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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Quantitative structure–activity relationships studies for prediction of antimicrobial activity of synthesized disulfonamide derivatives

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Abstract A new series of disulfonamides were synthesized and assayed as antimicrobial agents against *Staphylococcus aureus*, *Bacillus cereus*, and *Escherichia coli*. The quantitative structure–activity relationship analysis (QSAR) was applied to find out the correlation between experimentally evaluated antimicrobial activities with various parameters of the compounds using stepwise multiple liner regression method. The QSAR analysis revealed that the third-order average connectivity index ($^3\chi^A$) was found to have negative correlation. The best QSAR models were further validated by leave-one-out method of cross-validation.

Keywords Antimicrobial activity · Sulfonamides · Disulfonamides · QSAR

Introduction

Folate cofactors are essential components of several enzymatic reactions occurring in nearly all cells and are essential for life. Indeed, the first chemically synthesized antimicrobials—the sulfonamides or sulfa drugs—targeted one of these enzymes, namely, *dihydropteroate synthase* (Babaoglu *et al*., 2004; Woods, 1940). These sulfa drugs are still widely used, usually in combination with *dihydrofolate reductase* inhibitors, to treat common bacterial infections such as, urinary tract infections, nocardiosis, toxoplasmosis, blepharitis, conjunctivitis, septicemia, acute sinusitis, and chronic bronchitis, particularly in patients with penicillin allergy. In contrast to other types of medication, antibiotics ultimately lose their effectiveness as they are used over time and resistant strains of bacteria (Iliades *et al*., 2003; Lerner, 1998). In addition, the threat of bioterrorism using agents, such as weaponized *Bacillus anthracis* and *Yersinia pestis*, highlight the need for continuing research in infectious diseases and the search for new therapeutic agents (Greenfield and Bronze, 2003).

Quantitative structure–activity relationships (QSAR), establishing correlation between trends in chemical structure modification and respective changes of biological activity have been broadly used for the past few years mainly in medical research (Hansch and Leo, 1995; Hansch *et al*., 1995). This methodology allows cost savings by reducing the laboratory resources needed and the time required to create and investigate new drugs with certain desired biological activity. A large number of QSAR studies for sulfonamides have been developed for different biological properties, such as antimicrobial activity (Temiz *et al*., 2008), antifungal activity (Saiz *et al*., 2007; Deokar *et al*., 2008), antimalarial activity (Agrawal *et al*., 2001), antitumor activity (Jaiswal *et al*., 2004; Samanta *et al*., 2004), carbonic anhydrase inhibitors (Khadikar *et al*., 2005; Balaban *et al*., 2004), COX-2 inhibitors (Silakari *et al*., 2008), HIV-1 integrase inhibitors (Kumar Sahu *et al*., 2007; Ravichandran *et al*., 2007), matrix metalloproteinase (MMP) inhibitors (Gupta and Kumaran, 2005),

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and β_3-adrenergic receptor agonist (Hanumantharao *et al*., 2005; Kashaw *et al*., 2003).

Recently there has been considerable interest in new sulfonamides possessing antimicrobial activity (Patel *et al*., 2007; El-Sharief and Al-Raqa, 2007; Ezabadi *et al*., 2008). In our previous studies, aliphatic and aromatic disulfonamides were synthesized and evaluated for antimicrobial activity (Ozbek *et al*., 2007a, b; Alyar and Karacan, 2009; Alyar *et al*., 2007). In addition, methanesulfonic acid hydrazides and their hydrazones were obtained and screened for their antimicrobial and cytotoxic activity (Ienco *et al*., 1999; Dodoff *et al*., 1999; Alyar *et al*., 2008; Ozbek *et al*., 2009). Metal carbonyl complexes of these sulfonyl hydrazones were also reported (Ozdemir *et al*., 2003; Sert *et al*., 2004; Ozdemir *et al*., 2004; Ozdemir *et al*., 2006; Ozdemir and Olgun, 2008; Senturk *et al*., 2007; Senturk *et al*., 2003). In this article, as part of our ongoing studies, a series of novel aromatic sulfonamide derivatives were synthesized and characterized by elemental analysis and standard physicochemical methods. Their antimicrobial activity was screened against three bacteria, *Staphylococcus aureus*, *Bacillus cereus*, and *Escherichia coli*, by microdilution method. The QSAR analysis of the compounds was performed using various physicochemical and topological descriptors.

Experimental

Synthesis of the compounds

The nucleophilic substitution reaction of the aliphatic diamines with sulfonyl chlorides were carried out as follows: Tetrahydrofuran (THF) solution of aliphatic diamines was added slowly dropwise to the THF solution of sulfonyl chlorides, maintaining the temperature between −5 and −10°C. Then, the reaction mixture was stirred for 24 h at room temperature (completion of the reaction was monitored by TLC). After the completion of the reaction, the solvent was evaporated in vacuum. The solid residue was purified by column chromatography. The synthesized compounds were characterized by various spectrochemical techniques, and the data were found to be in agreement with those of the assigned molecular structures. The physicochemical characteristics and the molecular structure of our compounds are tabulated in Table 1.

Antimicrobial screening methods

Microdilution assays

E. coli ATCC 11230, *S. aureus* ATCC 25923, and *B. cereus* RSKK 863 cultures were obtained from Gazi University, Biology Department, and Refik Saydam Hygiene Center Culture Collection. Bacterial strains were cultured overnight at 310 K in Nutrient Broth. These stock cultures were stored in the dark at 277 K during the survey.

Microdilution broth susceptibility assay was used (Koneman *et al*., 1997). Stock solution of the test compounds were prepared in 10% dimethylsulfoxide (DMSO), and then serial dilutions of the test compounds were made in a concentration range from 25 to 1400 μg/ml. The 96-well plates were prepared by dispensing into each well 95 μl of nutrient broth and 5 μl of the inoculum. Then, 100 μl from each of the test compounds initially prepared at the concentration of 1400 μg/ml was added into the first wells. The last well containing 195 μl of nutrient broth without compound and 5 μl of the inoculum on each strip was used as negative control. The final volume in each well was 200 μl. The contents of the wells were mixed and the micro plates were incubated at 37°C for 24 h. All of the compounds tested in this study were screened two times against each microorganism. The MIC was defined as the lowest concentration of the compounds to inhibit the growth of microorganisms.

Disk diffusion method

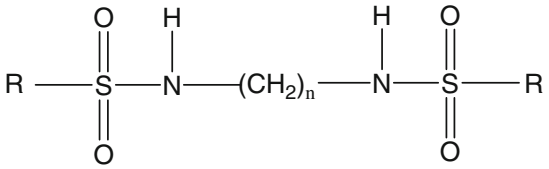
Bacterial susceptibility testing was performed by the disk diffusion method according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) (Bauer *et al*., 1966). The sterilized (autoclaved at 393 K for 30 min), liquefied Mueller–Hinton agar (313–323 K) was inoculated with the suspension of the microorganism (matched to 0.5 McFarland) and poured into a Petri dish to give a depth of 3–4 mm. The paper disks impregnated with the test compounds (60 μg) were placed on the solidified medium. Disks were placed on agar plates, and the cultures were incubated at 310 K for 24 h for bacteria. Inhibition zones formed on the medium were evaluated in millimeters. Ciprofloxacin (5 μg/disk) and Ampicillin (10 μg/disk) were used as standard drugs (positive control). DMSO-poured disk was used as negative control. Each assay in this experiment was repeated twice.

Result and discussion

In vitro antibacterial activity

In vitro antibacterial activity of the synthesized compounds was assayed on bacterial strains, Gram-positive *S. aureus*, *B. cereus*, and Gram negative *E. coli* with microdilution method. Antibacterial activity data (MIC) were converted

Table 1 Physicochemical data of disulfonamides derivatives



Compound	*n*	R	Molecular formula	Mol Wt	Mp (°C)	Yield (%)
Training set						
1	2	Ph–	$C_{14}H_{16}N_2O_4S_2$	340.41	173–174	72
2	3	Ph–	$C_{15}H_{18}N_2O_4S_2$	354.44	1174–175	77
3	4	Ph–	$C_{16}H_{20}N_2O_4S_2$	368.47	175–176	85
4	2	4-CH_3–ph–	$C_{16}H_{20}N_2O_4S_2$	367.47	158–161	72
5	3	4-CH_3–ph–	$C_{17}H_{22}N_2O_4S_2$	382.49	173–174	72
6	4	4-CH_3–ph–	$C_{18}H_{24}N_2O_4S_2$	396.52	183–184	72
7	2	2-CH_3–ph–	$C_{16}H_{20}N_2O_4S_2$	368.47	158–161	75
8	3	2-CH_3–ph–	$C_{17}H_{22}N_2O_4S_2$	382.49	173–174	78
9	4	2-CH_3–ph–	$C_{18}H_{24}N_2O_4S_2$	396.52	183–184	78
10	2	3-CH_3–ph–	$C_{16}H_{20}N_2O_4S_2$	368.47	158–161	80
11	3	3-CH_3–ph–	$C_{17}H_{22}N_2O_4S_2$	382.49	173–174	82
12	4	3-CH_3–ph–	$C_{18}H_{24}N_2O_4S_2$	396.52	183–184	80
13	2	4-CH_3O–ph–	$C_{16}H_{20}N_2O_6S_2$	400.46	195–196	80
14	2	CH_3–	$C_4H_{12}N_2O_4S_2$	216.27	74–75	75
15	3	CH_3–	$C_5H_{14}N_2O_4S_2$	230.30	77–78	85
16	4	CH_3–	$C_6H_{16}N_2O_4S_2$	244.32	79–80	85
17	5	CH_3–	$C_7H_{18}N_2O_4S_2$	258.35	81–82	75
18	2	CH_3–CH_2–	$C_6H_{16}N_2O_4S_2$	244.32	78–79	75
19	3	CH_3–CH_2–	$C_7H_{18}N_2O_4S_2$	258.35	80–81	75
20	4	CH_3–CH_2–	$C_8H_{20}N_2O_4S_2$	244.32	82–83	72
21	5	CH_3–CH_2–	$C_9H_{22}N_2O_4S_2$	258.35	84–85	72
22	2	CH_3–CH_2–CH_2–	$C_8H_{20}N_2O_4S_2$	272.38	94–95	75
23	3	CH_3–CH_2–CH_2–	$C_9H_{22}N_2O_4S_2$	286.40	121–122	88
24	4	CH_3–CH_2–CH_2–	$C_{10}H_{24}N_2O_4S_2$	300.43	126–128	84
25	3	CH_3–CH_2–CH_2–	$C_{11}H_{26}N_2O_4S_2$	314.46	116–118	88
26	4	CH_3–CH_2–CH_2–CH_2–	$C_{12}H_{28}N_2O_4S_2$	328.49	118–119	75
Test set						
27	3	4-CH_3O–ph–	$C_{17}H_{22}N_2O_6S_2$	414.49	200–201	80
28	5	Ph–	$C_{17}H_{22}N_2O_4S_2$	382.49	177–178	80
29	5	CH_3–CH_2–CH_2–	$C_{11}H_{26}N_2O_4S_2$	214.46	129–130	75
30	2	CH_3–CH_2–CH_2–CH_2–	$C_{10}H_{24}N_2O_4S_2$	300.43	120–121	75
31	2	3-CH_3O–ph–	$C_{16}H_{20}N_2O_6S_2$	400.46	195–196	80
32	3	3-CH_3O–ph–	$C_{17}H_{22}N_2O_6S_2$	414.49	200–201	80
33	2	2-CH_3O–ph–	$C_{16}H_{20}N_2O_6S_2$	400.46	195–196	80
34	3	2-CH_3O–ph–	$C_{17}H_{22}N_2O_6S_2$	414.49	200–201	80

Table 2 Comparison of observed and predicted antimicrobial activity of the compounds

	pMIC								
	Escherichia coli			*Bacillus cereus*			*Staphylococcus aureus*		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	3.510	3.537	0.027	3.370	3.408	0.038	3.380	3.404	0.024
2	3.490	3.522	0.032	3.360	3.394	0.034	3.285	3.391	0.106
3	3.480	3.508	0.028	3.358	3.381	0.023	3.240	3.370	0.130
4	3.530	3.537	0.007	3.400	3.408	0.008	3.400	3.404	0.004
5	3.520	3.508	0.012	3.380	3.381	0.001	3.300	3.370	0.070
6	3.500	3.493	0.007	3.350	3.166	0.184	3.260	3.360	0.100
7	3.700	3.670	0.032	3.560	3.342	0.218	3.638	3.527	0.111
8	3.680	3.654	0.026	3.542	3.328	0.214	3.600	3.513	0.087
9	3.640	3.625	0.015	3.505	3.298	0.207	3.540	3.486	0.054
10	3.580	3.581	0.001	3.480	3.254	0.226	3.522	3.445	0.077
11	3.570	3.566	0.004	3.440	3.240	0.200	3.480	3.432	0.048
12	3.550	3.551	0.001	3.410	3.225	0.185	3.470	3.418	0.052
13	3.560	3.522	0.038	3.460	3.196	0.264	3.490	3.391	0.099
14	2.990	3.012	0.022	2.876	2.682	0.194	2.990	2.917	0.073
15	2.970	2.997	0.027	2.864	2.668	0.196	2.925	2.904	0.021
16	2.950	2.968	0.018	2.840	2.638	0.202	2.900	2.877	0.023
17	2.940	2.954	0.014	2.828	2.624	0.204	2.880	2.863	0.017
18	2.720	2.662	0.058	2.660	2.330	0.330	2.660	2.592	0.068
19	2.700	2.662	0.038	2.642	2.330	0.312	2.642	2.592	0.050
20	2.690	2.678	0.011	2.638	2.345	0.293	2.637	2.606	0.031
21	2.670	2.677	0.007	2.580	2.345	0.235	2.610	2.606	0.004
22	3.258	3.158	0.100	3.179	2.829	0.350	3.003	3.053	0.050
23	3.104	3.128	0.024	3.058	2.800	0.258	3.009	3.025	0.016
24	3.119	3.114	0.005	2.950	2.785	0.165	2.933	3.012	0.079
25	3.116	3.056	0.060	2.917	2.726	0.191	2.861	2.958	0.097
26	2.857	3.041	0.184	2.850	2.712	0.138	2.829	2.944	0.115
Test set									
27	3.511	3.508	0.003	3.420	3.420	0.039	3.460	3.370	0.090
28	3.496	3.478	0.018	3.200	3.200	0.048	3.380	3.350	0.030
29	3.191	3.099	0.092	2.780	2.780	0.010	2.960	2.998	0.038
30	3.120	3.070	0.050	2.830	2.830	0.089	2.974	2.971	0.003
31	3.600	3.566	0.034	3.580	3.435	0.145	3.520	3.431	0.089
32	3.590	3.551	0.039	3.550	3.422	0.128	3.500	3.418	0.082
33	3.720	3.698	0.022	3.660	3.559	0.101	3.580	3.554	0.026
34	3.711	3.683	0.028	3.600	3.545	0.055	3.550	3.540	0.010

into the corresponding pMIC values (Table 2) to get the linear relationship in equations using the formula: pMIC = −logMIC(μM). Compound (**7**) was the most effective compound against *E. coli* with pMIC value of 3.70 in the training set. In general, the antimicrobial activity of the compounds was in the following order:

$$E.coli > B.cereus > S.aureus$$

The trend of antimicrobial activity shows that the activity against all bacterial strains was decreased when the length of the carbon chain between NH groups was increased. The aromatic disulfonamides were more active than aliphatic disulfonamides.

QSAR analysis

In order to identify the substituent effect on the antimicrobial activity, QSAR studies were performed using the linear regression analysis described by Hansch and Fujita

(Hansch and Fujita, 1964). The compounds were analyzed by physicochemical and topological parameters as independent variables and pMIC values as dependent variables. The chemical structure of molecules was set up with the Hyperchem 7.5 program and optimized with semi-empirical PM3 method. In order to prevent the structures locating at local minima, geometry optimization was run many times with different starting points for each molecule. Different quantum chemical descriptors including heat of formation, dipole moment, and energies of the frontier orbitals (HOMO and LUMO) were calculated by the Hyperchem 7.5 software (HyperChem 7.5, 2002). The topological parameters were calculated by Dragon 5.5 software (Dragon 5.5). Before generating model, intercorrelation of descriptors was taken into account, and highly correlated descriptors were removed. The values of the selected descriptors used in the regression analysis are presented in Table 3.

The first step in analyzing multivariate correlation is to construct correlation matrix, showing the interrelationship among the independent parameters and also their individual correlation with antimicrobial activity. The correlation matrix given in Table 4 indicates that there was high autocorrelation ($r > 0.7$) between the molecular discriptors. The topological descriptors were significantly correlated with ($r > 0.8$) antimicrobial activity of the compounds against all microorganisms. The third-order average connectivity index ($^3\chi^A$) exhibits the most correlation ($r > 0.97$) with all microorganisms, especially with *E. coli* ($r > 0.99$).

In this study, molecules were rationally divided into the training set (1–26) and test set (27–34). 2D-QSAR analysis was performed by stepwise multiple liner regression method using training set. The statistically significant QSAR models are given below:

QSAR model for antimicrobial activity against *E. coli*

$$\text{pMIC} = -14.585(\pm 0.422)^3\chi^A + 6.425(\pm 0.093) \quad (1)$$

where $n = 26$, $r^2 = 0.9801$, $s = 0.0504$, $F = 1194$, SPRESS = 0.050, $r^2_{cv} = 0.994$.

QSAR model for antimicrobial activity against *B. cereus*

$$\text{pMIC} = -13.670(\pm 0.408)^3\chi^A + 6.115(\pm 0.089) \quad (2)$$

where $n = 26$, $r^2 = 0.9781$, $s = 0.0487$, $F = 1124$, SPRESS = 0.048, $r^2_{cv} = 0.978$.

QSAR model for antimicrobial activity against *S. aureus*

$$\text{pMIC} = -13.537(\pm 0.636)^3\chi^A + 6.085(\pm 0.139) \quad (3)$$

where $n = 26$, $r^2 = 0.9082$, $s = 0.0760$, $F = 453$, SPRESS = 0.076, $r^2_{cv} = 0.947$.

All the statistical analyses were performed with SPSS software (Version 15, 2005). Leave-One-Out (LOO) cross-validation method was used to validate the predictive powers of all QSAR equations. The abbreviations for the statistical parameters given for each equation were: n (number of data points), r^2 (squared correlation coefficient), and s (standard error of estimate),r^2_{cv} (cross-validation correlation coefficient), SPRESS (sum of square standard error), and F (Fischer statistics).

The parameter r^2 is an indicator of the fit of the regression equation. Fisher test value reflects the ratio of the variance explained by the model and the variance due to the error in the model. The goodness of fit of Eqs. 1–3 is significant, possessing high r^2 values (>0.91), small standard deviations ($s < 0.07$) with high F values, exceeding the tabulated $F_{1,34,0.95} = 4.23$ (Draper and Smith 1966). The parameter r^2_{cv} is an indication of the predictive capability of the model (Jung *et al*., 2007; Sivakumar *et al*., 2007; Narasimhan *et al*., 2007). High cross-validated correlation coefficient $\left(r^2_{cv} > 0.9\right)$ and low predictive residual sum of square (SPRESS < 0.076) values indicate the robustness of the obtained QSAR models (Kadam and Roy, 2006; Tetko *et al*., 2001). Since the activity profiles of the compounds on target organisms are very similar to squared correlation coefficients ($r^2 = 0.91$–0.98), it is understandable that the best QSAR models are very similar.

Statistically, significant inverse relationship was observed between antimicrobial activity of disulfonamides against all microorganisms and third-order average connectivity index ($^3\chi^A$). The negative coefficient of $^3\chi^A$ in Eqs. 1–3 indicates that the lower the $^3\chi^A$ value, the higher the antimicrobial activity. For example, the compound (**7**) has the minimum third-order average connectivity index value ($^3\chi^A = 0.189$) in Table 3 and has the maximum antimicrobial activity against *E. coli* (pMIC = 3.70). Similarly, the compound (**21**) has the maximum third order average connectivity index value ($^3\chi^A = 0.259$) and has the minimum antimicrobial activity against *S. aureus* (pMIC = 2.61) in the training set. Kier–Hall Connectivity Indices are calculated from the Hydrogen-depleted molecular graph (Kier and Hall, 1986). One of them, the Average Connectivity index Chi-3 is defined as

$$\chi^{3A} = \chi^3/b$$

where, b is the number of bonds, the sum runs through all bonds in the Hydrogen-depleted molecule, and for each bond, $\delta_i\ \delta_j$ is the product of the vertex degrees of the end

Table 3 Values of selected descriptors used in the regression analysis

Compounds	$^{0}\chi^{A}$	$^{1}\chi^{A}$	$^{2}\chi^{A}$	$^{3}\chi^{A}$	$^{0}\chi^{v}$	$^{1}\chi^{v}$	$^{2}\chi^{v}$	$^{3}\chi^{v}$	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$
1	0.730	0.453	0.308	0.198	13.27	9.48	7.96	5.77	16.05	10.42	9.85	7.31	5.34
2	0.729	0.455	0.309	0.199	13.98	9.98	8.31	5.99	16.76	10.92	10.21	7.56	5.51
3	0.728	0.457	0.311	0.200	14.68	10.48	8.66	6.25	17.47	11.42	10.56	7.81	5.69
4	0.741	0.448	0.308	0.198	11.12	10.30	8.96	6.33	17.79	11.21	11.10	8.13	5.65
5	0.740	0.450	0.309	0.200	15.82	10.80	9.31	6.55	18.50	11.71	11.45	8.38	5.83
6	0.739	0.452	0.311	0.201	16.53	11.30	9.66	6.80	19.20	12.21	11.81	8.63	6.01
7	0.741	0.450	0.303	0.189	15.12	10.31	8.79	6.72	17.80	11.24	10.92	8.12	6.49
8	0.740	0.451	0.305	0.190	15.82	10.81	9.15	6.95	18.50	11.74	11.27	8.37	6.66
9	0.739	0.453	0.306	0.192	16.53	10.31	9.50	7.20	19.21	12.24	11.63	8.62	6.84
10	0.741	0.448	0.309	0.195	15.12	10.30	8.96	6.23	17.79	11.21	11.12	7.98	5.86
11	0.740	0.450	0.310	0.196	15.82	10.80	9.32	6.45	18.50	11.71	11.48	8.22	6.03
12	0.739	0.452	0.311	0.197	16.53	11.30	9.67	6.71	19.21	12.21	11.83	8.48	6.21
13	0.739	0.455	0.301	0.199	15.93	10.52	8.68	6.40	19.21	12.28	11.44	8.95	6.27
14	0.819	0.473	0.396	0.234	8.50	6.88	5.99	2.31	9.83	5.21	6.33	2.10	1.31
15	0.810	0.476	0.393	0.235	9.20	7.38	6.35	2.54	10.54	5.71	6.68	2.35	1.49
16	0.803	0.477	0.391	0.237	9.91	7.88	6.71	2.79	11.24	6.21	7.04	2.60	1.66
17	0.797	0.479	0.389	0.238	10.62	8.38	7.06	3.04	11.95	6.71	7.39	2.85	1.84
18	0.803	0.487	0.347	0.256	9.91	7.58	6.79	4.34	11.24	6.33	6.24	3.87	1.56
19	0.797	0.488	0.347	0.257	10.62	8.08	7.14	4.57	11.95	6.83	6.60	4.12	1.74
20	0.791	0.489	0.347	0.258	11.32	8.58	7.49	4.82	12.66	7.33	6.95	4.37	1.91
21	0.786	0.489	0.348	0.259	12.03	9.08	7.85	5.07	13.36	7.83	7.30	4.62	2.09
22	0.791	0.489	0.352	0.224	11.32	8.58	7.28	4.89	12.66	7.33	7.03	3.81	2.81
23	0.786	0.489	0.352	0.226	12.03	9.08	7.63	5.12	13.36	7.83	7.39	4.06	2.99
24	0.782	0.490	0.352	0.227	11.74	9.59	7.99	5.37	14.07	8.33	7.74	4.31	3.16
25	0.778	0.490	0.352	0.231	13.45	10.08	8.34	5.47	14.78	8.83	8.09	4.62	2.95
26	0.774	0.491	0.352	0.232	14.15	10.58	8.69	5.72	15.49	9.32	8.45	4.87	3.12
Test set													
27	0.738	0.456	0.302	0.200	16.64	11.02	9.03	6.63	19.22	12.78	11.79	9.20	6.45
28	0.727	0.458	0.312	0.202	15.39	10.98	9.02	6.50	18.76	11.92	10.92	8.06	5.87
29	0.778	0.490	0.352	0.228	13.45	10.08	8.34	5.62	14.78	8.83	8.09	4.56	3.34
30	0.782	0.490	0.352	0.230	14.74	9.58	7.99	5.24	12.07	8.33	7.74	4.37	2.77
31	0.739	0.455	0.302	0.196	15.932	10.524	8.687	6.330	19.209	12.281	11.460	8.823	6.313
32	0.738	0.456	0.303	0.197	16.639	11.024	9.041	6.558	19.916	12.781	11.813	9.073	6.489
33	0.739	0.456	0.297	0.187	15.932	10.536	8.568	6.427	19.209	12.315	11.303	8.767	6.982
34	0.738	0.458	0.299	0.188	16.639	11.036	8.922	6.656	19.916	12.815	11.656	9.017	7.159

Table 4 Correlation matrix for pMIC of *Ec*, *Bs*, *Sa* with topological descriptors

	$pMIC_{Ec}$	$pMIC_{Bs}$	$pMIC_{Sa}$	$^{0}\chi^{A}$	$^{1}\chi^{A}$	$^{2}\chi^{A}$	$^{3}\chi^{A}$	$^{0}\chi^{v}$	$^{1}\chi^{v}$	$^{2}\chi^{v}$	$^{3}\chi^{v}$	$^{0}\chi$	$^{1}\chi$	$^{2}\chi$	$^{3}\chi$	$^{4}\chi$
$pMIC_{Ec}$	1															
$pMIC_{Bs}$	0.995	1														
$pMIC_{Sa}$	0.975	0.979	1													
$^{0}\chi^{A}$	0.873	0.877	0.833	1												
$^{0}\chi^{A}$	0.893	0.891	0.917	0.840	1											
$^{0}\chi^{A}$	0.786	0.801	0.753	0.937	0.748	1										
$^{0}\chi^{A}$	0.990	0.989	0.975	0.887	0.897	0.773	1									
$^{0}\chi^{A}$	0.762	0.770	0.733	0.865	0.667	0.837	0.771	1								
$^{0}\chi^{A}$	0.755	0.756	0.708	0.881	0.638	0.835	0.776	0.944	1							
$^{0}\chi^{A}$	0.750	0.753	0.712	0.878	0.672	0.860	0.764	0.9363	0.988	1						
$^{0}\chi^{A}$	0.737	0.749	0.687	0.890	0.613	0.947	0.733	0.900	0.935	0.944	1					
$^{0}\chi^{A}$	0.858	0.864	0.832	0.949	0.799	0.916	0.867	0.941	0.963	0.967	0.935	1				
$^{0}\chi^{A}$	0.886	0.873	0.837	0.968	0.813	0.930	0.877	0.934	0.952	0.954	0.934	0.997	1			
$^{0}\chi^{A}$	0.908	0.910	0.896	0.945	0.899	0.879	0.918	0.897	0.907	0.919	0.859	0.979	0.979	1		
$^{0}\chi^{A}$	0.859	0.868	0.839	0.966	0.853	0.966	0.858	0.894	0.893	0.914	0.923	0.977	0.983	0.969	1	
$^{0}\chi^{A}$	0.943	0.948	0.926	0.962	0.881	0.919	0.945	0.891	0.890	0.895	0.892	0.970	0.976	0.979	0.974	1

atoms *i* and *j*. Connectivity indices Chi-m for 3 is defined as

$$\chi^3 = \sum_{k=1}^{K} (\Pi\delta_i)_k^{-1/2},$$

where, $(\Pi\ \delta_i)_k$ is the product of the vertex degrees of the atoms that form a connected subgraph with *m* edges, and *K* is the total number of such distinct connected sub graphs (the H-depleted molecular graph), each having *m* edges.

In order to confirm our results, we have predicted the antimicrobial activity of the disulfonamides in the test set using Eqs. 1–3. The comparison of the observed and the predicted values (Table 2) demonstrated that they are close to each other as evidenced by the low residual activity values. Furthermore, it is supported by the plot of $pMIC_{Ec}$ observed vs. $pMIC_{Ec}$ predicted (Fig. 1). It is important to note that all the equations are derived using the entire data set and no outliers were found during model development. Even though the sample size and "Rule of Thumb" allowed us to go for development of multi-parametric model in MLA, the high autocorrelation (Table 3) among parameters restricted us to opt for bi-parametric model (Narasimhan *et al*., 2006). In this study, the range of antimicrobial activities of the disulfonamides is within one order of magnitude. Bajaj *et al*. stated that the reliability of the QSAR models lies in its predictive ability even though the activity data are in the narrow range (Bajaj *et al*., 2005). The predictability of the QSAR models developed in this study is high evidenced by low residual values (Table 2).

Conclusion

In conclusion, a series of disulfonamide derivatives were synthesized in efficient yields and screened for their in vitro antimicrobial activity against *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli.* The SAR studies indicate that title compounds were the most effective against Gram-negative *Escherichia coli.* The trends of antimicrobial studies showed that decreasing the length of the carbon chain between NH groups will improve the activity. The QSAR analysis revealed that the antimicrobial activity of these synthesized derivatives against microorganism under test is mainly governed by the topological parameters, namely, third order average connectivity index ($^{3}\chi^{A}$). The obtained regression modes present a good capacity to explain the observed values of antimicrobial activity with high statistical significance and predictive capacity.

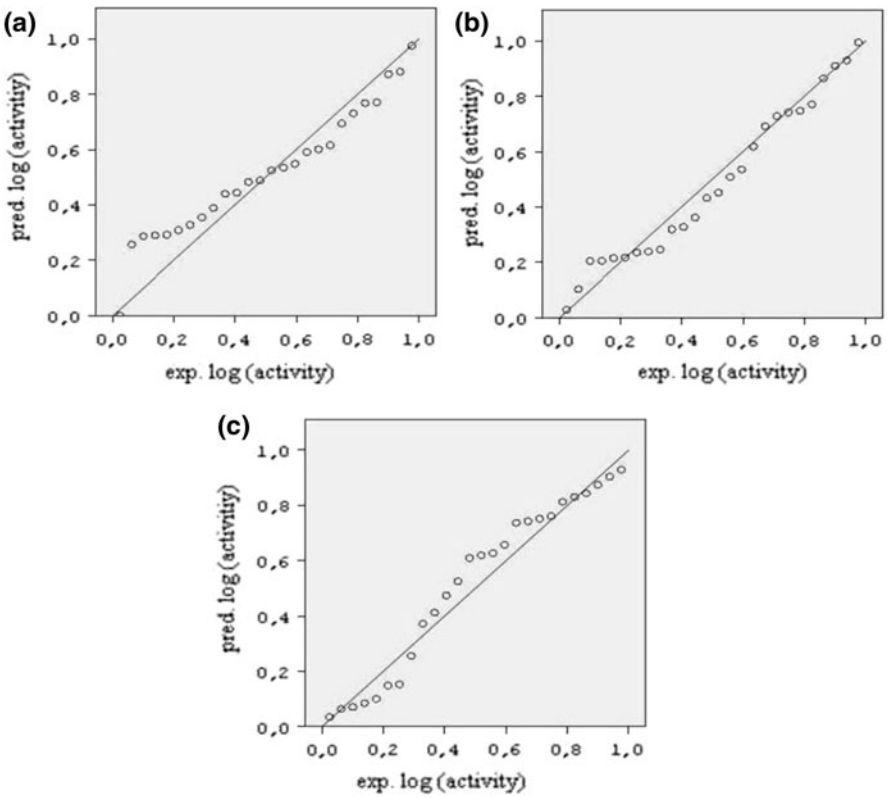


Fig. 1 **a** Plot of predicted $pMIC_{Ec}$ activity values against the experimental $pMIC_{Ec}$ values for the linear regression developed model by Eq. 1. **b** Plot of predicted $pMIC_{Bc}$ activity values against the experimental $pMIC_{Bc}$ values for the linear regression developed model by Eq. 2. **c** Plot of predicted $pMIC_{Sa}$ activity values against the experimental $pMIC_{Sa}$ values for the linear regression developed model by Eq. 3

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References

Agrawal VK, Srivastava R, Khadikar PV (2001) QSAR studies on some antimalarial sulfonamides. Bioorg Med Chem 9:3287–3293

Alyar S, Karacan N (2009) Synthesis, characterization, antimicrobial activity and structure–activity relationships of new aryldisulfonamides. J Enzym Inhib Med Chem 24:986–992

Alyar S, Ozbek N, Karacan N (2007) Synthesis and antimicrobial activity of new substituted arylsulfonamides. Drugs Future 32:126

Alyar S, Ozmen UO, Karacan N, Senturk OS, Udachin KA (2008) Tautomeric properties, conformations and structure of 2-hydroxyacetophenone methanesulfonylhydrazone. J Mol Struct 889:144–149

Babaoglu K, Qi J, Lee RE, White SW (2004) Crystal structure of 7,8-dihydropteroate, synthase from bacillus anthracis: mechanism and novel inhibitor design. Struct 12:1705–1717

Bajaj S, Sambi SS, Madan AK (2005) Prediction of anti-inflammatory activity of *N*-arylanthranilic acids: computational approach using refined Zagreb indices. Croat Chem Acta 78:165–174

Balaban AT, Basak SC, Beteringhe A, Mills D, Supuran CT (2004) QSAR study using topological indices for inhibition of carbonic anhydrase II by sulfanilamides and Schiff bases. Mol Divers 8:401–412

Bauer AW, Kirby WM, Sherris JC, Turck M (1966) Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol 45:493–496

Deokar HS, Puranik P, Kulkarni VM (2008) QSAR analysis of *N*-myristoyltransferase inhibitors: antifungal activity of benzofurans. Med Chem Res 18:206–220

Dodoff NI, Ozdemir U, Karacan N, Georgieva MC, Konstantinov SM, Stefanova ME (1999) Schiff bases of methanesulfonylhydrazine. Synthesis, spectroscopic characterization, conformational analysis, and biological activity. Z Naturforsch 54:1553–1562

Draper N, Smith H (1966) Applied regression analysis. Wiley, New York, p 17

El-Sharief AMS, Al-Raqa SY (2007) New types of mono and bis sulfonamides, tosylamino acids and thiosulfonic ester derived from autotoxin, bergapten and visnagin with biological interest. Phosphorus Sulfur 182:1557–1580

Ezabadi IR, Camoutsis C, Zoumpoulakis P, Geronikaki A, Sokovic M, Glamocilija J, Ciric A (2008) Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: synthesis, biological evaluation, lipophilicity, and conformational studies. Bioorg Med Chem 16:1150–1161

Greenfield RA, Bronze MS (2003) Prevention and treatment of bacterial diseases caused by bacterial bioterrorism threat agents. Drug Discov Today 8:881–888

Gupta SP, Kumaran S (2005) A quantitative structure–activity relationship study on some series of anthranilic acid-based matrix metalloproteinase inhibitors. Bioorg Med Chem 13:5454–5462

Hansch C, Fujita TJ (1964) A method for the correlation of biological activity and chemical structure. Am Chem Soc 86:1616–1626

Hansch C, Leo A (1995) Exploring QSAR. Fundamentals and applications in chemistry and biology. Am Chem Soc, Washington, DC

Hansch C, Leo A, Hoekman D (1995) Exploring QSAR. Hydrophobic, electronic and steric constants. Am Chem Soc, Washington, DC

Hanumantharao P, Sambasivarao SV, Soni LK, Gupta AK, Kaskhedikar SG (2005) QSAR analysis of thiazole benzenesulfonamide substituted 3-pyridylethanolamines as beta(3)-adrenergic receptor agonist. Bioorg Med Chem Lett 15:3167–3173

HyperChem 7.5 program (2002) Hypercube Inc., Toronto, Canada http://www.talete.mi.it/dragon_exp.htm, Italia (Milano Chemometrics and QSAR Group)

Ienco A, Mealli C, Paoli P, Dodoff N, Kantarci Z, Karacan N (1999) Structure and vibrational spectroscopy of methanesulfonic acid hydrazide: an experimental and theoretical study. New J Chem 23:1253–1260

Iliades P, Berglez J, Meshnick S, Macreadie I (2003) Promoter strength of folic acid synthesis genes affects sulfa drug resistance in *Saccharomyces cerevisiae* Microb. Drug Resist 9:249–255

Jaiswal M, Khadikar PV, Scozzafava A, Supuran CT (2004) Carbonic anhydrase inhibitors: the first QSAR study on inhibition of tumor-associated isoenzyme IX with aromatic and heterocyclic sulfonamides. Bioorg Med Chem Lett 14:3283–3290

Jung M, Tak J, Lee Y, Jung Y (2007) Design, synthesis, and discovery of stilbene derivatives based on lithospermic acid B as potent protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 17:1082–1090

Kadam RU, Roy N (2006) Comparative protein modeling and surface analysis of Leishmania sirtuin: a potential target for antileishmanial drug discovery. Bioorg Med Chem Lett 16:5136–5143

Kashaw SK, Rathi L, Mishra P, Saxena AK (2003) Development of 3D-QSAR models in cyclic ureidobenzenesulfonamides: human beta(3)-adrenergic receptor agonist. Bioorg Med Chem Lett 13:2481–2484

Khadikar PV, Sharma V, Karmarkar S, Supuran CT (2005) Novel use of chemical shift in NMR as molecular descriptor: a first report on modeling carbonic anhydrase inhibitory activity and related parameters. Bioorg Med Chem Lett 15:931–936

Kier LB, Hall LH (1986) Molecular connectivity in structure-activity analysis. Wiley, New York, pp 497–500

Koneman EW, Allen SD, Janda WM, Scherckenberger PC, Winn WC (1997) Color atlas and textbook of diagnostic microbiology. Lippincott-Raven, Philadelphia, p 253

Kumar Sahu K, Ravichandran V, Mourya VK, Agrawal RK (2007) QSAR analysis of caffeoyl naphthalene sulfonamid derivatives as HIV-1 integrase inhibitors. Med Chem Res 15:418–430

Lerner SA (1998) Resolving the antibiotic paradox: progress in understanding drug resistance and development of new antibiotics. Plenum Publishers, New York, pp 7–12

Narasimhan B, Kumari M, Jain N, Dhake AS, Sundaravelan C (2006) Correlation of antibacterial activity of some *N*-[5-(2-furanyl)-2-methyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3H-thieno[2,3-d]pyrimidin-4-ones with topological indices using Hansch analysis. Biorg Med Chem Lett 16:4951–4958

Narasimhan B, Mourya VK, Dhake AS (2007) QSAR studies of antibacterial ricinoleic acid derivatives. Khim Farm Zh 43:16–21

Ozbek N, Katircioglu H, Karacan N, Baykal T (2007a) Synthesis, characterization and antimicrobial activity of new aliphatic sulfonamide. Bioorg Med Chem 15:1509–5105

Ozbek N, Alyar S, Karacan N (2007b) Synthesis, characterization and antimicrobial activity of new butanesulfonamides. Drugs Future 32:128

Ozbek N, Kavak G, Ozcan Y, Ide S, Karacan N (2009) Structure, antibacterial activity and theoretical study of 2-Hydroxy-1-naphthaldehyde-*N*-methylethanesulfonylhydrazone. J Mol Struct 919:154–159

Ozdemir OU, Olgun G (2008) Synthesis, characterization and antibacterial activity of new sulfonyl hydrazone derivatives and their nickel(II) complexes. Spectrochim Acta A 70:641–645

Ozdemir U, Senturk OS, Sert S, Karacan N, Ugur F (2003) Photochemical reactions of metal carbonyls [M(CO)(6) (M = Cr, Mo and W), Re(CO)(5)Br, Mn(CO)(3)Cp] with 2-hydroxyacetophenone methanesulfonylhydrazone (apmsh). Trans Met Chem 28:243–246

Ozdemir U, Karacan N, Senturk OS, Sert S, Ugur F (2004) Synthesis and characterization of metal carbonyl complexes of M(CO)(6)(M = Cr, Mo, and W), Re(CO)(5)Br, and Mn(CO)(3)CP with—acetone-methanesulfonylhydrazone (amsh) and methanesulfonylhydrazone (msh). Synth React Inorg Met Org Chem 34:1057–1067

Ozdemir U, Senturk OS, Sert S, Karacan N, Ugur F (2006) Reaction of metal carbonyls with 2-hydroxy-1-naphthaldeyde methanesulfonylhydrazone and characterization of the substitution products. J Coord Chem 59:1905–1911

Patel PR, Ramalingan C, Park YT (2007) Synthesis and antimicrobial evaluation of guanylsulfonamides. Bioorg Med Chem Lett 17:6610–6614

Ravichandran V, Jain PK, Mourya VK, Agrawal RK (2007) QSAR study on some arylsulfonamides as anti-HIV agents. Med Chem Res 16:342–351

Saiz UL, Gonzalez MP, Collado IG, Hernandez GR (2007) Quantitative structure–activity relationship studies for the prediction of antifungal activity of *N*-arylbenzenesulfonamides against *Botrytis cinerea*. J Mol Graph Model 25:680–690

Samanta S, Srikanth K, Banerjee S, Debnath B, Gayen S, Jha T (2004) 5-N-Substituted-2-(substituted benzenesulphonyl) glutamines as antitumor agents. Part II: synthesis, biological activity and QSAR study. Bioorg Med Chem 12:1413–1423

Senturk OS, Ozdemir U, Sert S, Karacan N, Uğur F (2003) Synthesis and characterization of some metal carbonyls with 2-hydroxyacetophenone ethanesulfonylhydrazone. Inorg Chem Commun 6:926–929

Senturk OS, Ozdemir U, Sert S, Karacan N, Uğur F (2007) Photochemical reactions of metal carbonyls [M(CO)(6) (M = Cr, Mo, W), Re(CO)(5)Br, Mn(CO)(3)Cp] with salicylaldehyde ethanesulfonylhydrazone (Hsalesh). J Coord Chem 60:229–232

Sert S, Senturk OS, Ozdemir U, Karacan N, Ugur F (2004) Synthesis and characterization of the products from reaction of metal carbonyls [M(CO)(6) (M=Cr, Mo, W), Re(CO)(5)Br, Mn(CO)(3)Cp] with salicylaldehyde methanesulfonylhydrazone. J Coord Chem 57:183–188

Silakari P, Shrivastava SD, Silakari G, Kohli DV, Rambabu G, Srivastava S, Shrivastava SK, Silakari O (2008) QSAR analysis of 1,3-diaryl-4,5,6,7-tetrahydro-2H-isoindole derivatives as selective COX-2 inhibitors. Eur J Med Chem 43:1559–1569

Sivakumar PM, Seenivasan SP, Kumar V, Doble M (2007) Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives. Bioorg Med Chem Lett 17:1695–1700

SPSS for Windows (2005) Version 15

Temiz AO, Yıldız I, Ozkan S, Kaynak F, Akı-Sener E, Yalcin I (2008) Synthesis and biological activity of some new benzoxazoles. Eur J Med Chem 43:1423–1431

Tetko IV, Tanchuk VY, Villa AE (2001) Estimation of aqueous solubility of chemical compounds using E-state indices. J Chem Inf Comput Sci 41:1407–1421

Woods DD (1940) The relationship between *p*-aminobenzoic acid to the mechanism of action of sulphanilamide. Brit J Exp Pathol 21:74–90