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Synthesis, antimicrobial evaluation and QSAR studies of N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazides

Shashi Kumar[1], Rakesh Narang[1]*, Surendra Kumar Nayak[1], Sachin Kumar Singh[1], Balasubramanian Narasimhan[2]

[1]Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara-144401, India
[2]Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, India.

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ABSTRACT

A series of N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazide was synthesized starting from undec-2-enoic acid through multi-step reactions. Synthesized derivatives were evaluated for their *in vitro* antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans* by tube dilution method. The preliminary results showed the significance of *o*-NO_2, *m*-NO_2 and *m*-OCH_3 groups at phenyl ring in describing antimicrobial activity of synthesized compounds. QSAR studies revealed that second order molecular connectivity index ($^2\chi$) and Balaban topological index (J) are the key parameters for antimicrobial activity of synthesized hydrazide derivatives and can be cosidered as important factors for interaction with target site of different microorganisms. It is pertinent to note that multi-target QSAR models were more significant in demonstrating the antimicrobial activity than one-target QSAR models.

INTRODUCTION

In last 60 years the incidence of death rate due to multidrug resistant fungi, bacteria and other pathogenic microbial strains have become one of the serious health issue worldwide (Jee-Young *et al*., 2012, Jessica *et al*., 2015). Since multidrug resistant pathogenic strains flourish, the need for effectual treatment has inspired researchers for the development of novel antimicrobial molecules (Patel *et al*., 2012). Chemical compounds having azomethine –NHN=CH moiety (hydrazide-hydrazone) represent an important class for new drug development (Narang *et al*., 2012a). Literature study of hydrazide-hydrazone derivatives have been claimed to possess antifungal, antibacterial (Bayrak *et al*., 2009), antitubercular (Nayyar *et al*., 2007) trypnocidal (Leite *et al*., 2006), antimalarial (Gemma *et al*., 2006), antiviral (Narang *et al*., 2012b), anti-inflammatory (Bhandari *et al*., 2008) and anti-tumour (Lembege *et al*., 2008) activities. Moreover, isoniazid (antitubercular, Martins *et al*., 2014), nifuroxazide (antidiarrheal and antitumor, Yang *et al*., 2015), nifurtimox (antiamoebic, Jackson *et al*., 2010), furacin (antibiotic, Johnson *et al*., 2012) and furazolidone (Safaralizadeh *et al*., 2006, antibacterial) are hydrazide containing important biologically active drug molecules. Structure activity relationship study of hydrazide compounds revealed that conversion to hydrazone based molecules and substituents attached to aromatic moiety at a particular position affect the antimicrobial activity to a great extent. (Narang *et al*., 2012c). Undec-10-enoic (undecylenic acid) is eleven carbon straight chain unsaturated fatty produced by cracking of castor oil under pressure. It is a natural fungicide used for the treatment of skin infections such as athlete's foot, ringworm and jock itch. Undecylenic acid has also antiviral properties that are effective on skin infections caused by herpes simplex. (Ereaux *et al*., 1949) Quantitative structure–activity relationship (QSAR) is a significant part of chemometrics, used to correlate experimentally determined biological activities with structural descriptors of chemical compounds and to develop QSAR models (Hansch *et al*., 1964).

* *Corresponding Author*
Rakesh Narang, Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara-144401, India. Email: rakesh.15772[at]lpu.co.in

The developed QSAR models can be further utilized to estimate biological activity of compounds not synthesized in the laboratory (Narang *et al.*, 2013). In view of above findings and continuation of our research programme on antimicrobial evaluation of hydrazide-hydrazone derivatives (Narang *et al.*, 2013; Narang *et al.*, 2012b, 2012c; Narang *et al.*, 2011; Kumar *et al.*, 2010; Kumar *et al.*, 2009) we decided to synthesize hydrazone derivatives of undec-10-enoic acid, evaluated their antimicrobial activity and QSAR studies.

MATERIAL AND METHODS

Experimental

Progress of the reaction was checked by TLC on silica gel sheets (Merck silica gel-G) and purity of intermediates and final products was confirmed by single spot TLC. Melting points were determined in open glass capillaries on Popular India melting point apparatus. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Avance II 400 NMR spectrometer (400 MHz) at 298 K, in appropriate deuterated solvents. Chemical shifts were reported as δ (ppm) relative to tetramethylsilane (TMS) as internal standard. Infrared spectra (IR) were recorded as KBr pellet on Shimadzu FTIR spectrometer. The wave number is given in cm^{-1}. Mass spectra were recorded on Waters Micromass Q-ToF Micro instrument.

General procedure for synthesis of hydrazide derivatives of undecylinic acid (2-20, Scheme 1)

Synthesis of ethyl ester of undecylenic acid (2)

A solution of 0.065 mole of undec-10-enoic (**1**) and absolute ethanol (50 ml) was refluxed in presence of conc. sulphuric acid (4-5 drops) for 8-10 hr. The excess of acid was neutralized with saturated solution of sodium bicarbonate in water. Synthesized ester (**2**) was extracted by adding diethylether to the above solution and ether layer was separated. Further, ester of undec-10-enoic was obtained after evaporation of ether layer.

Synthesis of undec-10-ene hydrazide (3) from undec-10-enoate (2)

The ethanolic solution of synthesized ester (0.055 mol) and hydrazine hydrate (0.136 mol) was refluxed for 12-14 hr. The completion of the reaction was confirmed by TLC. The reaction mixture was cooled, filtered, washed with diethylether and dried to get undec-10-enehydrazide (**3**).

Synthesis of hydrazide derivatives of undecylenic acid (4-20) from undec-10-ene hydrazide (3)

A mixture of undec-10-ene hydrazide 0.005 mol and equimolar amount of appropriate aldehyde/acetophenone in ethanol was refluxed for (4-5 hr)/ (7-8 hr). Progress of reaction was monitored by TLC. The excess of ethanol was evaporated. The precipitates obtained were filtered off and washed with hexane. The synthesized undec-10-ene-hydrazide (**4-20**) derivatives were recrystallized from ethanol to get target pure product.

Analytical data

Undec-10-ene hydrazide (3)

Mp (^{o}C) 88-91; Yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84 (s, 1H), 5.75-5.85 (m, 1H), 4.91-5.01(m, 2H), 3.59 (s, 2H), 2.12-2.16 (t, 2H), 2.00-2.06 (m, 2H), 1.59-1.65 (m, 2H), 1.20-1.28 (m, 10H). IR (KBr pellets) cm^{-1}: 3315.74 (NH str., amide), 3045.70 (C-H str., alkene), 2920.32 (C-H str., alkane), 1674.27 (C=C str., alkene), 1631.83 (C=O str., amide), 1161.19 (C-N str.).

N′-(2-Chlorobenzylidene)undec-10-enehydrazide (5)

Mp (^{o}C) 48-51; Yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.25 (s, 1H), 8.17 (s, 1H), 7.95-7.96 (d, 1H), 7.26-7.39 (m, 3H), 5.75-5.85 (m, 1H), 4.90-5.01 (m, 2H), 2.73-2.77 (t, 2H), 2.00-2.05 (q, 2H), 1.30-1.40 (m, 12H). IR (KBr pellets) cm^{-1}: 3190.37 (NH str., amide), 3070.78 (C-H str., aromatic), 2960.69 (C-H str., aliphatic), 1674.43 (C=O str., amide), 1591.83 (C=C str., aromatic), 1148.61 (C-N str.), 750.33 (C-Cl str.). (ES^+): m/z 321 $[M+H]^+$

N′-(4-chlorobenzylidene) undec-10-enehydrazide (6)

Mp (^{o}C) 74-76; Yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 7.72 (s, 1H), 7.57-7.60 (d, 2H), 7.36-7.38 (d, 2H), 5.75-5.85 (m, 1H), 4.91-5.01 (m, 2H), 2.72-2.76 (t, 2H), 2.00-2.05 (q, 2H), 1.68-1.76 (m, 2H), 1.31-1.40 (m, 10H). IR (KBr pellets) cm^{-1}: 3207.73 (NH str., amide), 3057.27 (C-H str., aromatic), 2922.25 (C-H str., aliphatic), 1674.27 (C=C, aromatic), 1662.37 (C=O str., amide), 1162.89 (C-N str.), 827.49 (C-Cl str.).

N′-(2-hydroxybenzylidene)undec-10-enehydrazide (8)

Mp (^{o}C) 72-75; Yield 68%; ^{1}H NMR (400 MHz, CDCl3) δ: 9.74 (s, 1H), 8.35 (s, 1H), 8.08-8.09(d, 1H), 8.04 (d, 1H), 7.67-7.69 (t, 1H), 7.63-7.65 (t, 1H), 5.75-5.83 (m, 1H), 4.95-5.01 (m, 1H), 4.90-4.93 (m, 1H), 2.73-2.77 (t, 2H), 2.00-2.05 (q, 2H), 1.69-1.76 (m, 2H), 1.25-1.40 (m, 10H). IR (KBr pellets) cm^{-1}: 3410.41 (OH str.), 3186.51 (NH str., amide), 3080.42 (C-H str., aromatic), 2994.18 (C-H str., aliphatic), 1672.81 (C=O str., amide), 1614.47 (C=C str., aromatic), 1155.40 (C-N str.).

N′-(4-hydroxy-3-methoxybenzylidene)undec-10-enehydrazide (10)

Mp (^{o}C) 109-112; Yield 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 7.72 (s, 1H), 7.24-7.26 (d, 1H), 7.09-7.11 (d, 1H), 6.89-6.92 (d, 1H), 5.74-5.84 (m, 1H), 4.90-5.00 (m, 2H), 3.94 (s, 3H), 2.72-2.76 (t, 2H), 1.99-2.05 (q, 2H), 1.70-1.77 (m, 2H), 1.25-1.43 (m, 10H). IR (KBr pellets) cm^{-1}: 3196.15 (NH str., amide), 3063.42 (C-H str., aromatic), 2924.18 (C-H str., aliphatic), 1654.96 (C=O str., amide), 1600.97 (C=C, aromatic), 1278.85 (C-O-C asym. str., OCH_3), 1186.97 (C-N str.), 1116.82 (C-O-C sym. str, OCH_3) (ES^+): m/z 333 $[M+H]^+$

N′-(2-nitrobenzylidene)undec-10-enehydrazide (11)

Mp (^oC) 78-81; Yield 73%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (s, 1H), 8.35 (s, 1H), 8.08-8.09 (d, 1H), 8.04 (d, 1H), 7.67-7.69 (t, 1H), 7.63-7.65 (t, 1H), 5.75-5.83 (m, 1H), 4.95-5.01 (m, 1H), 4.90-4.93 (m, 1H), 2.73-2.77 (t, 2H), 2.00-2.05 (q, 2H), 1.69-1.76 (m,2H), 1.25-1.40 (m, 10H). IR (KBr pellets) cm^{-1}: 3211.53 (NH str., amide), 3072.71 (C-H str., aromatic), 2922.25 (C-H str., aliphatic), 1672.34 (C=O str., amide), 1519.96 & 1344.43 (N=O str.), 1190.8 (C-N str.).

N′-(4-nitrobenzylidene)undec-10-enehydrazide (12)

Mp (^oC) 105-108; Yield 79%; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.52 (s, 1H), 8.27-8.2 (d, 2H), 7.92 (s, 1H), 7.82-7.84 (d, 2H), 5.75-5.83 (m, 1H), 4.95-5.01 (m, 1H), 4.91-4.94 (m, 1H), 2.77-2.81 (t, 2H), 2.10 (q, 2H), 1.71-1.78 (m, 2H), 1.23-1.46 (m, 10H). IR (KBr pellets) cm^{-1}: 3188.44 (NH str., amide), 3086.21 (C-H str., aromatic), 2968.32 (C-H str., aromatic), 2924.18 (C-H str., alkane), 1668.48 (C=O str., amide), 1585.54 (C=C, aromatic), 1521.88 & 1336.71 (N=O str.), 1153.47 (C-N str.).

(E)-N'-((E)-3-phenylallylidene)undec-10-enehydrazide (16)

Mp (^oC) 81-84; Yield 46%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.58 (s, 1H), 7.60-7.62 (m, 1H), 7.45-7.47 (d, 2H), 7.26-7.38 (m, 3H), 6.86-6.88 (t, 2H), 5.79-5.81 (m, 1H), 4.90-5.01 (m, 2H), 2.65-2.69 (t, 2H), 2.00-2.06 (q, 2H), 1.65-1.73 (m, 2H), 1.25-1.39 (m, 10H). IR (KBr pellets) cm^{-1}: 3163.36 (NH str., amide), 3032.20 (C-H str., aromatic), 2920.32 (C-H str., aliphatic), 1672.34 (C=C str., aromatic), 1648.38 (C=O str., amide), 1626.05 (C=N, str.), 1112.96 (C-N str.).

N'-(1-phenylethylidene)undec-10-enehydrazide (17)

Mp (^oC) 120-123; Yield 50%; IR (KBr pellets) cm^{-1}: 3228.95(NH str., amide), 3184.58 (C-H str., aromatic), 3024.48 (C-H str., aromatic), 2922.25 (C-H str., alkane), 1680.05 (C=C str. aromatic), 1651.12 (C= O str.), 1286.56 (C-N), 2359.02 (C=N), 912.36 (C-H bending, alkenes), 1444.73 & 1373.36 (C-H bending, alkane), 1631.83 (C=C str., aromatic).

N′-(1-(3-nitrophenyl)ethylidene)undec-10-enehydrazide (18)

Mp (^oC) 83-86; Yield 52%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.25 (s, 1H), 8.57-8.58 (t, 1H), 8.21-8.24 (m, 1H), 8.09-8.11 (d, 1H), 7.56-7.60 (t, 1H), 5.75-5.83 (m, 1H), 4.90-5.00 (m, 2H), 2.77-2.81 (t, 2H), 2.31 (s, 3H), 2.00-2.05 (q, 2H), 1.70-1.77 (m, 2H), 1.25-1.42 (m, 10H). IR (KBr pellets) cm^{-1}: 3190.37 (NH str., amide), 3101.64 (C-H str., aromatic), 2924.18 (C-H str., aliphatic), 1668.27 (C=O str., amide), 1599.27 (C=C str., aromatic), 1147.69 (C-N str.), 1525.74 & 1350.22 (N=O).

N′-(1-(4-nitrophenyl)ethylidene)undec-10-enehydrazide (19)

Mp (^oC) 82-85; Yield 57%; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.14 (s, 1H), 8.24-8.26 (d, 2H), 7.89-7.91(d, 2H), 5.77-5.83 (m, 1H), 4.94-5.01 (m, 1H), 4.91-4.94 (m, 1H), 2.77-2.81 (t, 2H), 2.29 (s, 3H), 2.00-2.06 (q, 2H), 1.71-1.75 (m, 2H), 1.25-1.41 (m, 10H). IR (KBr pellets) cm^{-1}: 3190.37 (NH str., amide), 3099.71 (C-H str., aromatic), 2922.25 (C-H str., aliphatic), 1676.20 (C=O str., amide), 1579.75 (C=C str., aromatic), 1519.90 & 1340.57 (N=O str.), 1151.54 (C-N str.) (ES^+): m/z 346 $[M+H]^+$

N′-(1-(4-hydroxyphenyl)ethylidene)undec-10-enehydrazide (20)

Mp (^oC) 140-143; Yield 65%; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.12 (s, 1H), 9.56 (s, 1H), 7.56-7.62 (m, 2H), 6.75-6.77 (d, 2H), 5.73-5.80 (m, 1H), 4.90-4.99 (m, 2H), 3.34 (s, 3H), 1.98-2.01 (t, 2H), 1.57-1.62 (q, 2H), 1.28-1.33 (m, 12). IR (KBr pellets) cm^{-1}: 3215.44 (NH str., amide), 3049.56 (C-H str., aromatic), 2924.18 (C-H str., aliphatic), 1635.69 (C=O str., amide), 1593.25 (C=C str., aromatic), 1170.83 (C-N str.).

Antimicrobial studies

The antimicrobial activity was carried out against Gram-negative bacteria *E. coli*, Gram-positive bacteria *S. aureus*, *B. subtilis*, and fungal strains: *C. albicans and A. niger* by tube dilution method (Cappucino and Sherman, 1999). Ciprofloxacin and Fluconazole were used as a standard drug for antibacterial and antifungal evaluation.

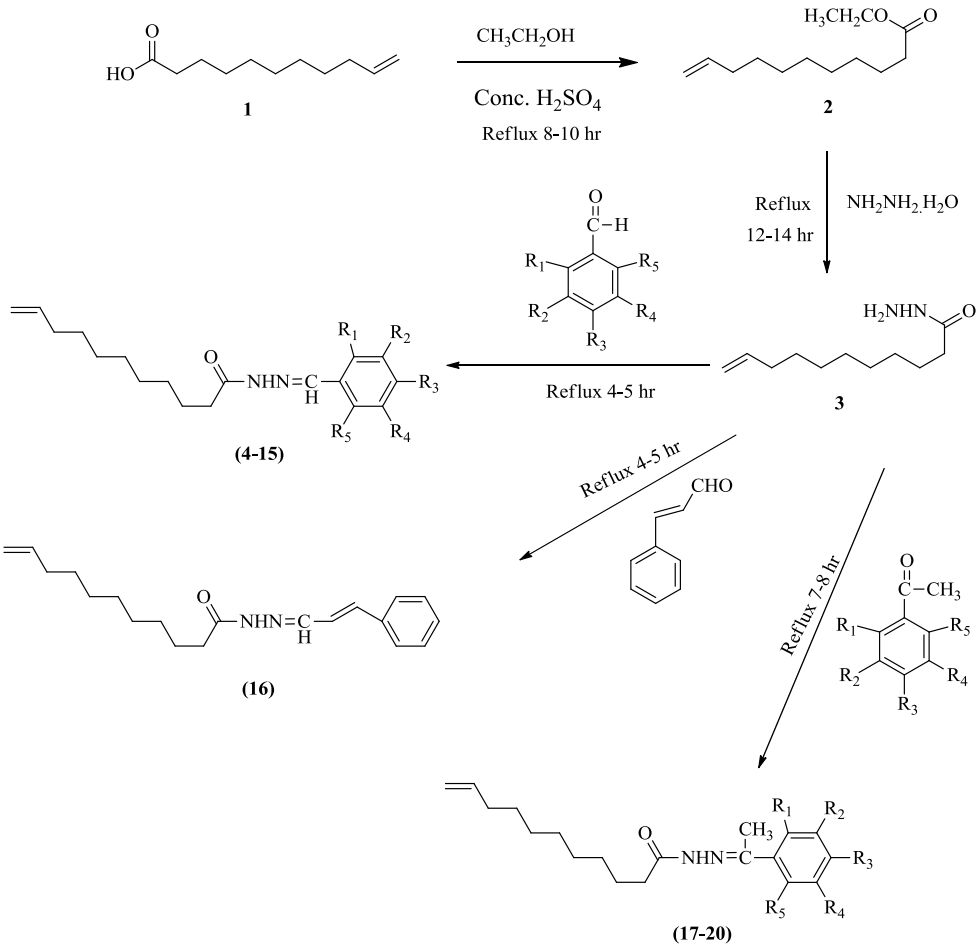
The synthesized derivatives and standard drugs were dissolved in dimethylsulphoxide to prepare stock solution of 100 µg/mL. Further, dilutions (50-3.125 µg/mL) were done in double strength nutrient broth – I.P. for bacteria and Sabouraud dextrose broth I.P. for fungi (Pharmacopoeia of India, 2007). The dilutions were incubated at 37 °C for all bacteria (24 hr), and *C. albicans* (48 hr), 25 °C for *A. niger* (7 days), and minimum inhibitory concentration (MIC) was determined.

QSAR studies

The QSAR study was performed to correlate antimicrobial activity with physicochemical parameters of synthesized hydrazide derivatives. The structures of synthesized hydrazide derivatives were first pre-optimized with the Molecular Mechanics Force Field method (MM^+) included in Hyperchem 6.03 (1993) and the resulting geometries were further refined by means of the semiempirical method PM3 (parametric method-3). Gradient norm limit of 0.01 kcal/A˚ was utilized for the geometry optimization.

TSAR 3.3 software for Windows (TSAR 3D Version 3.3, 2000) was used to calculate physicochemical parameters of lowest energy structures of synthesized hydazide derivatives. Further, the regression analysis was carried out using the SPSS software package (SPSS for Windows, 1999).

The predictive powers of the developed models were supported by cross-validated r^2 (q^2) using leave one out (LOO) cross-validation method (Schaper, 1999). The statistical qualities of equations were further confirmed by the parameters like standard error of estimate (s), correlation coefficient (r), variance ratio (F) at specified degrees of freedom, root mean square error (RMSE) and predicted error sum of square (PRESS) (Arora *et al.*, 2015, Narang *et al.*, 2012c).



Scheme 1: Synthetic scheme for synthesis of N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazide derivatives

Comp.	R_1	R_2	R_3	R_4	R_5
4	H	H	H	H	H
5	Cl	H	H	H	H
6	H	H	Cl	H	H
7	H	H	F	H	H
8	OH	H	H	H	H
9	H	H	OH	H	H
10	H	OCH_3	OH	H	H
11	NO_2	H	H	H	H
12	H	H	NO_2	H	H
13	H	H	$N(CH_3)_2$	H	H
14	H	H	OCH_3	H	H
15	H	OCH_3	OCH_3	H	H
17	H	H	H	H	H
18	H	NO_2	H	H	H
19	H	H	NO_2	H	H
20	H	H	OH	H	H

RESULTS AND DISCUSSION

Chemistry

The synthesis of intermediate (**2-3**) and N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazides (**4-20**) was carried out as per the reactions presented in **Scheme 1.** The starting material, undec-2-enoic acid was heated with absolute ethanol in catalytic amount of sulfuric acid to synthesize the ethyl ester of undec-2-enoic acid (**2**). The ethyl undec-10-enoate (**2**) was reacted with hydrazine hydrate in ethanol to synthesize the undec-10-enehydrazide, which was then condensed with corresponding aromatic aldehydes/ acetophenone to yield the target N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazides (**4-20**). The physicochemical characteristics of synthesized compounds are presented in Table 1.

Structures of synthesized compounds (**2-20**) were ascertained by their ^{1}H NMR, IR and mass spectral data. The emergence of singlet in the range of δ 9.14 to 10.52 ppm confirmed the presence of NH functionality in synthesized compounds. The singlet signal of CH proton in the range of δ 7.72-δ 8.35 ppm, confirmed the presence of N=CH bond in the synthesized compounds **5**, **6**, **8**, **10**, **11** and **12**.

Table 1: Physicochemical characteristic of synthesized derivatives.

Comp.	Mol. Formula	M. Wt.	Mp/Bp* (^oC)	R_f	% Yield
2	$C_{12}H_{22}O_2$	198	103-106	0.710[a]	80
3	$C_{11}H_{22}N_2O$	198	88-91	0.306[a]	73
4	$C_{18}H_{26}N_2O$	286	64-66	0.527[a]	62
5	$C_{18}H_{25}ClN_2O$	320	48-51	0.603[a]	52
6	$C_{18}H_{25}ClN_2O$	320	74-76	0.750[a]	58
7	$C_{18}H_{25}FN_2O$	304	56-59	0.466[b]	58
8	$C_{18}H_{26}N_2O_2$	302	72-75	0.534[a]	68
9	$C_{18}H_{26}N_2O_2$	302	98-101	0.289[e]	64
10	$C_{19}H_{28}N_2O$	332	109-112	0.237[c]	46
11	$C_{18}H_{25}N_3O_3$	331	78-81	0.532[a]	73
12	$C_{18}H_{25}N_3O_3$	331	105-108	0.518[a]	79
13	$C_{20}H_{31}N_3O$	329	75-78	0.478[a]	52
14	$C_{19}H_{28}N_2O_2$	316	59-61	0.454[a]	85
15	$C_{20}H_{30}N_2O_3$	346	99-101	0.388[d]	77
16	$C_{20}H_{28}N_2O$	312	81-84	0.450[c]	46
17	$C_{19}H_{28}N_2O$	300	120-123	0.525[a]	50
18	$C_{19}H_{27}N_3O_3$	345	83-86	0.400[f]	52
19	$C_{19}H_{27}N_3O_3$	345	82-85	0.384[a]	57
20	$C_{19}H_{28}N_2O_2$	316	140-143	0.269[a]	65

Mobile phase- Hexane: Ethylacetate (8:2) [a], Hexane: Ethylacetate (8.5:1.5) [b], Hexane: Ethylacetate (7:3) [c], Hexane: Ethylacetate (7.5:2.5) [d], Chloroform: Hexane: Ethylacetate (2:3:2) [e], Chloroform: Hexane: Ethylacetate (3:1:2) [f]

The singlet signal of CH_3 proton in compounds **18**, **19** and **20** at δ 2.29-3.34 ppm, confirmed attachment of acetophenone moieties with undec-10-enehydrazide. The appearance of multiplet in the range of δ 6.77–8.35 ppm revealed the presence of aromatic protons. The absence of -NH_2 protons signals in the region from δ 3 to 4 ppm further confirmed the synthesis of hydrazone derivatives. The presence singlet signal at δ 3.94 ppm confirmed the existence of methoxy group in compound **10**. The appearance of the stretching peak around 1630-1675 cm^{-1} indicated the presence of carbonyl group in synthesized hydrazide derivatives. The presence of aromatic ring was indicated by the appearance of the C=C str. band around 1600 cm^{-1} in synthesized hydrazide derivatives. The appearance of stretching band in the range of 3150-3280 cm^{-1} showed the presence of NH moiety in synthesized compounds. The appearance of C–Cl and C–F, bands at 750.33, 3410.41 cm^{-1} in compounds **5** and **8** showed the presence of chloro and hydroxy groups in their structures, respectively. The presence of methoxy group in compound **10** indicated by appearance of asymmetric C–O–C stretching and symmetric C–O–C stretching at 1278.85 cm^{-1} and 1116.82 $cm^{-1,}$ respectively. Further, the symmetric NO_2 stretching around 1340 cm^{-1} and asymmetric NO_2 stretching 1520 cm^{-1}, showed the presence of NO_2 functionality in synthesized derivatives (**11**, **12** and **19)**.

Antimicrobial evaluation

The synthesized undec-10-ene-hydrazide derivatives were evaluated for their *in vitro* antimicrobial activity against Gram-positive *S. aureus*, *B subtilis* and Gram-negative *E coli* and antifungal activity against *C. albicans* and *A. niger* by tube dilution method (Cappucino and Sherman, 1999). Double strength Nutrient broth I.P. and Sabouraud dextrose broth I.P. have been employed as media for growth of bacterial and fungal cells, respectively. The pMIC values of antimicrobial activity (in µM/ml) are presented in Table 2. In case of *B. subtilis*, compounds **15**, **18** and **19** were found to be more active than the other synthesized derivatives, each having $pMIC_{bs}$ values 1.44 µM/ml (Table 2). Against *S. aureus*, compounds **10**, **11, 12, 13**, **15**, **18** and **19** were found to be more active than the other synthesized derivatives with $pMIC_{sa}$ values of 2.05 µM/ml (Table 2) which is comparable to standard drug ciprofloxacin ($pMIC_{sa}$ = 2.61 µM/ml). Compounds **15**, **18** and **19** derivatives were found to be most potent against the Gram-negative bacteria, *E. coli* having $pMIC_{ec}$ value 1.44 µM/ml (Table 2).

On the other hand, results of antifungal activity showed that the compounds having NO_2 group (**11, 12** and **18**) and OCH_3 group (**10** and **15**) were most potent among the synthesized compounds against *C. albicans*, having $pMIC_{ca}$ value 2.05 µM/ml. In case of *A. niger*, compounds **18** and **19** showed highest inhibitory activity as compared to other synthesized derivatives with $pMIC_{an}$ value 1.74 µM/ml (Table 2). Results of antimicrobial data indicated that (Table 2) synthesized hydrazides have higher antifungal activity against *C. albicans*, in comparison to *A. niger*. Further, the antimicrobial results showed that compounds **11** and **18** having nitro substituent at *ortho* and *meta* position, respectively displayed highest antimicrobial potential among the synthesized derivatives.

In general, from antimicrobial activity data it is observed that compounds having NO_2 (**11, 12 and 18**) and OCH_3 (**10** and **15**) groups showed comparable antibacterial activity (pMIC= 2.05 µM/ml) against *S. aureus* and antifungal activity (pMIC=2.05 µM/ml) against *C. albicans* to that of standard drug Norfloxacin (pMIC=2.61 µM/ml) and Fluconazole (pMIC=2.64 µM/ml), respectively.

Structure activity relationship on the basis of antimicrobial activity results

1. The results of antimicrobial activity showed that substituted hydrazone derivatives (compounds **4-20**) have higher antimicrobial potency as compared to undec-

10-enoic acid, ester and hydrazide (compounds **1**, **2** and **3**).

2. The substitution of an electron-withdrawing nitro group at *ortho* and *meta* position of attached benzene ring (compounds **11** and **18**, respectively) make them highly potent antimicrobial compounds. The role of nitro group in potentiating antimicrobial activity is similar to the observation of Sharma *et al*. (**2004**).
3. Compound **16**, a cinnamaldehyde derivative improved activity (pMIC range 1.10-2.00 µM/ml) against tested strains. The presence of conjugated pie electrons in compound **16** can be involved in interaction with target site and this may be the reason of its good activity. This observation is similar to our earlier studies (Narasimhan *et al.* 2007).
4. The substitution of NH_2 group (compound **3**) with benzylidene/(1-phenyl-ethylidene) functionalities (compounds **4-20**) higher antibacterial and antifungal potency of the synthesized derivatives. This may be due to the enhancement of lipophilic character of synthesized compounds (**4-20**), which may allow them to easily infiltrate the cell wall.
5. In general, antimicrobial results indicated the importance of both NO_2 and OCH_3 in improving both antibacterial and antifungal activities. Presence of nitro and methoxy groups in compounds **10**, **11** and **18** causes maximum enhancement in both antibacterial and antifungal activities.
6. Antimicrobial activity results showed that the types and position of functional groups attached to phenyl ring have a significant effect on antimicrobial activity of synthesized hydrazone derivatives. The SAR results are summarized in Fig. 1.

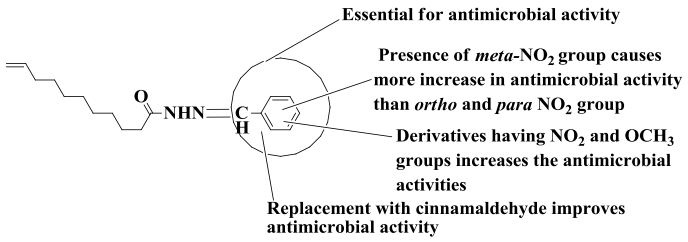


Fig. 1: Structural requirements for antimicrobial activity of synthesized hydrazide derivatives.

QSAR studies

Development of one-target QSAR models (ot-QSAR)

Quantitative structure activity relationship (QSAR) is one of the most influential method for the prediction of biological activity of chemical compounds. QSAR technique also important in finding quantitative relationships between the molecular structure and biological activity of investigated compounds (Mohsen *et al.*, 2010). In the present study, we have performed the QSAR studies by Hansch's analysis using the linear free energy relationship (LFER) model illustrated by Hansch and Fujita (1964).

In Hansch's approach, structural properties of compounds are calculated in terms of different physicochemical parameters and these parameters are correlated with biological activities through equation using regression analysis. Before using the biological activity data for QSAR study experimentally determined MIC values changed to –log MIC or pMIC (in micromole, Table 4) to obtain normal distribution of errors, all the values positive, and to get linear free energy relationship of antimicrobial activity values with different descriptors. Further, regression analysis was performed using calculated physicochemical parameters (Table 3 and 4) as independent variables and antimicrobial activity values as dependent variables (Table 2).

On the basis of intercorrelation between the independent variables and also their individual correlation with antimicrobial activity, different probable combinations of parameters were undertaken for linear regression (LR) and multiple linear regression (MLR) analysis. Statistically most significant QSAR models were chosen from hundreds of developed QSAR models. These models were developed in stepwise manner by forward selection method starting with best single physicochemical parameters and adding further important parameters as per their role in the equation that have the smallest standard deviation (s), until there is no other parameter outside the equation that gratifies the selection criterion.

The different physicochemical parameters *viz*. topological, electronic, thermodynamic, and spatial (Hansch and Fujita, 1964; Hansch *et al.*, 1973; Kier and Hall, 1976; Randic 1975; Balaban 1982; Wiener, 1947; Randic, 1993) were quantified using TSAR 3.3 software (TSAR 3D for Windows, Version 3.3, 2000) for synthesized hydazide derivatives and summarized in Table 3. The values of selected parameters are presented in Table 4.

In view of above facts, a data set of 20 synthesized hydrazide derivatives was used for model development. The predictive powers of derived QSAR models were confirmed by leave one out (LOO) method (Schaper, 1999), where a model is built with N - 1 compounds and N^{th} compound is predicted. Each compound was removed for model derivation and predicted in turn. The similar process was repeated by removal of a new compound until all the compounds have been removed once.

A correlation matrix was constructed for antibacterial activity against *S. aureus* is presented in Table 5. Both high and low colinearity was observed between different physicochemical properties. A highest interrelationship was observed between $^{2}\chi$ and $^{1}\chi$ (r = 0.992) and lowest interrelationship was observed between Log P and κ_3 (r = 0.053). The correlations of different parameters with antimicrobial activities are presented in Table 6. In general, a significant correlation (r > 0.7) was observed against all tested microbial strains (exception *B. subtilis*) with most of selected parameters except κ_3, $\kappa\alpha_3$ and HOMO (Table 6).

Table 2: pMIC values of synthesized N'-benzylidene/(1-phenylethylidene)undec-10-enehydrazide derivatives.

Comp.	$pMIC_{bs}$	$pMIC_{sa}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
1	1.17	0.87	0.87	0.87	0.87	0.97	0.87	0.93
2	1.20	0.90	0.90	1.20	1.20	1.00	1.20	1.08
3	1.20	0.90	1.20	0.90	0.90	1.10	0.90	1.02
4	1.36	1.96	1.36	1.96	1.36	1.56	1.66	1.60
5	1.41	2.00	1.41	2.00	1.70	1.61	1.85	1.70
6	1.41	2.00	1.41	2.00	1.41	1.61	1.70	1.65
7	1.09	2.00	1.39	2.00	1.68	1.49	1.84	1.63
8	1.40	2.00	1.40	2.00	1.70	1.60	1.85	1.70
9	1.40	2.00	1.40	2.00	1.70	1.60	1.85	1.70
10	1.42	2.05	1.42	2.05	1.72	1.63	1.88	1.73
11	1.42	2.05	1.42	2.05	1.72	1.63	1.88	1.73
12	1.42	2.05	1.42	2.05	1.42	1.63	1.73	1.67
13	1.42	2.05	1.42	2.05	1.42	1.63	1.73	1.67
14	0.80	2.00	1.40	2.00	1.40	1.40	1.70	1.52
15	1.44	2.05	1.44	2.05	1.44	1.64	1.74	1.68
16	1.10	2.00	1.40	2.00	1.40	1.50	1.70	1.58
17	1.39	1.40	1.40	1.39	1.39	1.40	1.39	1.39
18	1.44	2.05	1.44	2.05	1.74	1.64	1.90	1.74
19	1.44	2.05	1.44	1.74	1.74	1.64	1.74	1.68
20	1.40	2.00	1.40	2.00	1.70	1.60	1.85	1.70
S.D.	0.17	0.15	0.02	0.16	0.16	0.08	0.12	0.09
Std.	2.61[a]	2.61[a]	2.61[a]	2.64[b]	2.64[b]	2.61	2.64	2.62

S.D. Standard deviation of pMIC value of synthesized hydrazone [a] Norfloxacin [b] Fluconazole

Table 3 Brief description of some molecular descriptors used in the present study.

S. No.	Descriptor type	Molecular Description
1	Topological	Kier's molecular connectivity ($^0\chi$, $^0\chi^v$, $^1\chi$, $^1\chi^v$, $^2\chi$, $^2\chi^v$), Kier's alpha shape ($\kappa\alpha_1$) topological indices, Kier's shape (κ) topological indices, Randic topological index (R), Balaban topological index (J) and Wiener topological index (W)
2	Quantum	Total energy (Te), Ionization potential (I.P.), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ) and electronic energy (Ele.E)
3	Lipophilic	Log P (Octanol-water partition coefficient)
4	Spatial	Molecular surface area , Molar volume (Vm)
5	Structural	Molecular Weight (MW)

ot-QSAR model for antibacterial activity against S. aureus

$pMIC_{sa} = -0.323\ J + 3.119$ Eq. 1

$n = 20$

$r = 0.947$ $r^2 = 0.897$

$q^2 = 0.886$

$s = 0.140$ $F = 156.36$

$pMIC_{sa} = 0.058\ ^0\chi - 0.213\ J + 1.752$ Eq. 2

$n = 20$

$r = 0.957$ $r^2 = 0.916$

$q^2 = 0.900$

$s = 0.129$ $F = 93.16$

$RMSE = 0.181$ $PRESS = 0.654$

The developed QSAR model (Eq. 1) of synthesized undec-10-enoic acid hydrazide derivatives indicated that the Balaban topological index (J) is negatively correlated with antibacterial activity against *S. aureus*. This is clearly evident from Table 4, that compounds (**10**, **11**, **12**, **13**, **15**, **18** and **19**) having low J values, 3.45, 3.52, 3.47, 3.51, 3.57, 3.68 and 3.63 have highest $pMIC_{sa}$ values, *i.e.* 2.05 (Table 2). Additionally, compounds **1**, **2** and **3** with high J values 6.89, 6.89 and 6.94 have low $pMIC_{sa}$ activity values *i.e.* 0.87, 0.90 and 0.90, respectively against *S. aureus* (Table 2).

Although there is high interrelationship between J and other parameters, still we go for the development of biparametric models to get better r value. The maximum rise in value of regression coefficient (r = 0.957, Eq. 2) was achieved on combination of J and zero order molecular connectivity index ($^0\chi$). High r (0.957) and q^2 (0.900) values revealed the significance of $^0\chi$ and J (Eq. 2) in describing antibacterial activity against *S. aureus* of synthesized hydrazide derivatives.

The values of r and q^2 for Eq. 2 are 0.957 and 0.900, which showed that the resulted QSAR equation could explain and predict 95.7% and 90.0% of variances, respectively. Generally, when value of q^2 is greater than 0.5, the model are supposed to have strong predictive power. However, several studies recommended that a high q^2 appear to be a necessary, but not enough condition for an equation to have a good predictive power (Oltulu *et al.*, 2009).

Consequently, various other statistical approaches were used to validate the robustness and the practical applicability of the developed QSAR models. To demonstrate that the resulted equations have good prediction of antimicrobial activity, different parameters for evaluation of developed models have been used. Here, r^2, elucidate variance for given set, was employed to establish the robustness of model's fit performance. Low values of PRESS and RMSE further confirmed the strength of developed QSAR equations.

Moreover, low residual values indicated that experimental and predicted antimicrobial activities are very close to each other, also confirmed the robustness of developed models (Table 7 and 8).

Table 4: Value of selected descriptors used in the regression analysis.

Comp.	MM	Log P	MR	$^0\chi$	$^1\chi$	$^2\chi$	κ_3	$\kappa\alpha_3$	J	T.E.	LUMO	HOMO
1	184.31	3.42	54.12	9.94	6.27	4.66	12.00	11.37	6.89	-2326.71	1.02	-10.04
2	198.34	3.45	58.89	10.65	6.81	4.78	11.00	10.37	6.89	-2481.97	1.14	-10.02
3	198.35	2.54	60.43	10.65	6.81	4.78	11.00	10.33	6.94	-2446.55	1.01	-10.03
4	286.46	5.10	89.05	15.18	10.33	7.80	11.25	10.09	3.47	-3396.75	-0.33	-8.97
5	320.90	5.61	93.86	16.05	10.74	8.32	10.43	9.57	3.47	-3756.72	-0.50	-9.02
6	320.90	5.61	93.86	16.05	10.72	8.43	11.24	10.35	3.47	-3756.86	-0.59	-9.02
7	304.45	5.24	89.27	16.05	10.72	8.43	11.24	10.05	3.47	-3868.17	-0.58	-8.99
8	302.46	4.81	90.75	16.05	10.74	8.32	10.43	9.31	3.49	-3717.30	-0.45	-8.89
9	302.46	4.81	90.75	16.05	10.72	8.43	11.24	10.08	3.47	-3717.36	-0.34	-8.73
10	332.49	4.56	97.21	17.62	11.67	9.12	10.58	9.48	3.45	-4193.20	-0.37	-8.61
11	331.46	5.05	96.38	17.62	11.65	9.25	10.58	9.20	3.52	-4227.49	-1.28	-9.62
12	331.46	5.05	96.38	17.62	11.63	9.32	11.29	9.87	3.47	-4227.60	-1.45	-9.59
13	329.54	4.89	102.76	17.62	11.63	9.32	11.29	10.18	3.51	-3928.25	-0.06	-8.23
14	316.49	4.84	95.51	16.75	11.26	8.59	11.22	10.09	3.45	-3872.46	-0.10	-8.53
15	346.52	4.59	101.98	18.33	12.21	9.32	10.67	9.59	3.57	-4348.31	-0.20	-8.49
16	312.50	5.50	99.29	16.59	11.33	8.51	13.02	11.60	3.41	-3679.92	-0.61	-8.68
17	300.49	4.73	92.86	16.05	10.74	8.32	10.43	9.34	3.62	-3552.57	-0.07	-9.08
18	345.49	4.68	100.19	18.49	12.06	9.78	10.05	8.75	3.68	-4383.31	-0.99	-9.45
19	345.49	4.68	100.19	18.49	12.04	9.84	10.67	9.32	3.63	-4383.42	-1.30	-9.63
20	316.49	4.45	94.56	16.92	11.13	8.94	10.46	9.37	3.62	-3873.18	-0.10	-8.87

Table 5: Correlation matrix for antimicrobial activity of synthesized hydrazide derivatives against *S. aureus*.

	Log P	MR	$^1\chi$	$^2\chi$	κ_3	$\kappa\alpha_3$	J	W	LUMO	HOMO	pMICsa
Log P	1.000										
MR	0.797	1.000									
$^1\chi$	0.768	0.991	1.000								
$^2\chi$	0.752	0.978	0.992	1.000							
κ_3	0.053	-0.216	-0.265	-0.299	1.000						
$\kappa\alpha_3$	-0.171	-0.482	-0.540	-0.572	0.938	1.000					
J	-0.889	-0.952	-0.944	-0.930	0.177	0.439	1.000				
W	0.639	0.952	0.941	0.920	-0.178	-0.421	-0.855	1.000			
LUMO	-0.758	-0.812	-0.847	-0.868	0.187	0.480	0.813	-0.643	1.000		
HOMO	0.600	0.706	0.654	0.603	0.049	-0.081	-0.732	0.780	-0.244	1.000	
pMICsa	0.834	0.933	0.939	0.932	-0.164	-0.426	-0.947	0.846	-0.839	0.683	1.000

ot-QSAR model for antibacterial activity against E. coli

$pMIC_{ec} = 0.011\ MR + 0.381$ Eq. 3

n = 20

r = 0.934 $r^2 = 0.872$

$q^2 = 0.784$

s = 0.061 F=122.40

RMSE = 0.054

PRESS = 0.059

In case of Gram-negative bacteria *E. coli* developed QSAR equation (Eq. 3) displayed the importance of molecular refractive index (MR) in elucidating antimicrobial activity of synthesized derivatives. This is clearly evident from $pMIC_{ec}$ values of compounds **13**, **15, 18** and **19** with high antimicrobial activity (Table 4) have high values of MR *i.e.* 102.76, 101.98, 100.19 and 100.19 (Table 2), respectively.

ot-QSAR model for antifungal activity against C. albicans

$pMIC_{ca} = -0.289\ J + 2.983$ Eq. 4

n = 20

r = 0.919 $r^2 = 0.845$

$q^2 = 0.806$

s = 0.159 F = 97.27

RMSE = 0.192

PRESS = 0.739

QSAR analysis of synthesized derivatives showed that antifungal activity of undec-10-enoic acid hydrazide derivatives negatively correlated with J values (Eq. 4) against *C. albicans*. This fact can be further verified by high $pMIC_{ca}$ values ($pMIC_{ca}$ = 2.05) of compounds **10-13**, **15** and **18** (Table 2) and their respective small J values (Table 4).

ot-QSAR model for antifungal activity against A. niger

$pMIC_{an} = 0.136\ ^2\chi + 0.368$ Eq. 5

n = 20

r = 0.818

$r^2 = 0.669$

$q^2 = 0.601$

s = 0.156 F = 36.33

RMSE = 0.147 PRESS = 0.432

Eq. 5 showed the significance of second order molecular connectivity index ($^2\chi$) in demonstrating the antifungal activity of synthesized undec-10-enoic acid hydrazide derivatives against *A. niger*. Predictive ability of Eq. 5 can be further confirmed by high $^2\chi$ (Table 4) and $pMIC_{an}$ (Table 2) values of compounds **18** and **19**. Topological indices parameters (e.g. $^2\chi$, $^0\chi$) are numerical descriptors of a topology of a molecule.

These are highly sensitive to bonding pattern, symmetry, content of heteroatom as well as degree of complexity of atomic neighborhoods. Since, connectivity order of the constituent atoms in a molecule can be explained by topological descriptors hence the aforementioned fact revealed the role of topological indices, in estimating biological activity, *viz*. antimicrobial activity.

Table 6: Correlation of molecular descriptors with antimicrobial activity of synthesized hydrazide derivatives.

Mol. Descriptor	$pMIC_{bs}$	$pMIC_{sa}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
Log P	0.188	0.834	0.717	0.838	0.657	0.777	0.804	0.805
MR	0.353	0.933	0.934	0.894	0.763	0.937	0.883	0.928
$^{0}\chi$	0.392	0.924	0.910	0.875	0.804	0.934	0.889	0.929
$^{0}\chi^{v}$	0.377	0.914	0.909	0.876	0.766	0.924	0.874	0.916
$^{1}\chi$	0.361	0.939	0.925	0.896	0.798	0.940	0.900	0.937
$^{1}\chi^{v}$	0.364	0.930	0.927	0.891	0.779	0.937	0.889	0.930
$^{2}\chi$	0.406	0.932	0.910	0.879	0.818	0.943	0.898	0.938
$^{2}\chi^{v}$	0.407	0.919	0.917	0.874	0.776	0.938	0.877	0.925
κ_3	-0.523	-0.164	-0.293	-0.155	-0.487	-0.318	-0.305	-0.314
$\kappa\alpha_3$	-0.558	-0.426	-0.538	-0.399	-0.684	-0.559	-0.541	-0.558
R	0.329	0.893	0.904	0.856	0.732	0.897	0.847	0.889
J	-0.296	-0.947	-0.920	-0.919	-0.792	-0.929	-0.912	-0.938
W	0.290	0.846	0.845	0.812	0.649	0.840	0.783	0.828
T.E.	-0.400	-0.914	-0.878	-0.865	-0.822	-0.921	-0.890	-0.923
LUMO	-0.395	-0.839	-0.792	-0.770	-0.749	-0.850	-0.800	-0.842
HOMO	0.022	0.683	0.647	0.711	0.441	0.616	0.632	0.637

Table 7: Comparison of observed and predicted antibacterial and antifungal activity obtained by *ot*-QSAR models.

Comp.	$pMIC_{sa}$ (Eq. 2)			$pMIC_{ec}$ (Eq. 3)			$pMIC_{ca}$ (Eq. 4)			$pMIC_{an}$ (Eq. 5)		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.400	1.949	-0.549	1.400	1.379	0.021	1.390	1.935	-0.545	1.390	1.495	-0.105
2	0.900	0.894	0.006	0.900	1.014	-0.114	1.200	0.989	0.211	1.200	1.015	0.185
3	0.900	0.877	0.023	1.200	1.030	0.170	0.900	0.973	-0.073	0.900	1.015	-0.115
4	1.960	1.997	-0.037	1.360	1.338	0.022	1.960	1.978	-0.018	1.360	1.425	-0.065
5	2.000	1.997	0.003	1.410	1.389	0.021	2.000	1.978	0.022	1.700	1.495	0.205
6	2.000	1.997	0.003	1.410	1.389	0.021	2.000	1.978	0.022	1.410	1.509	-0.099
7	2.000	1.997	0.003	1.390	1.340	0.050	2.000	1.978	0.022	1.680	1.509	0.171
8	2.000	1.991	0.009	1.400	1.356	0.044	2.000	1.972	0.028	1.700	1.495	0.205
9	2.000	1.999	0.001	1.400	1.356	0.044	2.000	1.980	0.020	1.700	1.509	0.191
10	2.050	2.005	0.045	1.420	1.425	-0.005	2.050	1.985	0.065	1.720	1.604	0.116
11	2.050	1.983	0.067	1.420	1.416	0.004	2.050	1.965	0.085	1.720	1.621	0.099
12	2.050	1.999	0.051	1.420	1.416	0.004	2.050	1.979	0.071	1.420	1.631	-0.211
13	2.050	1.986	0.064	1.420	1.485	-0.065	2.050	1.968	0.082	1.420	1.631	-0.211
14	2.000	2.006	-0.006	1.400	1.407	-0.007	2.000	1.985	0.015	1.400	1.532	-0.132
15	2.050	1.966	0.084	1.440	1.477	-0.037	2.050	1.950	0.100	1.440	1.630	-0.190
16	2.000	2.018	-0.018	1.400	1.448	-0.048	2.000	1.997	0.003	1.400	1.521	-0.121
17	1.400	1.949	-0.549	1.400	1.379	0.021	1.390	1.935	-0.545	1.390	1.495	-0.105
18	2.050	1.929	0.121	1.440	1.457	-0.017	2.050	1.917	0.133	1.740	1.693	0.047
19	2.050	1.946	0.104	1.440	1.457	-0.017	1.740	1.931	-0.191	1.740	1.701	0.039
20	2.000	1.948	0.052	1.400	1.397	0.003	2.000	1.934	0.066	1.700	1.579	0.121

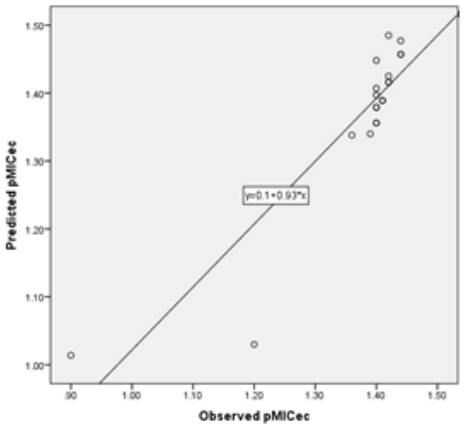


Fig. 2: Plot of predicted pMICec values against observed pMICec values for the linear regression developed model by Eq. 3.

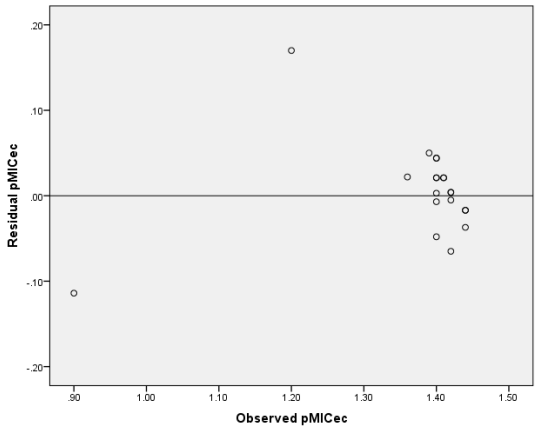


Fig. 3: Plot of residual pMICec values against observed pMICec values for the linear regression developed model Eq. 3.

Consequently, topological parameters utilized for estimating biological activities of chemical compounds can be employed for drug development (Lather and Madan, 2005). The cross-validation of the developed models was performed by leave one out (LOO) method (Schaper, 1999). As per studies done by Golbraikh and Troposha for a valid QSAR model, the value of cross validated r^2 (q^2) should be more than 0.5 (Golbraikh and Tropsha *et al.*, 2002). Consequentially, all the QSAR models developed in present study are statistically valid and reliable in predicting the antimicrobial activity of synthesized hydrazide derivatives. The plot of observed $pMIC_{ec}$ Vs predicted $pMIC_{ec}$ (Fig. 2) showed the accuracy of developed *ot*-QSAR model

(Eq. 3). To examine the presence of a systemic error in developed QSAR equation (Eq. 3), the observed $pMIC_{ec}$ values were plotted against the residuals $pMIC_{ec}$ values (Fig. 3). The presence of the residual points on both sides of zero indicated that no systemic error exists in the development of QSAR model. (Golbraikh and Tropsha *et al.*, 2002).

Usually for QSAR analysis, the biological activity data of synthesized molecules should lies in between 2–3 orders of magnitude. Although, in present study the range of antimicrobial activities of synthesized hydrazide derivatives is within one order of magnitude, though the low residual values (Table 7) evidenced the high predictability of developed QSAR models (Eqs. 1-5). This is in agreement with results suggested by earlier studies (Narasimhan *et al.*, 2007; Sharma *et al.*, 2006; Hatya *et al.*, 2006; Kumar *et al.*, 2006), which confirmed that the robustness of the QSAR model lies in its predictive ability, although the biological activity data existed in narrow range of magnitude. Moreover, Kim *et al.* (2007) recommended that developed QSAR models are acceptable if the value of standard deviation (S.D.) is not much higher than 0.3 (Table 2). Hence, the above facts justify the statistical acceptability of developed QSAR models (Eqs. 1-5).

Development of multi-target QSAR model (mt-QSAR)

Aforementioned *ot*-QSAR models showed that five different equations have to be used to predict the activity of synthesized derivatives against the respective bacterial and fungal strains. But results of our earlier studies recommended that use of *ot*-QSAR equations is not much practicable, when we have to predict the activity of synthesized compounds against more than one target.

As different *ot*-QSAR equations have to be used for different targets. Above facts inspired us to develop multi-target QSAR (*mt*- QSAR) models. In compare to *ot*-QSAR, the *mt*-QSAR model is a single equation that considers common and essential physicochemical parameters for elucidation of antimicrobial activity for different targets (Prado-Prado *et al.*, 2008; Gonzalez-Diaz *et al.*, 2007, 2008a; Gonzalez-Diaz and Prado-Prado 2008; Cruz-Monteagudo *et al.*, 2007). In the present research work three *mt*-QSAR models were developed, Eq. 6 for relating antibacterial activity of synthesized derivatives with *B. subtilis*, *S. aureus*, and *E. coli*, Eq. 7 for relating antifungal activity with *C. albicans* and *A. niger* as well a common *mt*-QSAR model (Eq. 8) for relating antimicrobial (overall antibacterial and antifungal) activity of synthesized udecanoic hydrazide derivatives with all the above mentioned microbial strains. In order to develop *mt*-QSAR equations, firstly we have calculated the average antibacterial, antifungal and antimicrobial activities values of synthesized compounds, presented in Table 2. Further, these average antimicrobial activity values were interrelated with the physicochemical parameters (Table 4) of synthesized compounds.

mt-QSAR model for antibacterial activity

$$pMIC_{ab} = 0.129\ {}^{2}\chi + 0.437 \qquad \text{Eq. 6}$$

n = 20

r = 0.943 $r^2 = 0.889$

$q^2 = 0.871$

s = 0.074F = 145.70

RMSE = 0.070

PRESS = 0.098

Eq. 6 showed the importance of ${}^{2}\chi$ in illustrating the overall antibacterial activity against all three tested bacterial strains. Developed *mt*-QSAR model (Eq. 6) once again evident that as the values of ${}^{2}\chi$ (Table 4) increases the value of $pMIC_{ab}$ enhances (Table 2). Moreover, statistical parameters indicated that *mt*-QSAR model (Eq. 6) have better predictive ability than *ot*-QSAR models, as in case of *ot*-QSAR model there is no statistical significant model was developed against *B. subtilis*.

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

Comp.	$pMIC_{ab}$ (Eq. 6)			$pMIC_{af}$ (Eq. 7)			$pMIC_{am}$ (Eq. 8)		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	0.970	1.036	-0.066	0.870	0.995	-0.125	0.930	1.031	-0.101
2	1.000	1.052	-0.052	1.200	0.995	0.205	1.080	1.049	0.031
3	1.100	1.052	0.048	0.900	0.982	-0.082	1.020	1.049	-0.029
4	1.560	1.441	0.119	1.660	1.774	-0.114	1.600	1.495	0.105
5	1.610	1.508	0.102	1.850	1.774	0.076	1.700	1.571	0.129
6	1.610	1.521	0.089	1.700	1.774	-0.074	1.650	1.586	0.064
7	1.490	1.521	-0.031	1.840	1.774	0.066	1.630	1.586	0.044
8	1.600	1.508	0.092	1.850	1.769	0.081	1.700	1.571	0.129
9	1.600	1.521	0.079	1.850	1.775	0.075	1.700	1.586	0.114
10	1.630	1.611	0.019	1.880	1.780	0.100	1.730	1.689	0.041
11	1.630	1.628	0.002	1.880	1.764	0.116	1.730	1.708	0.022
12	1.630	1.637	-0.007	1.730	1.775	-0.045	1.670	1.719	-0.049
13	1.630	1.637	-0.007	1.730	1.766	-0.036	1.670	1.719	-0.049
14	1.400	1.543	-0.143	1.700	1.780	-0.080	1.520	1.611	-0.091
15	1.640	1.636	0.004	1.740	1.752	-0.012	1.680	1.717	-0.037
16	1.500	1.532	-0.032	1.700	1.789	-0.089	1.580	1.599	-0.019
17	1.400	1.508	-0.108	1.390	1.740	-0.350	1.390	1.571	-0.181
18	1.640	1.696	-0.056	1.900	1.726	0.174	1.740	1.786	-0.046
19	1.640	1.704	-0.064	1.740	1.737	0.003	1.680	1.795	-0.115
20	1.600	1.588	0.012	1.850	1.739	0.111	1.700	1.663	0.037

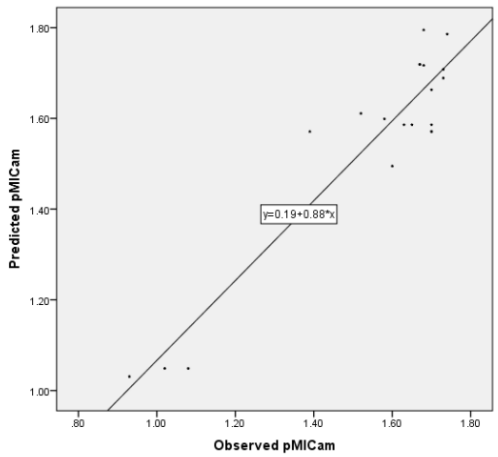


Fig. 4: Plot of predicted pMICam values against observed pMICam values for the linear regression developed model by Eq. 8.

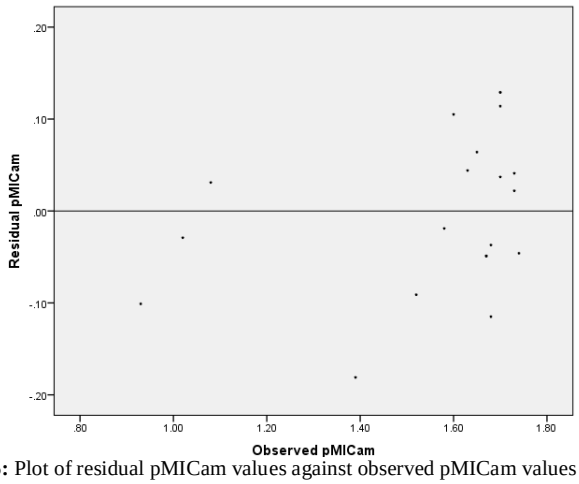


Fig. 5: Plot of residual pMICam values against observed pMICam values for the linear regression developed model Eq. 8.

mt-QSAR model for antifungal activity

$pMIC_{af}$ = -0.228 J + 2.566 Eq. 7

n = 20

r = 0.918 r^2 = 0.842

q^2 = 0.780

s = 0.132 F = 88.41

RMSE = 0.125

PRESS = 0.311

As in case of *C. albicans*, QSAR analysis of synthesized derivatives once again revealed that J values are negatively correlated with overall antifungal activity. This information can be further supported by high $pMIC_{af}$ values of compound **18** (MIC=1.90, Table 2) has small J values (3.68, Table 4).

mt-QSAR model for antimicrobial activity

$pMIC_{am}$ = 0.147 $^2\chi$ + 0.345 Eq. 8

n = 20

r = 0.938 r^2 = 0.880

q^2 = 0.866

s = 0.088 F = 132.53

RMSE = 0.084

PRESS = 0.142

The developed *mt*-QSAR model (Eq. 8) indicated that the $^2\chi$ is positively correlated with overall antimicrobial activity against all tested bacterial and fungal strains. This is clearly obvious from Table 4, that compounds (**10**, **11**, and **18)** having high $^2\chi$ values, 9.12, 9.25 and 9.78 have highest $pMIC_{am}$ activity values, *i.e.* 1.73, 1.73 and 1.74, respectively (Table 2). Moreover, compounds **1**, **2** and **3** with lowest $^2\chi$ values 4.66, 4.78 and 4.78 (Table 4) have lowest $pMIC_{am}$ activity values *i.e.* 0.93, 1.08 and 1.02, respectively (Table 2). Further, there is no statistically significant improvement in values of r and q^2 was observed, when we go for development of multiparametric models except *S. aureus* (Eq. 2).

The plot of observed $pMIC_{am}$ Vs predicted $pMIC_{am}$ (Fig. 4) showed the accuracy of developed *ot*-QSAR model (Eq. 8). To examine the presence of a systemic error in developed QSAR equation (Eq. 8), the observed $pMIC_{am}$ values were plotted against the residuals $pMIC_{am}$ values (Fig. 5). The presence of the residual points on both sides of zero indicated that no systemic error exists in the development of QSAR model (Golbraikh and Tropsha *et al.*, 2002).

CONCLUSION

In present study, a series of hydrazide derivatives of undecylenic acid (**4-20**) have been synthesized successfully in appreciable yields and evaluated for their *in vitro* antibacterial and antifungal activities against selected strains. The results of antimicrobial activity indicated that the NO_2 and OCH_3 groups improved the antimicrobial activity. The NO_2 group containing acetophenone derivatives have more antimicrobial activity as compare to NO_2 group containing aldehyde derivatives. Compounds having NO_2 (**11**, **12**, **18** and **19**) and OCH_3 (**10** and **15**) groups showed comparable antibacterial activity (pMIC= 2.05 µM/ml) against *S. aureus* and antifungal activity (pMIC=2.05 µM/ml) against *C. albicans* to that of standard drug Ciprofloxacin (pMIC=2.61 µM/ml) and Fluconazole (pMIC=2.64 µM/ml) respectively. QSAR studies showed that second order molecular connectivity index ($^2\chi$) and Balaban topological index (J) are the key parameters for antimicrobial activity of synthesized hydrazide derivatives. It is important to note that multi-target QSAR models were more significant in demonstrating the antimicrobial activity than one-target QSAR models.

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