Med Chem Res (2016) 25:1794–1812
DOI 10.1007/s00044-016-1603-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, antimicrobial activity, and QSAR studies on substituted oxadiazaboroles

Meryem Pir[1] · Hikmet Agirbas[1] · Fatma Budak[2] · Merve Ilter[1]

Received: 24 February 2016 / Accepted: 28 May 2016 / Published online: 7 July 2016

Abstract This paper presents the synthesis and in vitro antimicrobial activity studies of 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4**) and 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7**). The antimicrobial activities of the compounds were assessed against a panel of microorganisms including *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Streptococcus mutans,* and *Candida albicans*. Some of the oxadiazaboroles exhibited fair activities against these microorganisms. The *p*MIC values of the compounds were first correlated with Hammett polar substituent constant (σ) and lipophilic constant (π) and statistically significant correlations were obtained. Additionally, the *p*MIC values of the compounds were correlated with σ, π, and some theoretical descriptors and fair 2D-quantitative structure–activity relationship models with clogP, surface area approx, E_{LUMO}, μ, and E_{HOMO} as independent variables were obtained. Application of training and test sets to quantitative structure–activity relationship models gave good results. Squared correlation matrix of the theoretical descriptors used in the quantitative structure–activity relationship study showed no correlation between the descriptors.

Keywords Oxadiazaborole derivatives · Antimicrobial activity · QSAR

Electronic supplementary material The online version of this article (doi:10.1007/s00044-016-1603-1) contains supplementary material, which is available to authorized users.

✉ Hikmet Agirbas
agirbash@yahoo.com

[1] Department of Chemistry, Kocaeli University, Umuttepe 41300 Izmit, Turkey

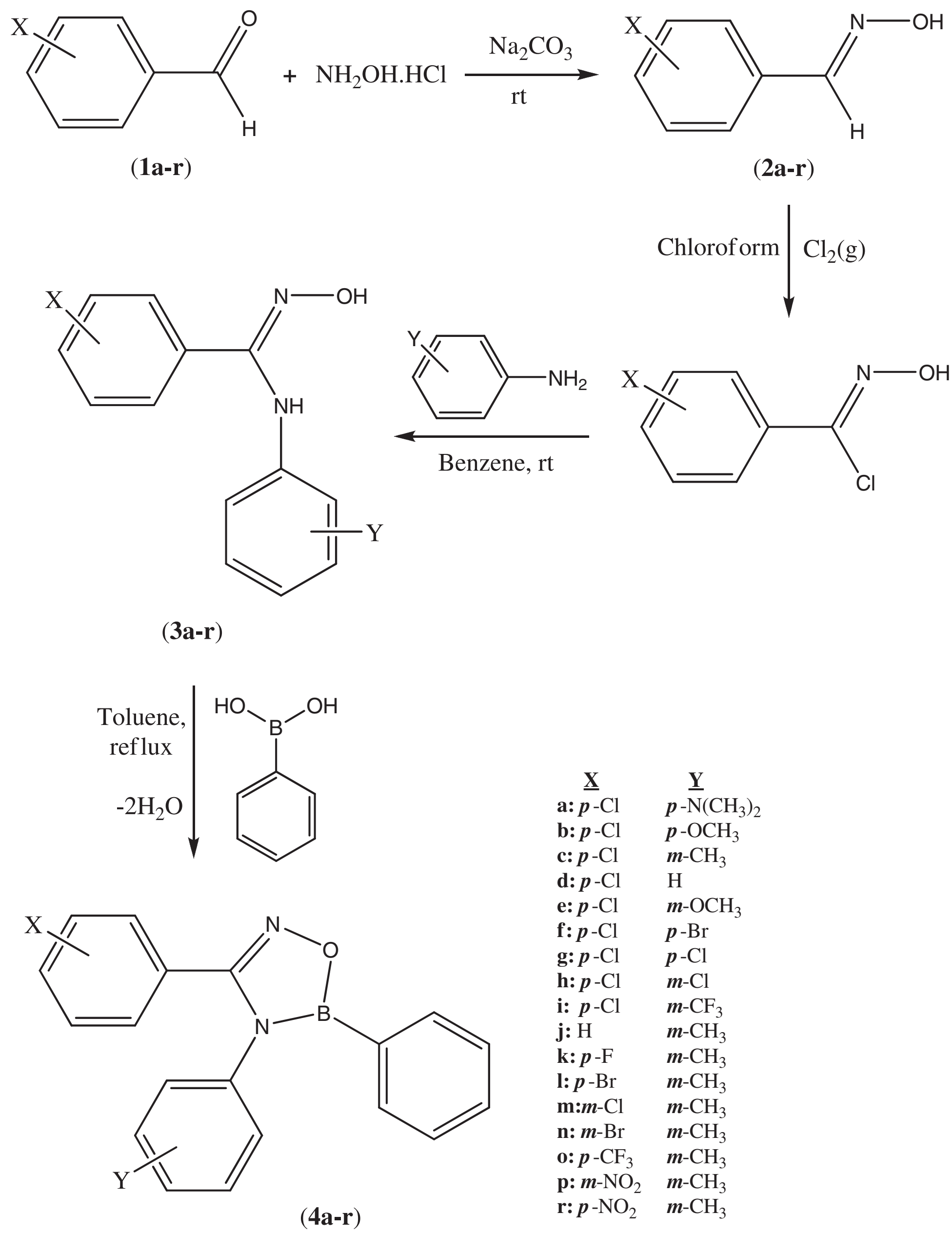
[2] Department of Microbiology, Kocaeli University, Umuttepe 41300 Izmit, Turkey

Introduction

Drug resistance is a natural response that is caused by antibiotic use. Hence, new drugs are needed to struggle with this resistance. Boron compounds are underexploited in medicinal chemistry and have tremendous potential in drug discovery. In the literature, boron-containing compounds have been identified as the agents that have potential biological activities (Ciaravino et al., 2013). Among these, it is worth mentioning the activities of the following compounds: heterocyclic aminoboron compounds (anti-tuberculosis agents) (Campbell-Verduyn et al., 2014), boron-containing GSK2251052 (antimicrobial agent) (Ross et al., 2013), oxaborole compounds (antibacterial prototypes) (Li et al., 2013), α-amino cyclic boronates (inhibitors of HCV NS3 protease) (Li et al., 2010), benzoxaborole compounds (anti-inflammatory agents) (Akama et al., 2009), and boronic acid esters (antibacterial agent with anti-inflammatory activity) (Baker et al., 2006).

Some heterocyclic boron compounds that contain B–N bonds also show biological activity (Das et al., 2012; Jabbour et al., 2004). Oxadiazaboroles possess a B–N bond and are readily obtained from an amidoxime and a boronic acid. On the basis of the biological activity displayed by other heterocyclic systems that contain B–N bonds, oxadiazaboroles should be interesting candidates for biological activity. Considering the structural characteristics of the 1,2,4,5-oxadiazaboroles, and the existence of the oxygen-, nitrogen-, and boron-containing five-membered nonaromatic heterocycles

Scheme 1 Synthesis of compounds (**4a**–**r**)



	X	Y
a:	*p*-Cl	*p*-$N(CH_3)_2$
b:	*p*-Cl	*p*-OCH_3
c:	*p*-Cl	*m*-CH_3
d:	*p*-Cl	H
e:	*p*-Cl	*m*-OCH_3
f:	*p*-Cl	*p*-Br
g:	*p*-Cl	*p*-Cl
h:	*p*-Cl	*m*-Cl
i:	*p*-Cl	*m*-CF_3
j:	H	*m*-CH_3
k:	*p*-F	*m*-CH_3
l:	*p*-Br	*m*-CH_3
m:	*m*-Cl	*m*-CH_3
n:	*m*-Br	*m*-CH_3
o:	*p*-CF_3	*m*-CH_3
p:	*m*-NO_2	*m*-CH_3
r:	*p*-NO_2	*m*-CH_3

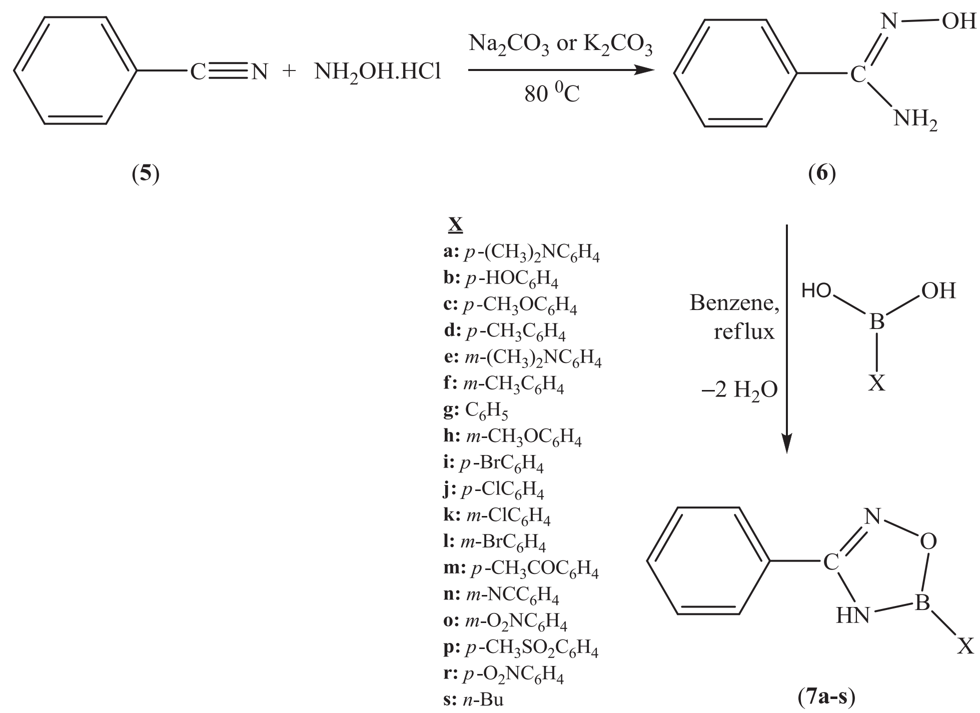
system, it is reasonable to expect physiological activities from these compounds. Therefore, the study of substituent effects on the antimicrobial activity of the oxadiazaboroles was thought to give a better understanding of their structure–antimicrobial activity relationships.

Some oxadiazaboroles were synthesized from amidoximes and phenylboronic acid (Yale, 1971; Dürüst et al., 2007). However, to our knowledge, no antimicrobial activity data of 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4**) and 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7**) was reported. We synthesized some series of new oxadiazaborole derivatives (Schemes 1 and 2) and determined their antimicrobial activities against some bacteria and fungi. We also applied 1D-quantitative structure–activity relationship (QSAR) and 2D-QSAR analysis to observe the relations of the molecular descriptors with the activities.

Synthesis

Synthesis of compounds (**2–4**, Scheme 1) starts with *p*-chlorobenzaldehyde, which was reacted with hydroxylamine hydrochloride to give *p*-chlorobenzaldehyde oxime (**2a–i**). Then, chlorination was followed: *p*-chlorobenzaldehyde oxime was reacted with chlorine gas in anhydrous chloroform at 0 °C, until a certain weight increase was obtained, to have 4-chloro-*N*-hydroxybenzimidoyl chloride. The solution was kept in the fridge overnight. Then the solvent was evaporated.

Scheme 2 Synthesis of compounds (**7a–s**)



The residue, 4-chloro-*N*-hydroxybenzimidoyl chloride, was reacted with substituted anilines in benzene at room temperature to give *N*-substituted-*p*-chlorobenzamidoximes (**3a–i**). *N*-(*m*-tolyl)-substituted benzamidoximes (**3j–r**) were synthesized by the literature method (Sümengen and Pelter, 1983). Then the compounds (**3a–r**) were reacted with phenylboronic acid in toluene to yield the corresponding 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4a–r**).

Synthesis of compounds **6** and **7**, outlined in Scheme 2, started with benzonitrile (**5**), which was reacted with hydroxylamine hydrochloride to afford benzamidoxime (**6**). This was followed by cyclodehydration reaction: benzamidoxime (**6**) was reacted with boronic acid derivatives in benzene to yield the corresponding 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7a–s**).

All the synthesized compounds were analyzed by their infrared radiation (IR), ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) spectra and the purity of compounds **4a–r** and **7a–s** was checked by elemental analysis.

Benzamidoxime was synthesized according to the literature methods A (Krüger, 1885) and B (Gosenca et al., 2013). Method B gives less amide impurity and high yield.

Biological activity

The synthesized compounds (**4** and **7**) have been evaluated for their in vitro antimicrobial activity against a panel of microorganisms, including three gram-positive bacteria (*S. aureus*, *E. faecalis*, and *S. mutans*), two gram-negative bacteria (*P. aeruginosa* and *E. coli*) and one fungi (*C. albicans*) by their minimal inhibitory concentrations (MIC) via broth microdilution susceptibility tests (CLSI, 2002, 2005, 2006). The biological activities of all the compounds are given in Table 1 and shown graphically in Figs. 1 and 2. Compounds **7k**, **7l**, and **7o** have been found to be the most active derivatives against fungi (*C. albicans*) at MIC value of 25 µg/mL among the tested compounds. All the compounds exhibited antimicrobial activity with MIC values between 25–800 µg/mL against *C. albicans*. **4i** is the most active compound against *S. aureus* (MIC 25 µg/mL). Additionally, compounds **4f**, **4g**, **4h**, **4i**, **4o**, and **7n** showed activity (MIC 25 µg/mL) against *S. mutans*. The results show that 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7**) are the most active derivatives against *P. aeruginosa* among the tested compounds (MIC 12.5–25 µg/mL). All compounds exhibited antibacterial activity with MIC values between 25–800 µg/mL against *S. aureus*, with MIC values between 50–800 µg/mL against *E. coli*; with MIC values between 12.5–200 µg/mL against *P. aeruginosa*; with MIC values between 50–800 µg/mL against *E. faecalis*; and with MIC values between 25–100 µg/mL against *S. mutans*.

QSAR analysis

We have carried out linear regression studies of molecular descriptors against the antimicrobial activity of compounds

Table 1 Antimicrobial activities of compounds (**4a–r**) and (**7a–s**)

Compound (substituents: X, Y)	Antibacterial and antifungal activities, μg/mL (μmol/mL)					
	S. aureus ATCC 25983	*E. faecalis* ATCC 29212	*P. aeruginosa* ATCC 27853	*E. coli* ATCC 25922	*S. mutans* ATCC 25175	*C. albicans* ATCC 90028
Ampicillin	0.78	0.78	–	6.25	≤0.25	–
Ciprofloxacin	0.25	0.25	0.25	0.04	–	–
4a (*p*-Cl, *p*-$N(CH_3)_2$)	800 (2.13)	100 (0.27)	100 (0.27)	800 (2.13)	50 (0.13)	800 (2.13)
4b (*p*-Cl, *p*-OCH_3)	800 (2.21)	800 (2.21)	200 (0.55)	800 (2.21)	50 (0.14)	800 (2.21)
4c (*p*-Cl, *m*-CH_3)	100 (0.29)	100 (0.29)	50 (0.14)	200 (0.58)	50 (0.14)	100 (0.29)
4d (*p*-Cl, H)	100 (0.30)	200 (0.60)	50 (0.15)	200 (0.60)	50 (0.15)	100 (0.30)
4e (*p*-Cl, *m*-OCH_3)	100 (0.28)	400 (1.10)	50 (0.14)	400 (1.10)	50 (0.14)	100 (0.28)
4f (*p*-Cl, *p*-Br)	200 (0.49)	200 (0.49)	100 (0.24)	200 (0.49)	25 (0.06)	400 (0.97)
4g (*p*-Cl, *p*-Cl)	200 (0.54)	200 (0.54)	50 (0.14)	200 (0.54)	25 (0.07)	800 (2.18)
4h (*p*-Cl, *m*-Cl)	50 (0.14)	50 (0.14)	50 (0.14)	100 (0.27)	25 (0.07)	50 (0.14)
4i (*p*-Cl, *m*-CF_3)	25 (0.06)	50 (0.12)	50 (0.12)	200 (0.50)	25 (0.06)	400 (1.00)
4j (H, *m*-CH_3)	200 (0.64)	100 (0.32)	50 (0.16)	100 (0.32)	50 (0.16)	200 (0.64)
4k (*p*-F, *m*-CH_3)	200 (0.61)	100 (0.30)	50 (0.15)	100 (0.30)	50 (0.15)	200 (0.61)
4l (*p*-Br, *m*-CH_3)	50 (0.13)	50 (0.13)	50 (0.13)	400 (1.02)	50 (0.13)	100 (0.26)
4m (*m*-Cl, *m*-CH_3)	50 (0.14)	50 (0.14)	50 (0.14)	100 (0.29)	50 (0.14)	100 (0.29)
4n (*m*-Br, *m*-CH_3)	50 (0.13)	50 (0.13)	50 (0.13)	100 (0.26)	50 (0.13)	100 (0.26)
4o (*p*-CF_3, *m*-CH_3)	50 (0.13)	50 (0.13)	50 (0.13)	100 (0.26)	25 (0.07)	100 (0.26)
4p (*m*-NO_2, *m*-CH_3)	200 (0.56)	200 (0.56)	100 (0.28)	100 (0.28)	100 (0.28)	200 (0.56)
4r (*p*-NO_2, *m*-CH_3)	200 (0.56)	200 (0.56)	100 (0.28)	200 (0.56)	50 (0.14)	200 (0.56)
7a (*p*-$(CH_3)_2NC_6H_4$)	100 (0.38)	50 (0.19)	12.5 (0.047)	50 (0.19)	100 (0.38)	200 (0.75)
7b (*p*-HOC_6H_4)	100 (0.42)	100 (0.42)	12.5 (0.052)	50 (0.21)	100 (0.42)	200 (0.84)
7c (*p*-$CH_3OC_6H_4$)	100 (0.39)	100 (0.39)	12.5 (0.050)	50 (0.20)	100 (0.39)	200 (0.79)
7d (*p*-$CH_3C_6H_4$)	100 (0.42)	100 (0.42)	12.5 (0.052)	100 (0.42)	100 (0.42)	200 (0.84)
7e (*m*-$(CH_3)_2NC_6H_4$)	100 (0.38)	100 (0.38)	12.5 (0.047)	50 (0.19)	50 (0.19)	200 (0.75)
7f (*m*-$CH_3C_6H_4$)	100 (0.42)	200 (0.84)	12.5 (0.052)	50 (0.21)	50 (0.21)	200 (0.84)
7g (C_6H_5)	100 (0.45)	100 (0.45)	12.5 (0.057)	50 (0.23)	100 (0.45)	200 (0.90)
7h (*m*-$CH_3OC_6H_4$)	100 (0.39)	100 (0.39)	12.5 (0.048)	100 (0.39)	50 (0.20)	200 (0.79)
7i (*p*-BrC_6H_4)	50 (0.17)	100 (0.33)	12.5 (0.042)	50 (0.17)	50 (0.17)	200 (0.66)
7j (*p*-ClC_6H_4)	50 (0.19)	100 (0.38)	12.5 (0.047)	50 (0.19)	50 (0.19)	100 (0.38)
7k (*m*-ClC_6H_4)	100 (0.38)	100 (0.38)	12.5 (0.047)	50 (0.19)	50 (0.19)	25 (0.09)
7l (*m*-BrC_6H_4)	50 (0.17)	100 (0.33)	12.5 (0.041)	100 (0.33)	50 (0.17)	25 (0.08)
7m (*p*-$CH_3COC_6H_4$)	50 (0.19)	100 (0.38)	12.5 (0.047)	50 (0.19)	50 (0.19)	200 (0.75)
7n (*m*-NCC_6H_4)	50 (0.20)	100 (0.40)	12.5 (0.050)	50 (0.20)	25 (0.10)	100 (0.40)
7o (*m*-$O_2NC_6H_4$)	50 (0.19)	50 (0.19)	12.5 (0.046)	100 (0.37)	50 (0.19)	25 (0.09)
7p (*p*-$CH_3SO_2C_6H_4$)	100 (0.33)	100 (0.33)	25 (0.082)	100 (0.33)	50 (0.17)	200 (0.66)
7r (*p*-$O_2NC_6H_4$)	50 (0.19)	100 (0.37)	12.5 (0.047)	50 (0.19)	50 (0.19)	100 (0.37)
7s (*n*-Bu)	100 (0.50)	100 (0.50)	12.5 (0.062)	50 (0.25)	50 (0.25)	200 (0.98)
Fluconazole	–	–	–	–	–	0.25

4a–r and **7a**–**s**. The results of the biological activities, reported as MIC values (Table 1), were converted to *p*MIC (– logMIC) on a molar basis and used as dependent variables to obtain the linear relationship. The *p*MIC values of compounds were first correlated with Hammett polar substituent constant (σ) (Hansch et al., 1991) or lipophilic constant (π) (Hansch et al., 1973), and statistically significant correlations were obtained (Table 2; Eqs. 2, 4, 5, 8, 14, 16, and 18). However, by application of the 2D statistical method, the correlation of *p*MIC values against σ and π independent variables gave two statistically significant 2D-QSAR models (Table 2; Eqs. 1 and 17).

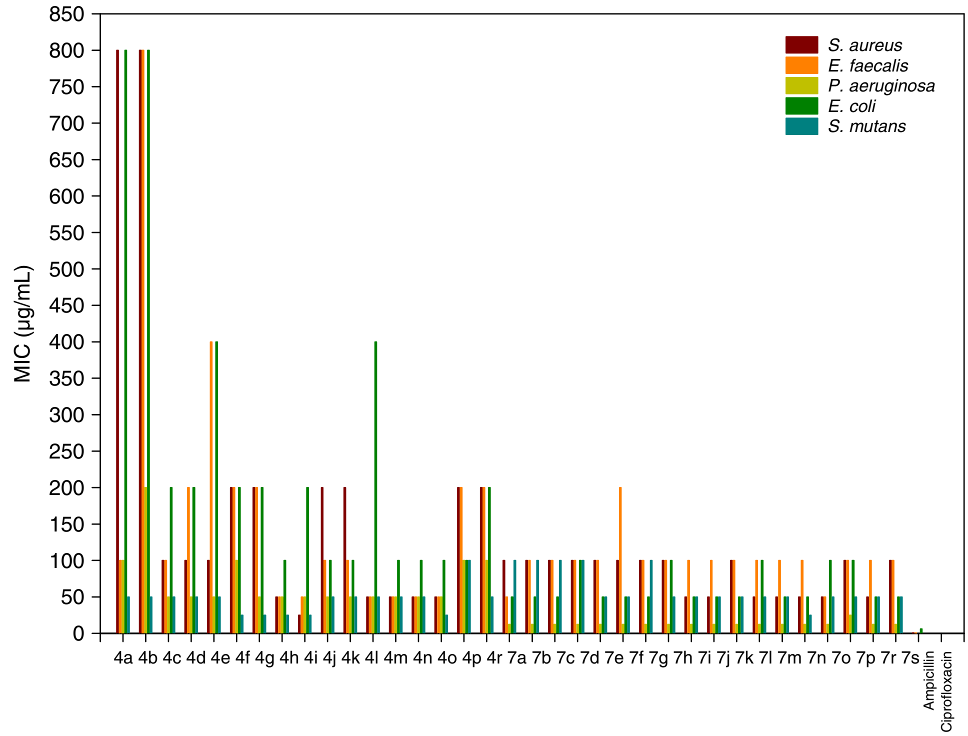


Fig. 1 Comparable chart for MIC values (μg/mL) of all compounds against bacterias

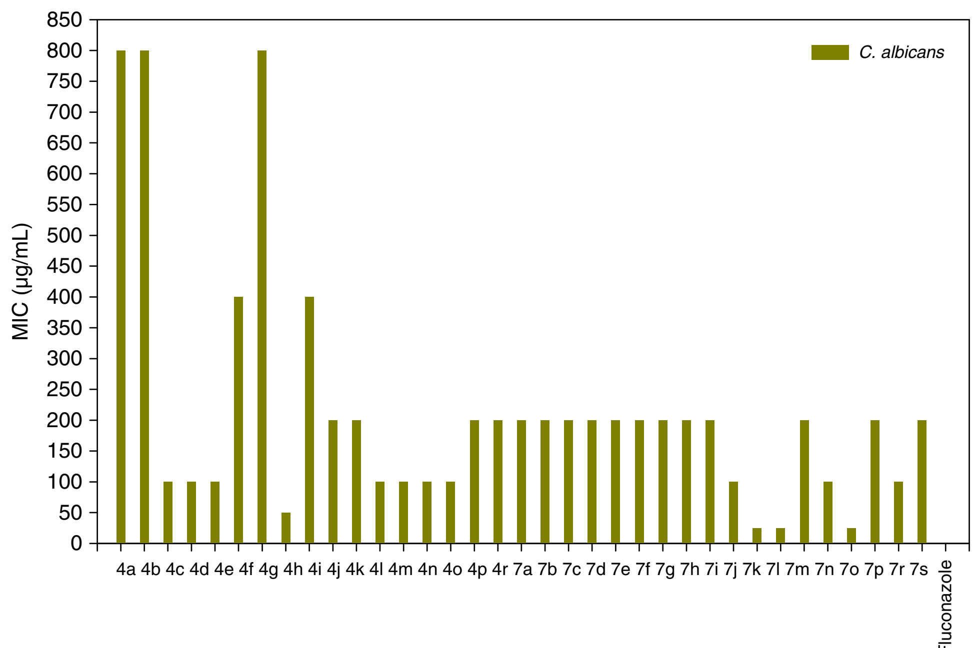


Fig. 2 Comparable chart for MIC values (μg/mL) of all compounds against fungi

Computer aid ranges from molecular design to architectural design (Agirbas, 2015) and also helps to check the experimental data. In order to add theoretical descriptors to the structure–antimicrobial activity relationship study, the geometrical optimization of all the compounds (**4a–r**, **7a–s**) was done by the ab initio (RHF/3-21G) method incorporated in the Hyperchem package (HyperChem, 2002). Theoretical descriptors, namely, surface area approx (SAA), molecular volume (MV), molar refractivity (MR), polarizability (polar), magnitude of dipolar moment (μ), and the calculated log of octanol–water partition coefficient (clogP) of the compounds were also computed by the Hyperchem software (RHF/3-21G) method (Table 3). E_{HOMO} (energies of the highest occupied molecular orbital) and E_{LUMO} (lowest unoccupied molecular orbital) were calculated by Gaussian 03W software (Frisch et al., 2004), using the DFT (B3LYP) method with

Table 2 Significant 2D–QSAR models obtained for antimicrobial activity of 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4a–r**) and 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7a–s**)

Microorganisms	Equations	Regression equation	Statistic parameter						
			n	r	r^2	r^2 adj.	s	P	F
S. aureus	1	$p\text{MIC}_{s.a.} = 0.26(\pm0.07)\sigma + 0.08(\pm0.05)\pi + 0.48(\pm0.03)$	17[a]	0.733	0.537	0.471	0.123	0.0045	8.131
	2	$p\text{MIC}_{s.a.} = 0.63(\pm0.08)\pi + 0.32(\pm0.05)$	8[b]	0.948	0.899	0.882	0.119	0.0003	53.639
	3	$p\text{MIC}_{s.a.} = 0.09(\pm0.05)\text{clogP} - 8.70(\pm2.70)E_{\text{LUMO}} - 1.52(\pm0.59)$	35	0.542	0.294	0.250	0.279	0.0038	6.673
E. faecalis	4	$p\text{MIC}_{E.f.} = 0.54(\pm0.02)\pi + 0.43(\pm0.01)$	8[b]	0.992	0.985	0.983	0.036	<0.0001	418.108
P. aeruginosa	5	$p\text{MIC}_{P.a.} = 0.24(\pm0.05)\pi + 0.69(\pm0.03)$	8[b]	0.884	0.782	0.746	0.072	0.0035	21.594
	6	$p\text{MIC}_{P.a.} = -0.005(\pm0.0005)\text{SAA} + 2.68(\pm0.16)$	35	0.873	0.763	0.756	0.151	<0.0001	106.614
	7	$p\text{MIC}_{P.a.} = 2.01(\pm1.74)E_{\text{HOMO}} - 0.006(\pm0.0006)\text{SAA} + 3.53(\pm0.75)$	35	0.879	0.773	0.759	0.150	<0.0001	54.522
	8	$p\text{MIC}_{P.a.} = 0.08(\pm0.02)\pi + 1.29(\pm0.01)$	17[a]	0.793	0.628	0.604	0.041	0.0001	25.360
E. coli	9	$p\text{MIC}_{E.c.} = -0.004(\pm0.0008)\text{SAA} + 1.60(\pm0.24)$	35	0.645	0.416	0.398	0.223	<0.0001	23.544
	10	$p\text{MIC}_{E.c.} = -0.003(\pm0.0008)\text{SAA} - 3.75(\pm2.19)E_{\text{LUMO}} + 0.68(\pm0.59)$	35	0.682	0.465	0.432	0.216	<0.0001	13.925
S. mutans	11	$p\text{MIC}_{S.m.} = 0.56(\pm0.15)\sigma + 6.76(\pm3.54)E_{\text{LUMO}} + 2.01(\pm0.74)$	17[a]	0.791	0.627	0.573	0.121	0.0010	11.763
	12	$p\text{MIC}_{S.m.} = 0.33(\pm0.07)\sigma - 0.03(\pm0.02)\mu + 0.74(\pm0.10)$	17[a]	0.774	0.599	0.542	0.125	0.0017	10.471
	13	$p\text{MIC}_{S.m.} = 0.004(\pm0.0006)\text{SAA} - 4.72(\pm1.65)E_{\text{LUMO}} - 1.31(\pm0.44)$	35	0.732	0.536	0.507	0.163	<0.0001	18.498
	14	$p\text{MIC}_{S.m.} = 0.41(\pm0.07)\pi + 0.83(\pm0.04)$	9[c]	0.898	0.806	0.778	0.084	0.0010	29.016
	15	$p\text{MIC}_{S.m.} = -3.22(\pm2.04)E_{\text{HOMO}} + 0.003(\pm0.0007)\text{SAA} - 1.49(\pm0.88)$	35	0.677	0.459	0.425	0.176	<0.0001	13.593
	16	$p\text{MIC}_{S.m.} = 0.31(\pm0.07)\sigma + 0.59(\pm0.03)$	17[a]	0.728	0.530	0.498	0.132	0.0009	16.897
C. albicans	17	$p\text{MIC}_{c.a.} = 0.47(\pm0.15)\sigma + 0.28(\pm0.10)\pi + 0.21(\pm0.07)$	17[a]	0.734	0.540	0.474	0.267	0.0043	8.222
	18	$p\text{MIC}_{c.a.} = 0.33(\pm0.05)\pi + 0.27(\pm0.03)$	8[b]	0.936	0.877	0.857	0.070	0.0006	42.955

[a] Compounds (**7a–r**)

[b] Compounds (**4j–r**)

[c] Compounds (**4a–i**)

3-21G basis set (Table 3). Several descriptors (Ferreira et al., 2009) were also calculated as shown below:

$$O(\text{ovality}) = \frac{\text{SA}}{4\pi\left(\frac{3\text{MV}}{4\pi}\right)_{2/3}}$$

$$\chi(\text{electronegativity}) = \frac{E_{\text{HOMO}} - E_{\text{LUMO}}}{2}$$

$$\eta(\text{hardness}) = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2}$$

$$\omega(\text{electrophilicity}) = \frac{\chi^2}{2\eta}$$

$$\eta^{-1}(\text{softness}) = \frac{1}{\eta}$$

When these theoretical descriptors were used as independent variables, seven significant correlation with pMIC values was obtained (Table 2; Eqs. 3, 6, 7, 9, 10, 13, and 15). However, with the application of the 2D statistical method, the correlation of pMIC values against the theoretical descriptors (E_{LUMO} and μ) and σ gave two statistically significant 2D-QSAR models (Table 2; Eqs. 11 and 12). The overall quality of 2D-QSAR models was shown by r and r^2 (correlation coefficients), s (standard deviations) of the regression equations, F value (F-statistical analysis; Fischer test), P (probability value), and n (number of data points). The predictability of each model was assessed by using the cross-validated correlation coefficient (r^2 adj). A value of r^2 adj >0.25 was considered for the structure–reactivity models.

To evaluate the predictive power of the model equations, MIC values were split into the training and test sets. The regression equations of the training sets gave fair internal cross-validation (r^2 adj) values and good coefficient of determination (r^2) values (Table 4). Good predicted values of the test sets were also obtained. The plot of the observed

Table 3 Theoretical descriptors of 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4a–r**) and 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7a–s**) used for the regression analyses

Compound	clogP	SAA ($Å^2$)	MV ($Å^3$)	MR ($Å^3$)	Polar ($Å^3$)	E_{HOMO} (au)	E_{LUMO} (au)	μ (D)	η	$η^{-1}$	ω	χ	*O*
4a	1.19	394.4	340.8	118.69	42.35	−0.3455	−0.1678	6.82	0.177	5.65	0.088	−0.177	1.6718
4b	1.15	366.3	319.6	111.44	39.80	−0.3596	−0.1801	5.67	0.179	5.58	0.089	−0.179	1.6206
4c	2.29	353.5	312.0	109.35	39.17	−0.3753	−0.2144	5.27	0.160	6.25	0.080	−0.160	1.5893
4d	2.14	330.0	295.5	105.07	37.33	−0.3812	−0.2160	5.14	0.165	6.06	0.082	−0.165	1.5383
4e	1.15	363.1	320.1	111.44	39.80	−0.3494	−0.2076	3.91	0.141	7.09	0.070	−0.141	1.6048
4f	2.19	351.8	317.4	112.60	39.96	−0.3609	−0.2179	3.46	0.143	6.99	0.071	−0.143	1.5636
4g	1.92	347.4	310.5	109.78	39.26	−0.3800	−0.2199	2.77	0.160	6.25	0.080	−0.160	1.5669
4h	1.92	347.3	310.4	109.78	39.26	−0.3807	−0.2197	4.62	0.161	6.21	0.080	−0.161	1.5667
4i	2.71	388.7	327.5	110.28	38.89	−0.3854	−0.2206	4.68	0.164	6.09	0.082	−0.164	1.6919
4j	2.52	336.1	296.9	104.63	37.24	−0.3733	−0.2102	5.70	0.163	6.13	0.081	−0.163	1.5618
4k	1.91	341.3	299.4	104.76	37.15	−0.3748	−0.2116	5.23	0.163	6.13	0.081	−0.163	1.5772
4l	2.57	357.9	318.9	112.17	39.87	−0.3710	−0.2097	5.25	0.161	6.21	0.080	−0.161	1.5857
4m	2.29	353.5	311.9	109.35	39.17	−0.3771	−0.2165	4.08	0.160	6.25	0.080	−0.160	1.5896
4n	2.57	357.8	318.9	112.17	39.87	−0.3653	−0.2126	4.49	0.152	6.58	0.076	−0.152	1.5853
4o	3.08	372.4	320.7	109.85	38.80	−0.3786	−0.2203	5.63	0.158	6.33	0.079	−0.158	1.6438
4p	−0.23	364.0	316.0	110.35	39.08	−0.3820	−0.2225	3.58	0.159	6.29	0.079	−0.159	1.6226
4r	−0.23	366.1	315.9	110.35	39.08	−0.3817	−0.2345	6.40	0.147	6.80	0.073	−0.147	1.6323
7a	1.01	298.9	251.2	84.49	30.76	−0.3479	−0.1748	5.33	0.086	11.55	0.043	−0.086	1.5525
7b	0.93	243.7	212.8	72.47	26.38	−0.3781	−0.2045	6.29	0.086	11.52	0.043	−0.086	1.4137
7c	0.96	271.1	230.7	77.24	28.22	−0.3718	−0.1955	6.36	0.088	11.34	0.044	−0.088	1.4910
7d	2.11	258.6	222.9	75.15	27.58	−0.3830	−0.2136	4.67	0.084	11.80	0.042	−0.084	1.4549
7e	1.01	298.9	251.3	84.49	30.76	−0.3401	−0.1890	6.30	0.075	13.24	0.037	−0.075	1.5522
7f	2.11	258.6	222.9	75.15	27.58	−0.3796	−0.2193	5.00	0.080	12.48	0.040	−0.080	1.4550
7g	1.96	235.0	206.1	70.87	25.74	−0.3920	−0.2241	4.72	0.083	11.91	0.041	−0.083	1.3928
7h	0.96	271.1	230.8	77.24	28.22	−0.3784	−0.1967	4.41	0.090	11.00	0.045	−0.090	1.4899
7i	2.01	256.8	228.3	78.40	28.37	−0.3808	−0.2152	5.24	0.082	12.07	0.041	−0.082	1.4218
7j	1.73	252.4	221.3	75.58	27.67	−0.3853	−0.2191	5.69	0.083	12.03	0.041	−0.083	1.4268
7k	1.73	252.3	221.3	75.58	27.67	−0.3788	−0.2260	3.04	0.076	13.08	0.038	−0.076	1.4264
7l	2.01	256.7	228.2	78.40	28.37	−0.3740	−0.2214	3.38	0.076	13.10	0.038	−0.076	1.4221
7m	1.89	280.1	240.6	80.42	29.50	−0.3648	−0.2273	7.59	0.068	14.54	0.034	−0.068	1.4978
7n	1.68	263.7	224.3	75.85	27.60	−0.3931	−0.2370	2.98	0.078	12.81	0.039	−0.078	1.4773
7o	−0.79	264.9	225.2	76.58	27.58	−0.4035	−0.2393	9.84	0.082	12.18	0.041	−0.082	1.4804
7p	0.36	309.4	254.4	84.53	28.72	−0.3889	−0.2347	7.87	0.077	12.96	0.038	−0.077	1.5940
7r	−0.79	265.0	225.0	76.58	27.58	−0.4042	−0.2416	7.76	0.081	12.30	0.040	−0.081	1.4814
7s	2.67	247.4	199.9	60.15	23.42	−0.4201	−0.2439	4.95	0.088	11.35	0.044	−0.088	1.4965

$p\mathrm{MIC}_{s.a}$ values against predicted ones, using regression equation of the training set (Table 4, Eq. 1), is shown in Fig. 3. This QSAR model has a squared correlation coefficient (r^2) of ~0.68. The predicted $p\mathrm{MIC}_{s.a.}$ values (determined from Eq. 1) with residuals are given in Table 5.

The correlation matrix for the descriptors is given in Table 6 and, as seen, cross-relations between the descri ptors are not observed. Therefore, the values of the descriptors allow its safe use in the multilinear regression relationship (Myers, 1987; Draper and Smith, 1981). The statistical calculations were performed by SigmaPlot program package.

Conclusion

A series of eighteen 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7**) were synthesized from the reactions of benzamidoxime (**6**) with boronic acid derivatives. Seventeen 3,4-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**4**)

Table 4 The results of the application of training and test sets to 2D–QSAR models (Eqs. 1–18 in Table 2)

Eq.	Training set	Regression equation of training set	Test set (MIC)	Predicted value (MIC)	Statistic parameter		
					r^2	r^2 adj.	s
1	**7a, 7b, 7d, 7e, 7f, 7h, 7i, 7j, 7l, 7m, 7o, 7r**	$p\text{MIC}_{s.a.} = 0.28\sigma + 0.10\pi + 0.50$	**7c** (100)	96	0.685	0.615	0.111
			7g (100)	70			
			7k (100)	51			
			7n (50)	59			
			7p (100)	86			
2	**4j, 4l, 4m, 4o, 4p, 4r**	$p\text{MIC}_{s.a.} = 0.60\pi + 0.36$	**4k** (200)	119	0.936	0.921	0.099
			4n (50)	52			
3	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\text{MIC}_{s.a.} = 0.42\text{clogP} - 11.70E_{\text{LUMO}} - 2.80$	**4a** (800)	816	0.492	0.436	0.249
			4j (200)	60			
			4o (50)	32			
			4p (200)	700			
			4r (200)	507			
			7a (100)	567			
			7b (100)	247			
			7c (100)	324			
			7e (100)	387			
			7h (100)	314			
			7o (50)	573			
			7p (100)	240			
			7r (50)	539			
			7s (100)	14			
4	**4j, 4l, 4m, 4o, 4p, 4r**	$p\text{MIC}_{E.f.} = 0.54\pi + 0.43$	**4k** (100)	103	0.984	0.980	0.043
			4n (50)	50			
5	**4j, 4l, 4m, 4o, 4p, 4r**	$p\text{MIC}_{P.a.} = 0.26\pi + 0.67$	**4k** (50)	65	0.843	0.804	0.070
			4n (50)	50			
6	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\text{MIC}_{P.a.} = -0.005\text{SAA} + 2.60$	**4a** (100)	88	0.742	0.728	0.157
			4j (50)	38			
			4o (50)	69			
			4p (100)	59			
			4r (100)	61			
			7a (12.5)	21			
			7b (12.5)	10			
			7c (12.5)	14			
			7e (12.5)	21			
			7h (12.5)	14			
			7o (12.5)	14			
			7p (25)	26.5			
			7r (12.5)	14			
			7s (12.5)	9			

Table 4 continued

Eq.	Training set	Regression equation of training set	Test set (MIC)	Predicted value (MIC)	Statistic parameter r^2	r^2 adj.	s
7	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\text{MIC}_{P.a.} = -3.34E_{\text{HOMO}} - 0.005\text{SAA} + 1.23$	**4a** (100)	145	0.753	0.725	0.158
			4j (50)	50			
			4o (50)	89			
			4p (100)	74			
			4r (100)	76			
			7a (12.5)	34			
			7b (12.5)	13			
			7c (12.5)	19			
			7e (12.5)	36			
			7h (12.5)	18			
			7o (12.5)	15			
			7p (25)	31			
			7r (12.5)	15			
			7s (12.5)	8			
8	**7a, 7b, 7d, 7e, 7h, 7k, 7l, 7m, 7n, 7o, 7p, 7r**	$p\text{MIC}_{P.a.} = 0.08\pi + 1.30$	**7c** (12.5)	13	0.662	0.628	0.045
			7f (12.5)	11			
			7g (12.5)	11			
			7i (12.5)	12.5			
			7j (12.5)	11			
9	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\text{MIC}_{E.c.} = -0.004\text{SAA} + 1.64$	**4a** (800)	325	0.450	0.420	0.226
			4j (100)	158			
			4o (100)	269			
			4p (100)	234			
			4r (200)	239			
			7a (50)	95			
			7b (50)	51			
			7c (50)	70			
			7e (50)	95			
			7h (100)	70			
			7o (100)	70			
			7p (100)	119			
			7r (50)	70			
			7s (50)	45			
10	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\text{MIC}_{E.c.} = -0.002\text{SAA} - 16.02E_{\text{LUMO}} - 2.34$	**4a** (800)	1000	0.698	0.665	0.172
			4j (100)	137			
			4o (100)	136			
			4p (100)	114			
			4r (200)	75			
			7a (50)	364			
			7b (50)	85			
			7c (50)	142			
			7e (50)	216			
			7h (100)	136			
			7o (100)	29			
			7p (100)	47			

Table 4 continued

Eq.	Training set	Regression equation of training set	Test set (MIC)	Predicted value (MIC)	Statistic parameter		
					r^2	r^2 adj.	s
			7r (50)	27			
			7s (50)	17			
11	**7a, 7b, 7d, 7e, 7h, 7k, 7l, 7m, 7n, 7o, 7p, 7r**	$p\mathrm{MIC}_{S.m.} = 0.56\sigma + 7.16E_{\mathrm{LUMO}} + 2.01$	**7c** (100)	88	0.683	0.613	0.115
			7f (50)	94			
			7g (100)	87			
			7i (50)	76			
			7j (50)	70			
12	**7a, 7b, 7d, 7e, 7h, 7k, 7l, 7m, 7n, 7o, 7p, 7r**	$p\mathrm{MIC}_{S.m.} = 0.31\sigma - 0.03\mu + 0.76$	**7c** (100)	82	0.679	0.609	0.116
			7f (50)	61			
			7g (100)	53			
			7i (50)	57			
			7j (50)	25			
13	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\mathrm{MIC}_{S.m.} = 0.004\mathrm{SAA} - 10.05E_{\mathrm{LUMO}} - 2.63$	**4a** (50)	87	0.637	0.597	0.146
			4j (50)	47			
			4o (25)	32			
			4p (100)	31			
			4r (50)	23			
			7a (100)	126			
			7b (100)	95			
			7c (100)	96			
			7e (50)	91			
			7h (50)	93			
			7o (50)	39			
			7p (50)	32			
			7r (50)	37			
			7s (50)	31			
14	**4c, 4d, 4f, 4h, 4i**	$p\mathrm{MIC}_{S.m.} = 0.48\pi + 0.77$	**4a** (50)	40	0.741	0.654	0.118
			4b (50)	45			
			4e (50)	45			
			4g (25)	20			
15	**4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4k, 4l, 4m, 4n, 7d, 7f, 7g, 7i, 7j, 7k, 7l, 7m, 7n**	$p\mathrm{MIC}_{S.m.} = -4.09E_{\mathrm{HOMO}} + 0.004\mathrm{SAA} - 1.80$	**4a** (50)	24	0.502	0.446	0.171
			4j (50)	27			
			4o (25)	22			
			4p (100)	22			
			4r (50)	21			
			7a (100)	40			
			7b (100)	45			
			7c (100)	39			
			7e (50)	43			
			7h (50)	37			
			7o (50)	33			
			7p (50)	28			
			7r (50)	33			
			7s (50)	25			

Table 4 continued

Eq.	Training set	Regression equation of training set	Test set (MIC)	Predicted value (MIC)	Statistic parameter		
					r^2	r^2 adj.	s
16	**7a, 7b, 7d, 7e, 7h, 7k, 7l, 7m, 7n, 7o, 7p, 7r**	$p\text{MIC}_{S.m.} = 0.28\sigma + 0.61$	**7c** (100)	74	0.577	0.535	0.126
			7f (50)	61			
			7g (100)	55			
			7i (50)	64			
			7j (50)	54			
17	**7a, 7b, 7d, 7e, 7h, 7k, 7l, 7m, 7n, 7o, 7p, 7r**	$p\text{MIC}_{c.a.} = 0.46\sigma + 0.37\pi + 0.28$	**7c** (200)	182	0.679	0.608	0.259
			7f (200)	86			
			7g (200)	117			
			7i (200)	52			
			7j (100)	58			
18	**4j, 4l, 4m, 4o, 4p, 4r**	$p\text{MIC}_{c.a.} = 0.31\pi + 0.30$	**4k** (200)	150	0.914	0.892	0.061
			4n (100)	106			

r^2 coefficient of determination, r^2 adj internal cross-validation, s standard deviation

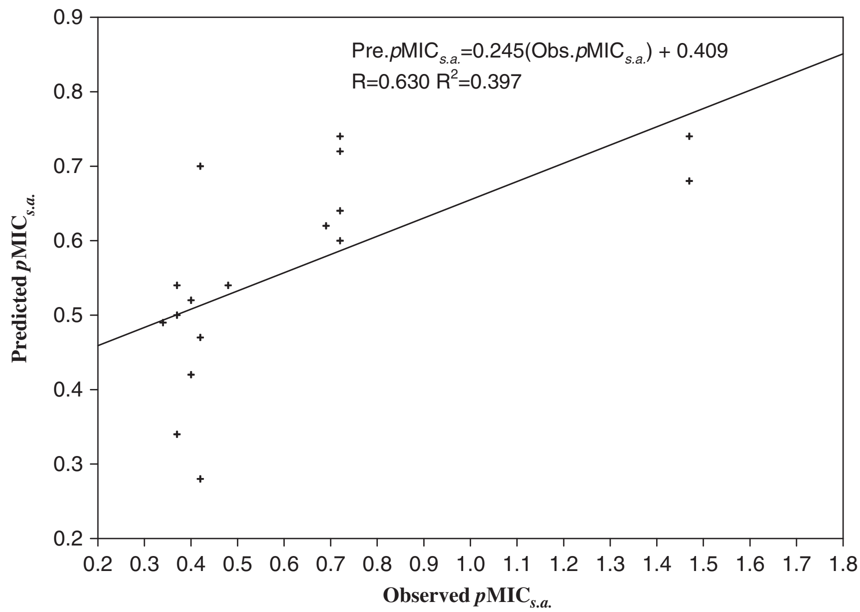


Fig. 3 The plot of observed versus predicted $p\text{MIC}_{s.a.}$ using the QSAR model (Table 4; Eq. 1)

were also synthesized from the reactions of substituted benzamidoximes (**3**) with phenylboronic acid. The antimicrobial activity studies of these oxadiazaboroles are not present in the literature. Antibacterial and antifungal activities of oxadiazaborole derivatives have been screened against three gram-positive bacteria, two gram-negative bacteria, and one fungi. Interestingly, all the compounds exhibited better results against *P. aeruginosa* (MIC of 12.5–200 µg/mL) than *S. aureus*, *E. faecalis*, *E. coli*, *S. mutans*, and *C. albicans*. These bacteria show the most dramatic resistance problems related to nosocomial infections and multiresistant strains (Kiska and Gilligan, 1999). Additionally, quantitative structure–activity relationship studies were carried out and this allowed us to draw the following conclusions about the antimicrobial activities of these synthesized oxadiazaboroles: (i) all oxadiazaboroles showed fair 2D correlations with some theoretical descriptors (clogP, SAA, E_{LUMO}, and E_{HOMO}) against *S. aureus*, *P. aeruginosa*, *E. coli*, and *S. mutans*; (ii) 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles (**7a–r**) showed fair 2D correlations with the electronic (σ) and lipophilic (π) descriptors against *S. aureus* and *C. albicans*; (iii) all oxadiazaboroles gave fair 1D correlations with the theoretical descriptor (SAA) against *P. aeruginosa* and *E. coli*; (iv) compounds (**4a–i, 4j–r,** and **7a–r**) showed fair 1D correlations with the electronic (σ) or lipophilic (π) descriptors against *S. aureus*, *E. faecalis*, *P. aeruginosa*, *S. mutans*, and *C. albicans.*

The QSAR study has given key information regarding the structural properties of 3,4,5-trisubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles and 3,5-disubstituted 4,5-dihydro-1,2,4,5-oxadiazaboroles, and may help to design more potent antimicrobial compounds in the future studies.

Experimental

Melting points were determined on the Electrothermal 9200 apparatus and are uncorrected. The FT IR spectra were recorded on the Bruker Alpha-P spectrometer in the region of 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on the Bruker DPX-400 (400 MHz) High Performance Digital FT-NMR Spectrometer using $CDCl_3$ and DMSO-d_6 with Me_4Si as an internal standard. Silica gel (Fluka or Merck) was used for column chromatography. Bands for the oxime NOH and C=N groups were followed in IR spectrum.

Table 5 Comparison of observed and predicted antibacterial activity obtained by equation (1)

Compound	$p\mathrm{MIC}_{s.a.}$ (Eq. 1)		
	Observed	Predicted	Residuals
7a	0.420	0.280	0.140
7b	0.370	0.340	0.030
7c	0.400	0.420	−0.020
7d	0.370	0.500	−0.130
7e	0.420	0.470	−0.050
7f	0.370	0.540	−0.170
7g	0.340	0.490	−0.150
7h	0.400	0.520	−0.120
7i	1.470	0.680	0.790
7j	0.720	0.640	0.080
7k	0.420	0.700	−0.280
7l	1.470	0.740	0.730
7m	0.720	0.600	0.120
7n	0.690	0.620	0.070
7o	0.720	0.720	0.000
7p	0.480	0.540	−0.060
7r	0.720	0.740	−0.020

Synthesis of *p*-chlorobenzaldehyde oxime (2a–i)

A solution of hydroxylamine hydrochloride (53 mmol, 3.7 g) in water (10 mL) and a solution of anhydrous sodium carbonate (27 mmol, 2.8 g) in water (15 mL) were mixed and stirred. *p*-Chlorobenzaldehyde (53 mmol, 7.5 g) in chloroform (20 mL) was added to this mixture. The reaction was stirred at room temperature for 24 h. After the reaction was complete, the chloroform phase was taken, the water phase was extracted with chloroform (15 mL) three times, and then the chloroform phase was collected and dried with anhydrous $CaCl_2$ overnight. The solvent was evaporated under vacuum. The precipitate was crystallized from ethyl acetate–petroleum ether (1:4) mixture to give *p*-chlorobenzaldehyde oxime (**2a–i**) (5.76 g, 70 %). Mp: 107.2–109.3 °C, Lit. (Liu et al., 1980): 105.5–108 °C; IR (ATR), υ (cm^{-1}): 3255 (NOH), 1594 (C=N).

Synthesis of *N*-phenyl-*p*-chlorobenzamidoxime (3d) (general procedure for 3a–i)

p-Chlorobenzaldehyde oxime (**2a–i**) (39 mmol, 6.08 g) was dissolved in anhydrous chloroform (100 mL). After cooling the solution in an ice bath, chlorine gas was passed through the solution until the determination of the 3.20-g weight increase. The solution was refrigerated for one night. Then the solution was evaporated under reduced pressure at 40 °C. The formed *p*-chloro-*N*-hydroxybenzimidoyl chloride was dissolved in dry benzene (30 mL), and to the solution aniline (78 mmol, 7.28 g) was added dropwise in dry benzene (20 mL) with constant stirring at room temperature for 24 h. After this the mixture was refrigerated for 1 h. The salt precipitated was removed by filtration. The residual solid was subjected to flash column chromatography (eluant:ethyl acetate:petroleum ether). The crude product was crystallized from ethyl acetate: petroleum ether (1:6) mixture to give *N*-phenyl-*p*-chlorobenzamidoxime (**3d**) (5.24 g, 54 %). Mp: 127–130 °C. IR (ATR), υ (cm^{-1}): 3390 (N–H), 3141 (NOH), 1611 (C=N); ^1H NMR (DMSO-d_6), δ (ppm): 10.67 (s, 1H, NOH); 8.36

Table 6 Correlation coefficients (r^2) of squared correlation matrix of the theoretical descriptors used in the QSAR study

clogP	1.000				
SAA	0.147	1.000			
E_{LUMO}	0.057	0.289	1.000		
μ	−0.508	−0.116	−0.220	1.000	
E_{HOMO}	0.087	0.432	0.808	−0.103	1.000
Variables	clogP	SAA	E_{LUMO}	μ	E_{HOMO}

(s, 1H, N–H); 7.35 (d, $J = 15.5$ Hz, aromatic, 4H); 7.05 (d, $J = 17.2$ Hz, aromatic, 2H); 6.78 (t, $J = 7.0$ Hz, aromatic, 1H); 6.62 (d, $J = 7.9$ Hz, aromatic, 2H).

*Spectroscopic and analytical data of compounds (**3**)*

*N-(p-dimethylaminophenyl)-p-chlorobenzamidoxime (**3a**)* yield: 55 %; mp: 205–208 °C; IR (ATR), υ (cm^{-1}): 3369 (N–H), 3198 (NOH), 1636 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.32 (s, 1H, NOH); 7.89 (s, 1H, N–H); 7.30 (d, $J = 19.6$ Hz, aromatic, 4H); 6.56–6.46 (m, aromatic, 4H); 2.74 (s, 6H, $N(CH_3)_2$).

*N-(p-methoxyphenyl)-p-chlorobenzamidoxime (**3b**)* yield: 47 %; mp: 185–186 °C; IR (ATR), υ (cm^{-1}): 3408 (N–H), 3137 (NOH), 1632 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.45 (s, 1H, NOH); 8.11 (s, 1H, N–H); 7.32 (d, $J = 19.6$ Hz, aromatic, 4H); 6.68–6.58 (dd, $J = 20.5$ Hz, 12.3 Hz, aromatic, 4H); 3.61 (s, 3H, OCH_3).

*N-(m-tolyl)-p-chlorobenzamidoxime (**3c**)*: 38 %; mp: 110–113 °C; IR (ATR), υ (cm^{-1}): 3383 (N–H), 3194 (NOH), 1632 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.38–6.37 (m, aromatic, 8H); 2.20 (s, 3H, CH_3).

*N-(m-methoxyphenyl)-p-chlorobenzamidoxime (**3e**)* yield: 42 %; mp: 66–69 °C; IR (ATR), υ (cm^{-1}): 3301 (N–H), 3169 (NOH), 1631 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.68 (s, 1H, NOH); 8.34 (s, 1H, N–H); 7.40–7.33 (m, aromatic, 4H); 6.96–6.91 (m, aromatic, 1H); 6.35 (d, $J = 8.2$ Hz, aromatic, 1H); 6.23 (s, aromatic, 1H); 6.15 (d, $J = 7.6$ Hz, aromatic, 1H); 3.54 (s, 3H, OCH_3).

*N-(p-bromophenyl)-p-chlorobenzamidoxime (**3f**)* yield: 37 %; mp: 186–187 °C; IR (ATR), υ (cm^{-1}): 3395 (N–H), 3085 (NOH), 1632 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.78 (s, 1H, NOH); 8.55 (s, 1H, N–H); 7.40–7.34 (m, aromatic, 4H); 7.22 (d, $J = 6.1$ Hz, aromatic, 2H); 6.56 (d, $J = 6.7$ Hz, aromatic, 2H).

*N-(p-chlorophenyl)-p-chlorobenzamidoxime (**3g**)* yield: 41 %; mp: 170–172 °C; IR (ATR), υ (cm^{-1}): 3394 (N–H), 3083 (NOH), 1629 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.76 (s, 1H, NOH); 8.55 (s, 1H, N–H); 7.40–7.36 (m, aromatic, 4H); 7.10 (d, $J = 8.7$ Hz, aromatic, 2H); 6.61 (d, $J = 8.7$ Hz, aromatic, 2H).

*N-(m-chlorophenyl)-p-chlorobenzamidoxime (**3h**)* yield: 44 %; mp: 135–137 °C; IR (ATR), υ (cm^{-1}): 3379 (N–H), 3193 (NOH), 1636 (C=N); ^{1}H NMR ($CDCl_3$), δ (ppm): 10.85 (s, 1H, NOH); 8.63 (s, 1H, N–H); 7.51–7.39 (m, aromatic, 4H); 7.07–7.01 (m, aromatic, 1H); 6.81–6.74 (m, aromatic, 2H); 6.44 (d, $J = 7.9$ Hz, aromatic, 1H).

*N-(m-trifluoromethylphenyl)-p-chlorobenzamidoxime (**3i**)* yield: 36 %; mp: 160 °C; IR (ATR), υ (cm^{-1}): 3387 (N–H), 3087 (NOH), 1633 (C=N); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.91 (s, 1H, NOH); 8.80 (s, 1H, N–H); 7.40–7.26 (m, aromatic, 5H); 7.08–6.99 (m, aromatic, 2H); 6.79–6.77 (m, aromatic, 1H).

Synthesis of 3-(*p*-chlorophenyl)-4,5-diphenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (4d) (general procedure for 4a–i)

N-phenyl-*p*-chlorobenzamidoxime (**3d**) (1.21 mmol, 0.300 g) and phenylboronic acid (1.36 mmol, 0.165 g) were dissolved in toluene (20 mL) and the solution was refluxed for 30 h in the presence of molecular sieves (4 Å). After extracting with acetone and filtering, the solvent was evaporated under reduced pressure. The residual was crystallized from ethyl acetate–petroleum ether (1:4) mixture to give 3-(*p*-chlorophenyl)-4,5-diphenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4d**) (0.240 g, 59 %). Mp: 201–202.8 °C. IR (ATR), υ (cm^{-1}): 1599 (C=N), 1371 (B–N), 1125 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55 (d, $J = 7.9$ Hz, aromatic, 2H); 7.45–7.38 (m, aromatic, 4H); 7.33–7.26 (m, aromatic, 6H); 7.17–7.13 (m, aromatic, 2H); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.0 (C=N); 137.2; 136.7; 134.3; 131.3; 130.5; 129.9; 128.9; 128.3; 128.2; 128.0; 124.7. Anal. calcd. for $C_{19}H_{14}BClN_2O$: C, 68.61; H, 4.24; N, 8.42; found: C, 68.39; H, 4.32; N, 8.35.

Synthesis of 3,5-diphenyl-4-(*m*-tolyl)-4,5-dihydro-1,2,4,5-oxadiazaborole (4j) (general procedure for 4j–r)

N-(*m*-tolyl)-benzamidoxime (**3j**) (1.33 mmol, 0.300 g) and phenylboronic acid (1.49 mmol, 0.181 g) were dissolved in toluene (20 mL) and the solution was refluxed for 30 h in the presence of molecular sieves (4 Å). After extracting with acetone and filtering, the solvent was evaporated under reduced pressure. The residual was crystallized from petroleum ether to give 3,5-diphenyl-4-(*m*-tolyl)-4,5-dihydro-1,2,4,5-oxadiazaborole (**4j**) (0.30 g, 72 %). Mp: 191–194 °C. IR (ATR), υ (cm^{-1}): 1601 (C=N), 1370 (B–N), 1125 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.57 (d, $J = 7.9$ Hz, aromatic, 2H); 7.44–7.22 (m, aromatic, 9H); 7.17 (d, $J = 7.6$ Hz, aromatic, 1H); 6.96 (d, $J = 7.0$ Hz, aromatic, 2H); 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.9 (C=N); 139.8; 137.4; 134.4; 131.1; 130.3; 129.5; 129.2; 128.9; 128.5; 128.5; 128.2; 126.3; 125.1; 21.5 (CH_3). Anal. calcd. for $C_{20}H_{17}BN_2O$: C, 76.95; H, 5.49; N, 8.97; found: C, 76.53; H, 5.37; N, 9.16.

*Spectroscopic and analytical data of compounds (**4**)*

*3-(p-chlorophenyl)-4-(p-N,N-dimethylaminophenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4a**)* yield: 75 %; mp: 208 –210 °C; IR (ATR), υ (cm^{-1}): 1601 (C=N), 1371 (B–N), 1126 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.59 (d, J = 7.3 Hz, aromatic, 2H); 7.43–7.26 (m, aromatic, 7H); 6.99 (d, J = 8.5 Hz, aromatic, 2H); 6.64 (d, J = 8.5 Hz, aromatic, 2H); 2.99 (s, 6H, $N(CH_3)_2$); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.5 (C=N); 149.9; 136.4; 134.4; 131.1; 130.5; 128.8; 128.5; 128.1; 125.6; 125.1; 112.8; 40.6 (CH_3). Anal. calcd. for $C_{21}H_{19}BClN_3O$: C, 67.14; H, 5.10; N, 11.19; found: C, 66.48; H, 5.28; N, 11.04.

*3-(p-chlorophenyl)-4-(p-methoxyphenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4b**)* yield: 61 %; mp: 197–199 °C; IR (ATR), υ (cm^{-1}): 1599 (C=N), 1369 (B–N), 1124 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55 (d, J = 7.0 Hz, aromatic, 2H); 7.44–7.25 (m, aromatic, 7H); 7.05 (d, J = 8.7 Hz, aromatic, 2H); 6.88 (d, J = 8.7 Hz, aromatic, 2H); 3.84 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.2 (C=N); 159.2; 136.6; 134.3; 131.2; 130.5; 129.9; 129.0; 128.9; 128.2; 124.8; 115.0; 55.7 (OCH_3). HRMS: *m/z* $(M + H)^{+}$ calcd. for $C_{20}H_{17}BClN_2O_2$: 363.1072; found: 363.1081 $(M + H)^{+}$. Anal. calcd. for $C_{20}H_{16}BClN_2O_2$: C, 66.24; H, 4.45; N, 7.73; found: C, 65.56; H, 4.76; N, 7.68.

*3-(p-chlorophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4c**)* yield: 57 %; mp: 182–184 °C; IR (ATR), υ (cm^{-1}): 1599 (C=N), 1369 (B–N), 1124 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55 (d, J = 9.3 Hz, aromatic, 2H); 7.42–7.39 (m, aromatic, 1H); 7.32–7.18 (m, aromatic, 8H); 6.96 (d, J = 6.1 Hz, aromatic, 2H); 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.0 (C=N); 140.0; 137.1; 136.6; 134.4; 131.2; 130.5; 129.7; 129.1; 128.9; 128.5; 128.2; 125.0; 124.8; 21.5 (CH_3). Anal. calcd. for $C_{20}H_{16}BClN_2O$: C, 69.30; H, 4.65; N, 8.08; found: C, 68.78; H, 4.58; N, 7.92.

*3-(p-chlorophenyl)-4-(m-methoxyphenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4e**)* yield: 60 %; mp: 170–172 °C; IR (ATR), υ (cm^{-1}): 1601 (C=N), 1367 (B–N), 1123 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.58 (d, J = 7.9 Hz, aromatic, 2H); 7.45–7.25 (m, aromatic, 8H); 6.92 (d, J = 10.8 Hz, aromatic, 1H); 6.75 (d, J = 9.6 Hz, aromatic, 1H); 6.67 (t, J = 2.0 Hz, aromatic, 1H); 3.73 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.9 (C=N); 160.6; 138.3; 136.7; 134.3; 131.3; 130.6; 130.4; 128.9; 128.2; 124.7; 120.2; 113.8; 113.8; 55.6 (OCH_3). Anal. calcd. for $C_{20}H_{16}BClN_2O_2$: C, 66.24; H, 4.45; N, 7.73; found: C, 65.67; H, 4.53; N, 7.63.

*3-(p-chlorophenyl)-4-(p-bromophenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4f**)* yield: 59 %; mp: 199–201 °C; IR (ATR), υ (cm^{-1}): 1598 (C=N), 1367 (B–N), 1123 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.56–7.42 (m, aromatic, 4H); 7.34–7.23 (m, aromatic, 5H); 7.04–7.0 (m, aromatic, 4H); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.7 (C=N); 137.0; 136.3; 134.3; 133.1; 131.5; 130.5; 129.5; 129.1; 128.3; 124.3; 122.1. ^{11}B NMR ($CDCl_3$), δ (ppm): 32.3. Anal. calcd. for $C_{19}H_{13}BBrClN_2O$: C, 55.46; H, 3.18; N, 6.81; found: C, 55.44; H, 3.34; N, 6.96.

*3-(p-chlorophenyl)-4-(p-chlorophenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4g**)* yield: 59 %; mp: 187–190 °C; IR (ATR), υ (cm^{-1}): 1597 (C=N), 1368 (B–N), 1122 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.56–7.52 (m, aromatic, 4H); 7.46–7.24 (m, aromatic, 5H); 7.10–7.07 (m, aromatic, 4H); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.8 (C=N); 136.9; 135.8; 134.3; 134.1; 131.4; 130.5; 130.2; 129.2; 129.1; 128.3; 124.3. Anal. calcd. for $C_{19}H_{13}BCl_2N_2O$: C, 62.17; H, 3.57; N, 7.63; found: C, 62.26; H, 3.68; N, 7.66.

*3-(p-chlorophenyl)-4-(m-chlorophenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4h**)* yield: 60 %; mp: 177.7–179 °C; IR (ATR), υ (cm^{-1}): 1599 (C=N), 1367 (B–N), 1124 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.54 (d, J = 8.2 Hz, aromatic, 2H); 7.47–7.25 (m, aromatic, 10H); 7.18 (t, J = 1.7 Hz, aromatic, 1H); 7.04 (m, aromatic, 1H); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.7 (C=N); 138.5; 137.0; 135.5; 134.3; 131.5; 130.9; 130.5; 129.1; 128.7; 128.4; 128.1; 126.3; 124.2. Anal. calcd. for $C_{19}H_{13}BCl_2N_2O$: C, 62.17; H, 3.57; N, 7.63; found: C, 62.24; H, 3.52; N, 7.63.
*3-(p-chlorophenyl)-4-(m-trifluoromethylphenyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4i**)* yield: 46 %; mp: 165–167 °C; IR (ATR), υ (cm^{-1}): 1598 (C=N), 1368 (B–N), 1119 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.66 (d, J = 7.9 Hz, aromatic, 1H); 7.55–7.42 (m, aromatic, 5H); 7.34–7.21 (m, aromatic, 7H); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.6 (C=N); 137.9; 137.1; 134.2; 132.6; 132.2; 131.6; 131.3; 130.6; 130.5; 129.2; 128.4; 125.2; 125.1; 125.0; 124.8; 124.0. Anal. calcd. for $C_{20}H_{13}BClF_3N_2O$: C, 59.97; H, 3.27; N, 6.99; found: C, 59.81; H, 3.23; N, 6.96.

*3-(p-fluorophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4k**)* yield: 62 %; mp: 188–190 °C; IR (ATR), υ (cm^{-1}): 1598 (C=N), 1370 (B–N), 1123 (B–O); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55 (d, J = 8.2 Hz, aromatic, 2H); 7.44–7.39 (t, J = 7.3 Hz, aromatic, 1H); 7.36–7.24 (m, aromatic, 5H); 7.18–6.94 (m, aromatic, 5H); 2.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.1 (C=N); 165.6; 162.2; 140.0; 137.2; 134.3; 131.4; 131.2; 131.2; 129.6; 129.0; 128.5; 128.2; 125.1; 122.4; 122.4; 115.9; 115.6; 21.5 (s, 3H, CH_3). Anal. calcd. for

$C_{20}H_{16}BFN_2O$: C, 72.76; H, 4.88; N, 8.48; found: C, 72.88; H, 5.02; N, 8.48.

*3-(p-bromophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4l**)* yield: 60 %; mp: 192–193 °C; IR (ATR), υ (cm^{-1}): 1598 (C=N), 1367 (B–N), 1122 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 7.55 (d, $J = 7.0$ Hz, aromatic, 2H); 7.43–7.41 (m, aromatic, 3H); 7.32–7.18 (m, aromatic, 6H); 6.95 (d, $J = 6.7$ Hz, aromatic, 2H); 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 160.1 (C=N); 140.1; 137.1; 134.4; 131.8; 131.2; 130.7; 129.7; 129.1; 128.5; 128.2; 125.2; 125.0; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{20}H_{16}BBrN_2O$: C, 61.42; H, 4.12; N, 7.16; found: C, 61.28; H, 4.22; N, 7.12.

*3-(m-chlorophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4m**)* yield: 75 %; mp: 130–133 °C; IR (ATR), υ (cm^{-1}): 1600 (C=N), 1370 (B–N), 1134 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 7.57 (d, $J = 9.3$ Hz, aromatic, 2H); 7.44–7.13 (m, aromatic, 9H); 6.96 (d, $J = 5.5$ Hz, aromatic, 2H); 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.8 (C=N); 140.0; 137.0; 134.5; 134.4; 131.3; 130.5; 129.8; 129.7; 129.4; 129.2; 128.4; 128.2; 128.0; 127.3; 125.0; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{20}H_{16}BClN_2O$: C, 69.30; H, 4.65; N, 8.08; found: C, 69.31; H, 4.46; N, 8.07.

*3-(m-bromophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4n**)* yield: 56 %; mp: 139–141 °C; IR (ATR), υ (cm^{-1}): 1600 (C=N), 1371 (B–N), 1131 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 7.61–7.55 (m, aromatic, 3H); 7.49–7.41 (dd, $J = 18.1$ Hz, 10.8 Hz, aromatic, 2H); 7.32–7.09 (m, aromatic, 6H); 6.96 (d, $J = 5.5$ Hz, aromatic, 2H); 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.6 (C=N); 140.0; 137.0; 134.4; 133.4; 132.2; 131.3; 130.0; 129.7; 129.2; 128.4; 128.2; 127.7; 125.0; 122.5; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{20}H_{16}BBrN_2O$: C, 61.42; H, 4.12; N, 7.16; found: C, 61.37; H, 4.16; N, 7.15.

*3-(p-trifluoromethylphenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4o**)* yield: 36 %; mp: 123–127 °C; IR (ATR), υ (cm^{-1}): 1601 (C=N), 1372 (B–N), 1126 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 7.58–7.40 (m, aromatic, 7H); 7.33–7.19 (m, aromatic, 4H); 6.97 (d, $J = 6.7$ Hz, aromatic, 2H); 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.8 (C=N); 140.2; 137.0; 134.4; 131.3; 129.8; 129.5; 129.3; 128.4; 128.2; 125.5; 125.5; 125.0; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{21}H_{16}BF_3N_2O$: C, 66.35; H, 4.24; N, 7.37; found: C, 66.28; H, 4.32; N, 7.39.

*3-(m-nitrophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4p**)* yield: 70 %; mp: 125–127 °C; IR (ATR), υ (cm^{-1}): 1599 (C=N), 1349 (B–N), 1138 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 8.24–8.21 (m, aromatic, 2H); 7.71 (d, $J = 8.7$ Hz, aromatic, 1H); 7.59–7.41 (m, aromatic, 4H); 7.33–7.21 (m, aromatic, 4H); 7.01 (d, $J = 7.0$ Hz, aromatic, 2H); 2.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.0 (C=N); 148.1; 140.4; 136.7; 134.9; 134.4; 131.5; 130.0; 129.7; 129.6; 128.4; 128.3; 128.1; 125.1; 125.0; 124.2; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{20}H_{16}BN_3O_3$: C, 67.25; H, 4.52; N, 11.76; found: C, 67.55; H, 4.60; N, 11.83.

*3-(p-nitrophenyl)-4-(m-tolyl)-5-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**4r**)* yield: 76 %; mp: 190–192 °C; IR (ATR), υ (cm^{-1}): 1598 (C=N), 1340 (B–N), 1122 (B–O); ^1H NMR ($CDCl_3$), δ (ppm): 8.13 (d, $J = 10.8$ Hz, aromatic, 2H); 7.57–7.53 (m, aromatic, 4H); 7.46–7.41 (m, aromatic, 1H); 7.33–7.21 (m, aromatic, 4H); 6.98 (d, $J = 5.8$ Hz, aromatic, 2H); 2.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$), δ (ppm): 159.2 (C=N); 148.8; 140.4; 136.7; 134.4; 132.6; 131.5; 130.1; 129.9; 129.5; 128.3; 128.3; 124.9; 123.7; 21.5 (s, 3H, CH_3). Anal. calcd. for $C_{20}H_{16}BN_3O_3$: C, 67.25; H, 4.52; N, 11.76; found: C, 67.48; H, 4.51; N, 11.84.

Synthesis of benzamidoxime (6) (general procedure)

Method A: A solution of hydroxylamine hydrochloride (200 mmol, 13.89 g) in ethanol (100 mL) and a solution of anhydrous sodium carbonate (100 mmol, 10.59 g) in boiling water (25 mL) were mixed and stirred. Benzonitrile (200 mmol, 20.62 g) in ethanol (25 mL) was added to this mixture. The reaction was refluxed at 80 °C for 21 h. The solvent was evaporated under reduced pressure. The residue was washed with water and extracted with chloroform. The solution was dried with anhydrous $CaCl_2$ and the solvent was evaporated under vacuum. The precipitate was crystallized from ethyl acetate–petroleum ether to give benzamidoxime (**6**) (11.88 g, 43 %). Mp: 75–77.5 °C, Lit. (Krüger, 1885): 79–80 °C; IR (ATR), υ (cm^{-1}): 3450, 3358 (NH_2), 3181 (N–OH), 1645 (C=N).

Method B (Gosenca et al., 2013): A solution of benzonitrile (3.6 mmol, 0.371 g), hydroxylamine hydrochloride (7.2 mmol, 0.50 g), and potassium carbonate (7.25 mmol, 1.0 g) were suspended in anhydrous ethanol (50 mL). The mixture was refluxed for 8 h. The precipitate was rapidly filtered off before cooling and the solvent was evaporated under vacuum. The crude pro duct was recrystallized from dichloromethane–petroleum ether to give benzamidoxime (**6**) (0.325 g, 66 %). Mp: 63–65 °C. IR (ATR), υ (cm^{-1}): 3450, 3357 (NH_2), 3181 (N–OH), 1642 (C=N).

Synthesis of 3,5-diphenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (7g) (general procedure for 7a–s)

Benzamidoxime (**6**) (22 mmol, 3.0 g) and phenylboronic acid (22 mmol, 2.86 g) were dissolved in benzene (150 mL) and the solution was refluxed overnight, then the solvent was evaporated under reduced pressure. The residual was crystallized from hexane to give 3,5-diphenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7g**) (4.57 g, 94 %). Mp: 164–164.5 °C, Lit. (Akcan, 2007): 154–156 °C; IR (ATR), υ (cm^{-1}): 3418, 3379 (N–H), 1601 (C=N), 1415 (B–N), 1200 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.46 (s, 1H, NH); 8.02–7.49 (m, aromatic, 10H); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.9 (C=N); 134.6; 131.8; 131.4; 129.6; 128.9; 127.4; 126.9. Anal. calcd. for $C_{13}H_{11}BN_2O$: C, 70.32; H, 4.99; N, 12.62; found: C, 70.26; H, 5.28; N, 12.53.

Spectroscopic and analytical data of compounds (7)

*5-(4-N,N-dimethylaminophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7a**)* yield: 91 %; mp: 198–200 °C; IR (ATR), υ (cm^{-1}): 3329 (N–H), 1608 (C=N), 1418 (B–N), 1234 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.13 (s, 1H, NH); 7.99–7.96 (m, aromatic, 2H); 7.78 (d, J = 8.7 Hz, aromatic, 2H); 7.58–7.55 (m, aromatic, 3H); 6.81 (d, J = 8.7 Hz, aromatic, 2H); 2.97 (s, 6H, N(CH$_3$)$_2$); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.6 (C=N); 152.8; 135.8; 131.2; 129.6; 127.7; 126.9; 112.1; 40.2 (CH$_3$). Anal. calcd. for $C_{15}H_{16}BN_3O$: C, 67.95; H, 6.08; N, 15.85; found: C, 68.27; H, 6.28; N, 15.90.

*5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7b**)* yield 82 %; mp: 197–198 °C; IR (ATR), υ (cm^{-1}): 3385 (N–H), 1608 (C=N), 1425 (B–N), 1204 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.23 (s, 1H, NH); 7.98–7.95 (m, aromatic, 2H); 7.80–7.76 (m, aromatic, 2H); 7.58–7.55 (m, aromatic, 3H); 6.92–6.89 (m, aromatic, 2H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.8 (Ar–O); 159.7 (C=N); 136.4; 131.3; 129.6; 127.5; 126.9; 118.6; 116.1. Anal. calcd. for $C_{13}H_{11}BN_2O_2$: C, 65.59; H, 4.66; N, 11.77; found: C, 65.18; H, 5.20; N, 11.41.

*5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7c**)* yield 78 %; mp: 145–148 °C; IR (ATR), υ (cm^{-1}): 3358 (N–H), 1603 (C=N), 1414 (B–N), 1236 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.27 (s, 1H, NH); 7.96–7.85 (m, aromatic, 4H); 7.55–7.52 (t, J = 3.8 Hz, aromatic, 3H); 7.06 (d, J = 8.4 Hz, aromatic, 2H); 3.79 (s, 3H, ArOCH$_3$); ^{13}C NMR (DMSO-d_6), δ (ppm): 162.3 (Ar–O); 159.8 (C=N); 136.3; 131.3; 129.6; 127.5; 126.9; 114.6; 55.7 (OCH$_3$). Anal. calcd. for $C_{14}H_{13}BN_2O_2$: C, 66.71; H, 5.20; N, 11.11; found: C, 66.75; H, 5.59; N, 11.33.

*5-(4-tolyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7d**)* yield 91 %; mp: 149–149.5 °C; IR (ATR), υ (cm^{-1}): 3377 (N–H), 1614 (C=N), 1416 (B–N), 1211 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.39 (s, 1H, NH); 8.00–7.97 (m, aromatic, 2H); 7.86 (d, J = 7.6 Hz, aromatic, 2H); 7.58–7.56 (t, J = 3.8 Hz, aromatic, 3H); 7.34 (d, J = 7.6 Hz, aromatic, 2H); 2.37 (s, 3H, ArCH$_3$); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.8 (C=N); 141.5; 134.6; 131.4; 129.6; 129.6; 127.4; 126.9; 21.9 (CH$_3$). Anal. calcd. for $C_{14}H_{13}BN_2O$: C, 71.23; H, 5.55; N, 11.87; found: C, 71.43; H, 5.57; N, 11.90.

*5-(3-N,N-dimetylaminophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7e**)* yield 82 %; mp: 95–96 °C; IR (ATR), υ (cm^{-1}): 3237 (N–H), 1599 (C=N), 1416 (B–N), 1234 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.35 (s, 1H, NH); 7.99–7.94 (m, aromatic, 2H); 7.58–7.56 (t, J = 3.5 Hz, aromatic, 3H); 7.39–7.24 (m, aromatic, 3H); 6.91–6.88 (m, aromatic, 1H); 2.96 (s, 6H, N(CH$_3$)$_2$); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.9 (C=N); 150.8; 131.4; 129.6; 129.5; 127.4; 126.9; 126.0; 122.3; 118.2; 115.8; 40.4 (CH$_3$). Anal. calcd. for $C_{15}H_{16}BN_3O$: C, 67.95; H, 6.08; N, 15.85; found: C, 67.20; H, 6.34; N, 15.43.

*5-(3-tolyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7f**)* yield 93 %; mp: 158–160 °C; IR (ATR), υ (cm^{-1}): 3239 (N–H), 1591 (C=N), 1422 (B–N), 1200 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.40 (s, 1H, NH); 7.99–7.94 (m, aromatic, 2H); 7.74–7.70 (t, J = 7.0 Hz, aromatic, 2H); 7.56–7.53 (m, aromatic, 3H); 7.39–7.33 (m, aromatic, 2H); 2.35 (s, 3H, ArCH$_3$); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.9 (C=N); 137.8; 135.1; 132.4; 131.6; 131.4; 129.6; 128.8; 128.7; 127.4; 126.9; 21.7 (CH$_3$). Anal. calcd. for $C_{14}H_{13}BN_2O$: C, 71.23; H, 5.55; N, 11.87; found: C, 71.71; H, 5.80; N, 11.94.

*5-(3-methoxyphenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7h**)* yield 27 %; mp: 115–117 °C; IR (ATR), υ (cm^{-1}): 3228 (N–H), 1604 (C=N), 1423 (B–N), 1233 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.45 (s, 1H, NH); 8.00–7.97 (m, aromatic, 2H); 7.59–7.41 (m, aromatic, 7H); 3.84 (s, 3H, ArOCH$_3$); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.9 (Ar–O); 159.7 (C=N); 131.4; 130.2; 129.6; 127.3; 126.9; 126.7; 119.4; 117.5; 55.7 (OCH$_3$). Anal. calcd. for $C_{14}H_{13}BN_2O_2$: C, 66.71; H, 5.20; N, 11.11; found: C, 66.98; H, 5.51; N, 10.88.

*5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (**7i**)* yield 56 %; mp: 228–229 °C; IR (ATR), υ (cm^{-1}): 3363 (N–H), 1587 (C=N), 1415 (B–N), 1203 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.50 (s, 1H, NH); 7.98–7.95 (m, aromatic, 2H); 7.89–7.85 (m, aromatic, 2H); 7.75–7.72 (m, aromatic, 2H); 7.59–7.56 (m, aromatic, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C=N); 136.5; 132.0; 131.5; 129.7; 127.2; 126.9; 125.9. Anal. calcd.

for $C_{13}H_{10}BBrN_2O$: C, 51.88; H, 3.35; N, 9.31; found: C, 51.49; H, 3.28; N, 9.25.

5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7j***) yield 84 %; mp: 220–222 °C; IR (ATR), υ (cm^{-1}): 3364 (N–H), 1595 (C=N), 1418 (B–N), 1204 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.50 (s, 1H, NH); 7.96–7.94 (t, $J = 1.7$ Hz, aromatic, 4H); 7.59–7.57 (t, $J = 3.2$ Hz, aromatic, 5H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C=N); 136.8; 136.3; 131.5; 129.6; 129.1; 127.2; 126.9. Anal. calcd. for $C_{13}H_{10}BClN_2O$: C, 60.87; H, 3.93; N, 10.92; found: C, 60.52; H, 3.89; N, 10.87.

5-(3-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7k***) yield 82 %; mp: 155–157 °C; IR (ATR), υ (cm^{-1}): 3381 (N–H), 1592 (C=N), 1408 (B–N), 1207 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.54 (s, 1H, NH); 7.99–7.96 (m, aromatic, 3H); 7.89 (d, $J = 7.3$ Hz, aromatic, 1H); 7.60–7.52 (m, aromatic, 5H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C=N); 134.0; 132.9; 131.6; 131.5; 131.0; 129.7; 127.2; 126.9. Anal. calcd. for $C_{13}H_{10}BClN_2O$: C, 60.87; H, 3.93; N, 10.92; found: C, 60.78; H, 4.11; N, 10.80.

5-(3-bromophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7l***) yield 77 %; mp: 158–160 °C; IR (ATR), υ (cm^{-1}): 3383 (N–H), 1605 (C=N), 1418 (B–N), 1209 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.52 (s, 1H, NH); 8.24–7.37 (m, aromatic, 10H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C=N); 139.9; 134.5; 133.2; 131.5; 131.4; 129.7; 127.2; 126.9; 122.8. Anal. calcd. for $C_{13}H_{10}BBrN_2O$: C, 51.88; H, 3.35; N, 9.31; found: C, 52.00; H, 2.89; N, 9.39.

5-(4-acetylphenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7m***) yield 74 %; mp: 205–207 °C; IR (ATR), υ (cm^{-1}): 3397 (N–H), 1549 (C=N), 1414 (B–N), 1202 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.57 (s, 1H, NH); 8.04 (s, aromatic, 4H); 7.96–7.93 (m, aromatic, 2H); 7.56–7.54 (m, aromatic, 3H); 2.60 (s, 3H, $COCH_3$); ^{13}C NMR (DMSO-d_6), δ (ppm): 198.7 (C=O), 160.1 (C=N); 139.2; 134.8; 131.5; 129.7; 128.7; 128.4; 127.2; 127.0; 27.5 (CH_3). Anal. calcd. for $C_{15}H_{13}BN_2O_2$: C, 68.22; H, 4.96; N, 10.61; found: C, 68.67; H, 5.07; N, 10.70.

5-(3-cyanophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7n***) yield 70 %; mp: 236–239 °C; IR (ATR), υ (cm^{-1}): 3381 (N–H), 1599 (C=N), 1429 (B–N), 1221 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.54 (s, 1H, NH); 8.28 (s, aromatic, 1H); 8.19 (d, $J = 7.3$ Hz, aromatic, 1H); 7.99–7.90 (m, aromatic, 3H); 7.72–7.67 (t, $J = 7.6$ Hz, aromatic, 1H); 7.56–7.54 (t, $J = 3.2$ Hz, aromatic, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C=N); 138.7; 138.0; 135.1; 131.6; 130.1; 129.7; 128.7; 127.1; 126.9; 119.3; 112.3 (C≡N). Anal. calcd. for $C_{14}H_{10}BN_3O$: C, 68.06; H, 4.08; N, 17.01; found: C, 68.20; H, 4.55; N, 16.52.

5-(3-nitrophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7o***) yield 53 %; mp: 241–243 °C; IR (ATR), υ (cm^{-1}): 3400 (N–H), 1610 (C=N), 1448 (B–N), 1215 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.71 (s, 1H, NH); 8.77 (s, aromatic, 1H); 8.39–8.29 (m, aromatic, 2H); 7.99–7.95 (m, aromatic, 2H); 7.83–7.78 (t, $J = 7.6$ Hz, aromatic, 1H); 7.60–7.58 (t, $J = 3.5$ Hz, aromatic, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.0 (C = N); 148.3; 140.6; 131.6; 130.6; 129.7; 128.8; 128.7; 127.0; 126.9; 126.3. Anal. calcd. for $C_{13}H_{10}BN_3O_3$: C, 58.47; H, 3.77; N, 15.74; found: C, 58.82; H, 3.77; N, 15.69.

5-(4-methanesulfonylphenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7p***) yield 82%; mp: 220–222.5 °C; IR (ATR), υ (cm^{-1}): 3389 (N–H), 1601 (C = N), 1408 (B–N), 1206 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.69 (s, 1H, NH); 8.21 (d, $J = 8.4$ Hz, aromatic, 2H); 8.10 (d, $J = 8.2$ Hz, aromatic, 2H); 8.00–7.97 (m, aromatic, 2H); 7.60–7.58 (t, $J = 3.5$ Hz, aromatic, 3H); 3.29 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.1 (C=N); 143.5; 135.4; 135.3; 131.6; 129.7; 128.7; 127.2; 127.1; 126.9; 44.0 (CH_3). Anal. calcd. for $C_{14}H_{13}BN_2O_3S$: C, 56.02; H, 4.37; N, 9.33; found: C, 55.96; H, 4.38; N, 9.61.

5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7r***) yield 51 %; mp: 257–259 °C; IR (ATR), υ (cm^{-1}): 3417, 3377 (N–H), 1602 (C=N), 1415 (B–N), 1200 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 10.73 (s, 1H, NH); 8.36 (d, $J = 8.4$ Hz, aromatic 2H); 8.20 (d, $J = 8.4$ Hz, aromatic, 2H); 7.99–7.96 (m, aromatic, 2H); 7.59–7.58 (m, aromatic, 3H); ^{13}C NMR (DMSO-d_6), δ (ppm): 160.1 (C=N); 149.8; 135.7; 131.6; 129.7; 127.0; 126.9; 123.6. Anal. calcd. for $C_{13}H_{10}BN_3O_3$: C, 58.47; H, 3.77; N, 15.74; found: C, 59.02; H, 3.83; N, 15.80.

5-butyl-3-phenyl-4,5-dihydro-1,2,4,5-oxadiazaborole (***7s***) yield 49 %; mp: 92–94 °C; IR (ATR), υ (cm^{-1}): 3260 (N–H), 2926 (CH_2), 1558 (C=N), 1427 (B–N), 1223 (B–O); ^{1}H NMR (DMSO-d_6), δ (ppm): 9.82 (s, 1H, NH); 7.88–7.85 (m, aromatic, 2H); 7.49–7.47 (m, aromatic, 3H); 1.53–1.11 (m, 6H, CH_2–CH_2–CH_2); 0.89–0.84 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6), δ (ppm): 159.2 (C=N); 131.1; 129.5; 127.5; 126.8; 27.3, 25.5 (CH_2–CH_2–CH_2); 14.4 (CH_3). Anal. calcd. for $C_{11}H_{15}BN_2O$: C, 65.39; H, 7.48; N, 13.86; found: C, 65.59; H, 8.05; N, 14.25.

Biological assays

The antibacterial activities of 35 oxadiazaboroles (**4a–r** and **7a–s**) have been determined by the broth microdilution susceptibility test, which is outlined by the Clinical and Laboratory Standards Institute M7–A7 (CLSI, 2006). MICs for each compound were determined against *S. aureus*

(ATCC 25983), *E. faecalis* (ATCC 29212), *P. aeruginosa* (ATCC 27853), and *E. coli* (ATCC 25922).

MIC values for each compound were also determined against *S. mutans* (ATCC 25175). The antibacterial activities of oxadiazaboroles also have been evaluated using Mueller–Hinton broth with 2–5 % lyophilized horse blood for the determination of the wells in the microdilution plate containing the lowest concentration that has completely inhibited visible bacterial growth as recommended by the standards of the Committee Laboratory Standards Institute (CLSI, 2005).

Sterile, disposable, multiwell microdilution plates (96 U-shaped wells) have been used for broth microdilution procedures. The stock solutions were prepared in pure ethanol (Sigma). In the concentrations studied, ethanol had no effect on the microorganisms.

The antifungal activities of the compounds were also determined by using broth microdilution susceptibility test outlined by Clinical and Laboratory Standards Institute M27–A2 (CLSI, 2002). MIC values for each compound were also determined against *C. albicans* (ATCC 90028). Also, sterile, disposable, multiwell microdilution plates (96 U-shaped wells) have been used for broth microdilution procedures. The stock solutions were prepared in pure ethanol (Sigma) and again ethanol has no effect on the microorganisms in the concentrations studied.

Dilutions of the compounds

For antibacterial activities, all the dilutions of oxadiazaborole solutions were done in the wells of microdilution plates by Mueller–Hinton Broth (Oxoid). For *S. mutans* antimicrobial activity tests, Mueller–Hinton Broth (Oxoid) with lyophilized horse blood was used. The concentrations of the compounds were 1600, 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39, 0.19, 0.09, and 0.04 µg/mL. Ampicillin and ciprofloxacin were used as reference compounds, which were obtained from the manufacturers.

For antifungal activity, all dilutions of the compounds were done with RPMI medium with L-glutamine buffered, pH 7, with MOPS (Sigma) in the wells of microdilution plates. The concentrations of the compounds are the same as above. The fluconazole was used as a reference compound, which was also obtained from the manufacturers.

Inoculum preparation

After the dilutions of oxadiazaborole solutions, standardized inoculum of each bacterium (*S. aureus*, *E. faecalis*, *P. aeruginosa*, and *E. coli*) (0.5 Mc Farland standard unit, 1×10^8 CFU/mL; colony forming unit/mL) was prepared. Then, the solutions were diluted once more (1/10), and final concentrations became 1×10^7 CFU/mL. Five microliters from each dilution was placed into each well containing 100 µL of dilutions of the compounds so that each well contained 5×10^5 CFU/mL of inoculum. All the inoculated plates were incubated at 35 °C for 16–20 h. The lowest concentration of the compounds that prevents visible growth was considered to be the MIC. To control the reliability of the results, ampicillin and ciprofloxacin were used as reference antimicrobial reagents. The parameters of these reagents were compared with the data obtained from the method applied in this study.

The bacteria (*S. mutans*) were cultivated on a sheep agar plate for 36–48 h at 37 °C in 5–10 % CO_2, and incubation was done in a candle extinction jar. After diluting the compounds, standardized inoculum of each bacterium (0.5 Mc Farland standard unit, 1×10^8 CFU/mL; colony forming unit/mL) was prepared in Brain-Heart Infusion broth. Then the compounds were diluted once more (1/10), and the final concentrations became 1×10^7 CFU/mL. Five microliters from each dilution was placed into each well containing 100 µL of dilutions of compounds so that each well contained 5×10^5 CFU/mL of inoculum. All the inoculated plates were incubated at 35 °C for 36–48 h with 5–10 % CO_2. The lowest concentration of compounds that prevents visible growth was considered to be the MIC. Ampicillin was used as reference antimicrobial reagent to compare its parameters with the data that result from the method applied in this work and to control the reliability of the latter.

For antifungal activity, *Candida* isolates were subcultured in SDA plates, incubated at 35 °C for 24–48 h prior to antifungal susceptibility testing, and passaged at least twice to ensure purity and viability. An inoculum suspension was prepared from individual five colonies (diameter 1 mm). The suspension was adjusted to 0.5 Mc Farland Standard ($1–5 \times 10^6$ CFU/mL) and further diluted to 1/20 ($1–5 \times 10^5$ CFU/mL), then to 1/50 ($0.5–2.5 \times 10^5$ CFU/mL) in RPMI medium. Hundred microliters from each dilution was placed into each well containing 100 µL of dilutions of compounds so that each well contained 1×10^3 CFU/mL of inoculum. The MIC plates were incubated at 37 °C for 48 h. The end point was determined when the concentration produced optically clear wells (MIC-0) compared with that of drug-free growth control. To control the reliability of the results, fluconazole was used as reference antifungal reagent. The parameter of this reagent was compared with the data obtained from the method applied in this study. Every experiment for the antibacterial and antifungal assays was replicated twice. MIC values for antimicrobial activities are given in Tables 1 and 2, respectively.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicting interests.

References

Agirbas A (2015) The use of digital fabrication as a sketching tool in the architectural design process–a case study. eCAADe 2:319–324

Akama T, Baker SJ, Zhang YK, Hernandez V, Zhou H, Sanders V, Freund Y, Kimura R, Maples KR, Plattner JJ (2009) Discovery and structure–activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis. Bioorg Med Chem Lett 19:2129–2132

Akcan M (2007) The ring closure reactions of amidoximes with phenylboronic acid. MSc Thesis (YÖK Number: 216538), Abant İzzet Baysal University at Bolu

Baker SJ, Akama T, Zhang YK, Sauro V, Pandit C, Singh R, Kully M, Khan J, Plattner JJ, Benkovic SJ, Lee V, Maples KR (2006) Identification of a novel boron-containing antibacterial agent (AN0128) with anti-inflammatory activity, for the potential treatment of cutaneous diseases. Bioorg Med Chem Lett 16:5963–5967

Campbell-Verduyn LS, Bowes EG, Li H, Vallee AM, Vogels CM, Decken A, Gray CA, Westcott SA (2014) Heterocyclic amino-boron compounds as antituberculosis agents. Heteroat Chem 25(2):100–106

Ciaravino V, Plattner J, Chanda S (2013) An assessment of the genetic toxicology of novel boron-containing therapeutic agents. Environ Mol Mutagen 54:338–346

CLSI (Clinical Laboratory Standards Institute) (formerly NCCLS) (2002) Reference method for broth dilution antifungal susceptibility testing of yeast, 2nd edn. CLSI, Wayne, PA, Approved standard, CLSI document M27 A2

CLSI (Clinical Laboratory Standards Institute) (2005) Performance standards for antimicrobial susceptibility testing. Fifteenth Informational Supplement LSI-M110-S15. CLSI: Wayne, PA

CLSI (Clinical Laboratory Standards Institute) (formerly NCCLS) (2006) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M-7, A-7, CLSI: Wayne, PA

Das BC, Tang XY, Rogler P, Evans T (2012) Design and synthesis of 3,5-disubstituted boron-containing 1,2,4-oxadiazoles as potential combretastatin A-4 (CA-4) analogs. Tetrahedron Lett 53:3947–3950

Draper NR, Smith H (1981) Applied regression analysis, 2nd edn. Wiley, New York

Dürüst Y, Dürüst N, Akcan M (2007) Potentiometric study of acid-base equilibria of 3,5-disubstituted 1,2,4,5-oxadiazaboroles in nonaqueous media. J Chem Eng Data 52:718–720

Ferreira AM, Krishnamurthy M, Moore BM, Finkelstein D, Bashford D (2009) Quantitative structure–activity relationship (QSAR) for a series of novel cannabinoid derivatives using descriptors derived from semi-empirical quantum-chemical calculations. Bioorg Med Chem 17:2598–2606

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheesemann JR, Montgomery Jr JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2004) Gaussian 03. Gaussian, Inc, Wallingford, CT, Revision B. 05

Gosenca M, Mravljak J, Gasperlin M, Obreza A (2013) The design, synthesis, and antioxidant activity of amphiphilic oximes and amidoximes. Acta Chim Slov 60(2):310–322

Hansch C, Leo A, Taft RW (1991) A survey of Hammett substituent constants and resonance and field parameters. Chem Rev 91:165–195

Hansch C, Leo A, Unger SH, Kim KH, Nikaitani D, Lien EJ (1973) Aromatic substituent constants for structure-activity correlations. J Med Chem 16(11):1207–1216

HyperChem 7.2 for Windows (2002) Hypercube, Inc., Gainesville, FL

Jabbour A, Steinberg D, Dembitsky VM, Moussaieff A, Zaks B, Srebnik M (2004) Synthesis and evaluation of oxazaborolidines for antibacterial activity against *Streptococcus mutans*. J Med Chem 47:2409–2410

Kiska DL, Gilligan PH (1999) Pseudomonas. Manual of clinical microbiology. ASM Press, Washington, DC

Krüger P (1885) Ueber abkömmlinge des benzenylamidoksimes. Chem Ber 18:1053

Li X, Zhang YK, Liu Y, Ding CZ, Li Q, Zhou Y, Plattner JJ, Baker SJ, Qian X, Fan D, Liao L, Ni ZJ, White GV, Mordaunt JE, Lazarides LX, Slater MJ, Jarvest RL, Thommes P, Ellis M, Edge CM, Hubbard JA, Somers D, Rowland P, Nassau P, McDowell B, Skarzynski TJ, Kazmierski WM, Grimes RM, Wright LL, Smith GK, Zou W, Wright J, Pennicott LE (2010) Synthesis and evaluation of novel α-amino cyclic boronates as inhibitors of HCV NS3 protease. Bioorg Med Chem Lett 20:3550–3556

Li X, Zhang YK, Plattner JJ, Mao W, Alley MRK, Xia Y, Hernandez V, Zhou Y, Ding CZ, Li J, Shao Z, Zhang H, Xu M (2013) Synthesis and antibacterial evaluation of a novel tricyclic oxaborole-fused fluoroquinolone. Bioorg Med Chem Lett 23:963–966

Liu KC, Shelton BR, Howe RK (1980) E-Oximes were prepared from the corresponding aldehydes. J Org Chem 45:3916–3918

Myers RH (1987) Classical and modern regression with application. PWS Publishers, Boston, MA

Ross JE, Scangarella-Oman N, Jones RN (2013) Determination of disk diffusion and MIC quality control guidelines for GSK2251052: a novel boron-containing antibacterial. Diagn Micr Infec Dis 75:437–439

Sümengen D, Pelter A (1983) The preparation and rearrangements of 3,4-disubstituted 1,2,4-oxadiazoline-5-thions. J Chem Soc 4:687–691

Yale HL (1971) Novel boron heterocycles. 2,3-dihydro-1,3,5,2-oxadiazaboroles, 1,2-dihydro-1,3,2-benzodiazoborine-3-oxide, and 3,4-dihydro-2*H*-1,2,4,3-benzothiadiazaborine-1,1-dioxide. J Heterocycl Chem 8(2):205–208