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Synthesis, antimicrobial evaluation and QSAR studies of novel piperidin-4-yl-5-spiro-thiadiazoline derivatives

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ABSTRACT

In an attempt to find a new class of antimicrobial agents, a series of new 1,3,4-thiadiazolines were synthesized from 2,6-diarylpiperidin-4-ones, via the corresponding 4′-phenylthiosemicarbazones. All the synthesized compounds (**23**–**39**) were virtually screened against bacterial (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*) and fungal strains (*Candida albicans*, *Rhizopus sp*, *Aspergillus niger* and *Aspergillus flavus*) by serial dilution method. QSAR study indicated that the increase in weakly polar component of solvent accessible surface area will favour antibacterial activity while increase in polarizability and decrease in ionisation potential and hydrogen bond donor will favour antifungal activity.

Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. Hence, the development of newer antimicrobial agents is essential to overcome the rapidly developing drug resistance and side effects.[1]

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Among the family of heterocyclic compounds, nitrogen containing heterocycles especially piperidin-4-ones gain considerable importance owing to their varied biological properties such as antiviral, antitumour,[2] analgesic,[3] local anaesthetic,[4,5] antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities.[6–8] The skeletal ring of piperidine nucleus can also be often found in the molecular framework of many synthetic and natural medicaments.[9] 1,3,4-Thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial,[10–13] antifungal,[12,13] antitubercular,[14–16] and analgesic[17] agents.

Furthermore, synthesis of novel chemical entities, which are still in resemblance with bioactive molecules by virtue of the presence of some critical structural features, is an essential component of the search for new leads in drug designing programs. Hence, a careful perusal of literature on antimicrobial agents and our continued interest in the development of simpler and more convenient synthetic routes for achieving the biologically challenging heterocyclic systems,[18] has induced us to synthesize a class of molecules having piperidinyl-thiadiazolines and to evaluate their antimicrobial activity. The role of structural features is determined from QSAR studies.

As illustrated in Scheme 1, piperidin-4-yl-5-spiro-thiadiazolines (**23**–**39**) were synthesized. Conversion of ketone into 4′-phenylthiosemicarbazones are primarily depends upon the substitution of active methylene carbons. The C-3, C-5 unsubstituted and C-3 substituted ketones yield the corresponding 4′-phenylthiosemicarbazone, respectively, within 3–6 h, depending on the nature and size of the substituent. But ketones with methyl substitution at C-3 and C-5 take more than 72 h for the conversion. Thiosemicarbazones undergo cyclisation reaction with freshly distilled acetic anhydride to yield the desired product **23**–**39** as shown in Scheme 1. Under acetylating condition, thiosemicarbazones **12**–**22** with acetic anhydride in 2:1 ratio refluxed for 12–48 h yields 4-acetyl-2-(*N*-phenylamino)-5-spiro-(*N*-acetyl-2,6-diarylpiperidin-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles (**23**–**33**) whereas in equal mol ratio (1:1) of thiosemicarbazones and acetic anhydrides refluxed for 12–15 h exclusively yields 4-acetyl-2-(*N*-phenylamino)-5-spiro-(2,6-diarylpiperidin-4-yl)-4,5-dihydro-[1,3,4] thiadiazoles (**34**–**39**). All the synthesized compounds **23**–**39** were characterised by MS, IR, ^{1}H, and ^{13}C NMR spectroscopy and single crystal X-ray diffraction studies.

In compounds **23**–**33**, due to the presence of acetyl moiety at the piperidine ring nitrogen site, the coupling constant values are changed abnormally from their parent piperidones whose conformations have been well established by using their coupling

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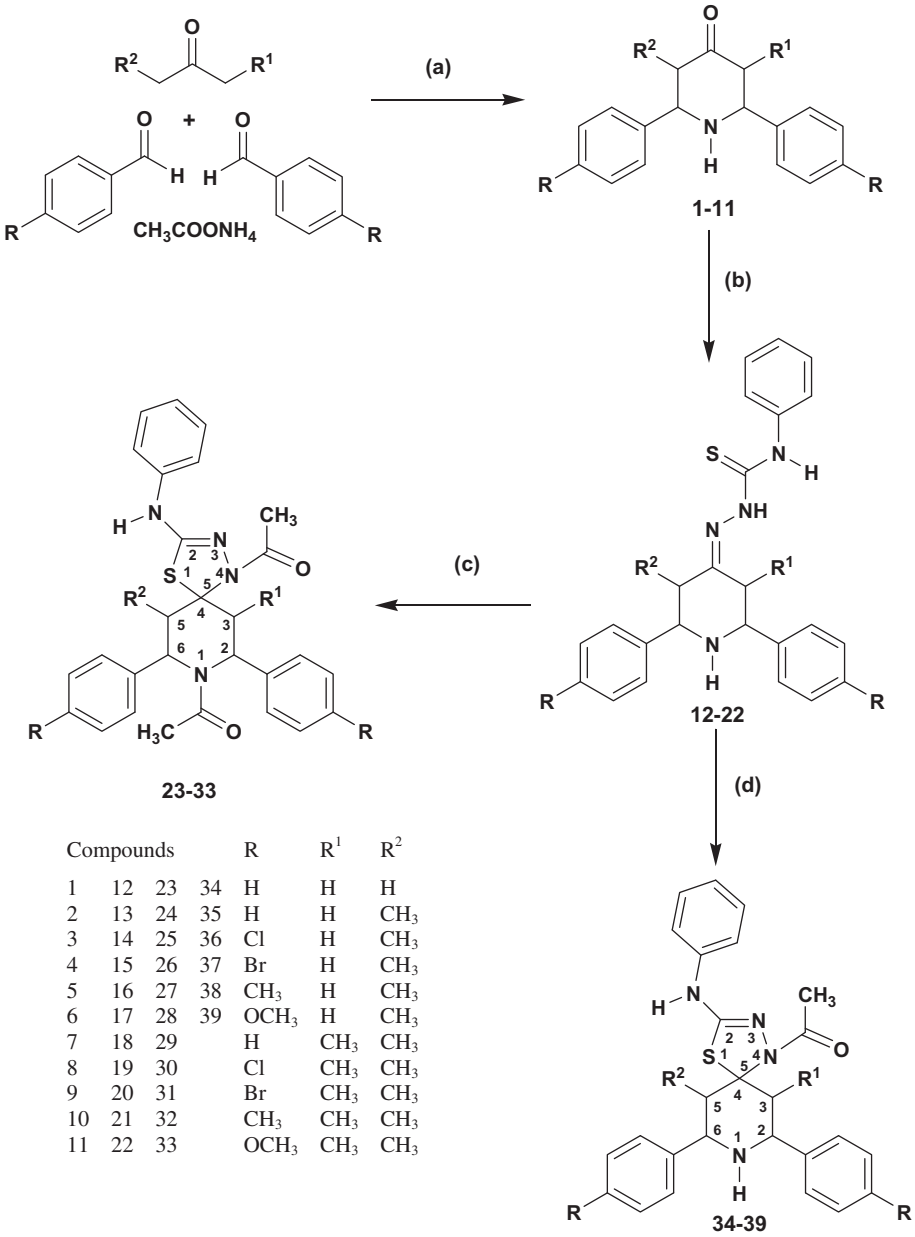

Compounds				R	R^1	R^2
1	12	23	34	H	H	H
2	13	24	35	H	H	CH_3
3	14	25	36	Cl	H	CH_3
4	15	26	37	Br	H	CH_3
5	16	27	38	CH_3	H	CH_3
6	17	28	39	OCH_3	H	CH_3
7	18	29		H	CH_3	CH_3
8	19	30		Cl	CH_3	CH_3
9	20	31		Br	CH_3	CH_3
10	21	32		CH_3	CH_3	CH_3
11	22	33		OCH_3	CH_3	CH_3

Scheme 1. Schematic representation showing synthesis of compounds **23**–**39**. Reagent and conditions: (a) EtOH/warm; (b) 4′-phenylthiosemicarbazide, H^+/MeOH, reflux, 3–72 h; (c) compounds **12**–**22** and Ac_2O (1:2), reflux, 12–48 h, 90 °C; (d) compounds **12**–**17** and Ac_2O (1:2), reflux, 12–15 h, 90 °C.

constants.[19] Hence, the observed vicinal coupling constants $^3J_{2,3} \approx 8.0$ Hz and $^3J_{5,6} \approx 7.0$ Hz suggest that compounds **23**–**33** are not in chair form. If it adopts a normal chair conformation with equatorial orientation of all substituents, the observed coupling constants $^3J_{2a,3a}$ and $^3J_{5a,6a}$ should be around 10.5 Hz. Moreover, the coupling constants are not favourable for boat conformation also. If it exists in a rigid boat form, the vicinal coupling constants should be about 4 Hz. Hence, the abnormal vicinal coupling constants indicate that piperidone ring adopts asymmetric non-chair conformation (see Supplementary data for more details) which is further confirmed from single crystal X-ray diffraction studies.

Of the synthesized compounds **23**–**33**, compounds **25** and **28** were suitable for single crystal XRD study. The ORTEP diagram of compound **25** is depicted in Figure 1. Analysis of torsion angles, asymmetry parameters and least-squares plane calculation[20] shows that the piperidine ring adopts a twist boat conformation with the puckering parameters and the smallest displacement asymmetry parameters[21] being $q^2 = 0.7369$ Å and $q^3 = -0.0490$ Å, total puckering amplitude, QT = 0.7385 (4) Å and $\theta = 93.80$ (3)°. The decrease in the N1–C28 bond length [1.352 (3) Å] when compared to C1–N1 [1.484 (3) Å] and C5–N1 (1.479 (3) Å) lengths indicates the effective conjugation between lone pair of nitrogen with carbonyl group. The torsion angles C1–N1–C28–C29 of 173.3(2)° and C5–N1–C28–O1 of −6.1 (3)° confirms the coplanar of N–$COCH_3$ group. The sum of the bond angles around N3 atom [359.3 (15)°] indicates the sp^2 hybridization. The torsion angles C27–C26–N2–N3 [−7.7 (3)°] and C27–C26–N2–C3 [−178.0 (2)°] indicate that atoms C27 and C26 lie in the plane of the five-membered ring (N2/N3/C19/S1/C3). The torsion angles C20–N6–C19–S1 [−170.02 (15)°], N3–C19–N6–S1 [8.1(19)°] and N6–C19–N3–N2 [−178.14 (18)°] also indicate that the substituted moiety at C18 lie in the plane of the ring to which it is attached. The ORTEP diagram of compound **28** is depicted in Figure 2.

In the case of compounds **34**–**39** the vicinal coupling constant values are similar to parent piperidones[19] which reveals that the piperidine ring in compounds **34**–**39** exist in chair conformation

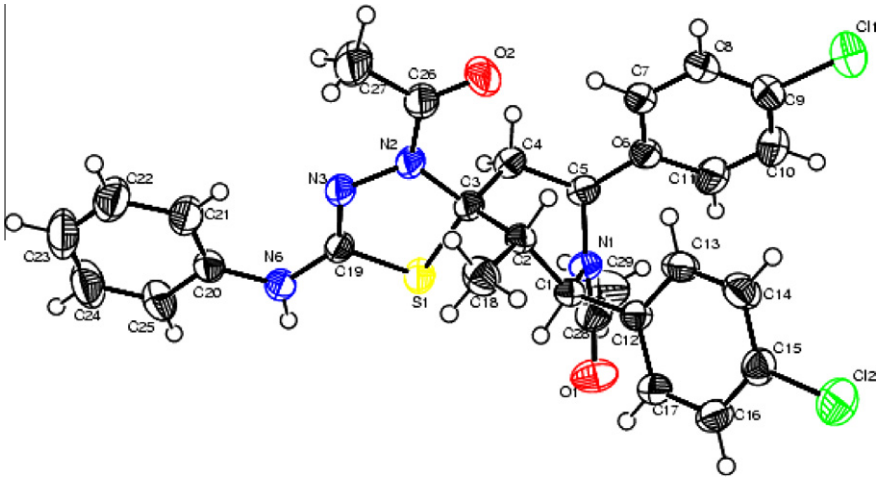

Figure 1. ORTEP diagram of compound **25**.

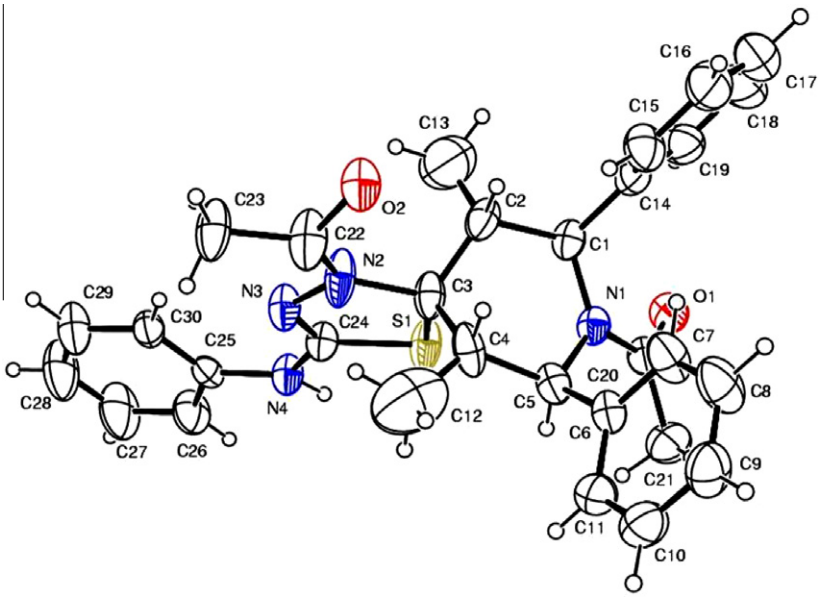

Figure 2. ORTEP diagram of compound **28**.

with equatorial orientation of aryl groups at C-2, C-6 and methyl group at C-3. Moreover the position of chemical shifts of compounds **34**–**39** suggests that the N–$COCH_3$ group of thiadiazoline moiety is oriented at equatorial disposition of C-4 carbon of six-membered heterocyclic ring akin to our earlier report[22] (Fig. 3) (see Supplementary data).

The synthesized compounds were tested against bacterial strains viz., *Staphylococcus aureus* (ATCC-25825), *Bacillus subtilis* (ATCC-451), *Salmonella typhi* (ATCC-24915), *Escherichia coli* (ATCC-25835) and *Klebsiella pneumonia* (ATCC-15490) and fungal strains viz. *Cryptococcus neoformans* (ATCC-3312), *Candida albicans* (ATCC-3122), *Rhizopus* sp. (ATCC-2915), *Aspergillus niger* (ATCC-598) and *Aspergillus flavus* (ATCC-485) using the literature precedent.[23] Ciprofloxacin and Amphotericin B were used as standard for bacteria and fungal strains, respectively.

The compounds with methyl substitution at C-3 and C-5 of piperidine showed remarkable increase in antimicrobial activity than the unsubstituted and methyl substitution at C-3 of piperidine ring. A close analysis of the screening results reveals that the halogen substitution at *para*-position of phenyl ring at C-2 and C-6 piperidine ring increased antimicrobial activity. It is to be noted that the presence of N-acetyl group in the piperidine ring shows improved antibacterial and antifungal activity, while, the replacement of methyl or methoxy group in place of halogens shows decrease in antimicrobial activity.

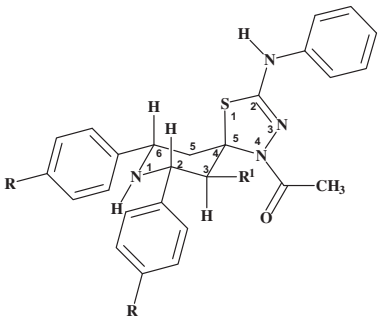

Figure 3. Conformation of compounds **34**–**39**.

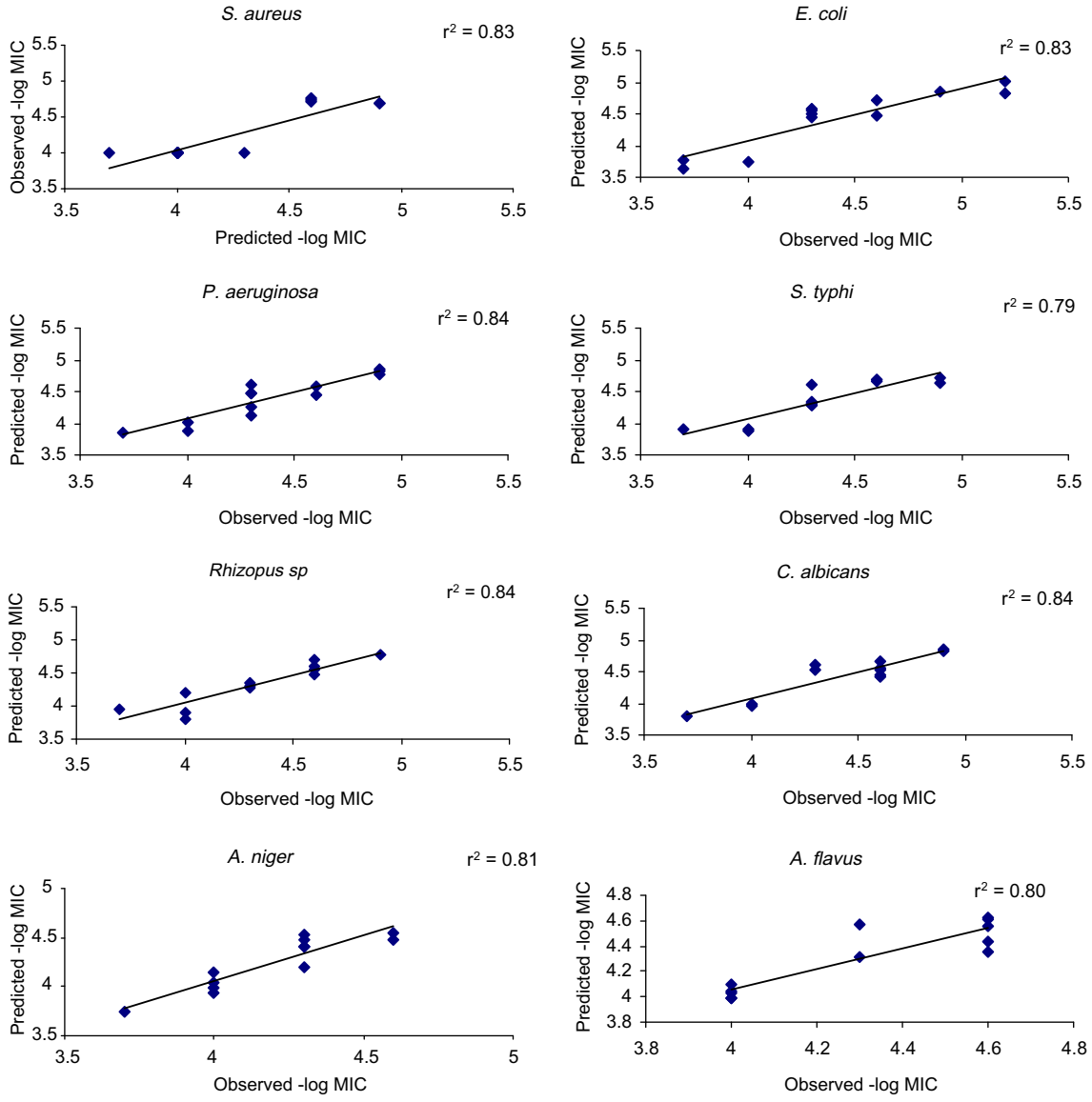

Figure 4. Comparison of observed and predicted activities of the compounds in the training set.

The quantitative structure–activity relationship (QSAR) analysis was undertaken to establish the relationship between antimicrobial activity of the synthesized compounds and their molecular descriptors. Structures of the synthesized compounds were sketched and cleaned up in Maestro.[24] The structures were processed using LigPrep[25] and minimized using MacroModel[26] with OPLS-2005 force field. Molecular descriptors were generated by QikProp[27] for each of the minimized compound reflecting Monte Carlo simulation studies.[28] The 'forward stepping' method was used to build QSAR equations in Strike[29] programme between pMIC activity of the synthesized compounds and their molecular descriptors. Combinations of descriptors were selected for analysis based on low interrelationship limit <0.50.[30] Based on structural variation and biological activity, compounds were divided into a training set of 13 compounds (75% of the dataset) and a test set of 4 compounds (25% of the dataset). Multiple linear regression method was used to identify the statistically important QSAR model on the basis of squared correlation coefficient (r^2), standard deviation (S.D), Fisher's value (F), Q (r/S.D) value and t-value for the training set. Robustness of the derived models were verified by using three different types of validation viz. (i) Leave one out (LOO) internal validation or cross-validation (q^2), (ii) external validation by predicting the activity of test set (four compounds) and (iii) randomization test.[31] Local Correlation Integral Outlier (LOCI) detection methodology by Strike was used to remove the outlier which uses a density-based approach to identify outliers within the data set.[29]

The experimental and predicted values of pMIC of training and test set compounds are given in Supplementary data. The final statistically valid QSAR models detailing statistical qualities and descriptors are tabulated in Tables 1 and 2, respectively. The graphs of predicted pMIC versus experimental pMIC for the training and test sets are depicted in Figures 4 and 5, respectively.

Eqs. 1–4 indicate the predominance of Weakly Polar component of Solvent accessible surface Area (WPSA) in describing the activity against all the bacterial strains taken in the present study. WPSA descriptor pertains to the surface area for all halogens, sulfur and phosphorous atoms, and correlates positively with the antibacterial activity. This justifies the increased antibacterial activity of the compounds substituted with halogens. From Eqs. 2 and 3 it can be stated that polarizability and PISA negatively correlates with pMIC of *E. coli* and *P. aeruginosa*, respectively. Descriptor PISA

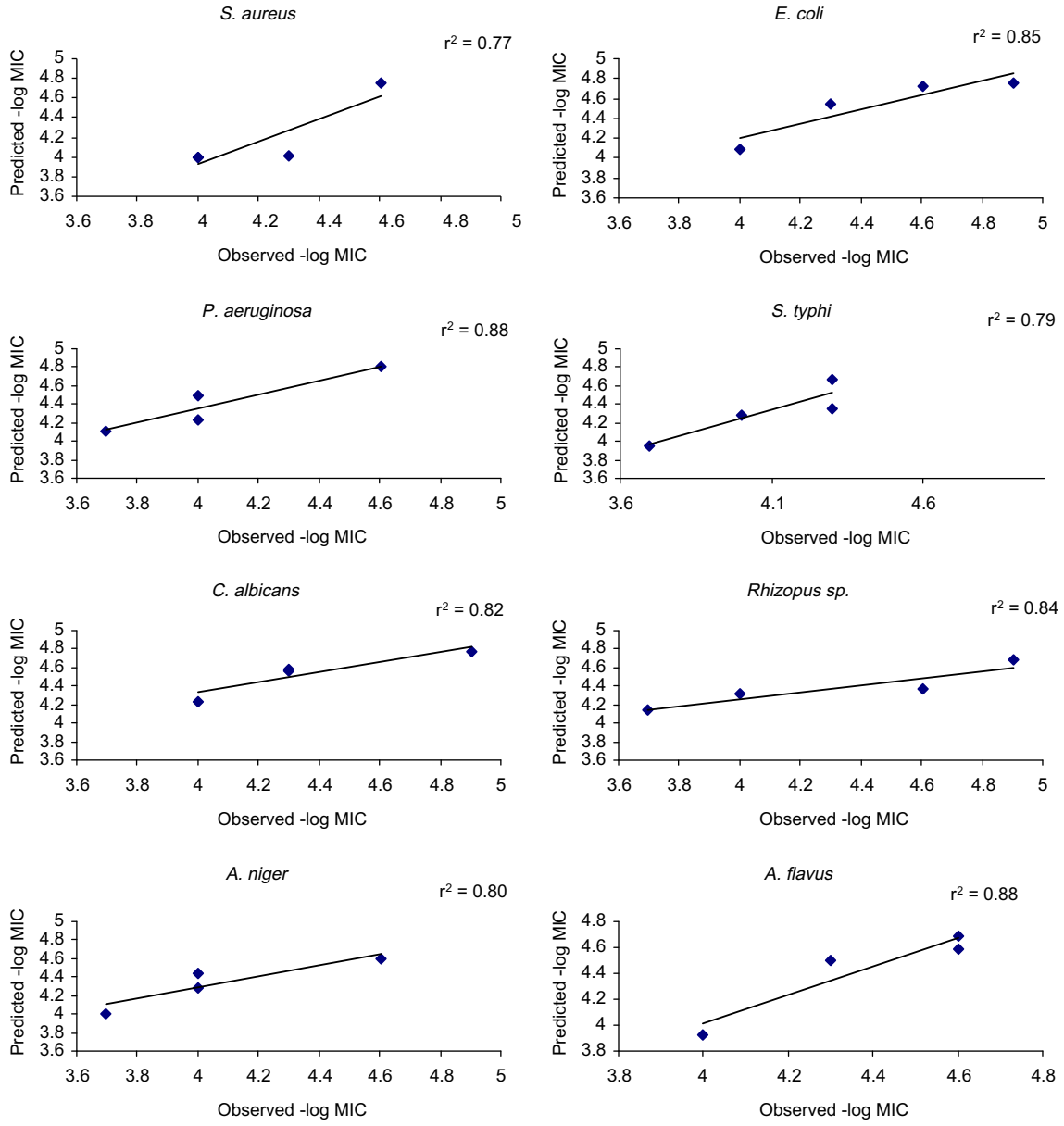

Figure 5. Comparison of observed and predicted activities of the compounds in the test set.

Table 1
QSAR statistics of modelled equations

Organism	*n*	r^2	R	S.D.	Q	q^2	*F* value	*P* value	Randomized r^2	r^2_{pred}
S. aureus	13	0.83	0.91	0.17	5.352	0.76	53.5 (1,11)	$1.514e^{-05}$	0.074	0.77
E. coli	12	0.83	0.91	0.23	3.957	0.72	21.6 (2, 9)	$3.690e^{-04}$	0.183	0.85
P. aeruginosa	13	0.84	0.92	0.17	5.411	0.71	25.3 (2,10)	$1.218e^{-04}$	0.138	0.88
S. typhi	12	0.79	0.89	0.18	4.944	0.66	17.3 (2,9)	$8.298e^{-04}$	0.184	0.79
C. albicans	12	0.84	0.92	0.16	5.750	0.79	53.4 (1,10)	$2.573e^{-05}$	0.085	0.82
Rhizopus sp.	12	0.84	0.92	0.15	6.133	0.71	23.8 (2,9)	$2.531e^{-04}$	0.178	0.84
A. niger	12	0.81	0.90	0.15	6.000	0.69	19.5 (2,9)	$5.347e^{-04}$	0.167	0.80
A. flavus	12	0.80	0.89	0.13	6.846	0.74	42.1 (1,10)	$6.989e^{-05}$	0.081	0.88

quantifies the π component of solvent accessible surface area, that is, it reflects hydrophobicity of the molecule due to aromatic region. As PISA is negatively correlated with pMIC, any substitution which decreases aromatic hydrophobicity of the molecule will favour the antibacterial activity against *P. aeruginosa*. This is also evident from the experimental results that compound **23** showed high PISA value and less activity against *P. aeruginosa*. In Eq. 4, descriptor hydrophobic surface area (FOSA) correlates positively with the antibacterial activity against *S. typhi*. FOSA represents the aliphatic portion of the solvent-accessible surface area that is composed of saturated carbons and the attached hydrogen.[32] This explains the increased biological activity of the compounds having methyl or methoxy substitutions. However *t*-value (Table 2) indicates that the halogens (WPSA) are more significant in increasing the biological activity when compared to methyl or methoxy substitutions (FOSA) which is in accordance with the experimental results.

Table 2
Best multiple linear regression model and *t*-values

Variable	Coefficient	S.E	*t*-value
Eq. 1 for S. aureus			
Intercept	3.997	0.061	65.495
WPSA	$4.759e^{-03}$	$6.507e^{-04}$	7.314
Eq. 2 for E. coli			
Intercept	−6.482	1.984	3.267
WPSA	$1.286e^{-03}$	$9.851e^{-04}$	1.306
Polarizability	$-2.008e^{-01}$	$3.723e^{-02}$	5.394
Eq. 3 for P. aeruginosa			
Intercept	5.615	$3.220e^{-01}$	17.435
PISA	$-3.234e^{-03}$	$7.169e^{-04}$	4.511
WPSA	$2.688e^{-03}$	$6.605e^{-04}$	4.069
Eq. 4 for S. typhi			
Intercept	3.699	$1.582e^{-01}$	23.383
FOSA	$2.121e^{-03}$	$7.135e^{-04}$	2.973
WPSA	$4.919e^{-03}$	$8.377e^{-04}$	5.872
Eq. 5 for C. albicans			
Intercept	−4.236	1.186	3.572
Polarizability	$1.608e^{-01}$	$2.200e^{-02}$	7.309
Eq. 6 for Rhizopus sp.			
Intercept	3.078	$4.234e^{-01}$	7.271
HB donor	$-5.734e^{-01}$	$9.380e^{-02}$	6.112
Log *P*	$3.966e^{-01}$	$8.405e^{-02}$	4.719
Eq. 7 for A. niger			
Intercept	1.717	1.014	1.693
Volume	$2.157e^{-03}$	$6.809e^{-04}$	3.167
HB donor	$-4.274e^{-01}$	$9.299e^{-02}$	4.596
Eq. 8 for A. flavus			
Intercept	40.912	6.906	7.112
IP	−5.276	$8.130e^{-01}$	6.489

In Eq. 5, polarizability has positive correlation with the antifungal activity against *C. albicans*. Polarizability is related to size and hydrophobicity of the compound. Sharma et al. observed that increasing the polarizability of the compounds with bulkier substitution increased the antifungal activity.[33] Hydrogen bond (HB) donor negatively correlates with the antifungal activity of the compounds against *Rhizopus* sp. and *A. niger* (Eqs. 6 and 7). In addition, Eq. 6 indicates that lipophilicity can increase the antifungal activity of the synthesized compounds against *Rhizopus* sp. This may be due to the increased facilitation of the permeability of the molecules through the fungal cell membrane.[34] Compound **26** had high lipophilicity value (6.126) and exhibits better activity against *Rhizopus sp*. From the Eq. 7 it can be stated that high molecular volume favours the antifungal activity against *A. niger* which is also evident from the experimental data. Further, a decrease in ionisation potential favours the antifungal activity against *A. flavus* (Eq. 8). Ionisation potential highly correlates with WPSA (see Supplementary data for more details) which implies that decrease in halogens is favourable for antifungal activity against *A. flavus*. As per the obtained Eq. 8, the compounds which are substituted with methyl or methoxy groups showed better antifungal activity against *A. flavus*.

In conclusion, QSAR analysis indicated that substituents like fluoro, chloro, bromo may increase the antibacterial potency of the compounds. While introducing bulkier substituents in the synthesized compounds, increasing the polarizability and hydrophobicity may increase the antifungal activity. The information presented here may effectively be used for designing newer compounds with improved antimicrobial potential.

Supplementary data

Detailed methodology of QSAR, complete experimental details and conformation studies are given. Supplementary crystallographic data for compounds **25** (CCDC No. 697341) and **28** (CCDC No. 686014) can be obtained free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html.

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References and notes

1. (a) Projan, S. J.; Shlaes, D. M. *Clin. Microbiol. Infect.* **2004**, *10*, 18; (b) Fidler, D. F. *Emerg. Infect. Dis.* **1998**, *4*, 169; (c) Oren, I.; Temiz, O.; Yalcin, I.; Sener, E.; Altanlar, N. *Eur. J. Pharm. Sci.* **1998**, *7*, 153; (d) Hong, C. Y. J. *Farmaco* **2001**, *56*, 41; (e) Macchiarulo, A.; Constantino, G.; Fringuelli, D.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. *Bioorg. Med. Chem.* **2002**, *10*, 3415; (f) Hatya, S. A.; Aki-sener, E.; Tekiner-Gulbas, B.; Yildiz, I.; Temiz-Arpaci, O.; Yalcin, I.; Altanlar, N. *Eur. J. Med. Chem.* **2006**, *41*, 1398.
2. El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-obaid, A. M. *J. Med. Chem.* **2000**, *43*, 2915.
3. Jerom, B. R.; Spencer, K. H. *Eur. Pat. Appl.* **1988**, EP 277794.
4. Perumal, R. V.; Adiraj, M.; Shanmugapandiyan, P. *Indian Drugs* **2001**, *38*, 156.
5. Hagenbach, R. E.; Gysin, H. *Experientia* **1952**, *8*, 184.
6. Mobio, I. G.; Soldatenkov, A. T.; Federov, V. O.; Ageev, E. A.; Sergeeva, N. D.; Lin, S.; Stashenku, E. E.; Prostakov, N. S.; Andreeva, E. L. *Khim. Farm. Zh.* **1989**, *23*, 421.
7. Katritzky, A. R.; Fan, W. J. *J. Org. Chem.* **1990**, *55*, 3205.
8. Ganellin, C. R.; Spickett, R. G. W. *J. Med. Chem.* **1965**, *8*, 619.
9. Daly, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic press: Sandiego, CA, 1998; p 141.
10. Modzelewska-Banachiewicz, B.; Banachiewicz, J.; Chodkowska, A.; Jagiello-Wójtowicz, E.; Mazur, L. *Eur. J. Med. Chem.* **2004**, *39*, 873.
11. Foroumadi, A.; Emami, S.; Hassanzadeh, A.; Rajaee, M.; Sokhanvar, K.; Moshafi, M. H.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4488.
12. Farghaly, A. A.; Bekhit, A. A.; Park, J. Y. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 53.
13. Kadi, A. A.; El-Brollosy, N. R.; Al-Deeb, O. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 235.
14. Solak, N.; Rollas, S. *Arkivoc xii* **2006**, 181.
15. Mamolo, M. G.; Falagiani, V.; Zampieri, D.; Vio, L.; Banfi, E.; Scialino, G., II *Farmaco* **2003**, *58*, 631.
16. Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Ranise, A.; Filippelli, W.; Rinaldi, B.; Capuano, A.; Falcone, G. *Bioorg. Med. Chem.* **2006**, *14*, 1698.
17. Foroumadi, A.; Emami, S.; Pournourmohammadi, S.; Kharazmi, A.; Shafiee, A. *Eur. J. Med. Chem.* **2005**, *40*, 1350.
18. (a) Balasubramanian, S.; Ramalingan, C.; Aridoss, G.; Parthiban, P.; Kabilan, S. *Med. Chem. Res.* **2004**, *13*, 297; (b) Balasubramanian, S.; Ramalingan, C.; Aridoss, G.; Kabilan, S. *Eur. J. Med. Chem.* **2005**, *40*, 694; (c) Balasubramanian, S.; Aridoss, G.; Parthiban, P.; Kabilan, S. *Biol. Pharm. Bull.* **2006**, *29*, 125; (d) Aridoss, G.; Balasubramanian, S.; Parthiban, P.; Kabilan, S. *Eur. J. Med. Chem.* **2007**, *42*, 851; (e) Aridoss, G.; Amirthaganesan, S.; Ashok kumar, N.; Kim, J. T.; Kabilan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542; (f) Aridoss, G.; Parthiban, P.; Ramachandran, R.; Prakash, M.; Kabilan, S.; Jeong, Y. T. *Eur. J. Med. Chem.* **2009**, *44*, 577.
19. Pandiarajan, K.; Sekar, R.; Anantharaman, R.; Ramalingam, V. *Indian J. Chem.* **1991**, *30B*, 490.
20. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
21. Nardelli, M. *Acta Crystallogr., Sect. C* **1983**, *39*, 1141.
22. Umamatheswari, S.; Kabilan, S. *J. Mol. Struct.* **2009**, *938*, 142.
23. Dhar, M. L.; Dhar, M. M.; Dhawan, B. N.; Mehrotra, B. N.; Ray, C. *Indian J. Exp. Biol.* **1968**, *6*, 232.
24. Maestro, Version 9.0, Schrödinger, LLC, New York, NY, 2009.
25. LigPrep, Version 2.3, Schrödinger, LLC, New York, NY, 2009.
26. MacroModel, Version 9.7, Schrödinger, LLC, New York, NY, 2009.
27. QikProp, Version 3.2, Schrödinger, LLC, New York, NY, 2009.
28. Duffy, E. M.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2000**, *122*, 2878.
29. Strike, Version 1.8, Schrödinger, LLC, New York, NY, 2009.
30. Dimov, N.; Osman, A.; Mekenyan, O. V.; Papazova, D. *Anal. Chim. Acta* **1994**, *298*, 303.
31. Roy, P. P.; Leonard, J. T.; Roy, K. *Chemom. Intell. Lab. Syst.* **2008**, *90*, 31.
32. Cao, Q.; Garib, V.; Yu, Q.; Connell, D. W.; Campitelli, M. *Chemosphere* **2009**, *76*, 453.
33. Sharma, P.; Kumar, A.; Sharma, S.; Rane, N. *Bioorg. Med. Chem. Lett.* **2007**, *15*, 937.
34. Purushottamachar, P.; Kulkarni, V. M. *Bioorg. Med. Chem.* **2003**, *11*, 3487.