.616	8.502	1.401	−7.977
7	3.984	1.099	0.612	16.372	8.444	5.379	14.890	7.320	1.462	−8.002
8	3.984	1.099	0.612	16.372	8.444	5.379	14.890	7.320	1.467	−7.998
9	3.011	1.219	0.582	19.326	10.096	6.094	17.759	8.890	1.523	−7.979
10	3.424	1.811	0.669	21.302	10.364	6.585	18.942	8.632	1.581	−8.292
11	5.423	0.781	0.243	21.044	14.352	12.071	19.926	13.331	1.778	−8.857
12	6.216	0.781	0.243	23.040	16.194	13.812	21.922	15.160	1.760	−8.991
13	7.009	0.781	0.243	25.037	18.056	15.584	23.919	17.011	1.737	−8.992
14	7.801	0.781	0.243	27.035	19.934	17.381	25.916	18.880	1.717	−8.991
15	2.865	0.781	0.230	15.059	9.000	7.111	13.425	7.604	1.886	−8.775
16	3.549	0.986	0.326	16.372	9.107	6.549	14.253	7.434	1.404	−8.803
17	3.609	1.184	0.472	15.390	7.695	5.120	13.530	6.320	1.472	−8.846
18	3.609	1.184	0.472	15.390	7.695	5.120	13.530	6.320	1.477	−8.839
19	2.636	1.303	0.441	18.340	9.333	5.864	16.392	7.867	1.535	−8.821
20	3.049	1.895	0.529	20.314	9.630	6.353	17.572	7.663	1.597	−9.266

Table 5 Correlation matrix for $pMIC_{ec}$ with molecular descriptors

	$pMIC_{ec}$	$^{0}\chi^{v}$	$^{2}\chi$	$^{3}\chi$	$^{3}\chi^{v}$	κ_3	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	J	HOMO
$pMIC_{ec}$	1.000										
$^{0}\chi^{v}$	−0.103	1.000									
$^{2}\chi$	0.076	0.781	1.000								
$^{3}\chi$	0.444	−0.437	0.181	1.000							
$^{3}\chi^{v}$	0.825	−0.285	0.025	0.702	1.000						
κ_3	−0.402	0.915	0.629	−0.615	−0.630	1.000					
$\kappa\alpha_1$	−0.214	0.981	0.816	−0.394	−0.383	0.947	1.000				
$\kappa\alpha_2$	−0.320	0.957	0.664	−0.596	−0.541	0.991	0.970	1.000			
$\kappa\alpha_3$	−0.386	0.923	0.618	−0.632	−0.616	0.999	0.948	0.994	1.000		
J	−0.544	0.424	0.071	−0.539	−0.634	0.617	0.502	0.589	0.618	1.000	
HOMO	0.508	0.203	−0.133	−0.264	0.442	−0.045	0.042	0.058	−0.010	−0.008	1.000

Table 6 Correlation of molecular descriptors with antimicrobial activity

Molecular descriptor	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{b}$	$pMIC_{f}$	$pMIC_{am}$
log P	−0.586	0.069	−0.236	−0.751	−0.623	−0.315	−0.803	−0.676
MR	−0.499	0.081	−0.089	−0.728	−0.542	−0.214	−0.746	−0.577
$^{0}\chi$	−0.448	0.134	−0.094	−0.727	−0.335	−0.163	−0.639	−0.482
$^{0}\chi^{v}$	−0.493	0.071	−0.103	−0.721	−0.530	−0.222	−0.735	−0.576
$^{1}\chi$	−0.437	0.137	−0.102	−0.724	−0.380	−0.160	−0.661	−0.493
$^{1}\chi^{v}$	−0.517	0.066	−0.095	−0.714	−0.575	−0.233	−0.754	−0.594
$^{2}\chi$	−0.243	0.224	0.076	−0.599	−0.102	0.042	−0.437	−0.232
$^{2}\chi^{v}$	−0.490	0.089	−0.056	−0.712	−0.549	−0.193	−0.740	−0.560
$^{3}\chi$	0.454	0.165	0.444	0.321	0.685	0.461	0.558	0.624
$^{3}\chi^{v}$	0.564	0.124	0.825	0.411	0.407	0.628	0.474	0.684
κ_1	−0.545	0.089	−0.195	−0.770	−0.435	−0.269	−0.718	−0.597
κ_2	−0.635	0.025	−0.326	−0.778	−0.584	−0.394	−0.800	−0.725
κ_3	−0.672	0.011	−0.402	−0.783	−0.596	−0.447	−0.809	−0.764
$\kappa\alpha_1$	−0.568	0.067	−0.214	−0.771	−0.490	−0.299	−0.747	−0.633
$\kappa\alpha_2$	−0.635	0.015	−0.320	−0.768	−0.604	−0.398	−0.804	−0.730
$\kappa\alpha_3$	−0.667	0.005	−0.386	−0.776	−0.610	−0.442	−0.812	−0.763
R	−0.437	0.137	−0.102	−0.724	−0.380	−0.160	−0.661	−0.493
J	−0.800	−0.270	−0.544	−0.523	−0.458	−0.713	−0.572	−0.794
W	−0.519	0.055	−0.145	−0.763	−0.522	−0.258	−0.759	−0.613
T_e	0.368	−0.156	0.073	0.650	0.130	0.107	0.484	0.356
LUMO	−0.072	−0.149	−0.262	−0.043	−0.502	−0.213	−0.284	−0.305
HOMO	0.087	−0.048	0.508	0.102	−0.267	0.201	−0.072	0.090
μ	0.493	0.062	0.332	0.402	0.590	0.380	0.562	0.575

antibacterial activity of substituted hydrazides and $^{3}\chi^{v}$. This is evidenced by the antibacterial activity data of substituted hydrazides (Table 2) and their $^{3}\chi^{v}$ values (Table 4). Compounds **8** and **10** with maximum $^{3}\chi^{v}$ values of 0.612 and 0.669 (Table 4) have maximum antibacterial activity against *E. coli* (compound **8**, $pMIC_{ec}$ 1.96; compound **10**, $pMIC_{ec}$ 2.06; Table 2). Similarly, the compounds **12** and **15** with minimum $^{3}\chi^{v}$ (0.243 and 0.230; Table 4) value have minimum antibacterial activity ($pMIC_{ec}$ 0.94 and 1.27; Table 2). The cross-validation of Eq. 1 was subsequently checked by employing "leave one out" (LOO) method. The q^2 value of Eq. 1 ($q^2 > 0.5$) justifies it to be a valid model according to the recommendations of Golbraikh and Tropsha (2002). The predictability of Eq. 1 is evidenced by the low residual values observed in Table 7 as well by the plot of predicted $pMIC_{ec}$ against observed

Table 7 Comparison of observed and predicted antimicrobial activity obtained by ot-QSAR models

Comp.	$pMIC_{ec}$ (Eq. 1)			$pMIC_{sa}$ (Eq. 2)			$pMIC_{ca}$ (Eq. 3)			$pMIC_{an}$ (Eq. 4)		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.30	1.44	−0.14	1.30	1.00	0.30	1.66	1.00	0.66	1.25	1.25	0.00
2	1.48	1.44	0.04	0.58	1.05	−0.47	0.58	0.85	−0.27	1.70	1.25	0.45
3	1.81	1.44	0.37	1.21	1.09	0.12	0.61	0.70	−0.09	0.61	1.25	−0.64
4	1.65	1.44	0.21	0.94	1.13	−0.19	0.70	0.55	0.15	0.70	1.25	−0.55
5	1.32	1.41	−0.09	1.02	0.82	0.20	1.32	1.41	−0.09	1.32	1.25	0.07
6	1.68	1.59	0.09	1.68	1.75	−0.07	1.37	1.46	−0.09	1.37	1.41	−0.04
7	1.66	1.86	−0.20	1.55	1.64	−0.09	1.67	1.57	0.10	1.70	1.56	0.14
8	1.96	1.86	0.10	1.66	1.63	0.03	1.96	1.57	0.39	1.66	1.56	0.10
9	1.70	1.81	−0.11	1.72	1.52	0.20	1.42	1.51	−0.09	1.59	1.65	−0.06
10	2.06	1.97	0.09	1.46	1.41	0.05	0.86	1.47	−0.61	2.06	2.10	−0.04
11	0.98	1.18	−0.20	0.98	1.04	−0.06	1.10	1.00	0.10	1.71	1.32	0.39
12	0.94	1.18	−0.24	0.94	1.07	−0.13	0.54	0.85	−0.31	1.20	1.32	−0.12
13	1.13	1.18	−0.05	0.99	1.12	−0.13	0.57	0.70	−0.13	1.20	1.32	−0.12
14	1.30	1.18	0.12	1.10	1.16	−0.06	0.60	0.55	0.05	1.51	1.32	0.19
15	1.27	1.15	0.12	0.96	0.84	0.12	1.41	1.43	−0.02	1.27	1.32	−0.05
16	1.32	1.33	−0.01	1.70	1.75	−0.05	1.93	1.47	0.46	1.93	1.47	0.46
17	1.77	1.60	0.17	1.31	1.62	−0.31	1.31	1.60	−0.29	1.31	1.62	−0.31
18	1.77	1.60	0.17	1.91	1.61	0.30	1.31	1.60	−0.29	1.61	1.62	−0.01
19	1.38	1.54	−0.16	1.98	1.50	0.48	1.98	1.53	0.45	1.98	1.71	0.27
20	1.42	1.71	−0.29	1.12	1.38	−0.26	1.42	1.49	−0.07	2.02	2.17	−0.15

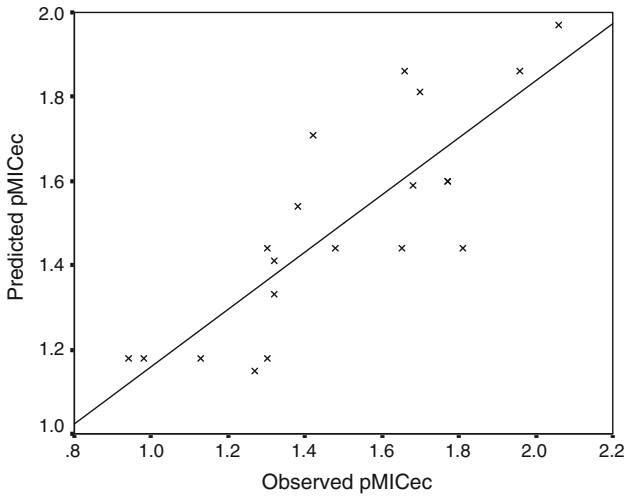


Fig. 1 Plot of predicted $pMIC_{ec}$ against the experimental $pMIC_{ec}$ for the linear regression model developed by Eq. 1

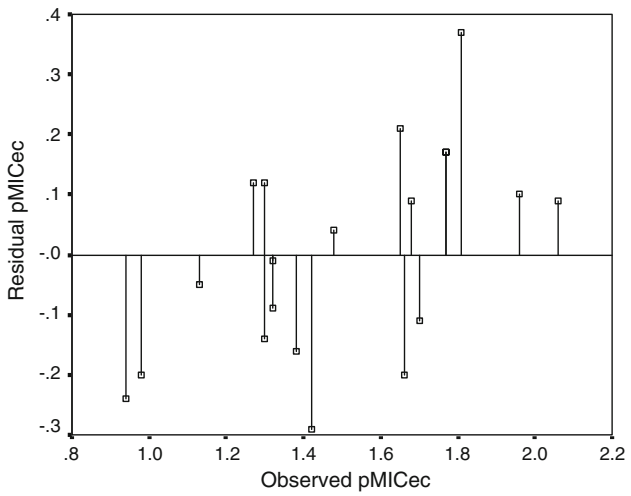


Fig. 2 Plot of residual $pMIC_{ec}$ against the experimental $pMIC_{ec}$ for the linear regression model developed by Eq. 1

$pMIC_{ec}$ (Fig. 1). Further, the plot of observed $pMIC_{ec}$ vs. residual $pMIC_{ec}$ (Fig. 2) indicated that there was no systemic error in model development as the propagation of error was observed on both sides of zero (Kumar *et al.*, 2007).

Similarly, monoparametric QSAR models (Eqs. 2–4) were developed to predict the antimicrobial potential of different substituted benzylidene hydrazides against *S. aureus*, *C. albicans* and *A. niger*.

ot-QSAR model for antibacterial activity against S. aureus

$$pMIC_{sa} = -1.889\,J + 4.398 \quad (2)$$

when $n = 20$, $r = 0.800$, $q^2 = 0.603$, $s = 0.236$, $F = 31.93$.

ot-QSAR model for antifungal activity against C. albicans

$$\mathrm{pMIC_{ca}} = -0.086\,\kappa_3 + 2.034 \quad (3)$$

when $n = 20$, $r = 0.783$, $q^2 = 0.584$, $s = 0.316$, $F = 28.51$.

ot-QSAR model for antifungal activity against A. niger

$$\mathrm{pMIC_{an}} = 0.764\,{}^3\chi + 0.718 \quad (4)$$

when $n = 20$, $r = 0.685$, $q^2 = 0.427$, $s = 0.296$, $F = 15.91$.

The model described in Eq. 2 indicated the importance of topological parameter, Balaban topological index, J ($r = 0.800$) in demonstrating antibacterial activity of substituted hydrazide derivatives against *S. aureus.* In case of *B. subtilis* the regression analysis did not yield valid QSAR model. For the antifungal activity of *C. albicans* the statistically significant relationship was observed with Kier's third order shape index (κ_3) (Table 6).

For the antifungal activity of *A. niger* the coefficient of third order molecular connectivity index, ${}^3\chi$, is positive indicating that as the value of ${}^3\chi$ increases, the antifungal activity of synthesized derivatives also increases. This is evidenced by the high ${}^3\chi$ values of compounds **9**, **10**, **18**, **19** and **20** (${}^3\chi = 1.219$, 1.811, 1.184, 1.303, 1.895; Table 4) which make them highly active with $\mathrm{pMIC_{an}}$ value of 1.59, 2.06, 1.61, 1.98 and 2.02 (Table 2), respectively. The predictability of Eqs. 2–4 was evidenced by the low residual values (Table 7).

Topological descriptors (${}^3\chi$) contain information about degree of branching and size of molecules. The topological descriptor characterizes the flexibility of alkyl chain and is connected closely with rearrangement of compounds. For molecule with more than one branched chain or with quaternary carbon atom in alkyl chain, the freedom of molecular skeleton decreases, where as the value of ${}^3\chi$ increase. The ${}^3\chi$ value for molecules having only one branch is smaller than those with many side chains. The positive coefficient in the models for ${}^3\chi$ means that molecule having higher degree of branching will have increased relative retention time (Fragkaki *et al.*, 2004). As the topological descriptor characterizes the shape of molecules so they play an important role in binding with receptor site.

As per 'rule of thumb' (Narasimhan *et al.*, 2006b) one can select one parameter for a five-compound data set in developing QSAR model. Even though the sample size and the 'Rule of Thumb' allowed us to go for development of tetra-parametric model in multiple linear regression analysis, the multi-colinearity among the parameters restricted us to mono-parametric models only.

In most of the QSAR studies, the biological activities of compounds span 2–3 orders of magnitude but in this study the range of antimicrobial activities of the synthesized compounds are within one order of magnitude. But it is important to note that the predictability of the QSAR models developed in this study is high evidenced by the low residual values. This is in accordance with results suggested by the Bajaj *et al.* (2005), who stated that the reliability of the QSAR model lies in its predictive ability even though the activity data are in the narrow range. Further, recent literature reveals that the QSAR have been applied to describe the relationship between narrow range of biological activity and physicochemical properties of the molecules (Narasimhan *et al.*, 2006b; Sharma *et al.*, 2006; Hatya *et al.*, 2006; Kumar *et al.*, 2006). When biological activity data lies in the narrow range, the presence of minimum standard deviation of the biological activity justifies its use in QSAR studies (Narasimhan *et al.*, 2007a; Kumar *et al.*, 2007; Kim *et al.*, 2007). The minimum standard deviation (Table 2) observed in the antimicrobial activity data justifies its use in QSAR studies.

Development of multi-target QSAR model

According to the above ot-QSAR models one should use five different equations with different errors to predict the activity of a new compound against the five microbial species. The ot-QSAR models, which are almost in all the literature, become unpractical or at less complicated to use when we have to predict to each compound results for more than one target. In these cases we have to develop one ot-QSAR for each target. However, very recently the interest has been increased in development of multi-target QSAR (mt-QSAR) models. In opposition to ot-QSAR, the mt-QSAR model is a single equation that considers the nature of molecular descriptors which are common and essential for describing the antimicrobial activity (Prado-Prado *et al.*, 2008; Gonzalez-Diaz *et al.*, 2007, 2008; Gonzalez-Diaz and Prado-Prado 2008; Cruz-Monteagudo *et al.*, 2007).

In this study we have attempted to develop three different types of mt-QSAR models viz. mt-QSAR model for describing antibacterial activity of synthesized compounds against *S. aureus, B. subtilis* and *E. coli*, mt-QSAR model for describing antifungal activity of synthesized compounds against *C. albicans* and *A. niger* as well a common mt-QSAR model for describing the antimicrobial activity of substituted hydrazide derivatives against all the aforementioned microorganisms.

In order to develop mt-QSAR models initially we have calculated the average antibacterial activity [$\mathrm{pMIC_b} = (\mathrm{pMIC_{sa}} + \mathrm{pMIC_{bs}} + \mathrm{pMIC_{ec}})/3$], antifungal activity [$\mathrm{pMIC_f} = (\mathrm{pMIC_{ca}} + \mathrm{pMIC_{an}})/2$] and antimicrobial activity values [$\mathrm{pMIC_{am}} = (\mathrm{pMIC_{sa}} + \mathrm{pMIC_{bs}} + \mathrm{pMIC_{ec}} + \mathrm{pMIC_{ca}} + \mathrm{pMIC_{an}})/5$] of substituted benzylidene hydrazide derivatives which are presented in Table 2. These

average activity values were correlated with the molecular descriptors of synthesized compounds (Table 6). The data depicted in Table 6 indicated that the $pMIC_b$, $pMIC_f$ and $pMIC_{am}$ are equally correlated with the molecular descriptors as compared to ot-MIC values, i.e., $pMIC_{sa}$, $pMIC_{bs}$, $pMIC_{ec}$, $pMIC_{ca}$ and $pMIC_{an}$.

mt-QSAR model for antibacterial activity

$$pMIC_b = -1.230\,J + 3.45 \quad (5)$$

when $n = 20$, $r = 0.713$, $q^2 = 0.488$, $s = 0.201$, $F = 18.56$.

In case of antibacterial mt-QSAR studies the developed model (Eq. 5) reveals the importance of Balaban topological index (J) in describing antibacterial activity of synthesized benzylidene hydrazide derivatives. The negative coefficient of Balaban topological index in Eq. 5 indicates that there is negative correlation between antibacterial activity of substituted hydrazides and Balaban topological index. This is evidence by low antibacterial activity values (1.08, 1.02, 0.92 and 1.17, Table 2) and their high J (1.729, 1.897, 1.778 and 1.886, Table 4) values of compounds **4**, **5**, **11** and **15**, respectively.

mt-QSAR model for antifungal activity

$$pMIC_f = -0.067\kappa\alpha_3 + 1.926 \quad (6)$$

when $n = 20$, $r = 0.812$, $q^2 = 0.609$, $s = 0.230$, $F = 34.88$.

Further, model depicted in Eq. 6 describes the statistically significant relationship between Kier's alpha third order shape index ($\kappa\alpha_3$) and antifungal activity of substituted hydrazide derivative. In this case also negative relationship was observed between $\kappa\alpha_3$ and antifungal activity of synthesized substituted hydrazide derivatives. The above fact can be proved by antifungal activity values (Table 2) and their respective $\kappa\alpha_3$ values (Table 4).

mt-QSAR model for antimicrobial activity

$$pMIC_{am} = 1.287\,J + 3.51 \quad (7)$$

when $n = 20, r = 0.794, q^2 = 0.614, s = 0.164, F = 36.65$.

Similarly, in case of antimicrobial studies, the developed mt-QSAR model Eq. 7 signifies the importance of Balaban topological index (J) in demonstrating the antimicrobial activity of synthesized derivatives. This is evidenced by antimicrobial activity data (Table 2) and their J values (Table 4).

Table 8 Comparison of observed and predicted antimicrobial activity obtained by mt-QSAR models

Comp.	$pMIC_b$ (Eq. 5)			$pMIC_f$ (Eq. 6)			$pMIC_{am}$ (Eq. 7)		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.35	1.24	0.11	1.46	1.16	0.30	1.39	1.19	0.20
2	1.38	1.27	0.11	1.14	1.04	0.10	1.28	1.23	0.05
3	1.71	1.30	0.41	0.61	0.93	−0.32	1.27	1.26	0.01
4	1.08	1.33	−0.25	0.70	0.81	−0.11	0.93	1.29	−0.36
5	1.02	1.12	−0.10	1.32	1.50	−0.18	1.14	1.07	0.07
6	1.68	1.73	−0.05	1.37	1.55	−0.18	1.56	1.71	−0.15
7	1.42	1.66	−0.24	1.69	1.62	0.07	1.53	1.63	−0.10
8	1.86	1.65	0.21	1.81	1.62	0.19	1.84	1.62	0.22
9	1.61	1.58	0.03	1.51	1.58	−0.07	1.57	1.55	0.02
10	1.86	1.51	0.35	1.46	1.57	−0.11	1.70	1.48	0.22
11	0.92	1.27	−0.35	1.41	1.18	0.23	1.11	1.22	−0.11
12	1.31	1.29	0.02	0.87	1.07	−0.20	1.13	1.25	−0.12
13	1.30	1.32	−0.02	0.89	0.95	−0.06	1.13	1.28	−0.15
14	1.30	1.34	−0.04	1.06	0.83	0.23	1.20	1.30	−0.10
15	1.17	1.14	0.03	1.34	1.53	−0.19	1.24	1.08	0.16
16	1.65	1.73	−0.08	1.93	1.58	0.35	1.76	1.71	0.05
17	1.46	1.65	−0.19	1.31	1.65	−0.34	1.40	1.62	−0.22
18	1.86	1.64	0.22	1.46	1.65	−0.19	1.70	1.61	0.09
19	1.58	1.57	0.01	1.98	1.61	0.37	1.74	1.54	0.20
20	1.32	1.49	−0.17	1.72	1.60	0.12	1.48	1.46	0.02

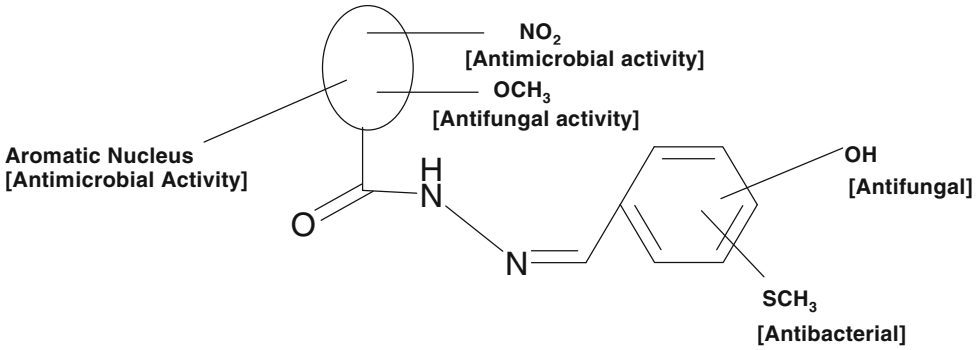


Fig. 3 Structural requirements for the antimicrobial activity of substituted benzylidene hydrazides

In order to confirm our results we have predicted the antibacterial, antimicrobial and antifungal activity values using mt-QSAR Eqs. 5–7, respectively. The comparison of observed and predicted values (Table 8) demonstrated that they are close to each other, evidenced by their low residual values.

Structure activity relationship (SAR) studies

1. The results of antimicrobial activity depicted that the presence of electron donating group, OCH_3, in compound **9** and **19**, increase the antifungal activity of benzylidene hydrazides. This is supported by results of Emami *et al.* (2008).
2. The presence of electron withdrawing group (NO_2) in compounds **10** and **20** made them highly active antimicrobial agents. The role of electron withdrawing group in increasing the antimicrobial activity is similar to the results of Sharma *et al.* (2006).
3. The synthesized compounds derived from 4-thiomethylbenzaldehyde have shown higher antibacterial activity (**1–10**) as compared to compounds derived from 3-hydroxybenzaldehyde (**11–20**).
4. The synthesized compounds derived from 3-hydroxybenzaldehyde have shown higher antifungal activity (**11–20**) as compared to compounds derived from 4-thiomethylbenzaldehyde (**1–10**).
5. The results of antimicrobial activity study demonstrate the importance of aromatic nucleus (compounds **6–10** and **16–20**; Table 2) in describing antimicrobial activity as compared to compounds containing aliphatic chain (compounds **1–5** and **11–15**).

The inference derived from above SAR is summarized in Fig. 3.

Conclusion

A novel series of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazide derivatives (**1–20**) was synthesized and tested for antimicrobial activity against *S. aureus, B. subtilis*, *E. coli, C. albicans* and *A. niger* The results of antimicrobial activity indicated that compounds having dinitro, methoxy, and methyl substituents were the most active ones. The results of MBC/MFC revealed that most of the synthesized compounds were bacteriostatic and fungistatic in nature except that compounds **9** and **16** were bactericidal for *S. aureus*, compounds **16** and **18** were bactericidal against *B. subtilis*, compounds **4**, **10** and **16** were bactericidal for *E. coli* and compounds **16**, **19** and **20** were found to fungicidal in case of *A. niger* and compound **16** was found to be active fungicidal agent against *C. albicans*. 3-Phenylacrylic acid-(3-hydroxybenzylidene)-hydrazide, **16**, was found to be bactericidal as well as fungicidal. The QSAR studies showed the importance of Balaban topological index (*J*), valence third order molecular connectivity index, $^3\chi^v$, and third order molecular connectivity index, $^3\chi$, in governing the antimicrobial activity of these synthesized compounds.

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