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Original article

Synthesis, biological evaluation and 2D-QSAR analysis of benzoxazoles as antimicrobial agents

Tugba Ertan [a], Ilkay Yildiz [a,*], Betul Tekiner-Gulbas [a], Kayhan Bolelli [a], Ozlem Temiz-Arpaci [a], Semiha Ozkan [b], Fatma Kaynak [b], Ismail Yalcin [a], Esin Aki [a]

[a] Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, TR-06100 Tandogan, Ankara, Turkey
[b] Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, 06330 Etiler, Ankara, Turkey

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Abstract

A new series of 5(or 6)-nitro/amino-2-(substituted phenyl/benzyl)benzoxazole derivatives (**1a–1m**, **2a–2l**) were synthesized and evaluated for antibacterial and antifungal activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and their drug-resistant isolate. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between >400 and 12.5 μg/ml. The results against *B. subtilis*, *P. aeruginosa*, drug-resistant *B. subtilis*, drug-resistant *E. coli*, and *C. albicans* isolate for these kinds of structures are quite encouraging. The 2D-QSAR analysis of a set of newly and previously synthesized benzoxazoles tested for growth inhibitory activity against *B. subtilis* ATCC 6633 was performed by using the multivariable regression analysis. The activity contributions for substituent effects of these compounds were determined from the correlation equation for predictions of the lead optimization.

Keywords: Antibacterial activity; Antifungal activity; Benzoxazoles; 2D-QSAR

1. Introduction

The dramatically rising prevalence of multidrug-resistant microbial infections in the past few decades has become a serious health care problem. In particular, the emergence of multidrug-resistant strains of Gram-positive bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermis* and vancomycin-resistant *Enterococcus* is a problem of ever-increasing significance [1–5]. In order to prevent this serious medical problem, the elaboration of the new types of the previously known drugs is a very actual task.

The benzoxazoles have been the aim of many researches for many years because they constitute an important class of heterocyclic compounds exhibiting substantial chemotherapeutic activities [6–33]. In the last few years, we reported some derivatives of benzoxazoles, which exhibited antimicrobial [14–16], antiviral [23,24], multidrug-resistance cancer cell activities [33] with inhibiting activity on eukaryotic topoisomerase II enzyme in cell-free system [25–27].

The goal of outset of this research was to develop new effective antimicrobial agents having benzoxazole nuclei. Herein, we have described the synthesis of a series of 2-(substituted phenyl and benzyl)benzoxazole derivatives which have a nitro group attached on position 5 or 6 of heterocylic nuclei binding them as a new class of synthetic antimicrobial agents along with their *in vitro* antimicrobial activity. Additionally, we also put an electron-donating group such as amine instead of nitro which is an electron-withdrawing group for the same position in order to be able to discuss the effect of substituent for biological activity.

In the drug design area, quantitative structure–activity relationship (QSAR) modelling is an area of research pioneered by Hansch and Leo [34] and Hansch and Fujita [35]. The QSAR

* Corresponding author. Tel.: +90 312 203 3069x2308; fax: +90 312 223 69 40.
E-mail address: iyildiz@pharmacy.ankara.edu.tr (I. Yildiz).

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method assumes that differences in the structural or physical properties measured experimentally account for differences in the observed biological or chemical properties [34–37]. A QSAR study usually leads to a predictive formula and attempts to model the activity of a series of compounds using measured or computed properties of the compounds.

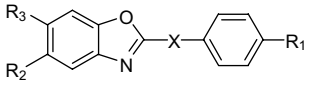
The other aim of this study is to derive quantitative structure–activity relationships (QSARs) from multivariable regression analysis (MRA) in order to investigate the quantitative effect of structural properties of the previously [10,38] and newly synthesized 5(or 6)-nitro/amino/methyl-2-(substituted phenyl/benzyl)benzoxazoles on their antibacterial activity against Gram-positive bacteria *Bacillus subtilis* ATCC 6633.

2. Results and discussion

2.1. Chemistry

The synthetic pathways for preparation of the target compounds listed in Table 1 are shown in Scheme 1. The synthesis of compounds (**1a–1m**) was performed by condensing of appropriate aminophenols and suitable acids in polyphoshoric acid. Reduction of the nitro group of **1a–1m** afforded **2a–2l**. Compounds **2b**, **2c**, **2g**, **2h–2j**, and **2l** were obtained from **1c**, **1d**, **1h–1l**, respectively, by using $NiCl_2 \cdot 6H_2O$ and Zn in methanol for reduction. Ten percent Pd–C was used to synthesize the other amines (**2a**, **2d–2f**, **2k**).

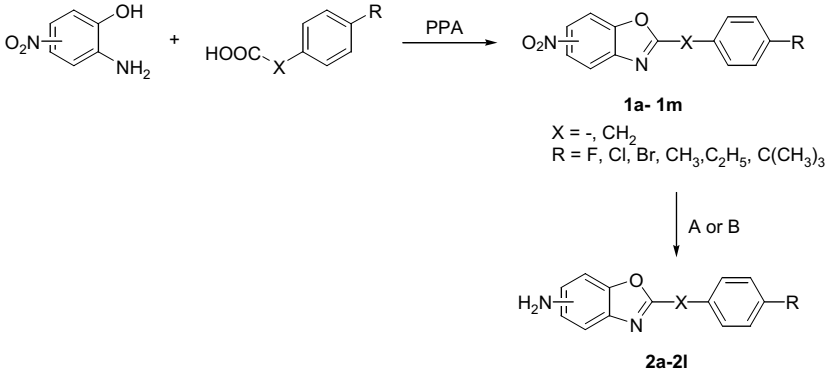
Table 1
The antimicrobial and antifungal activities of the synthesized compounds (**1a–1m**, **2a–2l**) and the control drugs (MIC in μg/ml)



Compound number	R_1	R_2	R_3	X	Microorganisms[a]										
					Gram negative					Gram positive				Fungi	
					Kp	*Kp*[b]	*Ec*	*Ec*[b]	*Pa*	*Bs*	*Bs*[b]	*Sa*	*Sa*[b]	*Ca*	*Ca*[b]
1a	$C(CH_3)_3$	H	NO_2	–	50	100	50	100	50	50	100	100	100	50	100
1b	H	H	NO_2	–	50	100	50	25	50	25	25	200	100	100	50
1c	F	H	NO_2	–	50	100	50	100	50	50	25	100	100	50	100
1d	Br	H	NO_2	–	50	100	50	25	50	12. 5	50	100	>400	100	50
1e	C_2H_5	H	NO_2	–	50	100	50	100	50	50	25	100	100	50	100
1f	H	NO_2	H	–	50	100	50	50	25	12. 5	25	200	>400	100	50
1g	C_2H_5	NO_2	H	–	50	100	50	100	50	50	25	100	100	50	100
1h	F	NO_2	H	–	50	100	50	100	50	50	25	100	100	50	100
1i	Br	H	NO_2	CH_2	50	100	50	100	25	25	25	100	100	50	100
1j	Cl	H	NO_2	CH_2	50	100	50	100	25	12. 5	25	200	100	100	50
1k	F	H	NO_2	CH_2	50	100	50	50	50	12. 5	100	100	100	100	50
1l	F	NO_2	H	CH_2	50	100	50	50	25	12. 5	50	100	100	100	50
1m	CH_3	NO_2	H	CH_2	50	50	50	50	50	50	50	50	50	50	25
2a	$C(CH_3)_3$	H	NH_2	–	50	100	50	100	25	25	25	100	100	50	50
2b	F	H	NH_2	–	50	100	50	100	50	50	50	100	100	50	50
2c	Br	H	NH_2	–	50	100	50	50	50	25	25	100	100	100	50
2d	C_2H_5	H	NH_2	–	50	100	50	100	50	50	100	100	100	50	50
2e	H	NH_2	H	–	50	100	50	50	50	12. 5	50	100	100	100	50
2f	C_2H_5	NH_2	H	–	50	100	50	100	50	12. 5	50	25	100	50	50
2g	F	NH_2	H	–	50	100	50	100	50	25	50	50	100	50	50
2h	Br	H	NH_2	CH_2	50	100	50	100	50	25	50	100	100	50	100
2i	Cl	H	NH_2	CH_2	50	100	50	100	25	12.5	25	100	100	50	50
2j	F	H	NH_2	CH_2	50	100	50	50	25	50	50	100	100	50	50
2k	CH_3	NH_2	H	CH_2	50	100	50	50	50	12. 5	25	100	100	100	50
2l	F	NH_2	H	CH_2	50	100	50	25	50	50	50	200	100	100	50
Rifampicin					16	256	8	64	32	64	256	0.5	8	–	–
Ampicillin trihydrate					2	256	8	256	4096	0.25	8	0.03	2	–	–
Gentamycin sulphate					8	64	0.5	1	2	1	512	0.06	1024	–	–
Ofloxacin					0.25	64	0.125	32	8	0.125	32	0.25	2	–	–
Fluconazole					–	–	–	–	–	–	–	–	–	1	64
Amphotericin B					–	–	–	–	–	–	–	–	–	1	1

[a] Abbreviations: *Kp*, *Klebsiella pneumoniae* RSHM 574; *Ec*, *Escherichia coli* ATCC 25922; *Pa*, *Pseudomonas aeruginosa* ATCC 25853; *Bs*, *Bacillus subtilis* ATCC 6633; *Sa*, *Staphylococcus aureus* ATCC 25923; *Ca*, *Candida albicans* ATCC 10231.

[b] *Kp*, *K. pneumoniae* isolate (resistant to trimethoprim sulfamethoxazole, amoxicilin clavulonat, ceftriaxone, cephepim, aztreonam); *Ec*, *E. coli* isolate (resistant to trimethoprim sulfamethoxazole, cephepim, tazobactam); *Bs*, *B. subtilis* isolate (resistant to ceftriaxone); *Sa*, *S. aureus* isolate (resistant to oxacillin, gentamycin, aztreonam, trimethoprim sulfamethoxazole); *Ca*, *C. albicans* isolate.



Scheme 1. Synthesis of the target benzoxazoles. Reagents: (A) 10% Pd–C, H_2, EtOH for compounds **2a**, **2d**–**2f**, **2k**; (B) $NiCl_2 \cdot 6H_2O$, Zn, MeOH for compounds **2b**, **2c**, **2g**–**2j**, **2l**.

2.2. In vitro antibacterial and antifungal activities

All the newly synthesized 5(or 6)-nitro/amino-2-(*p*-substituted phenyl/benzyl)benzoxazole derivatives (**1a**–**1m**, **2a**–**2l**) were assayed *in vitro* for antimicrobial activity against several Gram-positive, Gram-negative bacteria strains with its drug-resistant isolate and *Candida albicans* and its clinical isolate. The standard agents, rifampicin, ampicillin trihydrate, gentamycin, and ofloxacin for antibacterial activity and fluconazole and amphotericin B for antifungal activity were also screened under identical conditions for comparison. The MIC values were determined by the twofold serial dilution technique in Mueller–Hinton broth and Sabouraud dextrose agar for the antibacterial and antifungal assays, respectively [39].

According to the obtained data (Table 1), most of the synthesized compounds showed better antibacterial activity against Gram-positive bacteria *B. subtilis* and its drug-resistant isolate than the other tested microorganisms. Compounds **1a**, **1c**, **1e**, **1g**, **1h**, **1m**, **2b**, **2d**, **2j**, **2l** had comparable results with rifampicin, the other derivatives indicated one or more dilution better inhibitory effect against *B. subtilis* ATCC 6633. On the other hand, all of the compounds had more potent activity than rifampicin in drug-resistant *B. subtilis*. It should be noted that an H-acceptor group was enough for enhancing the activity of these series against *B. subtilis*. Besides, a halogen atom in the position of R_1 played an important role for increasing the potency as well. Having phenyl or benzyl group on second position of benzoxazole wasn't change the activity. None of the compounds exhibited more activity than the all tested standard drugs against *S. aureus* and its drug-resistant isolate. In particular, 5-amino-2-(*p*-ethylphenyl)benzoxazole, **2f**, came out with very significant activity at MIC value 25 μg/ml against *S. aureus*. Derivatives **1m**, 2-(*p*-methylbenzyl)-5-nitrobenzoxazole, and **2g**, 5-amino-2-(*p*-fluorophenyl)-benzoxazole (50 μg/ml) had a good inhibitory effect as well. It could be pointed out that there is no considerable difference for results about the preference of the phenyl or benzyl ring at position 2 of benzoxazole.

The antibacterial activity against Gram-negative bacteria *Klebsiella pneumoniae* and its isolate of tested compounds was found to be moderately active. Gentamycin and ofloxacin had more potent activity than the tested compounds in drug-resistant *K. pneumoniae* isolate except **1m** that indicated comparable inhibitory effect, while none of the synthesized structures showed a good inhibitory activity against *Escherichia coli* strains than the standard drugs, all of them were more active than ampicillin against drug-resistant *E. coli*. In particular, compounds **1b**, **1d**, and **2l** hopefully had a comparable inhibitory effect with ofloxacin. We could consider that switching the nitro group to the amine for 5th position of 2-benzylbenzoxazole structure or using a nitro group instead of amine at position 6 of 2-phenylbenzoxazole caused an increase in the antibacterial activity against drug-resistant *E. coli*. The tested compounds showed very important inhibitory effect against *Pseudomonas aeruginosa* with MIC values of 25–50 μg/ml as well. Among the tested compounds, derivatives **1f**, **1i**, **1j**, **1l**, **2a**, **2i**, and **2j** displayed very significant antibacterial activity against the Gram-negative enterobacter *P. aeruginosa*, which is effective in nosocomial infections and often resistant to antibiotic therapy, comparable to that of rifampicin. Additionally, all of the derivatives were found to be more potent than ampicillin.

On the other hand, although most of the tested compounds were found to be noticeably active against *C. albicans*, they exhibited less effect than the standard drugs. Surprisingly, all derivatives except **1a**, **1c**, **1e**, **1g**–**1i**, **2h** had comparable activity with fluconazole for *C. albicans* isolate. Structure–activity relationships suggested that substitution with the amine instead of the nitro at position R_2 or R_3 enhanced the potency. It could be pointed out that there has no any considerable result achieved about the preference of the phenyl or benzyl ring at position 2 of benzoxazole.

2.3. Structure–activity relationship of B. subtilis inhibitors with representative QSAR equation

The QSAR analysis in this study was performed using the extra-thermodynamic method, correlating the antibacterial activity against *B. subtilis* ATCC 6633 with various physicochemical parameters in order to reveal predictions for the lead optimization in the training set of compounds of newly synthesized 5(or 6)-nitro/amino-2-(substituted phenyl/benzyl)-

and previously synthesized [10,38] 5(or 6)-methyl-2-(substituted phenyl/benzyl)benzoxazoles.

Results of QSAR analysis obtained by the MRA of the training set of compounds given in Table 2 demonstrate that the best equation (Eq. (1)) is statistically significant.

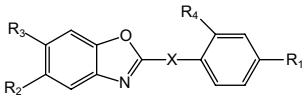
As can be deduced from Fig. 1, the goodness-of-fit of equation is very significant, possessing a high r (92.3%) and a small s (0.108) with an overall F test value of 31.028 at the significant level of $p < 0.05$. From a statistical point of view, equation has a sufficient number of DF (degrees of freedom, DF = 27) that can be judged significant for overall F statistics at the 5% level of probability.

In order to avoid the risk of chance correlation, some circumstances, which were pointed out by Kubinyi [40], have been taken into consideration in the study. Cross-validation was applied to the original data set and the resulting PRESS was calculated. The calculated overall PRESS values and for Eq. (1) is 0.131.

The obtained correlation equation was screened by using a test set (Table 3) concerning compounds **1b**, **1d**, **1f**, **1j**, **2f**, **2h**, **2i**, **2k**, **4k**–**4m** [10] that are not included in the developed model. The observed, calculated log 1/C values and residuals of the test set molecules obtained by Eq. (1) are given in Table 3. Fig. 2 represents the graph of the obtained *vs*. calculated log 1/C values of the test set molecules for the used model, which has an r value of 0.604.

The derived QSAR analysis revealed that the compounds possessing a methyl group at the positions 5 and 6 of benzoxazole moiety play a role in increasing the activity against *B. subtilis*. In addition, Eq. (1) demonstrates that substituent effects on the position R_4 is also important for the activity and holding a substituent possessing a minimum width property on this position like as alkyl groups enhance the potency. Furthermore, substituting position R_1 with a group enhancing the electron-withdrawing capability of the phenyl ring system plays a role in increasing the activity. Moreover, the best equation of these series structures has a molecular descriptor, which is superdelocalizability (S_r). S_r was originally derived as an index of reactivity of aromatic hydrocarbons [41]. The index is based on the idea that early interaction of the

Table 2
Training set of compounds, biological activity against *B. subtilis* and parameters used in Eq. (1)



Compound number	R_1	R_2	R_3	R_4	X	MIC (μg/ml)	IR_2	IR_3	σR_1	B_1R_4	S_r
1a	$C(CH_3)_3$	H	NO_2		–	50	0	0	−0.20	1	1.8749
1c	F	H	NO_2		–	50	0	0	0.06	1	1.5396
1e	C_2H_5	H	NO_2		–	50	0	0	−0.15	1	1.5075
1g	C_2H_5	NO_2	H		–	50	0	0	−0.15	1	1.4924
1h	F	NO_2	H		–	50	0	0	0.06	1	1.5427
1i	Br	H	NO_2		CH_2	25	0	0	0.23	1	1.5427
1k	F	H	NO_2		CH_2	12.5	0	0	0.06	1	0.4866
1l	F	NO_2	H		CH_2	12.5	0	0	0.06	1	0.4866
1m	CH_3	NO_2	H		CH_2	50	0	0	−0.17	1	1.5779
2a	$C(CH_3)_3$	H	NH_2		–	25	0	0	−0.20	1	0.6891
2b	F	H	NH_2		–	50	0	0	0.06	1	1.6413
2c	Br	H	NH_2		–	25	0	0	0.23	1	1.6413
2d	C_2H_5	H	NH_2		–	50	0	0	−0.15	1	1.2621
2e	H	NH_2	H		–	12.5	0	0	0	1	0.6697
2g	F	NH_2	H		–	25	0	0	0.06	1	1.6455
2j	F	H	NH_2		CH_2	50	0	0	0.06	1	1.7619
2l	F	NH_2	H		CH_2	50	0	0	0.06	1	1.7459
3a [38]	H	CH_3		H	–	12.5	1	0	0	1	1.5847
3b [38]	Cl	CH_3		H	–	12.5	1	0	0.23	1	1.5263
3c [38]	Br	CH_3		H	–	12.5	1	0	0.23	1	1.5263
3d [38]	NO_2	CH_3		H	–	6.25	1	0	0.78	1	1.2646
3e [38]	Cl		CH_3	H	–	12.5	0	1	0.23	1	1.5241
3f [38]	Br		CH_3	H	–	12.5	0	1	0.23	1	1.5241
4a [10]	H	CH_3		Cl	–	25	1	0	0	1.8	1.6075
4b [10]	H	CH_3		OCH_3	–	25	1	0	0	1.35	1.4705
4c [10]	H	CH_3		F	–	25	1	0	0	1.35	1.6304
4d [10]	H	CH_3		NO_2	–	25	1	0	0	1.7	1.4785
4e [10]	Cl	CH_3		Cl	–	25	1	0	0.23	1.8	1.4470
4f [10]	H		CH_3	Cl	–	25	0	1	0	1.8	1.6070
4g [10]	H		CH_3	OCH_3	–	25	0	1	0	1.35	1.5077
4h [10]	H		CH_3	F	–	25	0	1	0	1.35	1.6292
4i [10]	Cl		CH_3	Cl	–	25	0	1	0.23	1.8	1.4471
4j [10]	CH_3		CH_3	CH_3	–	50	0	1	−0.17	1.52	1.8861

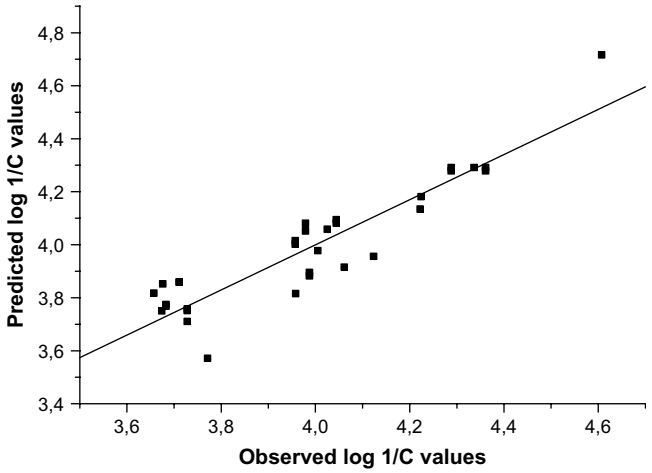


Fig. 1. Plot of observed *vs*. predicted log 1/*C* values of the training set compounds obtained from Eq. (1).

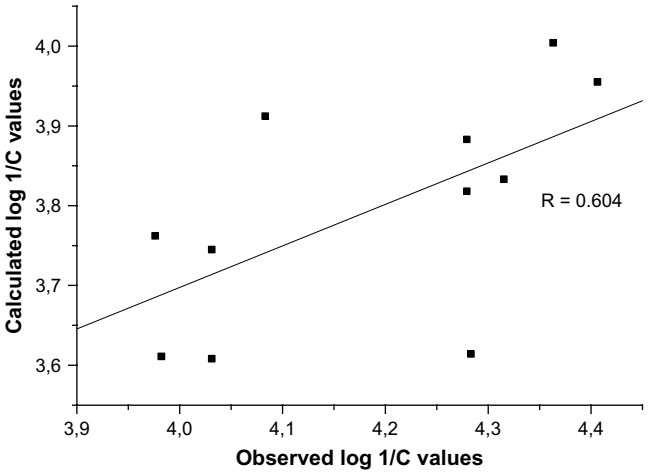


Fig. 2. Plot of observed *vs*. calculated log 1/*C* values of the test set compounds obtained by using Eq. (1).

molecular orbitals of reactants can be regarded as a mutual perturbation, the relative energies of orbitals changing together and maintaining a similar degree of overlap as reactants approach each other. The index is calculated by the sum

$$S_r = 2\sum_{j=1}^{m}\frac{C_{jr}^2}{e_j}$$

Here the term S_r is the superdelocalizability at position r, e_j is the bonding energy coefficient in the *j*th molecular orbital (eigenvalue), *c* is the molecular orbital coefficient at position r in the HOMO (highest occupied molecular orbital) and *m* is the index of the HOMO. This descriptor has been found to correlate highly to the activity of these sets of compounds.

3. Conclusion

In conclusion, the results against *B. subtilis*, *P. aeruginosa*, drug-resistant *B. subtilis*, drug-resistant *E. coli*, and *C. albicans* isolate for these kinds of structures are quite encouraging. According to 2D-QSAR study against *B. subtilis*, methyl group instead of nitro or amine at the positions 5 and 6 of benzoxazole moiety plays a role in increasing the activity. Moreover, substituting position R_1 with a group enhancing the electron-withdrawing capability of the phenyl ring system increases the potency. These observations could be guided to the lead optimization of the new candidate antibacterial agents.

4. Experimental

The chemicals were purchased from the commercial venders and were used without purification. The reactions were monitored and the purity of the products was checked by thin layer chromatography (TLC). Silica gel 60 F_{254} chromatoplates were used for TLC. All the melting points were measured with a capillary melting point apparatus (Buchi SMP 20 and Electrothermal 9100) and are uncorrected. Yields were calculated after recrystallization. The IR spectra were recorded on a Jasco FT/IR-420 spectrometer as KBr discs. The ^{1}H NMR spectra were recorded employing a VARIAN Mercury 400 MHz FT spectrometer, chemical shifts (δ) are in parts per million relative to TMS, and coupling constants (J) are reported in hertz. Mass spectra for compounds **1a**,

Table 3
Compounds, parameters, MIC values (μg/ml), observed, and calculated log 1/*C* values of the test set by using Eq. (1)

Compound number	R_1	R_2	R_3	R_4	X	MIC (μg/ml)	IR_2	IR_3	σR_1	B_1R_4	S_r	Observed log 1/*C*	Calculated log 1/*C*	Residuals
1b	H	H	NO_2		–	25	0	0	0	1	2.0546	3.983	3.610	0.373
1d	Br	H	NO_2		–	12.5	0	0	0.23	1	1.5396	4.407	3.954	0.453
1f	H	NO_2	H		–	12.5	0	0	0	1	2.0472	4.284	3.613	0.671
1j	Cl	H	NO_2		CH_2	12.5	0	0	0.23	1	1.4203	4.364	4.003	0.360
2f	C_2H_5	NH_2	H		–	12.5	0	0	−0.15	1	1.3394	4.280	3.817	0.463
2h	Br	H	NH_2		CH_2	25	0	0	0.23	1	1.6455	4.084	3.911	0.173
2i	Cl	H	NH_2		CH_2	12.5	0	0	0.23	1	1.8378	4.316	3.832	0.484
2k	CH_3	NH_2	H		CH_2	12.5	0	0	−0.17	1	1.1520	4.280	3.882	0.398
4k [10]	CH_3	CH_3		CH_3	–	25	1	0	−0.17	1.52	1.8453	3.977	3.761	0.217
4l [10]	OCH_3	CH_3		OCH_3	–	25	1	0	−0.27	1.35	1.9043	4.032	3.744	0.289
4m [10]	OCH_3		CH_3	OCH_3	–	25	0	1	−0.27	1.35	2.2047	4.032	3.607	0.425

1c, **1e**, **1g**, **2b**, **2d**, **2h–2j** were taken on a Waters Micromass ZQ by using ESI(+) method. Elemental analyses of compounds **1d**, **1i–1m**, which were not ionized on Waters Micromass ZQ, were taken on a Leco 932 CHNS-O analyzer. The results of the elemental analyses (C, H, N) were within ±0.4% of the calculated amounts.

*4.1. General procedure for the preparation of 2-(p-substituted phenyl/benzyl)-5(or 6)-nitrobenzoxazoles (**1a–1m**)*

The derivatives were synthesized by heating 0.01 mol appropriate *o*-aminophenol with 0.01 mol suitable acid in 24 g polyphosphoric acid (PPA) and stirring for 2–3 h. At the end of the reaction period, the residue was poured into an ice-water mixture and neutralized with an excess of 10 M NaOH solution extracted with ethyl acetate. Then, this solution was dried over anhydrous sodium sulphate and evaporated under diminished pressure. The residue was boiled with 200 mg charcoal in ethanol and filtered. After the evaporation of solvent in vacuo, the crude product was obtained and recrystallized from ethanol. In the present study, all the compounds except **1b** [42], **1f** [42], and **1h** [43] are new.

*4.2. General procedure for the preparation of 5(or 6)-amino-2-(p-substituted phenyl/benzyl)benzoxazoles (**2a–2l**)*

Compounds **2b**, **2c**, **2g–2j**, and **2l** were obtained from **1c**, **1d**, **1h–1l**, respectively, which (5 mmol) were treated with $NiCl_2 \cdot 6H_2O$ (15 mmol) and Zn (40 mmol) in methanol (25 ml) and refluxing the mixture at 60 °C for 2–4 h. The precipitate was filtered. The crude product was purified by recrystallization from methanol. The crystals were dried in vacuo. Compounds **1a**, **1e**, **1f**, **1g**, and **1m** (5 mmol) in ethanol (50 ml) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd–C (40 mg) until cessation of H_2 uptake to obtain compounds **2a**, **2d–2f**, and **2k**, respectively. The catalyst was filtered on a bed of Celite, washed with ethanol, and the filtrate was concentrated in vacuo. The crude product was purified by recrystallization from ethanol. The crystals were dried in vacuo. In the present study, all the compounds except **2c** [44], **2e–2g** [45], **2k** [37], and **2l** [37] are new.

*4.2.1. 2-(p-t-Butylphenyl)-6-nitrobenzoxazole (**1a**)*

Yield: 53%, mp 164–165 °C. IR (cm^{-1}): 3092, 2964, 1576–1608, 1497, 1528, 1342, 1119–1266, 661–916. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 7.57 (d, 2H, *J* 8.4 Hz), 7.81 (d, 1H, *J* 8.4 Hz), 8.19 (d, 2H, *J* 8.8 Hz), 8.29 (dd, 1H, *J* 8.8, 2.4 Hz), 8.46 (d, 1H, *J* 2.0 Hz). ESI(+) *m/e* 297.25 (M + 1, 100).

*4.2.2. 2-(p-Fluorophenyl)-6-nitrobenzoxazole (**1c**)*

Yield: 54%, mp 158–159 °C. IR (cm^{-1}): 3086, 1520–1600, 1496, 1520, 1343, 1123–1288, 1226, 627–922. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.30 (m, 2H), 7.84 (d, 1H, *J* 8.4 Hz), 8.28–8.35 (m, 3H), 8.49 (d, 1H, *J* 2.0 Hz). ESI(+) *m/e* 259.11 (M + 1, 100).

*4.2.3. 2-(p-Bromophenyl)-6-nitrobenzoxazole (**1d**)*

Yield: 51%, mp 162–164 °C. IR (cm^{-1}): 3099, 1593–1618, 1480, 1548, 1345, 1125–1280, 1073, 604–921. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72–7.74 (m, 2H), 7.85 (d, 1H, *J* 9.2 Hz), 8.15–8.18 (m, 2H), 8.35 (dd, 1H, *J* 8.8, 2.4 Hz), 8.50 (d, 1H, *J* 2.0 Hz). Anal. Found: C, 48.12; H, 2.196; N, 8.673. Calcd for $C_{13}H_7N_2O_3Br$: C, 48.93; H, 2.21; N, 8.78.

*4.2.4. 2-(p-Ethylphenyl)-6-nitrobenzoxazole (**1e**)*

Yield: 66%, mp 116–118 °C. IR (cm^{-1}): 3103, 2969, 1518–1607, 1497, 1551, 1343, 1124–1270, 733–921. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29–1.33 (m, 3H), 2.77 (q, 2H, *J* 7.6 Hz), 7.41 (d, 2H, *J* 8.4 Hz), 7.83 (d, 1H, *J* 8.8 Hz), 8.2 (d, 2H, *J* 8.4 Hz), 8.31–8.34 (m, 1H), 8.49 (d, 1H, *J* 2.0 Hz). ESI(+) *m/e* 269.17 (M + 1, 100).

*4.2.5. 2-(p-Ethylphenyl)-5-nitrobenzoxazole (**1g**)*

Yield: 70%, mp 128–130 °C. IR (cm^{-1}): 3036, 2969, 1526–1616, 1498, 1526, 1347, 1126–1267, 660–944. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, *J* 7.6 Hz), 2.77 (q, 2H, *J* 7.6 Hz), 7.40 (d, 2H, *J* 8.0 Hz), 7.67 (d, 1H, *J* 8.8 Hz), 8.18 (d, 2H, *J* 8.0 Hz), 8.31 (dd, 1H, *J* 9.2, 2.4 Hz), 8.63 (d, 1H, *J* 2.0 Hz). ESI(+) *m/e* 269.17 (M + 1, 100).

*4.2.6. 2-(p-Bromobenzyl)-6-nitrobenzoxazole (**1i**)*

Yield: 52%, mp 173–175 °C. IR (cm^{-1}): 3107, 1520–1616, 1485, 1520, 1344, 1145–1272, 690–941, 1011. ^1H NMR (400 MHz, $CDCl_3$): δ 4.61 (s, 2H), 7.39 (dd, 2H, *J* 8.0, 2.4 Hz), 7.58 (dd, 2H, *J* 8.4, 2.8 Hz), 7.92 (dd, 1H, *J* 8.8, 2.8 Hz), 8.27 (dd, 1H, *J* 8.8, 2.4 Hz), 8.67 (d, 1H, *J* 2.0 Hz). Anal. Found: C, 50.12; H, 2.649; N, 8.357. Calcd for $C_{14}H_9N_2O_3Br$: C, 50.48; H, 2.72; N, 8.41.

*4.2.7. 2-(p-Chlorobenzyl)-6-nitrobenzoxazole (**1j**)*

Yield: 75%, mp 119–121 °C. IR (cm^{-1}): 3107, 1524–1617, 1488, 1524, 1343, 1090–1273, 1090, 622–942. ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (s, 2H), 7.35 (s, 4H), 7.78 (dd, 1H, *J* 8.8, 2.8 Hz), 8.29 (dd, 1H, *J* 8.0, 2.0 Hz), 8.40 (d, 1H, *J* 2.8 Hz). Anal. Found: C, 57.77; H, 2.972; N, 9.625. Calcd for $C_{14}H_9N_2O_3Cl$: C, 58.25; H, 3.14; N, 9.70.

*4.2.8. 2-(p-Fluorobenzyl)-6-nitrobenzoxazole (**1k**)*

Yield: 60%, mp 109–110 °C. IR (cm^{-1}): 3105, 1510–1605, 1462, 1095–1307, 1344, 1213, 664–950. ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (s, 2H), 7.06 (m, 2H), 7.37 (m, 2H), 7.77 (dd, 1H, *J* 8.8, 1.2 Hz), 8.27 (m, 1H), 8.39 (d, 1H, *J* 1.6 Hz). Anal. Found: C, 61.19; H, 3.20; N, 10.18. Calcd for $C_{14}H_9N_2O_3F$: C, 61.77; H, 3.33; N, 10.29.

*4.2.9. 2-(p-Fluorobenzyl)-5-nitrobenzoxazole (**1l**)*

Yield: 81%, mp 88–90 °C. IR (cm^{-1}): 3104, 1507–1618, 1459, 1531, 1349, 1217, 1092–1276, 657–958. ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (s, 2H), 7.31 (m, 2H), 7.37 (m,

2H), 7.59 (d, 1H, *J* 8.0 Hz), 8.29 (dd, 1H, *J* 8.8, 2.4 Hz), 8.59 (d, 1H, *J* 2.0 Hz). Anal. Found: C, 60.95; H, 3.225; N, 10.20. Calcd for $C_{14}H_9N_2O_3F$: C, 61.77; H, 3.33; N, 10.29.

*4.2.10. 2-(p-Methylbenzyl)-5-nitrobenzoxazole (**1m**)*

Yield: 64%, mp 98–100 °C. IR (cm^{-1}): 2919, 1535–1617, 1456, 1535, 1345, 1131–1257, 668–955. ^1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 4.29 (s, 2H), 7.20 (d, 2H, *J* 8.0 Hz), 7.28 (dd, 2H, *J* 8.0, 2.8 Hz), 7.57 (d, 1H, *J* 9.2 Hz), 8.28 (dd, 1H, *J* 9.2, 2.4 Hz), 8.50 (d, 1H, *J* 2.0 Hz). Anal. Found: C, 66.72; H, 4.365; N, 10.31. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44.

*4.2.11. 6-Amino-2-(p-t-butylphenyl)benzoxazole (**2a**)*

Yield: 61%, mp 188–190 °C. IR (cm^{-1}): 3411, 3202, 2951, 1624, 1449, 1111–1267, 699–948. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 5.51 (s, 2H), 6.64 (dd, 1H, *J* 8.4, 2.0 Hz), 6.82 (s, 1H), 7.39 (d, 1H, *J* 8.4 Hz), 7.57 (d, 2H, *J* 8.4 Hz), 8.01 (d, 2H, *J* 8.0 Hz). ESI(+) *m/e* 269.17 (M + 1, 100).

*4.2.12. 6-Amino-2-(p-fluorophenyl)benzoxazole (**2b**)*

Yield: 45%, mp 224–225 °C. IR (cm^{-1}): 3400–3309, 3060, 1557–1633, 1497, 1130–1293, 1120, 651–948. ^1H NMR (400 MHz, $CDCl_3$): δ 5.49 (s, 2H), 6.65 (dd, 1H, *J* 8.4, 2.0 Hz), 6.83 (d, 1H, *J* 1.6 Hz), 7.40 (m, 3H), 8.11–8.15 (m, 2H). ESI(+) *m/e* 229.18 (M + 1, 100).

*4.2.13. 6-Amino-2-(p-ethylphenyl)benzoxazole (**2d**)*

Yield: 62%, mp 198–200 °C. IR (cm^{-1}): 3401, 2958, 1634, 1495, 1143, 824–840. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* 7.6 Hz), 2.68 (q, 2H, *J* 8.0 Hz), 5.44 (s, 2H), 6.64 (dd, 1H, *J* 8.4, 2.0 Hz), 6.81 (d, 1H, *J* 2.0 Hz), 7.39 (d, 3H, *J* 8.4 Hz), 7.99 (dd, 2H, *J* 8.4, 1.6 Hz). ESI(+) *m/e* 239.22 (M + 1, 100).

*4.2.14. 6-Amino-2-(p-bromobenzyl)benzoxazole (**2h**)*

Yield: 59%, mp 274–275 °C (decompose). IR (cm^{-1}): 3060, 2820, 1621, 1495, 1118–1259, 1089, 704–955. ^1H NMR (400 MHz, $CDCl_3$): δ 4.35 (s, 2H), 7.27–7.37 (m, 5H), 7.63 (d, 1H, *J* 2.0 Hz), 7.77 (d, 1H, *J* 8.4 Hz). Anal. Found: C, 54.86; H, 4.142; N, 9.289. Calcd for $C_{14}H_{11}N_2OBr$: C, 55.47; H, 3.66; N, 9.24.

*4.2.15. 6-Amino-2-(p-chlorobenzyl)benzoxazole (**2i**)*

Yield: 58%, mp 210–212 °C. IR (cm^{-1}): 3024, 2827, 2606, 2544, 1624, 1569, 1487, 1261–1119, 1092, 954–705, 600. ^1H NMR (400 MHz, DMSO + $CDCl_3$): δ 4.20 (s, 2H), 7.15–7.35 (m, 4H), 7.30–7.40 (dd, 1H, *J* 1.92, 8.42 Hz), 7.53 (s, 2H), 7.55–7.65 (d, 1H, *J* 8.43 Hz), 7.65–7.775 (d, 1H, *J* 1.77 Hz). ESI(+) *m/e* 259 (M + 1), 225 (100%), 147 (100%).

*4.2.16. 6-Amino-2-(p-fluorobenzyl)benzoxazole (**2j**)*

Yield: 45%, mp 115 °C. IR (cm^{-1}): 3343, 1631, 1567, 1509, 1494, 1272–1018, 957–736. ^1H NMR (400 MHz, $CDCl_3$): δ 3.70–3.85 (s, 2H), 4.20–4.30 (s, 2H), 6.60–6.70 (dd, 1H, *J* 8.43, 2.02 Hz), 6.75–6.80 (d, 1H, *J* 1,99 Hz), 7.00–7.10 (t, 2H, *J* 8.65 Hz), 7.30–7.40 (q, 2H, *J* 8.40 Hz), 7.40–7.45 (d, 1H, *J* 8.43 Hz). ESI(+) *m/e* 243 (M + 1, 100), 147 (100%).

4.3. Microbiology

Standard strains of *K. pneumoniae* RSHM 574, *P. aeruginosa* ATCC 25853, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, *S. aureus* ATCC 25923, *C. albicans* ATCC 10231 and clinical isolates of these microorganisms that are known to be resistant to various antimicrobial agents were included in the study. Resistance was determined by Kirby–Bauer Disk Diffusion method according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) [46] in the clinical isolates.

Standard powders of rifampicin, ampicillin trihydrate, gentamycin sulphate, ofloxacin, fluconazole and amphotericin B were obtained from the manufacturers. Stock solutions were dissolved in dimethylsulphoxide (ofloxacin), methanol (rifampicin), pH 8 phosphate-buffered saline (PBS) (ampicillin trihydrate) and distilled water (gentamycin sulphate, fluconazole and amphotericin B).

All bacterial isolates were subcultured in MHA plates and incubated overnight at 37 °C and all *Candida* isolates were subcultured in SDA plates at 35 °C for 24–48 h. The microorganisms were passaged at least twice to ensure purity and viability.

The solution of the synthesized compounds and standard drugs were prepared at 400, 200, 100, 50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39 μg/ml concentrations, at 4096, 2048, 1024, 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625 μg/ml concentrations in the wells of microplates by diluting in MHB, respectively. Bacterial susceptibility testing was performed according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) M100-S16 [39,47]. The bacterial suspensions used for inoculation were prepared at 10^5 cfu/ml by diluting fresh cultures at MacFarland 0.5 density (10^7 cfu/ml). Suspensions of the bacteria at 10^5 cfu/ml concentration were inoculated to the twofold diluted solution of the compounds. There were 10^4 cfu/ml bacteria in the wells after inoculations. MHB was used for diluting the bacterial suspension and for twofold dilution of the compound. DMSO (80%), EtOH (20%), methanol, DMSO, PBS, pure microorganisms and pure media were used in control wells. A 10 μl bacteria inoculum was added to each well of the microdilution trays. The trays were incubated at 37 °C in a humid chamber and MIC endpoints were read after 24 h of incubation. All organisms were tested in triplicate in each run of the experiments. The lowest concentration of the compound that completely inhibits macroscopic growth was determined and minimum inhibitory concentrations (MICs) were reported. All *Candida* isolates were subcultured in SDA plates, and incubated at 35 °C for 24–48 h prior to antifungal susceptibility testing, and passaged at least twice to ensure purity and viability. Susceptibility testing was performed in RPMI-1640 medium with L-glutamine buffered to pH 7 with MOPS and culture suspensions were prepared through the guideline of

CLSI M27-A [48]. The yeast suspensions used for inoculation were prepared at 10^4 cfu/ml by diluting fresh cultures at MacFarland 0.5 density (10^6 cfu/ml). Suspensions of the yeast at 10^4 cfu/ml concentration were inoculated to the twofold diluted solution of the compounds. There were 10^3 cfu/ml bacteria in the wells after inoculations. A 10 μl yeast inoculum was added to each well of the microdilution trays. The trays were incubated at 35 °C in a humid chamber and MIC endpoints were read after 48 h of incubation. All organisms were tested in triplicate in each run of the experiments. The lowest concentration of the compound that completely inhibits macroscopic growth was determined and minimum inhibitory concentrations (MICs) were reported.

4.4. QSAR analysis

Chemical structures and antibacterial activity against Gram-positive bacteria *B. subtilis* ATCC 6033 strains of the previously [10,38] and newly synthesized compounds shown as MIC values are given in Tables 2 and 3. The potency was defined as log 1/*C* where *C* was the MIC value expressed in molar concentration units. A training set including compounds **1a**, **1c**, **1e**, **1g**–**1i**, **1k**–**1m**, **2a**–**2e**, **2g**, **2j**, **2l**, **3a**–**3f** [38], **4a**–**4j** [10] and a test set consisting in compounds **1b**, **1d**, **1f**, **1j**, **2f**, **2h**, **2i**, **2k**, **4k**–**4m** [10] were considered. The variables used as independent descriptors in the QSAR analysis were hydrophobic, electronic, steric, and structural parameters. The structural variable I_x expresses a value of 1 for the presence of CH_2 group as a bridge element and 0 for the absence of it between phenyl and benzoxazole moiety. The screened physicochemical parameters in this QSAR study are log *P*, π for the hydrophobic effects, S_r, σ, *F* (field effect), *R* (resonance effect), as the electronic influences and Verloop's STERIMOL descriptors (*L*, B_1, B_4) for the steric interactions of the substituents R_1, R_2, R_3 and R_4. Additionally, H-bond donor, H-bond acceptor and the other Free–Wilson type structural indicator variables were also used for positions R_2 and R_3 such as IR_2a (IR_3a), IR_2b (IR_3b), IR_2c (IR_3c) represented a value of 1 for the presence of NO_2, NH_2, CH_3 and 0 for the absence, respectively. Values of the physicochemical parameters used in this QSAR study were taken from the Table of Hansch and Leo [49] except log *P* and S_r which were calculated by using the Acclerys's Cerius2 [50] program. The values of the parameters used in the correlation equation related to the activity among the candidate set of variables in the training set are shown in Table 2. Multivariable regression analysis (MRA) of the QSAR study was run on a PC using the BILIN [51].

MRA that involves finding the best fit of dependent variable (antibacterial activity) to a combination of independent variables (descriptors) is used by the least squares method. The tabulated $F_{(5,\ 30,\ 0.95)}$ and $F_{(5,\ 25,\ 0.95)}$ are 2.53, 2.60, respectively, whereas the overall *F* test values for the obtained equation was 31.028 which is statistically significant at the 5% level of probability [52]. The statistically significant correlation equation (Eq. (1)) obtained from MRA to describe the QSAR analysis is given below.

Table 4
Correlation matrix of the variables used in Eq. (1)

	IR_2	IR_3	σR_1	B_1R_4	S_r
IR_2	1.000	0.090	0.137	0.104	0.011
IR_3		1.000	0.000	0.223	0.045
σR_1			1.000	0.000	0.001
B_1R_4				1.000	0.042
S_r					1.000

$$\log 1/C = +0.329(\pm0.12)IR_{2c} + 0.315(\pm0.13)IR_{3c} + 0.577(\pm0.24)\sigma R_1 - 0.287(\pm0.18)B_1R_4 - 0.410(\pm0.12)S_r + 4.740(\pm0.25) \quad (1)$$

$n = 33$; $r = 0.923$; $s = 0.108$; $F = 31.028$; $Q^2 = 0.783$; s-PRESS = 0.131.

In the equation, the figures in parentheses are the standard errors of the regression coefficients, *n* is the number of compounds, *r* is the correlation coefficient, *F* is the significance test and *s* is the standard error of estimate.

In order to judge the validity of the predictive power of the QSAR analysis, the cross-validation method was also applied

Table 5
Observed and predicted log 1/*C* values with residuals obtained from Eq. (1)

Compound number	Observed log 1/*C*	Predicted log 1/*C*	Residuals
1a	3.773	3.568	0.205
1c	3.713	3.856	−0.143
1e	3.730	3.748	−0.018
1g	3.730	3.754	−0.024
1h	3.713	3.855	−0.142
1i	4.125	3.953	0.172
1k	4.338	4.288	0.050
1l	4.338	4.288	0.050
1m	3.730	3.707	0.022
2a	4.027	4.055	−0.027
2b	3.659	3.814	−0.155
2c	4.063	3.912	0.151
2d	3.678	3.849	−0.170
2e	4.226	4.178	0.048
2g	3.960	3.812	0.148
2j	3.685	3.765	−0.079
2l	3.685	3.771	−0.086
3a [38]	4.224	4.131	0.092
3b [38]	4.290	4.288	0.002
3c [38]	4.363	4.288	0.075
3d [38]	4.609	4.713	−0.104
3e [38]	4.290	4.276	0.014
3f [38]	4.363	4.276	0.087
4a [10]	3.989	3.892	0.097
4b [10]	3.981	4.078	−0.097
4c [10]	3.959	4.012	−0.054
4d [10]	4.007	3.974	0.033
4e [10]	4.046	4.091	−0.045
4f [10]	3.989	3.879	0.110
4g [10]	3.981	4.049	−0.068
4h [10]	3.959	3.999	−0.041
4i [10]	4.046	4.078	−0.031
4j [10]	3.676	3.747	−0.071

to the original data set by removing a compound from the data in such a way that each observation (compound) is deleted only once. For each reduced data set a model was developed and the response values of the deleted observations were predicted from this model and finally the resulting PRESS (predictive residual sum of squares) and Q^2 (the square of predictive power of coefficient) were calculated for the equation [53,54]. The search for the simple correlation coefficients which are given in Table 4 also reveals that there is no intercorrelation between the independent variables in any case entered in the correlation equations. The predicted log 1/*C* values with residuals of the training set determined from equation are given in Table 5.

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