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Quantitative structure–activity relationship studies for prediction of antimicrobial activity of synthesized 2,4-hexadienoic acid derivatives

Balasubramanian Narasimhan,* Vikramjeet Judge, Rakesh Narang, Ruchita Ohlan and Sucheta Ohlan

Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana 125001, India

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Abstract—A new series of 2,4-hexadienoic acid derivatives (S_1–S_{42}) has been synthesized and evaluated as antimicrobial agents against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus niger*. Quantitative structure–activity relationship (QSAR) investigation using Hansch analysis was applied to find out correlation between antimicrobial activities with physicochemical properties of the synthesized compounds. Various physicochemical descriptors and experimentally determined minimum inhibitory concentration values for different microorganisms were used as independent and dependent variables, respectively. The QSAR revealed that topological parameters especially molecular connectivity indices (χ^2, ${}^0\chi^v$, ${}^2\chi^v$) were found to have overall significant correlation with antimicrobial activity of 2,4-hexadienoic acid derivatives. The statistical results of training set, cross-validated r^2 and conventional r values gave reliability to the prediction of molecules with activity using QSAR models.

2,4-Hexadienoic acid (sorbic acid) obtained from *Sorbus aucuparia* L. Rosaceae[1] isolated by Hofmann Ann was found to possess antibacterial[2] and antifungal activity.[3] Further it enhances absorbance of ocular drugs[4] and increases antitubercular activity of pyrazinamide.[5] Sorbic acid is mainly used as preservative agent in pharmaceutical[6] and food products.[7] Sorbic acid is unsaturated at αβ and γδ position and its derivatives have also been studied for their antimicrobial activity by us[8] and others.[9]

Quantitative structure–activity relationship has been traditionally perceived as means of establishing correlation between trends in chemical structure modification and respective changes of biological activity.[10] QSAR is widely used in development of antimicrobial agents. Substituted pyrazinoic acid esters having 100 times more activity than pyrazinamide against *Mycobacterium tuberculosis*, in vitro, have been reported.[11]

In view of above and in continuation of our efforts in describing the contribution of QSAR in demonstrating biological activity,[12–18] we present here, a report on the application of QSAR to analyze antimicrobial potential of 2,4-hexadienoic acid derivatives using physicochemical descriptors. To our knowledge it is the first time the extensive QSAR has been studied on the 2, 4-hexadienoic acid derivatives.

The esters of 2,4-hexadienoic acid were achieved by reaction of 2,4-hexadienoic acid with corresponding alcohol in presence of mineral acid (Scheme 1). The synthetic route to the derived amides/anilides includes the reaction of 2,4-hexadienoyl chloride with corresponding amine/aniline in cold and normal conditions (Scheme 2). The precursor 2,4-hexadienoyl chloride was prepared by treatment of 2,4-hexadienoic acid with thionyl chloride. The physicochemical characteristics of synthesized 2, 4-hexadienoic acid derivatives are presented in Table 1. Structures of all the newly obtained 2,4-hexadienoic acid derivatives have been ascertained on the basis of their consistent IR and NMR spectral assignments.

It is important to note that the stereochemical configuration of 2,4-hexadienoic acid, i.e., 2*E*,4*E*-hexadienoic acid, is unaffected during the reaction which is evidenced

Keywords: 2,4-Hexadienoic acid derivatives; Antibacterial activity; Antifungal activity; QSAR; LOO method.
* Corresponding author. Tel.: +91 1662 263162; fax: +91 1662 267240; e-mail: naru2000us@yahoo.com

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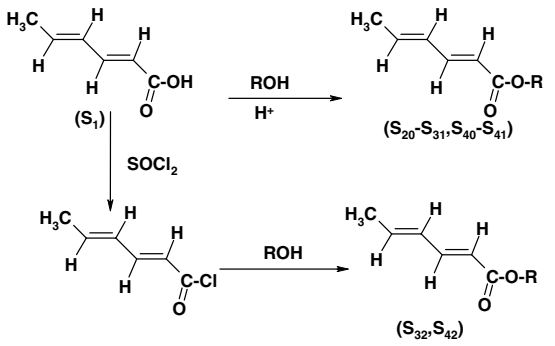
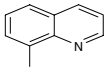
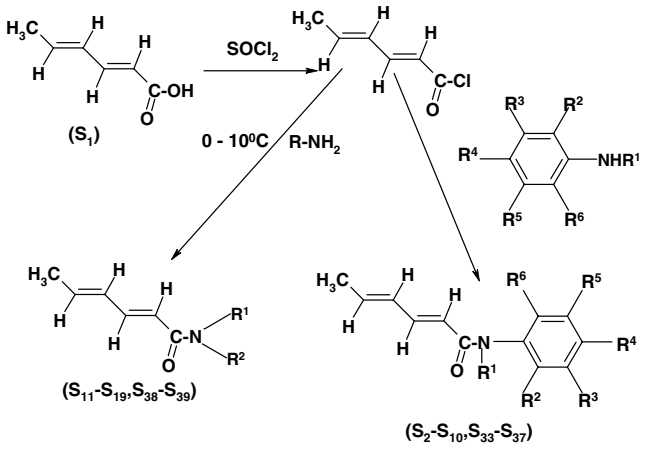


S_{20} = R = C_2H_5; S_{21} = R = C_3H_7; S_{22} = R = $(CH_3)_2CH$; S_{23} = R = C_4H_9;
S_{24} = R = $CH_3CH_2(CH_3)CH$; S_{25} = R = $(CH_3)_3C$; S_{26} = R = $(CH_3)_2CHCH_2$;
S_{27} = R = C_5H_{11}; S_{28} = R = $(CH_3)_2CHCH_2CH_2$; S_{29} = R = $CH_3(CH_2)_4CH_2$;
S_{30} = R = $CH_3(CH_2)_5CH_2$; S_{31} = R = CH_2=$CHCH_2$; S_{32} = R = C_6H_5; S_{40} = R = CH_3;
S_{41} = R = $C_6H_5CH_2$

S_{42} = R =



Scheme 1. Synthetic route for esters of 2,4-hexadienoic acid.



S_{11} = R^1, R^2 = H
S_{12} = R^1, R^2 = CH_3
S_{13} = R^1= C_2H_5, R^2 = H
S_{14} = R^1 = C_3H_7, R^2= H
S_{15} = R^1 = HOC_2H_4, R^2= H
S_{16} = R^1, R^2 = OHC_2H_4
S_{17} = R^1 = C_5H_{10}, R^2 = ----
S_{18} = R^1 = C_4H_8O, R^2 = ---
S_{19} = R^1 = NH_2, R^2 = H
S_{38} = R^1 = CH_3, R^2 = H
S_{39} = R^1 = $C_6H_5CH_2$, R^2 = H

S_2 = R^1, R^2, R^4,R^5,R^6 = H, R^3 = NO_2
S_3 = R^1, R^2, R^3,R^5,R^6 = H, R^4 = NO_2
S_4 = R^1, R^2, R^3,R^5,R^6 = H, R^4 = OCH_3
S_5 = R^1, R^2, R^4,R^5,R^6 = H, R^3 = Cl
S_6 = R^1, R^2, R^3,R^5,R^6 = H, R^4 = Cl
S_7 = R^1, R^2, R^4,R^5,R^6 = H, R^3 = CH_3
S_8 = R^1, R^2, R^3,R^5,R^6 = H, R^4 = Br
S_9 = R^1, R^3, R^4,R^5,R^6 = H, R^2 = NH_2
S_{10} = R^1, R^2, R^4,R^5,R^6 = H, R^3 = OH
S_{33} = R^1, R^2,R^3, R^4,R^5,R^6 = H
S_{34} = R^1, R^3, R^4,R^5,R^6 = H, R^2 = OCH_3
S_{35} = R^1, R^3, R^4,R^5,R^6 = H, R^2 = Cl
S_{36} = R^1, R^2, R^3,R^5,R^6 = H, R^4 = CH_3
S_{37} = R^2,R^3, R^4,R^5,R^6 = H, R^1 = C_6H_5

Scheme 2. Synthetic route for amides/anilides of 2,4-hexadienoic acid.

by the ^{1}H NMR coupling constant values of synthesized 2,4-hexadienoic acid derivatives which are within the range of J = 11–20, the coupling constant (J) values for trans compounds.[19]

The 2,4-hexadienoic acid derivatives were evaluated for their in vitro antibacterial activity against Gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and Gram negative *Escherichia coli* and in vitro antifungal activity against *Candida albicans* and *Aspergillus niger* by two-fold serial dilution method.[20] Double strength nutrient broth IP and Sabouraud dextrose broth IP[21] have been employed as media for growth of bacterial and fungal cells, respectively. The results of antimicrobial study are presented in Table 2. The results of antimicrobial studies indicated that the compounds *m*-nitrosorbanilide, *p*-nitrosorbanilide, *p*-chlorosorbanilide, *N*-phenylsorbanilide, and 8-quinolinyl sorbate (S_2, S_3, S_6, S_{37}, and S_{42}) were found to be the most active compounds. Further it is noteworthy to mention here that 2,4-hexadienoic acid derivatives were more active towards Gram-positive bacteria than the Gram-negative bacteria.

Table 1. Physicochemical characteristics of 2,4-hexadienoic acid derivatives

Compound	Mol. formula	Mol. Wt.	Mp/bp* (°C)	R_f	% yield
Training set					
S_1	$C_6H_8O_2$	112	133–136	0.65	—
S_2	$C_{12}H_{12}O_3N_2$	232	125–128	0.55	32.75
S_3	$C_{12}H_{12}N_2O_3$	232	98–101	0.64	58.18
S_4	$C_{13}H_{15}NO_2$	217	148–151	0.58	62.20
S_5	$C_{12}H_{12}NOCl$	221	126–129	0.67	50.10
S_6	$C_{12}H_{12}NOCl$	221	155–158	0.68	48.64
S_7	$C_{13}H_{15}NO$	201	122–125	0.71	55.00
S_8	$C_{12}H_{12}NOBr$	266	210–213	0.59	60.20
S_9	$C_{12}H_{14}N_2O$	202	173–176	0.41	20.29
S_{10}	$C_{12}H_{13}NO_2$	203	100–103	0.40	27.09
S_{11}	$C_6H_{10}NO$	111	118–121	0.25[a]	92.34
S_{12}	$C_8H_{13}NO$	139	115–118	0.35	47.90
S_{13}	$C_8H_{13}NO$	139	125–128	0.51	32.70
S_{14}	$C_9H_{15}NO$	152	41–44	0.47	55.90
S_{15}	$C_8H_{13}NO$	139	75–78	0.51	89.90
S_{16}	$C_{10}H_{17}NO$	167	112–115	0.21	30.10
S_{17}	$C_{11}H_{17}NO$	179	122–125	0.31	65.80
S_{18}	$C_{10}H_{15}NO_2$	181	49–52	0.24	57.40
S_{19}	$C_6H_{10}N_2O$	126	105–108	0.42	61.90
S_{20}	$C_8H_{12}O_2$	140	193–196*	0.70[a]	66.90
S_{21}	$C_9H_{14}O_2$	154	118–121	0.66[b]	35.00
S_{22}	$C_9H_{14}O_2$	154	106–109	0.23[b]	73.04
S_{23}	$C_{10}H_{16}O_2$	168	95–98	0.69[a]	40.20
S_{24}	$C_{10}H_{16}O_2$	168	100–103	0.29[b]	45.60
S_{25}	$C_{10}H_{16}O_2$	168	147–150	0.23[b]	55.00
S_{26}	$C_{10}H_{16}O_2$	168	111–114	0.59[c]	60.70
S_{27}	$C_{11}H_{18}O_2$	182	115–118	0.73[a]	50.20
S_{28}	$C_{11}H_{18}O_2$	182	161–164	0.77[a]	70.51
S_{29}	$C_{12}H_{20}O_2$	196	132–135	0.65[c]	62.52
S_{30}	$C_{13}H_{22}O_2$	210	112–115	0.82[a]	58.00
S_{31}	$C_9H_{12}O_2$	152	124–127	0.73[a]	57.80
S_{32}	$C_{12}H_{12}O_2$	188	75–78	0.69[a]	87.30
Test set					
S_{33}	$C_{12}H_{13}ON$	187	152–155	0.70	32.20
S_{34}	$C_{13}H_{15}NO_2$	217	110–113	0.73	46.08
S_{35}	$C_{12}H_{12}NOCl$	221	95–98	0.73	43.20
S_{36}	$C_{13}H_{15}NO$	201	128–131	0.72	54.47
S_{37}	$C_{18}H_{17}NO$	263	155–158	0.82	90.30
S_{38}	$C_7H_{11}NO$	125	110–113	0.20[b]	64.00
S_{39}	$C_{13}H_{15}NO$	201	110–113	0.18[a]	94.50
S_{40}	$C_7H_{10}O_2$	126	177–180*	0.66[a]	57.70
S_{41}	$C_{13}H_{14}O_2$	202	119–122	0.50[c]	40.20
S_{42}	$C_{15}H_{13}NO_2$	239	115–118	0.44	50.20

TLC mobile phase — Benz., EA (4:1); [a]Tol/$CHCl_3$ (7:3); [b]Benz., [c]EA/Hex (1:9).
* Boiling point should be added.

Table 2. Antimicrobial activity of 2,4-hexadienoic acid derivatives

Compound	$pMIC_{bs}$	$PMIC_{sa}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$
Training set					
S_1	0.95	0.85	0.75	0.95	0.90
S_2	1.46	1.30	1.22	1.32	1.40
S_3	1.41	1.22	1.22	1.27	1.27
S_4	1.34	1.19	1.19	1.30	1.35
S_5	1.30	1.20	1.14	1.30	1.40
S_6	1.35	1.20	1.14	1.30	1.30
S_7	1.32	1.21	1.10	1.21	1.21
S_8	1.32	1.43	1.10	1.33	1.30
S_9	1.31	1.20	1.16	1.21	1.16
S_{10}	1.27	1.05	1.00	1.27	1.16
S_{11}	1.00	0.90	0.90	1.10	0.95
S_{12}	1.14	1.10	0.94	1.20	1.10
S_{13}	1.05	0.94	0.84	1.10	1.05
S_{14}	1.14	1.00	0.88	1.09	1.00
S_{15}	1.04	0.99	0.94	1.09	0.95
S_{16}	1.20	1.10	1.04	1.30	0.90
S_{17}	1.21	1.11	0.95	1.16	1.20
S_{18}	1.26	1.16	0.92	1.20	1.10
S_{19}	1.00	0.85	0.80	1.00	0.95
S_{20}	1.05	0.89	0.89	1.11	1.00
S_{21}	1.15	0.98	0.89	1.15	1.09
S_{22}	1.20	1.09	0.97	1.20	1.25
S_{23}	1.13	1.00	0.97	1.13	1.13
S_{24}	1.13	0.88	0.97	1.13	1.08
S_{25}	1.30	1.13	1.08	1.27	1.13
S_{26}	1.13	1.00	0.97	1.13	1.20
S_{27}	1.20	1.10	1.00	1.30	1.16
S_{28}	1.26	1.20	1.00	1.16	1.16
S_{29}	1.20	1.00	0.95	1.29	1.20
S_{30}	1.30	1.23	1.10	1.23	1.23
S_{31}	1.10	0.88	0.93	1.09	1.10
S_{32}	1.23	1.02	1.13	1.25	1.32
SD[a]	0.13	0.14	0.12	0.09	0.14
Test Set					
S_{33}	1.18	0.97	0.97	1.18	1.13
S_{34}	1.24	1.20	1.10	1.30	1.20
S_{35}	1.25	1.15	1.09	1.25	1.20
S_{36}	1.26	1.21	1.00	1.26	1.46
S_{37}	1.42	1.30	1.23	1.32	1.40
S_{38}	1.10	1.00	0.84	1.10	1.10
S_{39}	1.21	1.15	1.00	1.21	1.21
S_{40}	1.10	1.00	0.90	1.10	1.00
S_{41}	1.16	1.20	1.00	1.21	1.15
S_{42}	1.89	1.89	1.89	1.28	1.42
SD	3.33[b]	3.33[b]	3.33[b]	2.64[c]	2.64[c]

[a] Standard deviation.
[b] Ciprofloxacin.
[c] Fluconazole.

The anilides with electron withdrawing group were generally more active than other derivatives (esters and amides). The presence of aromatic ring may be responsible for their higher activity which is further evidenced by higher activity of *N*-phenyl-substituted anilide (S_{37}). The importance of electron-withdrawing groups in enhancing the antimicrobial activity is supported by similar results observed by Sharma et al.[22] Importance of aromatic rings in improving the antimicrobial activity was further evidenced by low antimicrobial activity of simple amides (S_{11}, S_{12}). It is also important to note that the moderate increase in activity of benzyl sorbamide (S_{39}) may be attributed to the separation of aromatic ring and amide linkage by the presence of a CH_2 group. The positive contribution of aromatic ring may be due to the involvement of aromatic ring in enhancing the binding of molecules with the target.

In order to identify the substituent effect on the antimicrobial activity, quantitative structure–activity relationship (QSAR) studies were undertaken using the linear free energy relationship model described by Hansch and Fujita.[23] Biological activity data (MIC) were calibrated into their logarithmic values (pMIC) on molar basis and are listed in Table 2. QSAR studies were performed by linear regression analysis. The molecular descriptors are selected in such a way that they should cover different types viz., hydrophobic, electronic, steric, and topological descriptors. The calculated parameters used in the present study are (log *P*), molar refractivity (MR), Kier's molecular connectivity ($^0\chi$, $^0\chi^v$, $^1\chi$, $^1\chi^v$, χ^2, $^2\chi^v$) and shape (κ_1, $\kappa\alpha_1$) topological indices, Randic topological index (*R*), Balaban topological index (*J*), Wiener topological index (*W*), Total energy (T_e), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ), electronic energy (Ele.E), nuclear energy (Nu.E), and molecular surface area (SA).[24–30] The value of selected molecular descriptors of 2,4-hexadienoic acid derivatives used in linear regression analysis is depicted in Table 3.

In the present work, a training set consisting of 32 molecules (S_1–S_{32}) was used for linear regression model generation and a test set consisting of 10 molecules (S_{33}–S_{42}) was used for the evaluation of the predictive ability of the generated model. The reference drugs ciprofloxacin and fluconazole were not included in model generation as they belong to a different structural series.

Correlation analysis (Table 4) was performed on all the descriptors to find out colinearity among them. In general parameters showed high colinearity ($r > 0.8$). The high interrelationship was observed between $^1\chi$ and $^0\chi$ ($r = 0.988$), *R* and $^0\chi$ ($r = 0.988$), MR and $^1\chi$ ($r = 0.983$) and low interrelationship was observed between T_e and log *P* ($r = -0.485$).

The correlation of different parameters with antimicrobial activity of 2,4-hexadienoic acid derivatives is presented in Table 5. The above table indicated the predominance of topological parameter in describing the antimicrobial activity of 2,4-hexadienoic acid derivatives against *B. subtilis* in Eq. 1.

QSAR model for antibacterial activity against B. subtilis

$$pMIC_{bs} = 0.106(\pm 0.006)^2\chi + 0.701(\pm 0.027) \quad (1)$$

$n = 32$ $r = 0.961$ $q^2 = 0.913$ $S = 0.035$
$F = 361.93$

Here and thereafter, *n*, number of data points; *r*, correlation coefficient; r^2, squared correlation; *S*, standard error of estimate; *F*, Fischer ratio; q^2, cross-validated r^2 obtained by leave one out method.

Table 3. Molecular descriptors used in regression analysis

Compound	Log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	*R*	*W*
Training set										
S_1	1.47	33.28	6.41	4.66	3.77	2.29	2.89	1.22	3.77	79.00
S_2	2.49	67.10	12.67	9.29	8.13	4.98	6.87	3.18	8.13	606.00
S_3	2.49	67.10	12.67	9.29	8.13	4.98	6.86	3.18	8.13	630.00
S_4	2.28	66.24	11.80	9.44	7.76	5.00	6.13	3.10	7.76	535.00
S_5	3.05	64.58	11.10	9.22	7.22	4.99	5.97	3.36	7.22	434.00
S_6	3.05	64.58	11.10	9.22	7.22	4.99	5.96	3.35	7.22	442.00
S_7	3.00	64.82	11.10	9.03	7.22	4.89	5.97	3.24	7.22	434.00
S_8	3.32	67.40	11.10	10.03	7.22	5.39	5.96	3.82	7.22	442.00
S_9	1.75	64.48	11.10	8.60	7.24	4.69	5.86	2.96	7.24	426.00
S_{10}	2.25	61.47	11.10	8.47	7.22	4.62	5.97	2.92	7.22	434.00
S_{11}	0.60	35.11	6.41	4.80	3.77	2.36	2.89	1.29	3.77	79.00
S_{12}	1.10	44.90	7.98	6.66	4.68	3.19	3.72	2.12	4.68	143.00
S_{13}	1.19	44.75	7.82	6.42	4.81	3.38	3.39	1.78	4.81	150.00
S_{14}	1.66	49.27	8.53	7.13	5.31	3.88	3.74	2.18	5.31	200.00
S_{15}	0.41	46.29	8.53	6.58	5.31	3.49	3.74	1.90	5.31	200.00
S_{16}	0.21	57.48	10.81	8.39	6.76	4.56	4.81	2.66	6.76	357.00
S_{17}	1.82	57.04	9.52	8.20	6.34	4.93	4.87	3.27	6.34	284.00
S_{18}	0.75	53.97	9.52	7.90	6.34	4.50	4.87	2.82	6.34	284.00
S_{19}	0.59	39.59	7.11	5.30	4.31	2.61	3.01	1.39	4.31	110.00
S_{20}	1.84	42.80	7.82	6.33	4.81	3.27	3.39	1.64	4.81	150.00
S_{21}	2.31	47.32	8.53	7.04	5.31	3.77	3.74	2.05	5.31	200.00
S_{22}	2.26	47.22	8.69	7.20	5.16	3.66	4.23	2.37	5.16	192.00
S_{23}	2.71	51.93	9.23	7.75	5.81	4.27	4.10	2.41	5.81	261.00
S_{24}	2.72	51.74	9.40	7.91	5.70	4.20	4.35	2.54	5.70	245.00
S_{25}	2.33	51.86	9.61	8.13	5.45	3.98	5.37	3.42	5.45	236.00
S_{26}	2.71	51.80	9.40	7.91	5.66	4.13	4.57	2.91	5.66	252.00
S_{27}	3.10	56.53	9.94	8.45	6.31	4.77	4.45	2.76	6.31	334.00
S_{28}	3.04	56.47	10.10	8.62	6.16	4.63	4.93	3.23	6.16	324.00
S_{29}	3.50	61.13	10.65	9.16	6.81	5.27	4.80	3.11	6.81	420.00
S_{30}	3.90	65.73	11.36	9.87	7.31	5.77	5.16	3.47	7.31	520.00
S_{31}	2.24	47.22	8.53	6.62	5.31	3.38	3.74	1.80	5.31	200.00
S_{32}	3.18	57.83	10.23	8.01	6.83	4.39	5.34	2.62	6.83	364.00
Test Set										
S_{33}	2.53	59.78	10.23	8.10	6.83	4.48	5.34	2.74	6.83	364.00
S_{34}	2.28	66.24	11.80	9.44	7.77	5.01	6.05	3.07	7.77	503.00
S_{35}	3.05	64.58	11.10	9.22	7.24	5.00	5.86	3.29	7.24	426.00
S_{36}	3.00	64.82	11.10	9.03	7.22	4.89	5.96	3.24	7.22	442.00
S_{37}	4.46	84.45	14.21	11.44	9.83	6.56	7.85	4.23	9.83	829.00
S_{38}	0.85	40.00	7.11	5.72	4.31	2.82	3.01	1.50	4.31	110.00
S_{39}	2.63	64.61	10.93	8.81	7.33	4.94	5.68	3.09	7.33	458.00
S_{40}	1.50	38.05	7.11	5.63	4.31	2.68	3.01	1.41	4.31	110.00
S_{41}	3.28	62.67	10.93	8.72	7.33	4.83	5.68	2.98	7.33	458.00
S_{42}	3.27	71.75	12.79	10.04	8.81	5.66	7.24	3.64	8.81	666.00

Table 4. Correlation matrix of antibacterial activity of 2,4-hexadienoic acid derivatives against *B. subtilis*

Mol. descriptor	LOGBS	LOGP	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	κ_1	$\kappa\alpha_1$	*R*	*W*	T_e
LOGBS	1.000													
LOG *P*	0.534	1.000												
MR	0.921	0.609	1.000											
$^{0}\chi$	0.935	0.559	0.977	1.000										
$^{0}\chi^{v}$	0.898	0.678	0.973	0.946	1.000									
$^{1}\chi$	0.915	0.541	0.983	0.988	0.934	1.000								
$^{1}\chi^{v}$	0.845	0.665	0.956	0.914	0.980	0.922	1.000							
$^{2}\chi$	0.961	0.521	0.940	0.959	0.891	0.948	0.836	1.000						
$^{2}\chi^{v}$	0.886	0.649	0.910	0.872	0.955	0.849	0.928	0.875	1.000					
κ_1	0.858	0.598	0.931	0.964	0.937	0.933	0.913	0.859	0.835	1.000				
$\kappa\alpha_1$	0.794	0.609	0.885	0.908	0.929	0.869	0.917	0.775	0.835	0.982	1.000			
R	0.915	0.541	0.983	0.988	0.934	1.000	0.922	0.948	0.849	0.933	0.869	1.000		
W	0.906	0.562	0.956	0.978	0.904	0.979	0.884	0.936	0.812	0.935	0.866	0.979	1.000	
T_e	−0.904	−0.485	−0.941	−0.984	−0.909	−0.974	−0.883	−0.932	−0.823	−0.951	−0.896	−0.974	−0.967	1.000

Table 5. Correlation of molecular descriptors with antimicrobial activity of 2,4-hexadienoic acid derivatives

Mol. descriptor	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$
LOG *P*	0.421	0.534	0.503	0.482	0.729
MR	0.828	0.921	0.877	0.839	0.788
$^{0}\chi$	0.796	0.935	0.904	0.841	0.761
$^{0}\chi^{v}$	0.829	0.898	0.830	0.854	0.779
$^{1}\chi$	0.783	0.915	0.881	0.820	0.765
$^{1}\chi^{v}$	0.781	0.845	0.758	0.804	0.732
$^{2}\chi$	0.827	0.961	0.922	0.824	0.806
$^{2}\chi^{v}$	0.853	0.886	0.783	0.812	0.763
κ_1	0.720	0.858	0.836	0.810	0.676
$\kappa\alpha_1$	0.687	0.794	0.755	0.785	0.613
R	0.783	0.915	0.881	0.820	0.765
W	0.775	0.906	0.888	0.796	0.762
T_e	−0.768	−0.904	−0.872	−0.825	−0.711

The topological index, $^{2}\chi$, signifies the degree of branching, connectivity of atoms and the unsaturation in the molecule which accounts for variation in activity.[31] The coefficient of $^{2}\chi$ in the Eq. 1 is positive, indicating that the antibacterial activity of 2,4-hexadienoic acid derivatives against *B. subtilis* is directly proportional to the value of $^{2}\chi$. The compounds $\mathbf{S}_2$, $\mathbf{S}_3$, $\mathbf{S}_{37}$ and $\mathbf{S}_{42}$ having the $^{2}\chi$ values of 6.87, 6.86, 7.85 and 7.24 (Table 3), respectively, which are higher than those of many compounds in training as well as test set make them to be highly active against *B. subtilis* (Table 2). Similarly the compounds $\mathbf{S}_1$, $\mathbf{S}_{11}$, $\mathbf{S}_{19}$, $\mathbf{S}_{38}$ having minimum $^{2}\chi$ values 2.89, 2.89, 3.01, 3.01 (Table 3), respectively, have minimum activity (Table 2).

The QSAR model expressed by Eq. (1) was cross-validated by its high q^2 value ($q^2 = 0.913$) obtained by 'leave one out' (LOO) method. In order to confirm our results we have synthesized a test set consisting of ten 2,4-hexadienoic acid derivatives viz ($\mathbf{S}_{33}$–$\mathbf{S}_{42}$) and predicted their activities using Eq. 1. The comparison of observed and predicted values in case of test set (Table 6) demonstrated that the above-mentioned values are close to each other evidenced by low residual activity values. Similar results were observed when we predicted the activity of training set with the same equation. Further the plot of linear regression predicted $pMIC_{bs}$ against observed $pMIC_{bs}$ (Fig. 1) also favours the model expressed by Eq. 1.

Eqs. 2–5 are developed to predict the antimicrobial activity of 2,4-hexadienoic acid derivatives against *S. aureus*, *E. coli*, *C. albicans*, and *A. niger*.

QSAR model for antibacterial activity against S.aureus

$$pMIC_{sa} = 0.172(\pm 0.019)^{2}\chi^{v} + 0.622(\pm 0.052) \quad (2)$$

$n = 32$ $r = 0.853$ $q^2 = 0.694$ $s = 0.076$ $F = 80.45$

QSAR model for antibacterial activity against E. coli

$$pMIC_{ec} = 0.098(\pm 0.008)^{2}\chi + 0.537(\pm 0.037) \quad (3)$$

$n = 32$ $r = 0.922$ $q^2 = 0.829$ $s = 0.048$ $F = 170.39$

QSAR model for antifungal activity against C. albicans

$$pMIC_{ca} = 0.059(\pm 0.007)^{0}\chi^{v} + 0.728(\pm 0.052) \quad (4)$$

$n = 32$ $r = 0.854$ $q^2 = 0.685$ $s = 0.051$ $F = 80.82$

QSAR model for antifungal activity against A. niger

$$pMIC_{an} = 0.098(\pm 0.005)^{2}\chi + 0.681(\pm 0.064) \quad (5)$$

$n = 32$ $r = 0.806$ $q^2 = 0.609$ $s = 0.084$ $F = 55.64$

As in case of *B. subtilis* the antibacterial activity against *E. coli* (Eq. (3)) and antifungal activity against *A. niger* (Eq. (5)) indicated the predominance of topological parameter, second-order molecular connectivity index ($^{2}\chi$), in describing the antimicrobial activity of 2,4-hexadienoic acid derivatives.

Similar results were observed in case of *S. aureus* for which valence second-order molecular connectivity index ($^{2}\chi^{v}$) and *C. albicans* for which valence zero-order molecular connectivity index ($^{0}\chi^{v}$) were found to govern the antimicrobial activity.

As in case of Eq. 1, the predictive ability of Eqs. 2–5 against respective microorganisms is supported by the low residual activity values observed in case of test (Table 6) as well as training set (Figs. 1–5). Further the high q^2 values observed also supports the goodness of the QSAR models ($q^2 > 0.5$) described by Eqs. 2–5. The other statistically significant equations derived are presented in Table 7.

Table 6. Comparison of observed vs predicted antimicrobial activity of test set of 2,4-hexadienoic acid derivatives using corresponding QSAR models

Test set	$pMIC_{bs}$			$pMIC_{sa}$			$pMIC_{ec}$			$pMIC_{ca}$			$pMIC_{an}$		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
$\mathbf{S}_{33}$	1.18	1.27	−0.09	0.97	1.09	−0.12	0.97	1.06	−0.09	1.18	1.21	−0.03	1.13	1.20	−0.07
$\mathbf{S}_{34}$	1.24	1.34	−0.10	1.20	1.15	0.05	1.10	1.13	−0.03	1.30	1.28	0.02	1.20	1.27	−0.07
$\mathbf{S}_{35}$	1.25	1.32	−0.07	1.15	1.19	−0.04	1.09	1.11	−0.02	1.25	1.27	−0.02	1.20	1.26	−0.06
$\mathbf{S}_{36}$	1.26	1.33	−0.07	1.21	1.18	0.03	1.00	1.12	−0.12	1.26	1.26	0.00	1.46	1.27	0.19
$\mathbf{S}_{37}$	1.42	1.53	−0.11	1.30	1.35	−0.05	1.23	1.31	−0.08	1.32	1.40	−0.08	1.40	1.45	−0.05
$\mathbf{S}_{38}$	1.10	1.02	0.08	1.00	0.88	0.12	0.84	0.83	0.01	1.10	1.07	0.03	1.10	0.98	0.12
$\mathbf{S}_{39}$	1.21	1.30	−0.09	1.15	1.15	0.00	1.00	1.09	−0.09	1.21	1.25	−0.04	1.21	1.24	−0.03
$\mathbf{S}_{40}$	1.10	1.02	0.08	1.00	0.86	0.14	0.90	0.83	0.07	1.10	1.06	0.04	1.00	0.98	0.02
$\mathbf{S}_{41}$	1.16	1.30	−0.14	1.20	1.13	0.07	1.00	1.09	−0.09	1.21	1.24	−0.03	1.15	1.24	−0.09
$\mathbf{S}_{42}$	1.89	1.47	0.42	1.89	1.25	0.64	1.89	1.25	0.64	1.28	1.32	−0.04	1.42	1.39	0.03

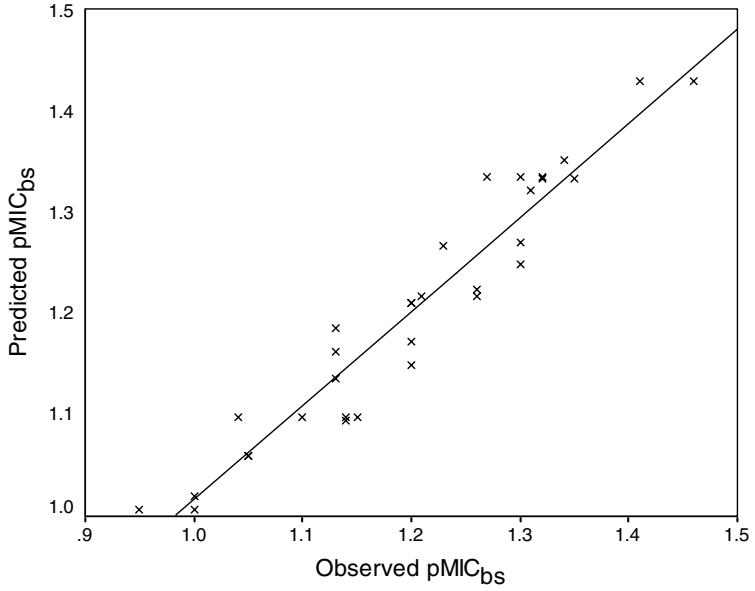


Figure 1. Plot of predicted $pMIC_{bs}$ values against experimental $pMIC_{bs}$ values for the linear regression developed model by Eq. 1.

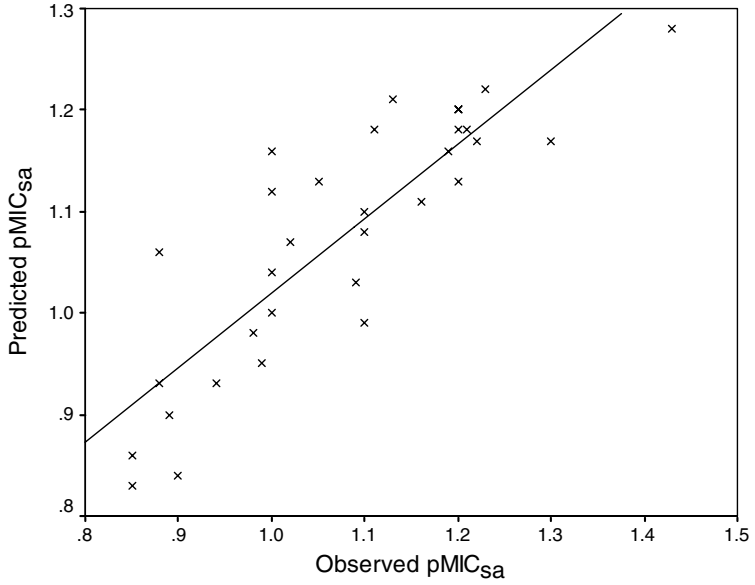


Figure 2. Plot of predicted $pMIC_{sa}$ values against experimental $pMIC_{sa}$ values for the linear regression developed model by Eq. 2.

It is worthwhile to mention here that no outliers were observed in the present study and also the q^2 value of the QSAR models developed was more than 0.5 which is the basic criteria on for qualifying the QSAR model to be a valid one. Even the 'rule of thumb' allowed us to go for a multiparametric model, the high interrelationship among the molecular descriptors made us to stick to a monoparametric model. The 'rule of thumb' gives information about the number of parameters to be selected for regression analysis in QSAR based on the number of compounds. According to this rule for QSAR model development one should select one parameter for a five-compound data set. The number of compounds in present study allowed us to go up to a maximum of octaparametric models, the high interrelationship (auto-correlation) between parameters restricted us to a single parametric model, being the auto-correlation of molecular descriptors prevents the significant improvement in the statistical parameters of the QSAR model in multiple linear regression (MLR) analysis.

The multicolinearity (auto-correlation) between the parameters[32] is indicated by the change in signs of the coefficients, a change in the values of previous coefficient, change of significant variable into insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model.

Generally for QSAR studies, the biological activities of compounds should span 2–3 orders of magnitude. But in the present study the range of activities of the

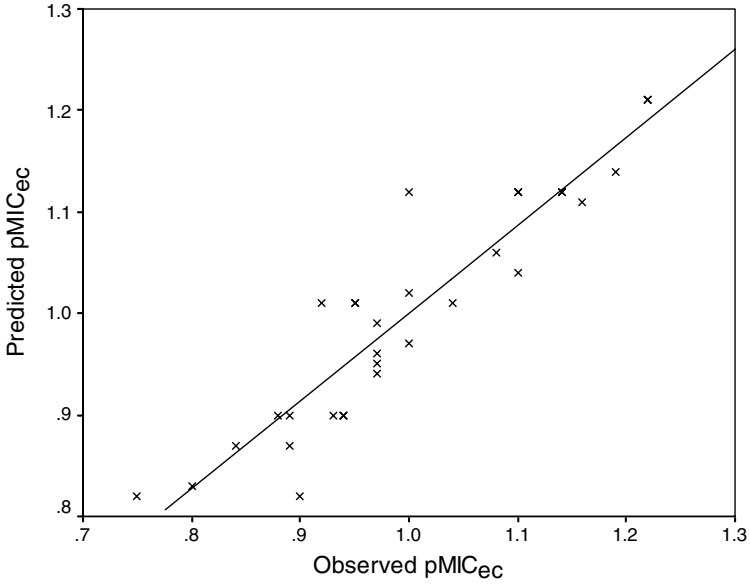


Figure 3. Plot of predicted $pMIC_{ec}$ values against experimental $pMIC_{ec}$ values for the linear regression developed model by Eq. 3.

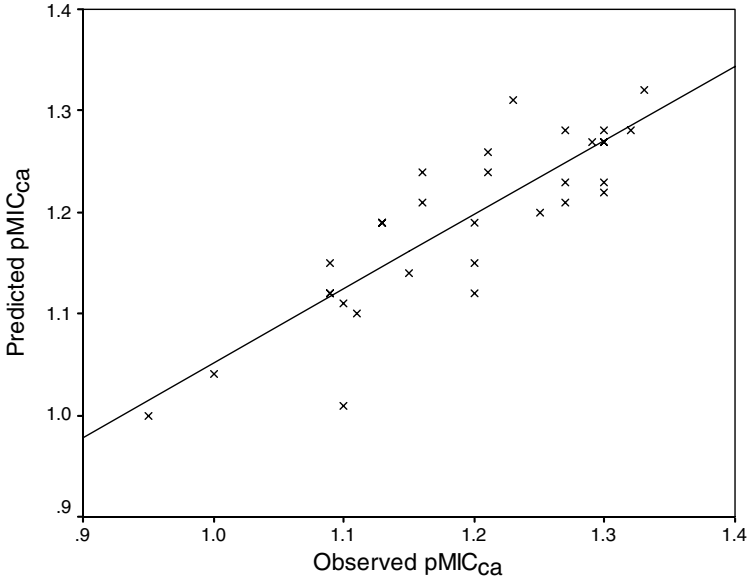


Figure 4. Plot of predicted $pMIC_{ca}$ values against experimental $pMIC_{ca}$ values for the linear regression developed model by Eq. 4.

compounds is within one order of magnitude except in case of 8-quinolinyl sorbate (S_{42}) where the order of magnitude is two. But it is important to note that the predictability of the QSAR models developed in the present study is very high as evidenced by the low residual values (Table 6). This is in accordance with results suggested by Bajaj et al.,[33] 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 has been applied to describe the relationship between narrow range of biological activity and physicochemical properties of the molecules.[34–36] When biological activity data lie in the narrow range, the presence of minimum standard deviation of the biological activity justifies its use in QSAR studies.[17] The minimum standard deviation (Table 2) observed in the antimicrobial activity data justifies its use in QSAR studies.

Summarizingly, a number of 2,4-hexadienoic acid derivatives have been synthesized in efficient yields. The synthesized compounds exhibited good in vitro antibacterial and antifungal profile. The trend of antimicrobial studies showed that these title compounds were highly effective against Gram-positive bacteria. Moreover, quantitative structure–activity relationship study revealed that antimicrobial activity of these synthesized derivatives against microorganisms under test was mainly governed by topological parameters, molecular connectivity indices (χ^2, $^0\chi^v$, $^2\chi^v$). The predictive ability of the developed QSAR models was established by the help of a test set which was excluded from model

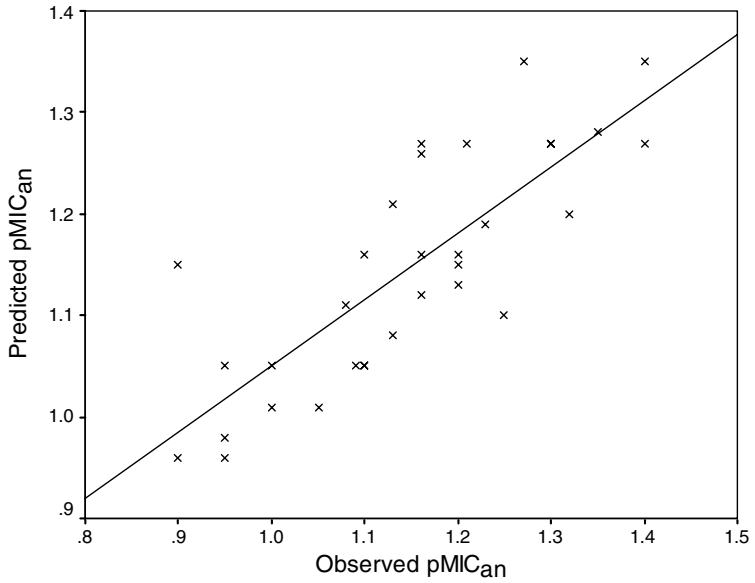


Figure 5. Plot of predicted $pMIC_{an}$ values against experimental $pMIC_{an}$ values for the linear regression developed model by Eq. 5.

Table 7. Regression analysis and quality of correlation for modeling antimicrobial activity of 2,4-hexadienoic acid derivatives

S.No.	QSAR Model (pMIC=)	*n*	*r*	q^2	*F*	*S*
	B. subtilis					
1	0.071 (±0.005) $^0\chi$ + 0.516 (±0.048)	32	0.935	0.860	207.72	0.045
2	0.012 (±0.001) MR + 0.558 (±0.050)	32	0.921	0.830	167.86	0.050
3	0.095 (±0.008) $^1\chi$ + 0.623 (±0.047)	32	0.915	0.816	153.83	0.051
4	0.095 (±0.008) *R* + 0.623 (±0.047)	32	0.915	0.816	153.83	0.051
	S. aureus					
5	0.084 (±0.010) $^0\chi^v$ + 0.412 (±0.083)	32	0.829	0.644	66.17	0.081
6	0.012 (±0.002) MR + 0.415 (±0.083)	32	0.828	0.646	65.59	0.081
7	0.104 (±0.013) $^2\chi$ + 0.584 (±0.063)	32	0.827	0.645	65.09	0.082
8	0.068 (±0.010) $^0\chi$ + 0.409 (±0.094)	32	0.796	0.592	51.75	0.088
	E. coli					
9	0.066 (±0.006) $^0\chi$ + 0.360 (±0.056)	32	0.904	0.789	134.35	0.053
10	0.0007 (±0.00) *W* + 0.780 (±0.023)	32	0.888	0.761	111.53	0.057
11	0.088 (±0.009) $^1\chi$ + 0.463 (±0.054)	32	0.881	0.743	104.06	0.058
12	0.088 (±0.009) *R* + 0.463 (±0.054)	32	0.881	0.743	104.06	0.058
	C. albicans					
13	0.050 (±0.006) $^0\chi$ + 0.713 (±0.057)	32	0.841	0.661	72.64	0.053
14	0.008 (±0.001) MR + 0.737 (±0.055)	32	0.839	0.660	71.19	0.054
15	−0.0002 (±0.000) T_e + 0.755 (±0.055)	32	0.825	0.623	64.10	0.058
16	0.070 (±0.009) $^2\chi$ + 0.859 (±0.043)	32	0.824	0.632	63.40	0.056
	A. niger					
17	0.011 (±0.002) MR + 0.536 (±0.088)	32	0.788	0.581	49.20	0.087
18	0.077 (±0.011) $^0\chi^v$ + 0.542 (±0.090)	32	0.779	0.566	46.16	0.089
19	0.088 (±0.014) $^1\chi$ + 0.610 (±0.084)	32	0.765	0.537	42.27	0.091
20	0.088 (±0.014) *R* + 0.610 (±0.084)	32	0.765	0.537	42.27	0.091

development. Further the QSAR models were cross-validated by their high q^2 values obtained by leave one out technique.

Experimental. Melting points were determined on Elico melting point apparatus and are uncorrected. The purity of each compound was ascertained by single spot TLC on silica gel G. The IR spectra were recorded on KBr pellets on a Perkin Elmer IR spectrometer. The wave number is given in cm^{-1}. The ^1H NMR spectra were performed on Bruker Avance II 400 NMR spectrometer in $CDCl_3$ solution; all values are reported in δ ppm.

*General procedure for preparation of esters of 2,4-hexadienoic acid (**S**$_{20}$–**S**$_{31}$, **S**$_{40}$, and **S**$_{41}$).* A mixture of 2,4-hexadienoic acid (0.08 mol) and appropriate alcohol

(0.74 mol) was heated under reflux in presence of mineral acid until the completion of reaction. Once the reaction has been completed, the reaction mixture was added to 200 mL ice-cold water and the ester formed was extracted with ether (50 mL). The ether layer was separated and on evaporation yielded the crude ester which was then recrystallized from alcohol.

*General procedure for synthesis of amides (**S**$_2$–**S**$_{19}$ and **S**$_{33}$–**S**$_{39}$).* The acid chloride of 2,4-hexadienoic acid was prepared by reaction of 2,4-hexadienoic acid with thionyl chloride. The solution of corresponding amine (0.1 mol)/ aniline (0.1 mol) in ether (50 mL) was added dropwise to a solution of acid chloride (0.1 mol) in ether (50 mL) maintained at 0–10 °C/room temperature. The solution was stirred for 30 min and the precipitated amide was separated by filtration. The crude amide was recrystallized from alcohol. In case of anilides, the precipitates of crude anilide were treated with water and ether layer was separated, washed successively with 5% hydrochloric acid, 4% sodium carbonate and water to remove residual aniline. Evaporation of ether layer yielded anilides which were recrystallized from alcohol took place.

Structure of synthesized compounds was confirmed on the basis of their spectroanalytical data.

*Analytical data for compound **S**$_4$.* ^{1}H NMR ($CDCl_3$): δ 7.47–7.53 (m, 4H, ArH), 7.25–7.29 (t, 1H, terminal CH of CH═CH─C═O, J_{trans} = 16 Hz), 6.82–6.85 (d, 1H, CH adjacent to C═O), 5.87–5.90 (m, 1H, CH of ═CH─CH_3, J_{trans} = 12 Hz), 1.83–1.87 (d, 3H, CH_3 of CH_3─CH═). IR (KBr pellets): cm^{-1} 1608.27 (C═C), 1660.2 (C═O), 3080.0 (CH), 3299.7 (NH).

*Analytical data for compound **S**$_{11}$.* ^{1}H NMR ($CDCl_3$): δ 7.31–7.37 (dd, 1H, central CH of ═CH─CH─CH═), 7.27 (s, 2H, NH_2), 6.22–6.26 (m, 1 H, CH of ═CH─C═O, J_{trans} = 16 Hz), 5.75–5.79 (d, 1H, CH of CH_3─CH═, J_{trans} = 16 Hz), 1.83 (d, 3H, CH_3). IR (KBr pellets): cm^{-1} 1611.4 (C═C), 1637.9 (C═O), 2969.5 (CH), 3100 (NH).

*Analytical data for compound **S**$_{12}$.* ^{1}H NMR ($CDCl_3$): δ 6.14–6.26 (d, 1H, CH of ═CH─C═O), 5.75–5.79 (d, 1H, CH of CH_3─CH═, J_{trans} = 16 Hz), 6.19–6.22 (d, 1H, CH of R─CH─C═O, J_{trans} = 12 Hz), 2.75 (s, 6H, CH_3 of $N(CH_3)_2$), 1.83–1.91 (d, 3H, CH_3 of CH_3─CH═). IR (KBr pellets): cm^{-1} 1637.5 (C═O), 3026.2 (NH), 2925.7 (C─H).

*Analytical data for compound **S**$_{20}$.* ^{1}H NMR ($CDCl_3$): δ 7.22–7.28 (dd, 1H, central CH of R═CH─CH═CH─C═O), 6.09–6.22 (d, 1H, CH of R═CH─C═O, J_{trans} = 12 Hz), 5.75–5.79 (m, 1H, CH of CH_3─CH═, J_{trans} = 16 Hz), 4.17–4.22 (m, 2H, CH_2 of O─CH_2─CH_3), 1.84–1.87 (d, 3H, CH_3 of CH_3─CH═), 1.29 (t, 3H, CH_3 of O─CH_2─CH_3). IR (KBr pellets): cm^{-1} 1140.6 (C─O), 1619.6 (C═C), 1713.4 (C═O), 2937.8 (C─H).

*Analytical data for compound **S**$_{22}$.* ^{1}H NMR ($CDCl_3$): δ 7.29–7.37 (t, 1H, terminal CH of CH═CH─C═O), 6.19–6.23 (t, 1H, terminal CH of CH─CH═CH─C═O, J_{trans} = 16 Hz), 5.75–5.78 (m, 1H, CH of ═CH─CH_3, J_{trans} = 12 Hz), 4.04–4.07 (m, 1H, CH of $CH(CH_3)_2$), 1.86–1.88 (d, 3H, CH_3 of CH_3─CH═), 1.15–1.32 (d, 6H, CH_3 of $(CH_3)_2$). IR (KBr pellets): cm^{-1} 1151.5 (C─O), 1640 (C═C), 1713.6 (C═O), 2981.2 (C─H).

*Analytical data for compound **S**$_{23}$.* ^{1}H NMR ($CDCl_3$): δ 7.51–7.54 (t, 1H, terminal CH of CH═CH ─C═O), 6.15–6.20 (d, 1H, CH adjacent to C═O, J_{trans} = 20 Hz), 5.75–5.78 (m, 1H, CH of ═CH─CH_3,J_{trans} = 12 Hz), 1.86–1.85 (d, 3H, CH_3 of CH_3─CH═CH), 1.25–1.45 (m, 2H, CH_2 of CH_3CH_2), 0.88–0.90 (t, 3H, CH_3 of $O(CH_2)_3CH_3$). IR (KBr pellets): cm^{-1} 1265.3 (C─O), 1644.4 (C═C), 1722.4 (C═O), 2934.6 (C─H).

*Analytical data for compound **S**$_{24}$.* ^{1}H NMR ($CDCl_3$): δ 7.23–7.37 (t, 1H, terminal CH of CH═CH─C═O), 6.15–6.18 (d, 1H, CH adjacent to C═O, J_{trans} = 12 Hz), 5.74–5.79 (m, 1H, CH of CH_3─CH═, J_{trans} = 20 Hz), 1.84–1.88 (d, 3H, CH_3 of CH_3─CH), 1.52–1.65 (m, 2H, CH_2 of CH_3─CH_2), 1.22–1.24 (d, 3H, CH_3 of OCH CH_3), 0.89–0.93 (t, 3H, CH_3 of CH_2─CH_3). IR (KBr pellets) : cm^{-1} 1263.9 (C─O), 1613.1 (C═C), 1722.1 (C═O), 2935.8 (C─H).

*Analytical data for compound **S**$_{33}$.* ^{1}H NMR ($CDCl_3$): δ 7.26–7.73 (m, 5H, ArH), 7.07–7.11 (t, 1H, NH), 1.83–1.87 (d, 3H, CH_3), 5.90–5.93 (m, 1H, CH of CH_3─CH═, J_{trans} = 12 Hz), 6.03–6.20 (m, 2H, terminal CH of ═CH─CH═CH─). IR (KBr pellets): cm^{-1}1495.6 (C═C, aromatic), 1610 (C═C), 1657.7 (C═O), 3054.4 (CH), 3302 (NH).

*Analytical data for compound **S**$_{35}$.* ^{1}H NMR ($CDCl_3$): δ 7.25–7.33 (m, 4H, ArH), 7.00–7.03 (d, 1H, CH adjacent to C═O, J_{trans} = 12 Hz), 6.17–6.23 (t, 1H, terminal CH of CH─CH═CH─C═O), 5.92–5.96 (m, 1H, CH of ═CH─CH_3, J_{trans} = 16 Hz), 1.86–1.93 (d, 3H, CH_3 of CH_3─CH─). IR (KBr pellets): cm^{-1} 1473.1 (C═C, aromatic), 1617.7(C═C, aliphatic), 1659.8 (C═O), 3025.7 (C─H, aromatic), 3265.6 (NH).

Antibacterial assay. A 24-h fresh culture was obtained by inoculation of respective bacteria in double strength nutrient broth-IP followed by incubation at 37 ± 1 °C. The stock solution of synthesized 2,4-hexadienoic acid derivatives was serially diluted in tube containing 1 mL of sterile double strength nutrient broth—IP to get a concentration of 50 to 3.125 μg/mL and then inoculated with 100 μL of suspension of respective organisms in sterile saline (*S. aureus*, *B. subtilis* and *E. coli)*. The inoculated tubes were incubated at 37 ± 1 °C for 24 h and minimum inhibitory concentrations (MIC) were determined. From the observed MIC values, the exact MIC values were determined by making suitable dilution of stock solution.

Antifungal assay. The antifungal activity of synthesized 2,4-hexadienoic acid derivatives against the fungal species *C. albicans* and *A. niger* was determined by serial dilution method similar to *Antibacterial assay* using Sabouraud dextrose broth-IP. The inoculated tubes

were incubated at 37 ± 1 and 25 ± 1 °C for a period of 2 and 7 days in case of *C. albicans* and *A. niger*, respectively.

QSAR studies. The details of molecular descriptors are available in literature and therefore they are not discussed over here.[23–29] The structures of 2,4-hexadienoic acid derivatives are first pre-optimized with the Molecular Mechanics Force Field (MM^+) procedure included in Hyperchem 6.03,[37] and the resulting geometries are further refined by means of the semiempirical method PM3 (parametric Method-3). We chose a gradient norm limit of 0.01 kcal/Å for the geometry optimization. The lowest energy structure was used for each molecule to calculate physicochemical properties using TSAR 3.3 software for windows.[38] Further the regression analysis was performed using the SPSS software package.[39] The predictive powers of the equation were validated by determination of cross-validated r^2 (q^2) using leave one out (LOO) cross-validation method.[40]

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