Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Medicinal Chemistry 41 (2006) 833–840
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://france.elsevier.com/direct/ejmech

Original article

Synthesis and QSAR studies on 5-[2-(2-methylprop1-enyl)-1*H* benzimidazol-1yl]-4,6-diphenyl-pyrimidin-2-(5*H*)-thione derivatives as antibacterial agents

P. Sharma *, A. Kumar, M. Sharma

School of chemical sciences, Devi-Ahilya university, Indore 452 017, India

Received 9 September 2005; received in revised form 22 February 2006; accepted 2 March 2006
Available online 26 May 2006

Abstract

A new series of 5-[2-(2-methylprop1-enyl)-1*H* benzimidazol-1yl]-4,6-diphenyl-pyrimidin-2-(5*H*)-thione derivatives [**3a**–**q**] has been synthesized and subjected to evaluate their antibacterial properties. All the synthesized compounds of the series displayed, remarkable activity in comparison to standard drug (ampicillin). A number of descriptors were tested to adjudge a quantitative correlation between activity and structural features. However, significant correlations have emerged between activity and physicochemical parameters viz. polarizability parameter (MR). Moreover, results are interpreted on the basis of multiple regression and cross-validation methodology.

Keywords: Phase transfer catalysis; Physicochemical parameters; Quantitative structure–activity relationship (QSAR); 5-[2-(2-methylprop1-enyl)-1*H* benzimi dazol-1yl]-4,6-diphenyl- pyrimidin-2-(5*H*)-thiones

1. Introduction

Interest in benzimidazole-containing structures stems from their widespread occurrence in molecules that display a plethora of useful biological properties. Substituted benzimidazole derivatives have found commercial application in veterinarian medicine as anthelmintic agents and in such diverse human therapeutic areas as antiulcers [1], antihypertensives [2], antivirals [3], antifungals [4], anticancers [5] and antihistaminics [6] to name just a few. In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly qualify them as 'privileged sub-structures' for drug design [7]. Benzimidazoles are the component of vitamin B12 and are related to the DNA base purine and the stimulant caffeine. Bisbenzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity [8] and can act as ligands to transition metals for modeling biological systems [9]. The advent of high-throughput screening technologies has impacted significantly on the methodologies that are used for the synthesis of medicinal compounds. The implementation in the laboratory of high-throughput synthetic techniques to increase the number of molecules generated by chemists is now a prerequisite to competitive advantage in the field. The parallel synthesis of benzimidazole libraries is a good example of this trend and several publications describing methodologies for this application, both in solution phase and on solid supports, have appeared in the literature [10–13].

However, little progress has been made in deducing antimicrobial behavior of benzimidazole derivatives [14], which need to be investigated thoroughly. It has been observed that resistance of several bacteria against commercially available drugs increases tremendously. As a result, there is an urgent need for new antibiotic agents, which would fight against bacterial infections. These threats have rekindled our interest in search of new compounds and in continuation of our previous work on heterocyclic systems [15–19], we herein report a novel method of synthesis of 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazol-1yl]-4,6-diphenyl-pyrimidin-2-(5*H*)-thione derivatives under the phase transfer catalysis conditions vis-a-vis exploration of their antibacterial activity.

* Corresponding author.
E-mail address: drpratibhasharma@yahoo.com (P. Sharma).

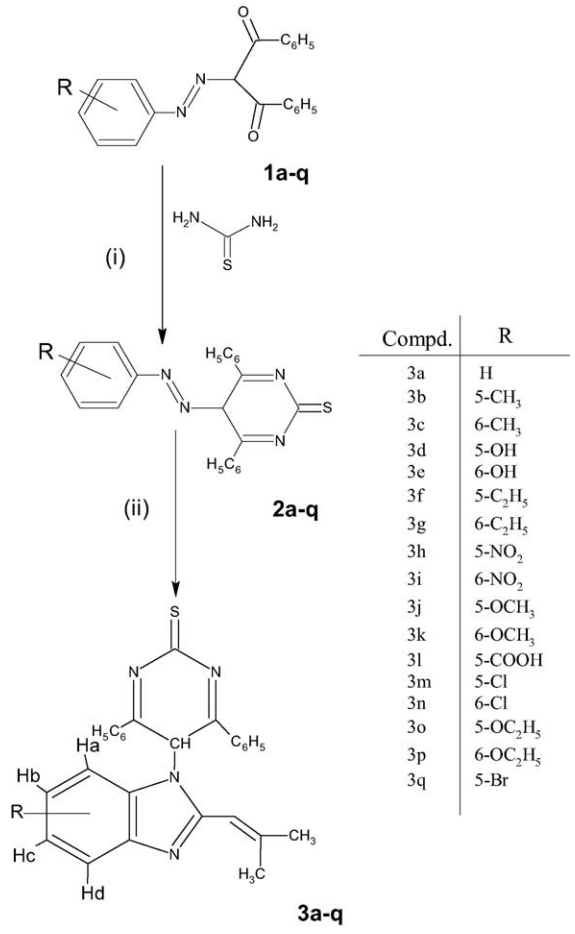
0223-5234/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.ejmech.2006.03.022

Quantitative structure–activity relationship (QSAR) studies have been investigated on the basis of the fact that the biological activity of a compound is a function of its physicochemical properties [20–22]. Physicochemical parameters, which represent structural features of the compounds—for example, hydrophobicity (lipophilicity) and steric properties—govern the biological activity to a greater extent. For the sake of present purpose, QSAR analysis of synthesized benzimidazole compounds was performed based on the assumption of linear additive contributions of the different physicochemical properties. Multiple regression analysis was applied to generate QSAR models and to obtain statistical parameters, i.e. correlation coefficient (r), standard deviation (s), F-test, cross validated correlation coefficient (r^2_{CV}), sum of square standard error (SPRESS), predicted residual sum of squares (PRESS) and sum of the squares of response value (SSY). These statistical data were utilized in order to have a judicious interpretation for effective QSAR models. The best-derived QSAR model was used to predict the activity of the tested compounds and to suggest structural features, which could be incorporated in order to manifest enhanced biological activity.

2. Results and discussion

2.1. Chemistry

The synthesis of 5-[2-(2-methylprop1-enyl)-1*H* benzimidazol-1yl]-4,6-diphenyl- pyrimidin-2-(5*H*)-thione derivatives (**3a–q**) was carried out under phase transfer catalytic conditions as per Scheme 1. The key intermediate 4,6-diphenyl-5-[(2-phenyldiazenyl) pyrimidin-2(5*H*)-thione] derivatives (**2a–q**) was prepared by condensation of 1,3-diphenyl-2-(aryldiazenyl) propane-1,3-diones which is obtained by reported method [23] (**1a–q**) with phenyl thiourea [24]. Compound **2(a–q)** upon treatment with dimethylvinylidene carbene (which was generated in situ as an intermediate product of 3-chloro-3-methyl-1-butyne) in the presence of aqueous potassium hydroxide under phase transfer catalysis conditions resulted in the insertion-cyclization of carbene fragment into N=N moiety of precursor to yield the required 4,6-diphenyl-5[2-(2-methylprop1-enyl)-1*H*-benzimidazol-1yl] pyrimidin-2-(5*H*)-thione derivatives (**3a–q**). Energy minimized geometry of the highest active 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6-diphenyl-6-ethoxypyrimidene-2-(5*H*)-thione(**3o**)is shown in Fig. 1.



Compd.	R
3a	H
3b	5-CH_3
3c	6-CH_3
3d	5-OH
3e	6-OH
3f	5-C_2H_5
3g	6-C_2H_5
3h	5-NO_2
3i	6-NO_2
3j	5-OCH_3
3k	6-OCH_3
3l	5-COOH
3m	5-Cl
3n	6-Cl
3o	5-OC_2H_5
3p	6-OC_2H_5
3q	5-Br

Scheme 1. Reagents and conditions: (i) C_2H_5ONa/C_2H_5OH, stirring, 1 h; (ii) 50% KOH, BTEAC, 3-chloro-3-methyl-1-butyne, benzene, stirring, 30 min.

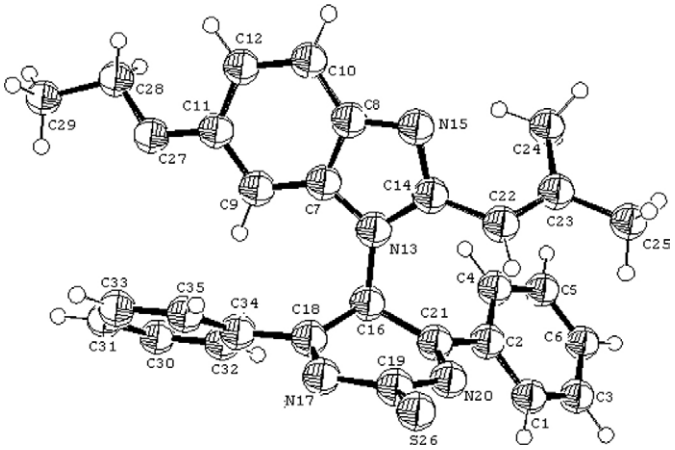


Fig. 1. ORTEP diagram of compound 3O (PM3 optimized geometry). The atom numbers are arbitrary.

2.2. Biological activities

The in vitro antibacterial activity of the 5-[2-(2-methylprop1-enyl)-1*H*- benzimidazole-1yl]-4,6-diphenyl pyrimidene-2-(5*H*)-thione derivatives has been investigated against several representative pathogenic bacteria. Minimal inhibitory concentration (MIC) was determined by means of standard twofold serial dilution method using nutrient agar media [25]. Inocula containing approximately 10^7CFU ml^{-1} of bacteria were prepared from broth culture in log phase. Bacterial plates were incubated at 37 °C for 24 h. Four microbial strains i.e. *Bacillus subtilis*, *Staphylococcus aureus, Escherichia coli* and *Pseudomonas diminuta* were used in antimicrobial assay. Ampicillin trihydrate was also screened under similar conditions as reference antibacterial drug. All the synthesized compounds have been found to delineate profound antimicrobial potency as compared to reference drug within a MIC range of

Table 1
The in vitro antimicrobial activity of 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6-diphenyl pyrimidine-2-(5*H*)-thione derivatives(**3a–q**)

Compound	R	–logMIC in μg ml^{-1}			
		SA	BS	PD	EC
3a	H	3.984	3.974	3.956	3.947
3b	5-CH_3	4.189	4.160	4.140	4.133
3c	6-CH_3	4.160	4.133	4.121	4.108
3d	5-OH	4.041	4.030	4. 010	4.00
3e	6-OH	4.020	4.00	3.991	3.982
3f	5-C_2H_5	4.820	4.711	4.662	4.624
3g	6- C_2H_5	4.665	4.624	4.551	4.519
3h	5-NO_2	4.402	7.380	4.338	4.319
3i	6-NO_2	4.380	4.359	4.317	4.301
3j	5-OCH_3	4.345	4.295	4.280	4.269
3k	6-OCH_3	4.325	4.269	4.261	4.252
3l	5-COOH	4.265	4.233	4.214	4.203
3m	5-Cl	4.290	4.256	4.237	4.224
3n	6-Cl	4.273	4.239	4.220	4.208
3o	5-OC_2H_5	5.200	5.078	4.902	4.835
3p	6-OC_2H_5	5.060	4.865	4.835	4.777
3q	5-Br	4.630	4.521	4.534	4.505
A	–	3.907	4.606	4.429	4.605

A: *ampicilin*; SA: *S. aureus;* BS: *B. subtilis;* PD: *P. diminuta*; EC*: E. coli*.

3–48 μg ml^{-1}. The screening results depicted in Table 1, reveals that reported compounds showed a remarkable effect on the bacteriocidal/bacterostatic potency, as per the pattern shown below:

S.aureus > *B.subtilis* > *P.dimunata* > *E.coli*

It is deduced from the data that the compounds having electron-withdrawing groups i.e. NO_2, Cl and alkylated hydroxyl substitution tends to enhance the antibacterial activity. In general, it has been observed that antimicrobial results follow the pattern:

3o > 3p > 3f > 3g > 3q > 3j > 3k > 3l > 3m > 3n > 3d > 3e > 3c > 3b > 3a

Table 2
Values of selected descriptors calculated for 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6-diphenyl pyrimidine-2-(5*H*)-thione derivatives (**3a–q**)

Compound	$HOMO_{ene}$	$LUMO_{ene}$	ddene	log *P*	MR
3a	–8.811	–1.973	–0.061	6.885	1.103
3b	–8.768	–1.948	–0.288	6.316	0.565
3c	–8.767	–1.958	–0.038	6.316	0.565
3d	–8.767	–1.958	–0.038	6.953	0.285
3e	–8.726	–1.858	–0.558	5.885	0.285
3f	–8.791	–1.957	–0.246	6.845	1.030
3g	–8.774	–1.957	–0.407	6.845	1.030
3h	–10.967	–5.782	0.875	2.525	0.736
3i	–10.817	–5.638	1.887	2.525	0.736
3j	–8.685	–1.919	–0.143	6.065	0.787
3k	–8.705	–1.838	–0.738	6.065	0.787
3l	–8.927	–2.092	1.578	5.834	0.693
3m	–8.864	–2.008	0.381	6.556	0.603
3n	–8.771	–1.949	0.610	6.556	0.603
3o	–8.650	–1.927	–0.178	6.594	1.247
3p	–8.702	–1.836	–0.700	6.594	1.247
3q	–8.893	–2.061	0.347	6.706	0.888
A	–8.956	–0.228	0.675	–1.204	9.114

A: ampicillin.

2.3. QSAR analysis

In order to deduce the correlation of observed activity, in terms of MIC (μg ml^{-1}) of reported compounds with different structural parameters, systematic QSAR investigations have been carried out using the model proposed by Hansch and co-workers [26].

The activity data (MIC) represents the concentration of compounds that inhibited visible growth in various bacterial species. The same are further expressed as –log MIC on molar basis and used as dependent variables to get linear relationship in QSAR model. The calculated parameters used in the present studies include molar refractivity (MR), dipole–dipole energy (ddene), and partition coefficient (*P*). The above-mentioned parameters were calculated using Chem 3D 6.0 software [27]. Further, HOMO and LUMO energies were calculated by semi-empirical PM3 [28] studies using MOPAC 6.0 package [29]. The MR and partition coefficient were calculated by chempro-pro server and ddene values were calculated by MM2 server available in Chem 3D 6.0.

The best fit between –log MIC values and these explaining parameters were obtained through multiple regression analysis (MRA) employing the method of least square. Calculated parameters and correlation matrix needed is shown in Tables 2 and 3.

Out of a number of parametric evaluations, only molar refractivity exhibited a good correlation ($r^2 > 0.89$) with biological activity.

The resulting mono-parametric models are depicted in Eqs. (1)–(4), along with statistical parameters of the regression. No outliers have been detected and the equations were derived using the entire data set ($N = 17$).

QSAR model for *S. aureus*

$$-\log \text{MIC} = [3.664(\pm 0.156)] + \text{MR}[1.047(\pm 0.200)] \quad (1)$$
$$N = 17,\ \text{r} = 0.945,\ \text{s} = 0.118,\ \text{F} = 125.94$$

QSAR model for *B. subtilis*

$$-\log \text{MIC} = [3.732(0.095)] + \text{MR}[0.799(\pm 0.122)] \quad (2)$$
$$N = 17,\ r = 0.963,\ \text{s} = 0.072,\ \text{F} = 195.86$$

QSAR model for *P. diminuta*

$$-\text{logMIC} = [3.700(\pm 0.106)] + \text{MR}[0.821(\pm 0.136)] \quad (3)$$
$$N = 17,\ r = 0.965,\ \text{s} = 0.080,\ \text{F} = 166.906$$

QSAR model for *E. coli*

$$-\text{logMIC} = [3.729(\pm 0.113)] + \text{MR}[0.868(\pm 0.144)] \quad (4)$$
$$N = 17,\ r = 0.957,\ \text{s} = 0.086,\ \text{F} = 165.267$$

Further, in order to have improvement in statistics the bi- and tri-parametric correlations have been tested. However, no statistically significant combinations were obtained.

The *F*-value obtained in Eqs. (1)–(4) is found to be statistically significant at 99% level. Similarly, cross validation of obtained equations were checked by employing the Leave

Table 3
Correlation matrix of used molecular descriptors

	MR	$HOMO_{ene}$	$LUMO_{ene}$	ddene	Log*P*	*S.A*	*B.S*	*P.D*	*E.C*
MR	1.000								
$HOMO_{ene}$	0.007	1.000							
$LUMO_{ene}$	0.015	0.997	1.000						
ddene	0.103	0.675	0.660	1.000					
Log*P*	0.005	0.959	0.963	0.640	1.000				
SA	0.945	0.058	0.034	0.166	0.098	1.000			
BS	0.957	0.007	0.016	0.124	0.055	0.995	1.000		
PD	0.958	0.004	0.032	0.164	0.028	0.988	0.991	1.000	
EC	0.963	0.023	0.004	0.129	0.066	0.995	0.997	0.98	1.000

one out (LOO) [30] method ($r^2_{cv} > 0.83$). The calculated activities (activities obtained from the derived Eqs. (1)–(4) by VALSTAT [31]) and predicted activities (activities calculated by LOO method [29]) of the synthesized compounds were in accordance with the observed activities as shown in Figs. 1 and 2.

PRESS (predicted residual sum of squares) is an important cross-validation parameter, which is a good approximation of the real predictive error of the models. Its value being less than SSY (sum of the squares of response value) points out that the model predicts better than chance and can be considered statistically important. In the present case all the proposed models have PRESS << SSY demonstrating them to be better than chance and statistically significant (Fig. 3).

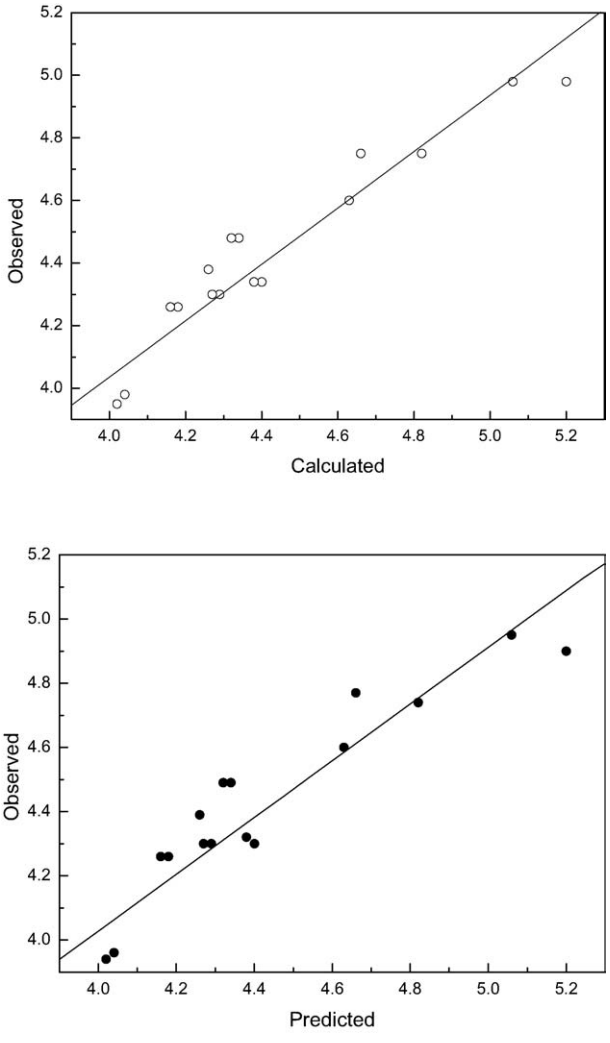


Fig. 2. Plots of observed vs. calculated and observed vs. predicted activity of 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6-diphenyl pyrimidine-2-(5*H*)-thione derivatives (**3a–q**) against *S. aureus*.

To have a dependable QSAR model, PRESS/SSY should be smaller than 0.4. Thus, the data presented in Table 4 show ratio of PRESS/SSY ranging 0.11–0.16 indicating that all the proposed models are reliable QSAR models.

Since, molar refractivity accounts for the polarizability and thus for the size and polarity of the groups as indicated by Eqs. (1)–(4), suggesting that MR plays significant role towards the expressed biological activities, which is possible due to steric interactions occurring in polar spaces.

3. Experimental section

3.1. General

All the chemicals used were of analytical grade purity. Melting points were taken in open capillary tubes using an electric melting point apparatus. All the melting points reported are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker advance DRX 300 instrument using TMS as an internal stranded. IR spectra were run on a Perkin Elmer model 377-spectrophotometer using KBr pellets. Analytical thin layer chromatography was performed using E. Merck Silica gel-G 0.50 mm plates (Merck No. 5700).

3.2. Synthesis of 4,6-diphenyl-5-[(2-phenyldiazenyl) pyrimidin-2(5H)-thione] (2a–q)

In a 250 ml round bottom flask equimolar quantities of 1,3-diphenyl-2-(aryldiazenyl) propane-1,3-diones (**1a–q**) and thiourea were taken together in the presence of freshly prepared sodium ethoxide solution (2.3 g sodium metal in 50 ml absolute ethanol). These were stirred for 3–4 h at room temperature to obtain crystals of required 4,6-diphenyl-5-[(2-phenyldiazenyl) pyrimidin-2(5*H*)-thione]derivatives (**2a–q**) in good yields (75–80%), filtered at the pump and dried. Systematic methodology of synthetic pathway is depicted in Scheme 1.

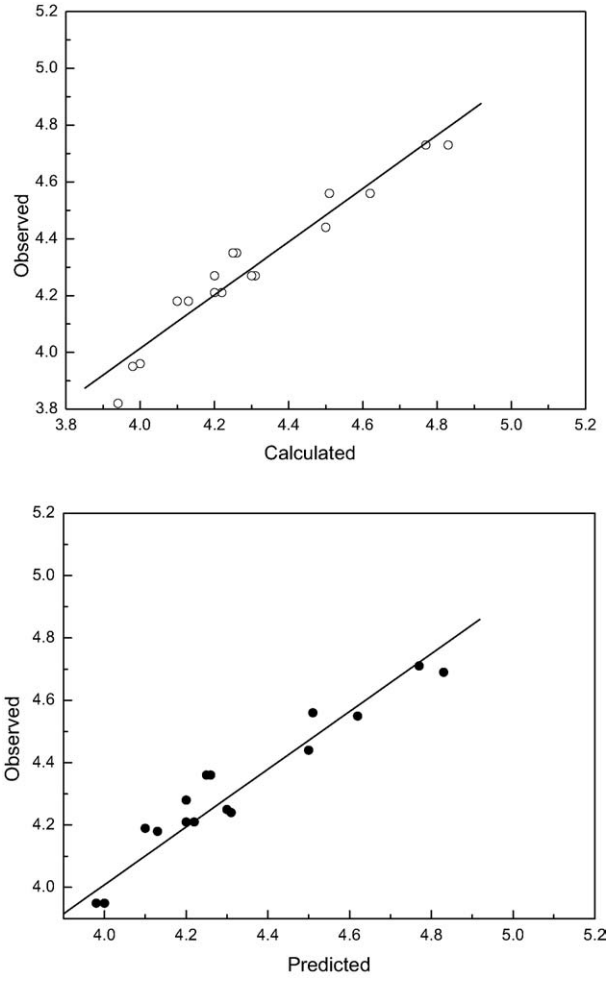


Fig. 3. Plots of observed vs. calculated and observed vs. predicted activity of 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6-diphenyl pyrimidine-2-(5*H*)-thione derivatives(**3a–q**) against *E. coli*.

*3.2.1. Synthesis of 5-[2-(2-methylprop1-enyl)-1H-benzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione derivatives (**3a–q**)*

In a 100 ml three-necked bolt-head flask fitted with dropping funnel and a mechanical stirrer, a mixture of 50% of aqueous potassium hydroxide (15 ml), benzyl triethyl ammonium chloride (BTEAC) (1.32 mg, 2.5 mmol), benzene (5 ml) was taken and stirred thoroughly for 30 min. To this, a pertinent 4,6-diphenyl-5-[(2-phenyldiazenyl) pyrimidin-2(5*H*)-thione] (2.5 mmol) (**2a–q**) was added slowly and stirred for further 5-7 hrs under nitrogen atmosphere. While stirring was going on, 3-chloro-3-methyl-1-butyne (25 mmol) in benzene (5 ml) was added slowly to the mixture. The contents were diluted with water (120 ml), followed by extraction with ether (120 ml) to afford crude product. It was purified on an alumina column using benzene as an eluent so as to yield finally 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazole-1yl]-4,6–diphenyl pyrimidine-2-(5*H*)-thione derivatives (**3a–q**). Structures of the synthesized compounds have been ascertained on the basis of spectral analytical data.

*3.2.2. 5-[2-(2-Methylprop1-enyl)-1H-benzimidazol-1yl]-4,6-diphenylpyrimidin-2-(5H)-throne [**3a**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3114 (C–H, sp^2), 2950 (C–H, sp^3), 1681 (C=S), 1621 (C=C/C=N), 1605, 1536, 1444 (C⋯C, ring stir), 952, 856, 740 (sub. phenyl).

^{1}H NMR (δppm): 1.71 (s, 6H, 2 × CH_3, isopropenyl), 3.70 (s, CH, pyrimidine) 6.13 (s, CH, methine), 7.26 (t, 2H,H_b, H_c, $J = 8.0$ Hz), 7.40 (s, 10H, 2 × C_6H_5), 7.70 (d, 2H, H_a, H_d, $J = 8.0$ Hz),. m.p. 135–36 °C; Yield: 79%; Found (Calcd.)(%) C: 74.43 (74.63); H: 5. 03 (5.10); N: 12.77 (12.89); S: 7.18 (7.38).

*3.2.3. 5-[2-(2-Methylprop1-enyl)-1H-5-methyl-benzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3b**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3116 (C–H, sp^2), 2955 (C–H, sp^3), 1684 (C=S), 1623 (C=C/C=N), 1622, 1531, 1440 (C⋯C, ring str), 951, 852, 743 (sub. phenyl).

^{1}H NMR (δppm): 1.73 (s, 6H, 2 × CH_3, isopropenyl), 2.35 (t, 3H, CH_3) 3.72 (s, CH, pyrimidine) 6.15 (s, CH, methine), 7.26 (t, 2H, H_b), 7.40 (s, 10H, 2 × C_6H_5), 7.50 (d,H_a), 7.58 (d, H_d). m.p. 133–34 °C; Yield: 77%; Found (Calcd.) C: 74.77% (74.97%); H: 5.10 (5.39); N: 12.25 (12.49); S: 7.02 (7.15).

*3.2.4. 5-[2-(2-Methylprop1-enyl)-1H-6-methylbenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3c**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3112 (C–H, sp^2), 2953 (C–H, sp^3), 1684 (C=S), 1625 (C=C/C=N), 626, 1537, 1448 (C⋯C, ring str), 957, 855, 742 (sub. phenyl).

^{1}H NMR (δppm): 1.77 (s, 6H, 2 × CH_3, isopropenyl), 2.33 (s, 3H, CH_3) 3.75 (s, CH, pyrimidene), 6.12 (s, CH, methine). 7.06 (d, H_c), 7.47 (s, 10H, 2 × C_6H_5), 7.50 (d, H_a), 7.58 (d, H_d). m.p. 131–32 °C; Yield: 74%; Found (Calcd.) (%) 74.73 (74.97); H: 5.12 (5.39); N: 12.28 (12.49); S: 7.09 (7.15).

Table 4
Cross-validation parameters

Equation	Compound used	PRESS	SSY	PRESS/SSY	S_{PRESS}	SDEP	r^2_{CV}	r^2_{bsp}
1	**17**	0.319	1.988	0.160	0.146	0.137	0.844	0.913
2	**17**	0.114	1.116	0.102	0.087	0.082	0.897	0.929
3	**17**	0.125	0.943	0.132	0.103	0.097	0.878	0.926
4	**17**	0.084	0.552	0.152	0.095	0.090	0.884	0.902

*3.2.5. 5-[2-(2-Methylprop-1-enyl)-1H-5-hydroxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3d**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$);3112 (C–H, sp^2), 2953 (C–H, sp^3), 1684 (C=S), 1625 (C=C/C=N), 628, 1539, 1447 (C⋯C, ring str), 954, 855, 746 (sub. phenyl).

^{1}H NMR (δppm): 1.75 (s, 6H, 2 × CH_3, isopropenyl), 3.71 (s, CH, pyrimidine) 6.14 (s, CH, methine), 7.25 (d, H_b), 7.42 (s, 10H, 2 × C_6H_5), 7.51 (d, H_a), 7.51 (d, H_d), 11.2 (bs, O–H). m.p. 131–32 °C; Yield: 80%; Found (Calcd.) (%) C: 71.77 (71.98); H: 4.80 (4.92); N: 12.21 (12.44); S: 7.01 (7.12).

*3.2.6. 5-[2-(2-Methylprop1-enyl)-1H-6-hydroxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3e**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3111 (C–H, sp^2), 2952 (C–H, sp^3), 1683 (C=S), 1624 (C=C/C=N), 628, 1539, 1447 (C⋯C, ring str), 958, 857, 746 (sub. phenyl).

^{1}H NMR (δppm): 1.72 (s, 6H, 2 × CH_3, isopropenyl), 2.34 (s, 3H, CH_3) 3.71 (s, CH, pyrimidene), 6.12 (s, CH, methine).7.04 (d, H_c), 7.47 (s, 10H, 2 × C_6H_5), 7.50 (d, H_a), 7.58 (d, H_d), 11.0 (bs, O-H). m.p. 135–36 °C; Yield: 77%; Found (Calcd.) (%) C: 71.72 (71.98); H: 4.71 (4.92); N: 12.23 (12.44); S: 6.99 (7.12).

*3.2.7. 5-[2-(2-Methylprop-1-enyl)-1H-5-ethylbenzimidazole-1-yl]4,6-diphenyl- pyrimidin-2-(5H)-thione [**3f**]*

This was prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3120 (C–H, sp^2), 2955 (C–H, sp^3), 1685 (C=S), 1618 (C=C/C=N), 1623, 1531, 1440 (C⋯C, ring str), 954, 858, 743 (sub. phenyl).

^{1}H NMR (d ppm): 1.24 (t.3H, CH_3), 1.72 (s, 6H, 2 × CH_3, isopropenyl), 2.59 (q, 2H, CH_2) 3.71 (s, CH, pyrimidine), 6.16 (s, CH, methine), 7.12 (d, H_b), 7.44 (s, 10H, 2xC_6H_5), 7.56 (d, H_a), 7.65 (d, H_d). m.p.138–39 °C; Yield: 75%; Found (Calcd.) (%) C: 75.12 (75.29); H: 5.44 (5.66); N: 11.98 (12.11); S: 6.75 (6.93).

*3.2.8. 5-[2-(2-Methylprop1-enyl)-1H-6-ethylbenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3g**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3113 (C–H, sp^2), 2952 (C–H, sp^3), 1681 (C=S), 1620 (C=C/C=N), 1622, 1533, 1443 (C⋯C, ring str), 953, 855, 746 (sub. phenyl).

^{1}H NMR (δppm): 1.20 (t.3H, CH_3), 1.73 (s, 6H, 2xCH_3, isopropenyl), 2.30 (q, 2H, CH_2), 3.77 (s, CH, pyrimidine), 6.13 (s, CH, methine), 7.11 (d, H_c), 7.49 (s, 10H, 2 × C_6H_5), 7.66 (d, H_a), 7.57 (d, H_d), m.p. 130–31 °C; Yield: 81%; Found (Calcd.) (%) C: 75.12 (75.29); H: 5.40 (5.66); N: 12.01 (12.11); S: 6.78 (6.93).

*3.2.9. 5-[2-(2-Methylprop1-enyl)-1H-5-nitrobenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3h**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3119 (C–H, sp^2), 2958 (C–H, sp^3), 1687 (C=S), 1626 (C=C/C=N), 1625, 1534, 1443 (C⋯C, ring str), 958, 857, 745 (sub. phenyl).

^{1}H NMR (δppm): 1.73 (s,6H,2 × CH_3,isopropenyl), 3.77 (s, CH, pyrimidine), 6.11 (s, CH, methine), 7.41 (s, 10H, 2 × C_6H_5), 7.96 (d, H_a), 8.19 (d, H_b), 8.63 (d, H_d). m.p. 139–40 °C; Yield: 72%; Found (Calcd.) (%) C:67.44 (67.62); H: 4.28 (4.41); N: 14.41 (14.60); S: 6.45 (6.69).

*3.2.10. 5-[2-(2-Methylprop1-enyl)-1H-6-nitrobenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3i**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3115 (C–H, sp^2), 2955 (C–H, sp^3), 1682 (C=S), 1629 (C=C/C=N), 1624, 1531, 1443 (C⋯C, ring str), 958, 857, 746 (sub. phenyl).

^{1}H NMR (δppm): 1.71 (s, 6H, 2 × CH_3, isopropenyl), 3.76 (s, CH, pyrimidine), 6.13 (s, CH, methine), 7.48 (s, 10H, 2 × C_6H_5), 7.96 (d, H_d), 8.20 (d, H_c), 8.63 (d, H_a). m.p. 129–31 °C; Yield: 72%; Found (Calcd.) (%) C: 67.46 (67.62); H: 4.20 (4.41); N: 14.48 (14.60); S: 6.48 (6.69).

*3.2.11. 5-[2-(2-Methylprop1-enyl)-1H-5-methoxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3j**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3119 (C–H, sp^2), 2958 (C–H, sp^3), 1687 (C=S), 1626 (C=C/C=N), 1625, 1534, 1443 (C⋯C, ring str), 955, 853, 744 (sub. phenyl).

^{1}H NMR (δppm): 1.74 (s, 6H, 2 × CH_3, isopropenyl), 3.68 (t.3H, CH_3), 3.75 (s, CH, pyrimidine), 6.13 (s, CH, methine), 6.77 (d, H_b), 7.21 (d, H_d) 7.43 (s, 10H, 2 × C_6H_5), 7.59 (d,H_a). m.p. 135–36 °C; Yield: 79%; Found (Calcd.) (%) C: 72.13 (72.39); H: 5.05 (5.21); N: 11.93 (12.06); S: 6.75 (6.90).

*3.2.12. 5-[2-(2-Methylprop1-enyl)-1H-6-methoxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3k**]*

Prepared according to the general procedure as in Section 4.2.

IR ($v = cm^{-1}$); 3110 (C–H, sp^2), 2951 (C–H, sp^3), 1682 (C=S), 1623 (C=C/C=N), 1624, 1535, 1446 (C⋯C, ring str), 951, 852,743 (sub. phenyl).

^{1}H NMR (δppm): 1.71 (s, 6H, 2 × CH_3, isopropenyl), 3.71 (t.3H, CH_3), 3.78 (s, CH, pyrimidine), 6.10 (s, CH, methine), 6.72 (d, H_c), 7.25 (d, H_a)7.43 (s, 10H, 2xC_6H_5), 7.61 (d, H_d). m.p. 134–35 °C; Yield: 79%; Found (Calcd.) (%) C: 72.15 (72.39); H: 5.09 (5.21); N: 11.92 (12.06); S: 6.79 (6.90).

*3.2.13. 5-[2-(2-Methylprop1-enyl)-1H-5-carboxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3l**]*

Prepared according to the general procedure as in Section 4.2.

IR (v = cm^{-1}); 3115 (C–H, sp^2), 2954 (C–H, sp^3), 1685 (C=S), 1625 (C=C/C=N), 1622, 1534, 1446 (C⋯C, ring str), 954, 851, 742 (sub. phenyl).

^{1}HNMR (δppm): 1.73 (s, 6H, 2 × CH_3, isopropenyl), 3.70 (s, CH, pyrimidine), 6.13 (s, CH, methine), 7.21 (d, H_b), 7.41 (s, 10H, 2 × C_6H_5), 7.56 (d, H_a), 7.54 (d, H_d). 11.0 (bs, O-H) m.p. 136–37 °C; Yield: 73%; Found (Calcd.) (%) C: 69.98 (70.27); H: 4.41 (4.63); N: 11.46 (11.71); S: 6.48 (6.70).

*3.2.14. 5-[2-(2-Methylprop1-enyl)-1H-5-chlorobenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3m**]*

Prepared according to the general procedure as in Section 4.2. IR (v = cm^{-1}); 3115 (C–H, sp^2), 2952 (C–H, sp^3), 1685 (C=S), 1626 (C=C/C=N), 625, 1534, 1445 (C⋯C, ring str), 956, 857, 745 (sub. phenyl).

^{1}H NMR (δppm): 1.72 (s,6H,2 × CH_3,isopropenyl), 3.75 (s, CH, pyrimidine), 6.14 (s, CH, methine), 7.44 (s, 10H, 2 × C_6H_5), 7.27 (d, H_b), 7.64 (d,H_a), 7.71 (d, H_d). m.p. 130–31 °C; Yield: 75%;(%); Found (Calcd.) (%) C: 68.99 (69.14); H: 4.39 (4.51); N: 11.77 (11.95); S: 6.62 (6.84).

*3.2.15. 5-[2-(2-Methylprop1-enyl)-1H-6-chlorobenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3n**]*

Prepared according to the general procedure as in Section 4.2.

IR (v = cm^{-1}); 3115 (C–H, sp^2), 2951 (C–H, sp^3), 1683 (C=S), 1624 (C=C/C=N), 1623, 1538, 1446 (C⋯C, ring str), 951, 857,743 (sub. phenyl).

^{1}H NMR (δppm): 1.73 (s, 6H, 2xCH_3, isopropenyl), 3.71 (s, CH, pyrimidine), 6.11 (s, CH, methine), 7.41 (s, 10H, 2 × C_6H_5), 7.29 (d, H_c), 7.63 (d, H_d), 7.72 (d, H_a). m.p. 135–36 °C; Yield: 78%; Found (Calcd.) (%) C: 68.95 (69.14); H: 4.35 (4.51); N: 11.72 (11.95); S: 6.60 (6.84).

*3.2.16. 5-[2-(2-Methylprop1-enyl)-1H-5-ethoxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2- (5H)-thione [**3o**]*

Prepared according to the general procedure as in Section 4.2.

IR (v = cm^{-1}); 3120 (C-H,sp^2), 2953 (C-H,sp^3), 1682 (C=S), 1623 (C=C/C=N), 624, 1533, 1441 (C⋯C, ring str), 952, 852, 741 (sub. phenyl).

^{1}H NMR (δppm): 1.33 (t.3H, CH_3), 1.70 (s, 6H, 2xCH_3, isopropenyl), 3.71 (s, CH, pyrimidine), 3.98 (q, 2H, CH_2) 6.16 (s, CH, methine), 6.77 (d, H_b), 7.21 (d, H_d), 7.47 (s, 10H, 2 × C_6H_5), 7.59 (d, H_a). m.p. 135–36 °C; Yield: 76%; Found (Calcd.) (%) C: 72.59 (72.78); H: 5.20 (5.48); N: 11.75 (11.91); S: 6.59 (6.70).

*3.2.17. 5-[2-(2-Methylprop1-enyl)-1H-6-ethoxybenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3p**]*

Prepared according to the general procedure as in Section 4.2.

IR (v = cm^{-1});3114 (C–H, sp^2), 2951 (C–H, sp^3), 1684 (C=S), 1626 (C=C/C=N), 1624, 1532, 1447 (C⋯C, ring str), 954, 858,744 (sub. phenyl).

^{1}H NMR (δppm): 1.31 (t.3H, CH_3), 1.72 (s, 6H, 2xCH_3, isopropenyl), 3.74 (s, CH, pyrimidine), 3.40 (q, 2H, CH_2)6.12 (s, CH, methine), 6.75 (d, H_c), 7.21 (d,H_a), 7.49 (s, 10H, 2xC_6H_5), 7.60 (d, H_d) m.p. 136–37 °C; Yield: 75%; Found (Calcd.) (%) C: 72.61 (72.78); H: 5.12 (5.20); N: 11.78 (11.91); S: 6.58 (6.70).

*3.2.18. 5-[2-(2-Methylprop1-enyl)-1H-5-bromobenzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5H)-thione [**3q**]*

Prepared according to the general procedure as in Section 4.2.

IR (v = cm^{-1}); 3118 (C–H, sp^2), 2957 (C–H, sp^3), 1686 (C=S), 1625 (C=C/C=N), 1624, 533, 1442 (C⋯⋯C, ring str), 951, 854,739 (sub. phenyl).

^{1}H NMR (δppm): 1.70 (s, 6H, 2 × CH_3, isopropenyl), 3.72 (s, CH, pyrimidine), 6.13 (s, CH, methine), 7.49 (s, 10H, 2 × C_6H_5), 7.28 (d, H_b), 7.66 (d,H_a), 7.70 (d, H_d). m.p. 138–39 °C; Yield:79%; Found (Calcd.) (%) C: 63.01 (63.16); H: 4.02 (4.12); N:10.76 (10.91); S: 6.11 (6.24).

To conclude, a series of compounds incorporating pyrimidine and benzimidazole heterocyclic nuclei viz. 5-[2-(2-methylprop1-enyl)-1*H*-benzimidazol-1yl]-4,6-diphenyl pyrimidin-2-(5*H*)-thione derivatives, has been synthesized as potent antimicrobial agents. Furthermore, QSAR studies performed on these compounds have revealed that the presence of electron-attracting group increases the antibacterial activity. Substitution of bulky group with higher polarizability probably enhances the potency of these compounds as antibacterial agents. Molar refractivity exhibited a good correlation ($r^2 > 0.89$) with biological activity.

References

[1] H.G. Cheon, E.K. Yum, S.S. Kim, Arch. Pharm. Res. 19 (1996) 126.
[2] K. Kubo, Y. Kohara, Y. Yoshimura, Y. Inada, Y. Shibouta, Y. Furukawa, T. Kato, K. Nishikawa, T. Naka, J. Med. Chem. 36 (1993) 2343.
[3] R. Zou, K. Ayres, J. Drach, L. Townsend, J. Med. Chem. 39 (1996) 3477.
[4] C.J. Going, V.W. Mayer, Mut. Res. 343 (1995) 185.
[5] J.Z. Stefanska, R. Gralewska, B.J. Starosciak, Z. Kazimierczuk, Pharmazie 54 (1999) 879.
[6] F. Bordi, M. Mor, G. Morini, P.B. Plazzi, A. Caretta, Farmaco 49 (1994) 153.
[7] J.S. Mason, I. Morize, P.R. Menard, D.L. Cheney, C. Hulme, R.F. Labaudiniere, J. Med. Chem. 42 (1999) 3251.
[8] J. Mann, A. Baron, Y. Opoku-Boahen, E. Johansson, G. Parkinson, L.R. Kelland, S. Neidle, J. Med. Chem. 44 (2001) 138.
[9] E. Bouwman, W.L. Driessen, J. Reedijk, Coord. Chem. Rev. 104 (1990) 143.
[10] Y.C. Chi, C.M. Sun, Synlett (2000) 591.
[11] W. Huang, R.M. Scarborough, Tetrahedron Lett. 40 (1999) 2665.
[12] Z. Wu, P. Rea, G. Wickham, Tetrahedron Lett. 41 (2000) 9871.
[13] J.B. Thomas, M.J. Fall, J.B. Cooper, J.P. Burgess, F.I. Carroll, Tetrahedron Lett. 38 (1997) 5099.
[14] H.V. Welchinskaya, I.I. Kuzmenko, I.G. Kudryavtseva, N.I. Sharikina, E.A. Kovalenko, V.S. Podgorsky, Int. J. Bio.Macro 26 (1999) 243.
[15] P. Sharma, S. Sharma, N. Rane, Bioorg. Med. Chem. 12 (2004) 3135.
[16] P. Sharma, N. Rane, V.K. Gurram, Bioorg. Med. Chem. Lett. 14 (2004) 4185.
[17] P. Sharma, A. Kumar, A. Mandloi, Synth. Commun. 33 (2003) 3.
[18] P. Sharma, A. Kumar, N. Rane, V. Gurram, Tetrahedron 61 (2005) 4273.

[19] P. Sharma, A. Kumar, S. Sharma, N. Rane, Bioorg. Med. Chem. Lett. 17 (2005) 937.
[20] C. Hansch, T. Fujita, J. Am. Chem. Soc. 86 (1964) 1616.
[21] J.S.M. Free, J.W. Wilson, J. Med. Chem. 7 (1964) 395.
[22] H. Kubinyi, in: R. Mannhold, P. Krogsgaard-Larsen, H. Timmerman (Eds.), VCH Publishers, NewYork, 1993, pp. 21–137 (vol 1).
[23] P. Sharma, A. Kumar, S. Sharma, Indian J. Chem. 43B (2004) 385.
[24] B.S. Furniss, A.J. Hannaford, V. Roger, P.W.G. Smith, A.K. Tatchell, In Vogel's Textbook of Organic Chemistry, Longmann, 1984.
[25] P.R. Muray, E.J. Baron, M.A. Faller, F.C. Tenoveer, R.H. Yolke, Manual of Clincal Microbiolgy, 6th ed, ASM, Washington, 1995.
[26] C. Hansch, A. Leo, D. Hoekman, In Exploring QSAR: 450 Hydrophobic, Electronic and Steric Constants, ACS, Washington, DC, 1995.
[27] Cambridge Soft corp., 100 Cambridge Park, MA 02140-2317, USA.
[28] J.P. Stewart, J. Comput. Chem. 10 (1989) 209.
[29] J.P. Stewart, MOPAC 6.0. QCPE 455, Indiana University, Bloomington, 1990 (IN 47405).
[30] I.V. Tetko, V.Y. Tanchuk, A.E.J. Villa, Chem. Inf. Comput. Sci. 41 (2001) 1407.
[31] Valstat software developed at department of pharmacy SGSITS, 23, park road, indore, India (available on request).