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ORIGINAL ARTICLE

Synthesis, antimicrobial evaluation and QSAR studies of gallic acid derivatives

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Abstract A series of gallic acid derivatives (**1–33**) was synthesized and characterized by physicochemical and spectral means. The synthesized compounds were evaluated *in vitro* for their antimicrobial activity against different Gram positive and Gram negative bacterial and fungal strains by the tube dilution method. Results of antimicrobial screening indicated that compound **6** was the most active antimicrobial agent ($pMIC_{am}$ = 1.92 μM/mL). The results of QSAR studies demonstrated that antibacterial, antifungal and overall antimicrobial activities of synthesized gallic acid derivatives were governed by the electronic parameters, cosmic total energy (Cos E.) and nuclear energy (Nu. E.).

1. Introduction

After the discovery of penicillin by Alexander Fleming, antibiotics were regarded as wonder drugs for curing virtually all infections. However, the careless use and overconsumption of antibiotics in both human and veterinary medicine have led to the emergence of antibiotic-resistant bacterial strains. Of major concern is the development of antibiotic resistance in *Staphylococcus aureus*, primarily because *S. aureus* is frequently associated with hospital and community-acquired infections. Infections with multi-drug resistant *S. aureus* have become responsible for huge healthcare costs and are projected to be responsible for more deaths this year in the United States than HIV/AIDS. Despite this increasing problem of antibiotic resistance, the number of different antibiotics available is dwindling and there are only a handful of new antibiotics in the drug development pipeline. Therefore, there is an urgent need for new antibacterial drugs preferably with new modes of action to potentially avoid cross-resistance (Jang et al., 2011).

The antimicrobial potential of simple organic acids is well established in the literature *viz*. sorbic acid (Narasimhan et al., 2003), cinnamic acid (Narasimhan et al., 2004), anacardic acid (Narasimhan and Dhake, 2006a), veratric acid (Narasimhan et al., 2009), myristic acid (Narasimhan et al., 2006b), caprylic acid (Chaudhary et al., 2008), anthranilic acid (Mahiwal et al., 2012) and dodecanoic acid (Sarova et al., 2011). The literature reports reveal that the gallic acid and its derivatives possess wide spectrum of biological activities like antimicrobial (Chanwitheesuk et al., 2007), anticancer (Saxena et al., 2008), antiviral (Thapa et al., 2012), anti-inflammatory (Arunkumar et al., 2009), analgesic (Krogh et al., 2000) and anti-HIV activities (Kratz et al., 2008).

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QSAR models are highly effective in describing the structural basis of biological activity. The success of QSAR approach can be explained by the insight offered into 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 (Sawant et al., 2012).

In light of abovementioned facts and in continuation of our research efforts in the field of synthesis, antimicrobial evaluation and QSAR studies (Sigroha et al., 2012; Kumar et al., 2010, 2012; Judge et al., 2012a,b; Narang et al., 2012a,b), we hereby report the synthesis, antimicrobial evaluation and QSAR studies of gallic acid derivatives.

2. Material and methods

All reagents and solvents used in the study were of analytical grade and procured locally. The progress of the reaction was monitored by TLC and products were purified through recrystallization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate. The spectral studies, IR and ^{1}H NMR were determined by standard methods. Infra red (IR) spectra were recorded on FTIR Bruker ATR instrument and was recorded in cm^{-1}. The ^{1}HNMR spectra were recorded in DMSO-*d6* on a Bruker DRX-300 FTNMR instrument. Elemental analysis was performed on a Perkin–Elmer 2400 C, H, N analyzer.

2.1. General procedure for the synthesis of 3,4,5-trihydroxybenzoyl chloride

Thionyl chloride (0.3 mol) was added gradually to gallic acid (0.25 mol) in a round bottom flask. After addition of thionyl chloride, the mixture was stirred for 4 h and heated to 80 °C for 30 min in water bath. The excess of thionyl chloride was removed by distillation.

2.2. General procedure for the synthesis of amides/anilides of gallic acid

The solution of corresponding amine/aniline (0.1 mol) in ether (50 mL) was added dropwise to a solution of 3,4,5-trihydroxybenzoyl chloride (0.1 mol, synthesized in previous step) in ether (50 mL) maintained at 0–10 °C (Scheme 1). The solution was stirred for 30 min and the precipitated amide/anilide was separated by filtration. The crude amide was recrystallized with alcohol. In case of anilides, the precipitated crude anilide was treated with 5% hydrochloric acid, 4% sodium carbonate and water to remove residual aniline and the resultant anilide was recrystallized with alcohol.

*2.3. General procedure for the synthesis of esters of gallic acid (**3–6**, **10**, **19**, **23**, **24**, **26** and **32**)*

A solution of different alcohols in ether (50 mL) was added to a solution of 3,4,5-trihydroxybenzoyl chloride (0.05 mol) in ether (50 mL). The mixture was heated on a water bath until no further evolution of hydrogen chloride was observed. The mixture was cooled to room temperature and evaporation of solvent yielded the crude ester which was purified by recrystallization with alcohol.

*2.4. General procedure for the synthesis of esters of gallic acid (**2** and **12**)*

A mixture of gallic acid (0.08 mol) and appropriate alcohol (0.74 mol) was heated under reflux in the presence of sulfuric acid (Scheme 1) till the completion of reaction. Then, the reaction mixture was poured in 200 mL ice cold water, neutralized with sodium bicarbonate solution followed by extraction of ester with ether (50 mL). The ether layer was separated, which on evaporation yielded the esters of gallic acid.

*2.4.1. Compound **1***

IR (ATR) cm^{-1}: 1190 and 1457 (C—O str. and O—H in plane bending, phenol), 1624 (C=O str., 2^0 amide), 3071 (C—H str., aromatic), 1558 (C=C skeletal str., phenyl), 771 (C—Cl str., C_6H_4Cl); ^{1}H NMR (DMSO-d_6): δ 6.63–7.51 (m, 6H, aromatic), 8.69 (s, 1H, NH of amide); Anal. Calculated for $C_{13}H_{10}ClNO_4$: C, 55.83; H, 3.60; N, 5.01; Found: C, 55.81; H, 3.63; N, 5.00.

*2.4.2. Compound **3***

IR (ATR) cm^{-1}: 3618 (O—H str., phenol), 1709 (C=O str., ester), 3074 (C—H str., aromatic), 1545 (C=C skeletal str., phenyl), 1337 (NO_2 sym. str., Ar—NO_2); ^{1}H NMR (DMSO-d_6): δ 6.91–8.13 (m, 6H, aromatic); Anal. Calculated for $C_{13}H_9NO_7$: C, 53.62; H, 3.12; N, 4.81; Found: C, 53.65; H, 3.10; N, 4.85.

*2.4.3. Compound **5***

IR (ATR) cm^{-1}: 3609 (O—H str., phenol), 1741 (C=O str., ester), 1464 (CH_2 scissoring, cyclohexane), 1022 (ring str., cyclohexane), 3074 (C—H str., aromatic), 1544 (C=C skeletal str., phenyl); ^{1}H NMR (DMSO-d_6): δ 6.72–6.92 (m, 2H, aromatic), 1.13–1.73 (m, 10H, cyclohexane), 3.59 (m, 1H, α to —O—C=O); Anal. Calculated for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39; Found: C, 61.94; H, 6.37.

*2.4.4. Compound **6***

IR (ATR) cm^{-1}: 3621 (O—H str., phenol), 1740 (C=O str., ester), 3067 (C—H str., aromatic), 1546 (C=C skeletal str., phenyl), 1395 (ring str., quinoline), 745 (C—H out of plane bending, quinoline), 1626 (C=N str., quinoline); ^{1}H NMR (DMSO-d_6): δ 7.54–7.55 (m, 2H, aromatic), 7.72–8.03 (m, 6H, CH_2); Anal. Calculated for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71; Found: 64.67; H, 3.71; N, 4.74.

*2.4.5. Compound **7***

IR (ATR) cm^{-1}: 3619 (O—H str., phenol), 1648 (C=O str., 2^0 amide), 3027 (C—H str., aromatic), 1548 (C=C skeletal str., phenyl), 2932 (C—H str., alkane); ^{1}H NMR (DMSO-d_6): δ 7.10–7.14 (m, 2H, aromatic), 2.31–3.39 (m, 13H, aliphatic), 8.22 (s, 1H, NH of amide); Anal. Calculated for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53; Found: C, 61.68; H, 7.53; N, 5.51.

*2.4.6. Compound **14***

IR (ATR) cm^{-1}: 1181 and 1443 (C—O str. and O—H in plane bending, phenol), 1630 (C=O str., 2^0 amide), 3066 (C—H str., aromatic), 1587 (C=C skeletal str., phenyl), 1310 (NO_2 sym. str., Ar—NO_2), 2838 (CH_3 str., Ar—CH_3); ^{1}H NMR

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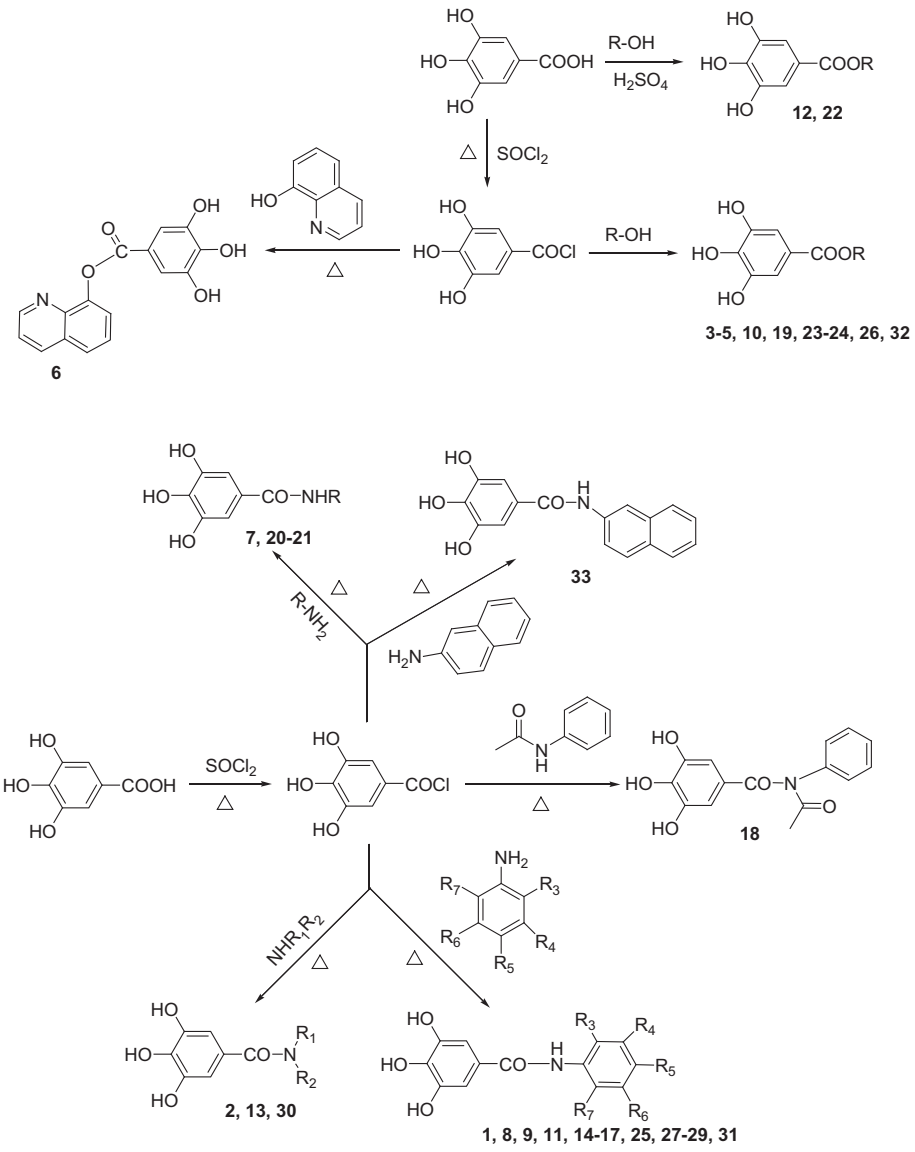

Scheme 1 Scheme for the synthesis of gallic acid derivatives.

(DMSO-d_6): δ 7.13–7.44 (m, 5H, aromatic), 2.34 (s, 3H, CH_3); Anal. Calculated for $C_{14}H_{12}N_2O_6$: C, 55.27; H, 3.98; N, 9.21; Found: C, 55.30; H, 4.00; N, 9.22.

2.4.7. Compound **22**

IR (ATR) cm^{-1}: 3605 (O—H str., phenol), 1761 (C═O str., ester), 3092 (C—H str., aromatic), 1513 (C═C skeletal str., phenyl), 2912 (C—H str., alkane); ^1H NMR (DMSO-d_6): δ 6.91 (m, 2H, aromatic), 4.29 (m, 2H, CH_2), 2.08 (t, 3H, CH_3); Anal. Calculated for $C_9H_{10}O_5$: C, 54.55; H, 5.09; Found: C, 54.59; H, 5.06.

2.4.8. Compound **27**

IR (ATR) cm^{-1}: 1254 and 1432 (C—O str. and O—H in plane bending, phenol), 1624 (C═O str., 2^0 amide), 3070 (C═H str., aromatic), 1572 (C═C skeletal str., phenyl), 1344 (NO_2 sym. str., Ar═NO_2); ^1H NMR (DMSO-d_6): δ 6.58–7.41 (m, 6H, aromatic), 7.96 (s, 1H, NH of amide); Anal. Calculated for $C_{13}H_{10}N_2O_6$: C, 53.80; H, 3.47; N, 9.65; Found: C, 53.83; H, 3.51; N, 9.62.

2.4.9. Compound **28**

IR (ATR) cm^{-1}: 1255 and 1436 (C—O str. and O—H in plane bending, phenol), 1626 (C═O str., 2^0 amide), 3065 (C—H str., aromatic), 1545 (C═C skeletal str., phenyl), 746 (C—Cl str., C_6H_3Cl); ^1H NMR (DMSO-d_6): δ 6.21–7.34 (m, 5H, aromatic), 7.50 (s, 1H, NH of amide); Anal. Calculated for $C_{13}H_9Cl_2NO_4$: C, 49.71; H, 2.89; N, 4.46; Found: C, 49.69; H, 2.92; N, 4.42.

2.4.10. Compound **30**

IR (ATR) cm^{-1}: 1242 and 1466 (C—O str. and O—H in plane bending, phenol), 1636 (C═O str., 3^0 amide), 3170 (C—H str., aromatic), 1551 (C═C skeletal str., phenyl), 2972 (C—H str., alkane); ^1H NMR (DMSO-d_6): δ 6.73–6.98 (m, 2H, aromatic), 3.55 (m, 2H, CH_2), 2.08 (t, 3H, CH_3); Anal. Calculated for

Table 1 Physicochemical properties of synthesized gallic acid derivatives (**1**–**33**).

Comp.	Mol. Formula	M. Wt.	m.p. (°C)	R_f Value*	% Yield
1	$C_{13}H_{10}ClNO_4$	279	178–180	0.52	66.5
2	$C_9H_{11}NO_4$	197	105–107	0.49	65.0
3	$C_{13}H_9NO_7$	291	151–153	0.50	78.5
4	$C_{13}H_{10}O_5$	246	171–173	0.53	81.3
5	$C_{13}H_{16}O_5$	252	183–185	0.63	71.4
6	$C_{16}H_{11}NO_5$	297	258–260	0.72	76.2
7	$C_{13}H_{19}NO_4$	253	96–98	0.69	60.5
8	$C_{15}H_{15}NO_4$	273	168–170	0.57	62.8
9	$C_{14}H_{13}NO_4$	259	221–223	0.83	69.8
10	$C_{17}H_{24}O_5$	308	198–200	0.71	74.4
11	$C_{13}H_{12}N_2O_4$	260	165–167	0.67	83.0
12	$C_8H_8O_5$	184	135–137	0.87	77.5
13	$C_{19}H_{15}NO_4$	321	250–252	0.47	64.2
14	$C_{14}H_{12}N_2O_6$	304	156–158	0.55	80.4
15	$C_{13}H_{10}N_2O_6$	290	207–209	0.84	66.8
16	$C_{13}H_9ClN_2O_6$	324	191–193	0.77	70.3
17	$C_{13}H_{10}N_2O_6$	290	182–184	0.91	55.0
18	$C_{15}H_{13}NO_5$	287	195–197	0.85	68.5
19	$C_{14}H_{12}O_5$	260	234–236	0.73	73.2
20	$C_{13}H_{10}N_2O_5$	274	222–224	0.66	49.7
21	$C_{14}H_{11}NO_5$	272	249–251	0.97	58.3
22	$C_9H_{10}O_5$	198	242–244	0.82	67.4
23	$C_{10}H_{12}O_5$	212	122–124	0.76	55.5
24	$C_{12}H_{16}O_5$	240	134–136	0.53	76.4
25	$C_{14}H_{13}NO_5$	275	208–210	0.48	64.0
26	$C_{11}H_{14}O_5$	226	141–143	0.68	68.7
27	$C_{13}H_{10}N_2O_6$	290	187–189	0.91	76.7
28	$C_{13}H_9Cl_2NO_4$	314	194–196	0.88	75.3
29	$C_{13}H_9Cl_2NO_4$	314	233–235	0.81	56.5
30	$C_{11}H_{15}NO_4$	225	121–123	0.61	67.7
31	$C_{13}H_9ClN_2O_6$	324	249–251	0.70	50.4
32	$C_{13}H_{11}NO_5$	261	255–257	0.63	78.5
33	$C_{17}H_{13}NO_4$	295	208–210	0.76	73.9

* TLC mobile phase: Benzene:Chloroform (7:3).

$C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22; Found: C, 58.70; H, 6.73; N, 6.25.

2.5. In vitro antimicrobial activity

2.5.1. Determination of minimum inhibitory concentration

The antimicrobial activity of the synthesized compounds was tested against Gram-positive bacteria: *S. aureus* MTCC 2901, *Bacillus subtilis* MTCC 2063, and Gram negative bacterium: *Escherichia coli* MTCC 1652 and fungal strains: *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 8189 using the tube dilution method (Cappucino and Sherman, 1999). Dilutions of test and standard compounds were prepared in double strength nutrient broth—I.P. (bacteria) or 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*), and the results were recorded in terms of minimum inhibitory concentration (MIC).

2.5.2. Determination of minimum bactericidal/fungicidal concentration

The minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were determined by sub culturing 100 μL of culture from each tube (which remained clear in the MIC determination) on 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).

2.6. QSAR Studies

The structures of gallic derivatives were first pre-optimized with the Molecular Mechanics Force Field (MM^+) procedure included in Hyperchem 6.03 (Hyperchem 6.0, 1993) and the resulting geometries were further refined by means of the semi-empirical 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 (TSAR 3D Version 3.3, 2000). Further, the regression analysis was performed using the SPSS software package (SPSS for Windows, 1999).

The predictive powers of the equations were validated by the leave one out (LOO) cross validation method (Agrawal et al., 2006), where a model is built with N-1 compounds and Nth compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance is obtained from the cross-validated r^2 method which is defined as

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Table 2 Antimicrobial activity (pMIC in μM/mL) of synthesized gallic acid derivatives against different microorganisms.

S. No.	$pMIC_{ec}$	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{an}$	$pMIC_{ca}$	$pMIC_{ab}$	$pMIC_{af}$	$pMIC_{am}$
1	1.35	1.35	1.35	1.35	1.95	1.35	1.65	1.47
2	0.90	1.20	1.20	1.80	1.50	1.10	1.65	1.32
3	1.37	1.37	1.97	1.37	1.97	1.57	1.67	1.61
4	1.29	1.29	1.29	1.29	1.90	1.29	1.60	1.41
5	1.30	1.30	1.30	1.30	1.30	1.30	1.30	1.30
6	1.98	1.98	1.98	1.68	1.98	1.98	1.83	1.92
7	1.31	1.31	1.31	1.31	1.91	1.31	1.61	1.43
8	1.04	1.34	1.34	1.34	1.34	1.24	1.34	1.28
9	1.32	1.32	1.32	1.32	1.32	1.32	1.32	1.32
10	1.69	1.39	1.99	1.39	1.69	1.69	1.54	1.63
11	1.32	1.32	1.92	1.02	1.62	1.52	1.32	1.44
12	1.47	0.87	1.77	0.57	1.47	1.37	1.02	1.23
13	1.41	1.41	2.01	1.41	1.71	1.61	1.56	1.59
14	1.39	1.39	1.99	1.09	1.69	1.59	1.39	1.51
15	1.37	1.37	1.67	1.37	1.37	1.47	1.37	1.43
16	1.41	1.41	1.72	1.41	1.72	1.51	1.57	1.53
17	1.37	1.37	1.67	1.06	1.67	1.47	1.37	1.43
18	1.11	1.11	1.72	1.11	1.41	1.31	1.26	1.29
19	1.32	1.62	1.62	1.32	1.32	1.52	1.32	1.44
20	1.34	1.34	1.34	1.04	1.64	1.34	1.34	1.34
21	1.34	1.04	1.04	1.34	1.34	1.14	1.34	1.22
22	1.50	1.20	1.50	1.20	1.20	1.40	1.20	1.32
23	1.53	1.23	1.23	1.23	1.23	1.33	1.23	1.29
24	1.28	1.28	1.58	1.28	1.28	1.38	1.28	1.34
25	1.34	1.34	1.34	1.04	1.64	1.34	1.34	1.34
26	1.26	1.26	1.56	1.56	1.56	1.36	1.56	1.44
27	1.37	1.37	1.67	1.37	1.37	1.47	1.37	1.43
28	0.80	1.40	1.40	1.10	1.40	1.20	1.25	1.22
29	1.40	1.40	1.70	1.10	0.80	1.50	0.95	1.28
30	1.26	1.56	1.26	1.26	1.26	1.36	1.26	1.32
31	1.41	1.41	1.41	1.41	1.41	1.41	1.41	1.41
32	1.06	1.36	1.36	1.06	1.36	1.26	1.21	1.24
33	1.71	2.01	2.01	1.71	1.71	1.91	1.71	1.83
S.D.	0.22	0.21	0.28	0.23	0.27	0.19	0.20	0.16
Std.	2.61*	2.61*	2.61*	2.64**	2.64**	–	–	–

S.D. = Standard deviation; Std. = Standard.
* Norfloxacin.
** Fluconazole.

$$q^2 = 1 - \Sigma(Y_{predicted} - Y_{actual})^2 / \Sigma(Y_{actual} - Y_{mean})^2$$

where, $Y_{predicted}$, Y_{actual} and Y_{mean} are predicted, actual and mean values of target property (pMIC), respectively. $\Sigma(Y_{predicted} - Y_{actual})^2$ is the predictive residual error sum of squares.

3. Results and discussion

3.1. Chemistry

Gallic acid derivatives (**1–33**) were synthesized as outlined in Scheme 1. The physicochemical properties of the synthesized compounds are presented in Table 1. The structures of all the newly synthesized compounds were confirmed by the IR, ^{1}H NMR and elemental analysis which were in full agreement with their structures.

3.2. In vitro antimicrobial activity

The synthesized gallic acid derivatives were evaluated for their *in vitro* antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and antifungal activity against *C. albicans* and *A. niger* by the tube dilution method. From the recorded pMIC values (Table 2), it was observed that compound **6** was found to be most active against *C. albicans* and *E. coli*, having $pMIC_{ca}$ and $pMIC_{ec}$ value 1.98 μM/mL. Compound **33** was found to be most active against *S. aureus* having $pMIC_{sa}$ value 2.01 μM/mL. The compound **2** was found to be most active against *A. niger* having $pMIC_{an}$ value 1.80 μM/mL and compounds **13** and **33** were found to be most potent against *B. subtilis* having $pMIC_{bs}$ value 2.01 μM/mL.

In general, the results of MBC/MFC studies (Table 3) revealed that the synthesized compounds were bacteriostatic and fungistatic in action as their MFC and MBC values were 3-fold higher than their MIC values (a drug is considered to be bacteriostatic/fungistatic when its MFC and MBC values are 3-fold higher than its MIC value) (Rodriguez-Arguelles et al., 2005).

3.3. Structure–activity relationship

From the antimicrobial activity results of the synthesized gallic acid derivatives, the following structure–activity relationship can be withdrawn:

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Table 3 Minimum bactericidal/fungicidal (MBC/MFC in μM/mL) of synthesized gallic acid derivatives against different microorganisms.

S. No.	*E. coli*	*S. aureus*	*B. subtilis*	*A. niger*	*C. albicans*
1	> 0.18	> 0.18	> 0.18	> 0.18	> 0.18
2	> 0.25	> 0.25	> 0.25	> 0.25	> 0.25
3	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
4	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20
5	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20
6	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
7	> 0.20	> 0.20	> 0.20	> 0.20	> 0.20
8	> 0.18	> 0.18	> 0.18	> 0.18	> 0.18
9	> 0.19	> 0.19	> 0.19	> 0.19	> 0.19
10	> 0.16	> 0.16	> 0.16	> 0.16	> 0.16
11	> 0.19	> 0.19	> 0.19	> 0.19	> 0.19
12	> 0.27	> 0.27	> 0.27	> 0.27	> 0.27
13	> 0.16	> 0.16	> 0.16	> 0.16	> 0.16
14	> 0.16	> 0.16	> 0.16	> 0.16	> 0.16
15	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
16	> 0.15	> 0.15	> 0.15	> 0.15	> 0.15
17	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
18	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
19	> 0.19	> 0.19	> 0.19	> 0.19	> 0.19
20	> 0.18	> 0.18	> 0.18	> 0.18	> 0.18
21	> 0.18	> 0.18	> 0.18	> 0.18	> 0.18
22	> 0.25	> 0.25	> 0.25	> 0.25	> 0.25
23	> 0.24	> 0.24	> 0.24	> 0.24	> 0.24
24	> 0.21	> 0.21	> 0.21	> 0.21	> 0.21
25	> 0.18	> 0.18	> 0.18	> 0.18	> 0.18
26	> 0.22	> 0.22	> 0.22	> 0.22	> 0.22
27	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
28	> 0.16	> 0.16	> 0.16	> 0.16	> 0.16
29	> 0.16	> 0.16	> 0.16	> 0.16	> 0.16
30	> 0.22	> 0.22	> 0.22	> 0.22	> 0.22
31	> 0.15	> 0.15	> 0.15	> 0.15	> 0.15
32	> 0.19	> 0.19	> 0.19	> 0.19	> 0.19
33	> 0.17	> 0.17	> 0.17	> 0.17	> 0.17
Std.	0.019*	0.019*	0.019*	0.040**	0.040**

* Norfloxacin.
** Fluconazole.

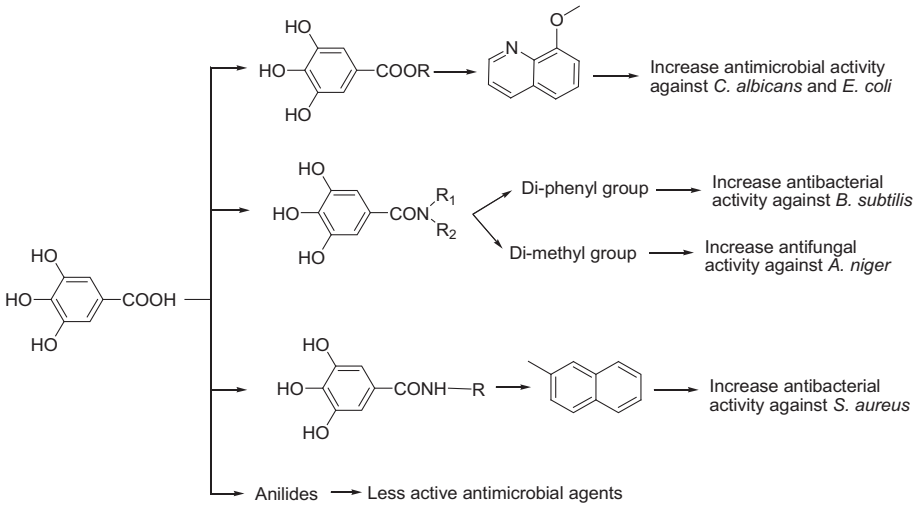

Figure 1 SAR of antimicrobial activity of synthesized gallic acid derivatives.

- Esters and amides of gallic acid were more potent antimicrobial agents than anilides. The high antimicrobial activity of esters is also supported by results of Mahiwal et al. (2012).
- In case of antimicrobial activity of gallic acid derivatives against *E. coli* and *C. albicans*, quinolin-8-yl 3,4,5-trihydroxybenzoate (**6**) was found to be the most potent antimicrobial agent, which indicated that esters having bulky aromatic group will be more potent antimicrobial agents against *E. coli* and *C. albicans*. This fact is supported by findings of Sarova et al. (2011).
- In case of antibacterial activity of gallic acid derivatives against *S. aureus*, 3,4,5-trihydroxy-*N*-(naphthalen-2-yl) benzamide (**33**) having bicyclic aromatic ring (naphthalene) was found to be the most potent antibacterial agent.
- In case of antibacterial activity of gallic acid derivatives against *B. subtilis*, 3,4,5-trihydroxy-*N*,*N*-diphenylbenzamide (**13**) and 3,4,5-trihydroxy-*N*-(naphthalen-2-yl) benzamide (**33**) having two phenyl substituents and bicyclic aromatic ring (naphthalene), respectively were found to be the most potent antibacterial agents, which indicated that amides having bulky aromatic group will be more potent antibacterial agents against *B. subtilis*. These results are in accordance with the results of Mahiwal et al. (2012).
- Results of antifungal activity against *A. niger* indicated that 3,4,5-trihydroxy-*N*,*N*-dimethylbenzamide (**2**) was found to be the most potent one and the activity decreased upon increase in carbon chain length as evidenced by low antifungal activity of 3,4,5-trihydroxy-*N*,*N*-diethylbenzamide (**30**).
- The anilide formation does not improve the antimicrobial profile of 2-amino benzoic acid as none of the synthesized anilides were found to be active.
- From the abovementioned antimicrobial activity results, it can be concluded that different structural requirements are necessary for different gallic acid derivatives to become active against different microbial targets. This is in accordance with the results obtained by Sortino et al. (2007).

The above mentioned findings are summarized in Fig. 1.

3.4. QSAR Studies

In the present study, we have performed the quantitative structure–activity relationship study by conventional Hansch's analysis using the linear free energy relationship model (LFER) (Hansch and Fujita, 1964). In this approach, structural features of drug molecules are quantified in terms of different parameters and these structural features are correlated to quantified biological activity through equation using regression analysis. Biological activity data determined as MIC values were first transformed into pMIC values (i.e. −log MIC, Table 2) and used as dependent variable in the QSAR study.

Table 4 Values of selected parameters used in QSAR studies of synthesized gallic acid derivatives.

Comp.	Cos E	Log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	*J*	Nu. E	LUMO	HOMO	μ
1	4.29	2.47	69.20	13.99	10.41	1.63	16570.80	−0.58	−8.89	1.38
2	21.63	0.52	49.51	10.88	7.85	2.29	11657.10	−0.37	−9.36	4.45
3	22.84	2.56	69.77	15.57	10.39	1.63	19586.30	−1.22	−9.63	7.38
4	15.04	2.61	62.45	13.12	9.20	1.63	15381.10	−0.80	−9.43	1.90
5	12.78	2.51	63.68	13.12	9.93	1.63	17232.10	−0.53	−9.27	0.47
6	26.82	2.69	76.37	15.69	11.22	1.42	20727.80	−0.75	−9.08	1.80
7	6.51	2.27	67.69	13.54	10.44	2.08	16624.40	−0.50	−9.38	3.84
8	0.47	2.89	74.48	14.86	11.14	1.69	18580.00	−0.62	−8.58	4.21
9	0.80	2.42	69.44	13.99	10.21	1.63	16694.40	−0.64	−8.64	3.92
10	11.04	3.97	81.85	16.44	13.24	1.76	25766.80	−0.72	−9.38	2.49
11	−2.05	1.17	69.10	13.99	9.79	1.70	17053.00	−0.43	−8.52	2.33
12	18.10	0.92	42.67	10.01	6.81	2.23	10089.70	−0.59	−9.31	3.45
13	23.22	3.88	89.07	17.10	12.63	1.55	24815.90	−0.39	−8.80	3.27
14	8.64	2.38	76.76	16.44	11.40	1.71	21698.10	−1.02	−9.39	7.77
15	10.36	1.91	71.72	15.57	10.48	1.63	19409.60	−1.17	−9.52	7.76
16	12.20	2.43	76.52	16.44	11.60	1.70	21335.40	−1.33	−9.45	5.36
17	13.18	1.91	71.72	15.57	10.48	1.62	19594.00	−1.04	−9.53	5.34
18	1.55	1.95	73.96	15.57	11.15	1.86	20732.20	−0.32	−9.18	3.68
19	14.52	2.70	67.28	13.83	9.91	1.58	16856.20	−0.80	−9.44	2.66
20	−6.44	1.09	67.27	14.70	10.07	1.66	18028.80	−0.79	−9.27	4.18
21	−6.44	1.09	67.27	14.70	10.07	1.66	18028.80	−0.79	−9.27	4.18
22	14.61	1.27	47.42	10.72	7.52	2.22	11420.10	−0.55	−9.14	3.16
23	8.31	1.68	51.83	11.59	8.39	2.25	12979.60	−0.72	−9.38	2.38
24	10.44	2.46	61.09	13.00	9.80	2.16	15595.20	−0.74	−9.39	2.50
25	0.64	1.70	70.86	14.70	10.62	1.62	18266.40	−0.47	−8.44	2.85
26	10.69	2.14	56.41	12.29	9.10	2.21	14508.10	−0.75	−9.40	2.81
27	2.68	1.91	71.72	15.57	10.48	1.75	20285.30	−1.11	−9.36	3.81
28	2.47	2.99	74.00	14.86	11.53	1.64	18145.80	−0.82	−8.99	5.86
29	3.09	2.99	74.00	14.86	11.53	1.68	18450.90	−0.77	−9.11	2.57
30	17.51	1.21	59.01	12.29	9.27	2.36	14837.40	−0.12	−9.17	3.33
31	5.53	2.43	76.52	16.44	11.60	1.66	21290.00	−1.06	−9.47	6.63
32	1.16	1.82	67.15	13.99	9.70	1.63	16868.50	−0.77	−8.47	3.27
33	4.68	2.96	80.85	15.69	11.45	1.33	19999.00	−0.70	−8.47	3.80

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The different molecular descriptors used in the QSAR study (independent variables) like log of octanol–water partition coefficient (log *P*), molar refractivity (MR), Kier's molecular connectivity ($^0\chi$, $^0\chi^v$, $^1\chi$, $^1\chi^v$, $^2\chi$, $^2\chi^v$) and shape (κ_1, κ_1, κ_2, κ_3) topological indices, Randic topological index (*R*), Balaban topological index (*J*), Wiener topological index (*W*), Total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment () and electronic energy (Ele. E) (Hansch and Fujita, 1964; Kier and Hall, 1976; Randic, 1975, 1993; Balaban, 1982; Wiener, 1947) were calculated for gallic acid derivatives and values of selected descriptors are presented in Table 4.

Our previous studies in the field of QSAR studies (Narang et al., 2012a,b; Judge et al., 2012a,b; Kumar et al., 2009, 2010), indicated that the multi-target QSAR (*mt*-QSAR) models are better than one-target QSAR (*ot*-QSAR) models in describing the antimicrobial activity. So, in the present study we have developed multi-target QSAR models to describe the antimicrobial activity of synthesized gallic acid derivatives.

According to the *ot*-QSAR models, one should use five different equations with different errors to predict the activity of a new compound against five microbial species. However, very recently the interest has been increased in the development of multi-target QSAR (*mt*-QSAR) models. As opposed 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 antibacterial and antifungal activity (Gonzalez-Diaz et al., 2008, 2007; Cruz-Monteagudo et al., 2007; Gonzalez-Diaz and Prado-Prado, 2008).

In the present study, we attempted to develop three different types of *mt*-QSAR models *viz*. the *mt*-QSAR model for describing antibacterial activity of synthesized compounds *against S. aureus*, *B. subtilis* and *E. coli*, the *mt*-QSAR model for describing antifungal activity against *C. albicans* and *A. niger* as well as a common *mt*-QSAR model for describing the antimicrobial (overall antibacterial and antifungal) activity of synthesized gallic acid derivatives by calculating their average antibacterial activity, antifungal activity and antimicrobial activity values which are presented in Table 2.

In the present study, a dataset of 33 gallic acid derivatives (**1–33**) was used for linear regression model generation. The standard drugs norfloxacin and fluconazole were not included in model generation because of dissimilarity in structure with synthesized compounds. Different outliers were identified in case of antibacterial, antifungal and antimicrobial activities and the models have been developed after removal of the outliers (compound numbers in brackets) *i.e.* antibacterial (**2**, **6**, **8**, **12**, **18**, **21**, **22**, **28**, **32** and **33**), antifungal (**1**, **5**, **6**, **7**, **12**, **19**, **22**, **23**, **27**, **29**, **30** and **33**) and antimicrobial (**3**, **6**, **8**, **18**, **21**, **26**, **28**, **29**, **32** and **33**). In multivariate statistics, it is common to define three types of outliers (Furusjo et al., 2006).

1. *X*/*Y* relation outliers are substances for which the relationship between the descriptors (*X* variables) and the dependent variables (*Y* variables) is not the same as in the (rest of the) training data.
2. *X* outliers are substances whose molecular descriptors do not lie in the same range as the (rest of the) training data.
3. *Y* outliers are only defined for training or test samples. They are substances for which the reference value of response is invalid.

As there was no difference in the activity (Table 2) as well as the molecular descriptor range (Table 4) of these outliers when compared to other gallic acid derivatives, these outliers belong to the category of *Y* outliers (Substances for which the reference value of response is invalid).

In order to develop mt-QSAR models, initially we calculated the average antibacterial, antifungal and antimicrobial activity values of gallic acid derivatives which are presented in Table 2. These average antibacterial activity values were correlated with the molecular descriptors of synthesized compounds (Table 5). In general, high colinearity ($r > 0.5$) was observed between different parameters. The high interrelationship was observed between topological parameters, zero order molecular connectivity index ($^0\chi$) and Kier's first order shape index (κ_1) ($r = 0.987$) and low interrelationship was observed for electronic parameters, energy of highest occupied molecular orbital (HOMO) and nuclear energy (Nu. E) ($r = -0.059$).

From the correlation matrix (Table 5), it was observed that electronic parameter, nuclear energy (Nu. E) was found to be dominating descriptor for antibacterial activity of the synthesized compounds (Eq. (1)).

3.4.1. LR-mt-QSAR model for antibacterial activity

$$\mathrm{pMIC_{ab}} = 0.000028\ \mathrm{Nu.E} + 0.915 \quad (1)$$

$n = 23 \quad r = 0.785 \quad q^2 = 0.559 \quad s = 0.072 \quad F = 33.80$

Here and thereafter, *n* – number of data points, *r* – correlation coefficient, q^2 – cross validated r^2 obtained by the leave one out method, *s* – standard error of the estimate and *F* – Fischer statistics.

Table 5 Correlation matrix for the antibacterial activity of synthesized gallic acid derivatives.

	$\mathrm{pMIC_{ab}}$	Cos E	Log *P*	MR	$^0\chi$	$\kappa 1$	*J*	Nu. E	LUMO	HOMO	μ
$\mathrm{pMIC_{ab}}$	1.000										
Cos E	0.326	1.000									
Log *P*	0.511	0.478	1.000								
MR	0.711	0.090	0.582	1.000							
$^0\chi$	0.724	0.086	0.436	0.936	1.000						
$\kappa 1$	0.714	0.098	0.422	0.915	0.987	1.000					
J	−0.334	0.081	−0.314	−0.659	−0.658	−0.559	1.000				
Nu. E	0.785	0.186	0.587	0.937	0.942	0.933	−0.544	1.000			
LUMO	−0.320	−0.068	−0.078	−0.218	−0.499	−0.505	0.343	−0.330	1.000		
HOMO	−0.131	−0.427	−0.111	0.158	−0.062	−0.126	−0.187	−0.059	0.641	1.000	
μ	0.375	0.133	−0.101	0.352	0.587	0.630	−0.196	0.405	−0.669	−0.409	1.000

Table 6 Comparison of observed and predicted antimicrobial activity obtained by mt-QSAR models.

Comp.	$pMIC_{ab}$			$pMIC_{af}$			$pMIC_{am}$		
	Obs	Pre	Res	Obs	Pre	Res	Obs	Pre	Res
1	1.35	1.38	−0.03	1.65	1.37	0.28	1.47	1.38	0.09
2	1.10	1.24	−0.14	1.65	1.59	0.06	1.32	1.28	0.04
3	1.57	1.47	0.10	1.67	1.61	0.06	1.61	1.45	0.16
4	1.29	1.35	−0.06	1.60	1.51	0.09	1.41	1.36	0.05
5	1.30	1.40	−0.10	1.30	1.48	−0.18	1.30	1.40	−0.10
6	1.98	1.50	0.48	1.83	1.66	0.17	1.92	1.47	0.45
7	1.31	1.39	−0.08	1.61	1.40	0.21	1.43	1.38	0.05
8	1.24	1.44	−0.20	1.34	1.33	0.01	1.28	1.43	−0.15
9	1.32	1.39	−0.07	1.32	1.33	−0.01	1.32	1.39	−0.07
10	1.69	1.64	0.05	1.54	1.46	0.08	1.63	1.58	0.05
11	1.52	1.40	0.12	1.32	1.30	0.02	1.44	1.39	0.05
12	1.37	1.20	0.17	1.02	1.55	−0.53	1.23	1.25	−0.02
13	1.61	1.62	−0.01	1.56	1.61	−0.05	1.59	1.56	0.03
14	1.59	1.53	0.06	1.39	1.43	−0.04	1.51	1.49	0.02
15	1.47	1.46	0.01	1.37	1.45	−0.08	1.43	1.44	−0.01
16	1.51	1.52	−0.01	1.57	1.47	0.10	1.53	1.48	0.05
17	1.47	1.47	0.00	1.37	1.49	−0.12	1.43	1.45	−0.02
18	1.31	1.50	−0.19	1.26	1.34	−0.08	1.29	1.47	−0.18
19	1.52	1.39	0.13	1.32	1.50	−0.18	1.44	1.39	0.05
20	1.34	1.43	−0.09	1.34	1.24	0.10	1.34	1.41	−0.07
21	1.14	1.43	−0.29	1.34	1.24	0.10	1.22	1.41	−0.19
22	1.40	1.24	0.16	1.20	1.50	−0.30	1.32	1.27	0.05
23	1.33	1.28	0.05	1.23	1.42	−0.19	1.29	1.31	−0.02
24	1.38	1.36	0.02	1.28	1.45	−0.17	1.34	1.36	−0.02
25	1.34	1.43	−0.09	1.34	1.33	0.01	1.34	1.42	−0.08
26	1.36	1.33	0.03	1.56	1.45	0.11	1.44	1.34	0.10
27	1.47	1.49	−0.02	1.37	1.35	0.02	1.43	1.46	−0.03
28	1.20	1.43	−0.23	1.25	1.35	−0.10	1.22	1.42	−0.20
29	1.50	1.44	0.06	0.95	1.36	−0.41	1.28	1.42	−0.14
30	1.36	1.33	0.03	1.26	1.54	−0.28	1.32	1.35	−0.03
31	1.41	1.52	−0.11	1.41	1.39	0.02	1.41	1.48	−0.07
32	1.26	1.39	−0.13	1.21	1.34	−0.13	1.24	1.39	−0.15
33	1.91	1.48	0.43	1.71	1.38	0.33	1.83	1.45	0.38

The developed QSAR model for antibacterial activity (Eq. (1)) indicated that there is a positive correlation between nuclear energy and antibacterial activity of the synthesized compounds. This means that antibacterial activity of synthesized gallic acid derivatives will increase with increase in their Nu. E values and vice versa, which is evidenced by low antibacterial activity value of compound **2** ($pMIC_{ab}$ = 1.10 μM/mL, Table 2) having low Nu. E value (11657.10, Table 4).

The developed QSAR model (Eq. (1)) was cross validated by q^2 value (q^2 = 0.559) obtained by the leave one out (LOO) method. The value of q^2 more than 0.5 indicated that the model developed is a valid one (Golbraikh and Tropsha, 2002). As the observed and predicted antibacterial activity values are close to each other (Table 6), the *mt*-QSAR model for antibacterial activity (Eq. (1)) is a valid one. The plot of predicted $pMIC_{ab}$ against observed $pMIC_{ab}$ (Fig. 2) also favors the developed model expressed by Eq. (1).

In case of antifungal activity, electronic parameter, cosmic total energy (Cos E) was found most dominant in expressing antifungal activity of the synthesized compounds. So, the QSAR model for antifungal activity (Eq. (2)) was developed using Cos E

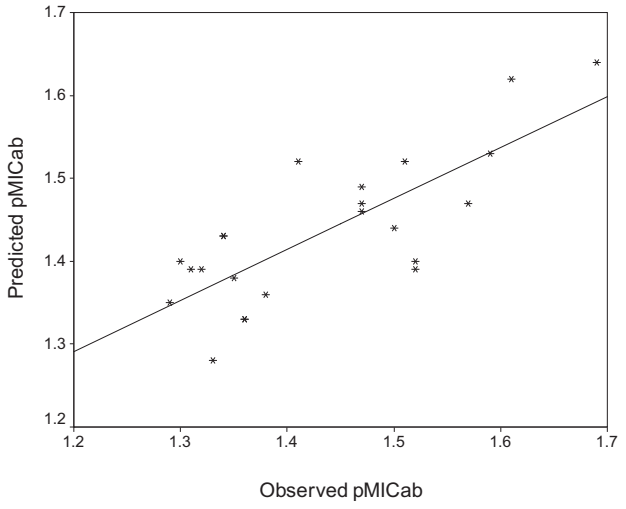

Figure 2 Plot of observed $pMIC_{ab}$ against predicted $pMIC_{ab}$ obtained by Eq. (1).

3.4.2. LR-mt-QSAR model for antifungal activity

$$pMIC_{af} = 0.0125\ Cos\ E + 1.321 \quad (2)$$

n = 21 r = 0.786 q^2 = 0.539 s = 0.089 F = 3.78

As in case of antibacterial activity, antifungal activity of the synthesized compounds is also positively correlated with their

Cos E values which means that antifungal activity of the synthesized compounds will increase with increase in their Cos E values (Tables 2 and 5).

The validity and predictability of the QSAR model for antifungal activity *i.e.* Eq. (2) was cross validated by q^2 value ($q^2 = 0.539$) obtained by the leave one out (LOO) method and by comparison of the observed and predicted antifungal activity values (Table 6), which indicated that the *mt*-QSAR model for antifungal activity (Eq. (2)) is a valid one.

Electronic parameter, nuclear energy (Nu. E) was found to be most effective in describing antimicrobial activity of the synthesized compounds (Eq. (3)).

3.4.3. LR-mt-QSAR model for antimicrobial activity

$$pMIC_{am} = 0.0000211\ \text{Nu. E} + 1.033 \quad (3)$$

$n = 23 \quad r = 0.848 \quad q^2 = 0.671 \quad s = 0.054 \quad F = 53.57$

As in case of antibacterial activity, antimicrobial activity of the synthesized compounds is positively correlated with nuclear energy (Nu. E) which means that antimicrobial activity of the synthesized compounds will increase with increase in their Nu. E values (Tables 2 and 5).

The validity of the QSAR model for antimicrobial activity (Eq. (3)) is indicated by their high q^2 value (0.671) as well as the low residual values (Table 6). Further, the plot of observed $pMIC_{am}$ *vs* residual $pMIC_{am}$ (Fig. 3) 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).

It is important to note a fact that the high residual values observed in case of outliers justify their removal before development of QSAR models.

It was observed from *mt*-QSAR models [Eq. (1–3)] that the antibacterial, antifungal and the overall antimicrobial activities of the synthesized gallic acid derivatives were governed by electronic parameters, nuclear energy (Nu. E) and cosmic total energy (Cos E).

Generally for QSAR studies, the biological activities of compounds should span 2–3 orders of magnitude. But in the present study the range of antimicrobial activities of the synthesized compounds is within one order of magnitude. This is in accordance with results suggested by 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. 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., 2007). The minimum standard deviation (Table 2) observed in the antimicrobial activity data justifies its use in QSAR studies.

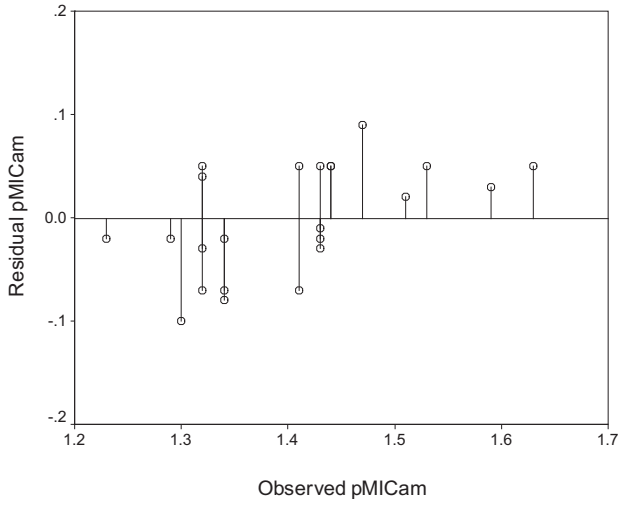

Figure 3 Plot of observed $pMIC_{am}$ against residual $pMIC_{am}$ obtained by Eq. (3).

4. Conclusion

A series of gallic acid derivatives (**1–33**) was synthesized and evaluated *in vitro* for its antimicrobial activity by the tube dilution method. Results of antimicrobial screening indicated that esters and amides of gallic acid were more potent than anilides and compound **6** was the most active antimicrobial agent ($pMIC_{am} = 1.92\ \mu M/mL$). Results of MBC/MFC studies indicated that the synthesized compounds were bacteriostatic and fungistatic in action. The results of QSAR studies demonstrated that antibacterial, antifungal and overall antimicrobial activities of synthesized gallic acid derivatives were governed by the electronic parameters, cosmic total energy (Cos E) and nuclear energy (Nu. E.).

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