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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antimicrobial evaluation, and QSAR analysis of 2-isopropyl-5-methylcyclohexanol derivatives

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Abstract A series of 2-isopropyl-5-methylcyclohexanol derivatives were synthesized and evaluated for their antibacterial activity against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative *Escherichia coli* and in vitro antifungal activity against *Candida albicans* and *Aspergillus niger*. The results of antimicrobial activity demonstrated that the compounds **10**, **20**, and **21** were the most active ones among the synthesized compounds. The QSAR studies revealed the importance of dipole moment (μ), total energy (Te), and topological parameters (κ_1 and κ_3) in describing the antimicrobial activity of 2-isopropyl-5-methylcyclohexanol derivatives.

Keywords 2-Isopropyl-5-methylcyclohexanol esters · Antimicrobial activity · QSAR

Introduction

During the past two decades, the frequency of systemic infection has increased dramatically along with the number of invasive, mostly opportunistic, microbial species carrying infectious diseases. Fungal infections are the important cause of morbidity and mortality in hospitalized patients: candidiasis is the fourth most common blood culture isolates at US hospitals, pulmonary aspergillosis is the leading cause of death in bone marrow transplant recipients, and *Pneumocystis carinii* pneumonia is the leading cause of death in AIDS patients in North America and Europe (Garcia-Domenech *et al.*, 2003).

The number of cases of multidrug resistant bacterial infections is increasing at an alarming rate. Clinicians have to become reliant on few antimicrobial drugs available in the market but that is not sufficient as microbial species are getting resistant very fastly. In order to meet these challenges, there is need for the development of novel antimicrobial drugs to which the microbes have never been presented before (Emami *et al.*, 2008).

2-Isopropyl-5-methylcyclohexanol (menthol) is obtained from the dried leaves of *Mentha piperata* (peppermint) and *Mentha arvensis* (Family-Labiatae) and by extraction from other natural sources such as *citronella java* oil, spanish pennyroyal oil, eucalyptus oil as well as from other plant sources (Galeotti *et al.*, 2002).

2-Isopropyl-5-methylcyclohexanol has been reported to possess wide variety of biological activities viz. Acaricidal (Kim *et al.*, 2008), acetyl cholinesterase inhibitor (Miyazawa *et al.*, 1997), anesthetic (Haeseler *et al.*, 2002), analgesic (Macpherson *et al.*, 2006), antiacne (Miyazawa *et al.*, 1997), antiallergenic (Miyazawa *et al.*, 1997), antiasthmatic (Tamaoki *et al.*, 1995), antibacterial (Kotan *et al.*, 2007), anticancer (Beck *et al.*, 2007), antiepileptic (Garcia *et al.*, 2006), antifungal (Dambolena *et al.*, 2008), anti-inflammatory (Juergens *et al.*, 1998), antimicrobial (Trombetta *et al.*, 2005), antioxidant (Mimica-Dukic *et al.*, 2003), antiplasmid (Schelz *et al.*, 2006), antispasmodic (Hawthorn *et al.*, 1988), central nervous system stimulant (Silva *et al.*, 2007), hepatoprotective (Janbaz and Gilani 2002), immunomodulator (Sidell *et al.*, 1991), and sedative (Desousa *et al.*, 2007) activities.

QSAR analysis applies statistical methods to describe relationship between chemical structure and biological

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activities of a series of analogs quantitatively (Wang *et al.*, 2006). Quantitative structure–activity relationship has been traditionally perceived as means of establishing correlation between trends in chemical structure modification and the respective changes of biological activity (Yao *et al.*, 2004). Thus, QSAR studies have a predictive ability and simultaneously provide deeper insight into the mechanism of drug receptor interaction (Vasanthanthan *et al.*, 2006).

In view of above and in continuation of our studies in development of antimicrobial agents (Narasimhan *et al.*, 2003, 2004, 2006a, b, c, 2007a, b, c; Kumar *et al.*, 2007; Ohlan *et al.*, 2007), we hereby report the synthesis, antimicrobial activity, and QSAR studies of esters of 2-isopropyl-5-methylcyclohexanol (**1**–**26**).

Experimental

Melting points (°C) were determined using Elico melting point apparatus and are uncorrected. The FTIR spectra were recorded in KBr pellets on Perkin Elmer IR spectrophotometer. ^{1}H NMR was recorded on Bruker Avance II 400 NMR spectrophotometer using $CDCl_3$ as a solvent and TMS as an internal standard (chemical shift in δ, ppm). The purity of compounds was checked by thin layer chromatography (TLC) on silica gel G plates. The spots were detected by exposure to iodine vapors.

General procedure for synthesis of acid chloride

0.25 mol of acid with 0.35 mol of thionyl chloride were taken in a 500-ml round-bottomed flask equipped with a stir bar. Bubbles evolved out from the light yellow solution immediately. The mixture was stirred at room temperature for 10 min and then heated under reflux for 30 min, during which time the mixture turned brown. Then the solution was heated up to 80°C and stirred for 3 h. The excess thionyl chloride was removed by distillation.

General procedure for synthesis of esters of (1R,2S,5R)-2-isopropyl-5 methylcyclohexanol (**1**–**26**)

0.25 mol of (−)-2-isopropyl-5-methylcyclohexanol dissolved in 90 ml of tetrahydrofuran and 2 ml of pyridine were stirred to dissolve completely. Then acid chloride was slowly dropped into the solution. The mixture was refluxed for appropriate time and temperature until evolution of HCl ceased. Reaction progress was monitored by TLC using a 9:1 hexane/acetone mobile phase solution, and visualization of TLC plate was accomplished in iodine chamber. On completion of reaction, the mixture leaving the pyridine hydrochloride in the reaction vessel itself was transferred into a separating funnel containing hexane (100 ml) and was shaken vigorously. The hexane solution was washed with aq. $NaHCO_3$ solution and then water. After that the mixture was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield the esters.

Compound **1**: IR (KBr pellets): cm^{-1} 3050.00 (CH str., aromatic), 2955.77 (CH str., aliphatic), 1692.52 (CO str., ester), 1584.94 (COO^- asymmetric str.), 1384.16 (COO^- symmetric str.); ^{1}H NMR($CDCI_3$): δ 7.40–7.53 (m, 5H, Ar–H), 4.93–4.94 (m, 1H, C_1 of 2-isopropyl-5-methylcyclohexanol), 2.15 (m, 1H, C_2 of 2-isopropyl-5-methylcyclohexanol), 1.53–1.74 (m, 7H, C_3–C_6 of 2-isopropyl-5-methylcyclohexanol), 1.01–1.05 (d, 9H, terminal CH_3); compound **7**: IR (KBr pellets): cm^{-1} 3080.00 (CH str., aromatic), 2956.83 (CH str., aliphatic), 1721.60 (CO str., α,β-unsaturated acid), 1591.59 (COO^- asymmetric str.), 1384.06 (COO^- symmetric str.), 743.46 (C–Cl str., Ar.-Cl); ^{1}H NMR (DMSO): δ 7.38–7.54 (m, 4H, Ar–Cl), 4.32–4.36 (m, 1H, C_1 of 2-isopropyl-5-methylcyclohexanol), 2.17 (m, 1H, C_2 of 2-isopropyl-5-methylcyclohexanol), 1.57–1.73 (m, 7H, C_3–C_6 of 2-isopropyl-5-methylcyclohexanol), 1.00–1.08 (d, 9H, terminal CH_3); compound **10**: IR (KBr pellets): cm^{-1} 3084.91 (CH str., aromatic), 2958.34 (CH str., aliphatic), 1735.44 (CO str., ester), 1592.61 (COO^- asymmetric str.), 1535.83 (NO_2 asymmetric str., aromatic nitro group), 1351.29 (COO^- symmetric str.), 719.47 (C–C out of plane bending, monosubstituted benzene); ^{1}H NMR ($CDCI_3$): δ 8.49–8.97 (m, 4H, Ar NO_2), 4.44–4.46 (m, 1H, C_1 of 2-isopropyl-5-methylcyclohexanol), 2.18 (m, 1H, C_2 of 2-isopropyl-5-methylcyclohexanol), 1.42–1.72 (m, 7H, C_6–C_6 of 2-isopropyl-5-methylcyclohexanol), 1.01–1.09 (d, 9H, terminal CH_3); compound **14**: IR (KBr pellets): cm^{-1} 3050.00 (CH str., aromatic), 2920.00 (CH str., aliphatic), 1670.00 (CO str., ester), 1521.35 (COO^- asymmetric str.), 1384.03 (COO^- symmetric str.), 1257.27 (COC str., Araalkyl ether); ^{1}H NMR($CDCI_3$): δ 7.26–7.50 (m, 4H, $ArOCH_3$), 3.80 (s, 3H, OCH_3), 1.23–2.29 (m, 8H, C_2–C_6 of 2-isopropyl-5-methylcyclohexanol), 1.01–1.09 (d, 9H, terminal CH_3); compound **15**: IR (KBr pellets): cm^{-1} 3095.30 (CH str., aromatic), 2956.66 (CH str., aliphatic), 1721.59 (CO str., ester), 1591.35 (COO^- asymmetric str.), 1365.57 (COO^- symmetric str.), 1226.44 (COC str., Araalkyl ether); ^{1}H NMR($CDCI_3$): δ 6.90–7.98 (m, 4H, $ArOCH_3$), 3.88 (m, 1H, C_1 of 2-isopropyl-5-methylcyclohexanol), 3.85 (s, 3H, OCH_3 of $ArOCH_3$), 2.17 (m, 1H, C_2 of 2-isopropyl-5-methylcyclohexanol), 1.45–1.97 (m, 7H, C_3–C_6 of 2-isopropyl-5-methylcyclohexanol), 0.96–1.09 (d, 9H, terminal CH_3); compound **17**: IR (KBr pellets): cm^{-1} 3040.00 (CH str., aromatic), 2956.46 (CH str., aliphatic), 1692.88 (CO str., ester), 1540.00 (COO^- asymmetric str.), 1384.10 (COO^- symmetric str.), 695.52 (C–C out of plane bending, monosubstituted benzene); ^{1}H NMR($CDCI_3$): δ 7.24–7.90 (m, 4H,

$ArCH_3$), 2.39–2.41 (s, 3H, CH_3 of $ArCH_3$), 1.33–2.41 (m, 8H, C_2–C_6 of 2-isopropyl-5-methylcyclohexanol).

Antimicrobial evaluation

Antibacterial assay

A 24-h fresh culture was obtained by inoculation of respective bacteria in double strength nutrient broth—IP, followed by incubation at 37 ± 1°C The stock solution of synthesized 2-isopropyl-5-methylcyclohexanol derivatives was serially diluted in tube containing 1 ml of sterile double strength nutrient broth—IP (Pharmacopoeia of India, 1996) to get a concentration of 50–0.78 µg/ml and then inoculated with 100 µl of suspension (with a count of 10^5 cfu/ml) of respective microorganisms (Gram-positive *S. aureus* MTCC 1430, *B. subtilis* MTCC 2423, Gram-negative *E. coli* MTCC 739) in sterile saline. The inoculated tubes were incubated at 37 ± 1°C for 24 h, and minimum inhibitory concentrations (MICs) were determined. From the observed MIC values, the exact MIC values were determined by making suitable dilution of the stock solution.

Antifungal assay

The antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol derivatives against the fungal species *C. albicans* MTCC 227 and *A. niger* MTCC 2425 was determined by serial dilution method similar to antibacterial assay using Sabouraud dextrose broth—IP. The inoculated tubes were incubated at 37 ± 1°C and 25 ± 1°C for a period of 2 and 7 days in case of *C. albicans* and *A. niger*, respectively.

QSAR studies

Data set is the set of molecules whose biological activity is regressed with its molecular descriptor values. In the present study, the synthesized 2-isopropyl-5-methylcyclohexanol derivatives (**1–26**) are selected as data set. Descriptor is any molecular property which is characteristic of a molecule and can be utilized to determine new QSAR. The number of descriptors selected for the present study fell into four categories, viz. electronic, steric, lipophilic, and topological (Sharma *et al.*, 2004; Randic, 1975; Balaban, 1982; Wiener, 1947; Sortino et al., 2007) (Table 3). The structure of 2-isopropyl-5-methylcyclohexanol derivatives was optimized by energy minimization. The lowest energy structure was used for each molecule to calculate the physicochemical parameters using TSAR 3.3 software for Windows (TSAR 3D Version 3.3, 2000). Further, the regression analysis was performed using the SPSS software package (SPSS for windows, Version 10.05, 1999).

Cross-validation

The predictive powers of the equations were validated by leave one out (LOO) cross-validation method (Schaper, 1999), where a model is built with $N - 1$ compounds and Nth compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance is obtained from cross-validated (or predictive q^2) method which is defined as

$$q^2 = 1 - \frac{\sum (Y_{\text{predicted}} - Y_{\text{actual}})^2}{\sum (Y_{\text{actual}} - Y_{\text{mean}})^2},$$

where $Y_{\text{predicted}}$, Y_{actual}, and Y_{mean} are the predicted, actual, and mean values of target property (pMIC), respectively. $\Sigma(Y_{\text{predicted}} - Y_{\text{actual}})^2$ is the predictive residual error sum of squares.

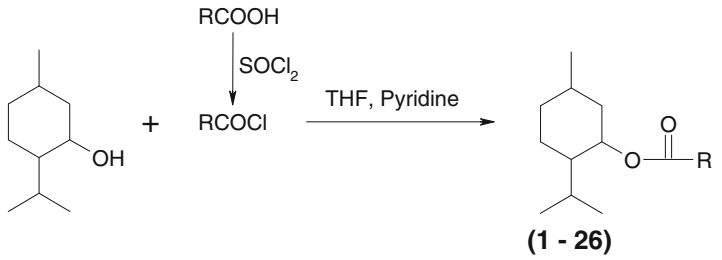
Results and discussion

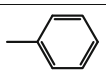
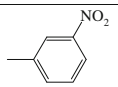
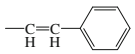
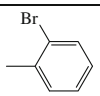
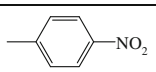
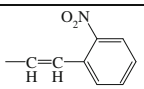
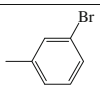
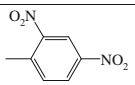
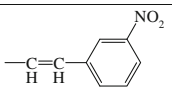
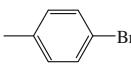
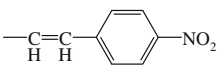
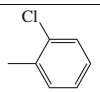
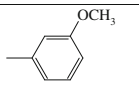
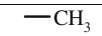
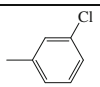
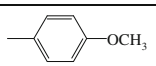
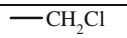
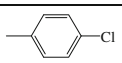
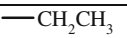
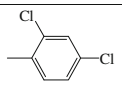
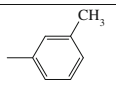
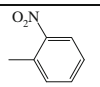
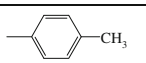
The esters of 2-isopropyl-5-methylcyclohexanol were prepared by the refluxing various aliphatic and aromatic acid chlorides with 2-isopropyl-5-methylcyclohexanol as depicted in the Scheme 1. The acid chlorides, in turn, were prepared by the reaction of different acids with thionyl chloride. The physicochemical properties and the elemental analyses for the synthesized compounds are presented in Table 1. The purity of compounds was ascertained by single spot TLC on silica gel G. The spectral characterization (IR and NMR) were found in agreement with the assigned molecular structure.

The synthesized esters derivative of 2-isopropyl-5-methylcyclohexanol have shown characteristic peaks in the region 1721–1670 cm^{-1} corresponding to the C=O group of ester. The IR bands corresponding to COO^- asymmetric stretching were present around 1592–1521 cm^{-1} and COO^- symmetric stretching were present at 1384–1351 cm^{-1}, which confirmed the formation of ester linkage. The presence of CH stretching at 2958–2920 cm^{-1} depicts the existence of aliphatic alkyl groups in the synthesized compounds, and IR bands at 3040–3095 cm^{-1} confirm the existence of aromatic group in the synthesized compounds.

The IR band at 743.46 cm^{-1} corresponding to C–Cl stretching confirms the presence of monochlorinated benzene nucleus in compound **7**. The presence of IR band at 1226.44 and 1257.27 cm^{-1} supports the existence of

Scheme 1 General procedure for synthesis of esters of (1R,2S,5R)-2-isopropyl-5-methyl cyclohexanol (**1–26**)



Comp.	R	Comp.	R	Comp.	R
1.		10.		19.	
2.		11.		20.	
3.		12.		21.	
4.		13.		22.	
5.		14.		23.	
6.		15.		24.	
7.		16.		25.	
8.		17.		26	
9.		18.			

methoxy group in compounds **15** and **14**. The asymmetric stretching band at 1535.83 cm^{-1} depicts the presence of aromatic nitro group in compound **10** which was not seen in all other synthesized compounds.

The presence of signals at δ 0.96–1.09 ppm reveals the presence of terminal CH_3 group in the synthesized 2-isopropyl-5-methylcyclohexanol derivatives. The multiplet signals at δ 7.24–7.90 ppm depict the presence of aromatic phenyl nucleus in the synthesized derivatives. The presence of singlet at δ 3.80 and 3.85 ppm in compounds **14** and **15** depicts the presence of OCH_3 group in the synthesized compounds. A singlet at δ 2.39–2.41 ppm supports the presence of CH_3 group on aromatic nucleus in compound **17** which confirms the attachment of aromatic acid with 2-isopropyl-5-methylcyclohexanol via an ester linkage.

These NMR and IR spectral characterization supports the fact that acid groups were attached to the 2-isopropyl-5-methylcyclohexanol through an ester linkage. Moreover, the absence of signals at δ 11.0 and 4.0 ppm confirms the absence of any residual acid or 2-isopropyl-5-methylcyclohexanol in the synthesized compounds thus confirming the completion of reaction.

The synthesized esters were evaluated for their in vitro antibacterial activity against Gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and Gram-negative *Escherichia coli* and in vitro antifungal activity against *Candida*

Table 1 Physicochemical characteristics of synthesized 2-isopropyl-5-methylcyclohexanol derivatives

Comp.	Mol. formula	M. Wt.	MP/BP* (°C)	Ref. value	% Yield	Elemental analyses			
						C (found)	H (found)	N (found)	O (found)
1	$C_{17}H_{24}O_2$	260	54–56	0.34[e]	65.3	78.42 (78.45)	9.29 (9.25)	–	12.29 (12.30)
2	$C_{17}H_{23}BrO_2$	339	78–80	0.41[c]	54.2	60.18 (60.21)	6.83 (6.79)	–	9.43 (9.45)
3	$C_{17}H_{23}BrO_2$	339	83–85	0.38[d]	56.3	60.18 (6.22)	6.83 (6.80)	–	9.43 (9.43)
4	$C_{17}H_{23}BrO_2$	339	80–82	0.60[a]	57.8	60.18 (60.14)	6.83 (6.85)	–	9.43 (9.40)
5	$C_{17}H_{23}ClO_2$	295	90–92	0.51[b]	57.6	69.26 (69.29)	7.86 (7.83)	–	10.85 (10.82)
6	$C_{17}H_{23}ClO_2$	295	95–97	0.44[c]	61.6	69.26 (69.27)	7.86 (7.85)	–	10.85 (10.84)
7	$C_{17}H_{23}ClO_2$	295	92–94	0.47[c]	64.4	69.26 (69.24)	7.86 (7.88)	–	10.85 (10.87)
8	$C_{17}H_{22}Cl_2O_2$	330	101–103	0.40[d]	47.8	62.01 (61.05)	6.73 (6.79)	–	9.72 (9.69)
9	$C_{17}H_{23}NO_4$	305	68–70	0.52[b]	68.8	66.86 (66.82)	7.59 (7.64)	4.59 (4.56)	20.96 (20.91)
10	$C_{17}H_{23}NO_4$	305	63–65	0.38[e]	59.6	66.86 (66.89)	7.59 (7.64)	4.59 (4.62)	20.96 (20.91)
11	$C_{17}H_{23}NO_4$	305	62–64	0.42[c]	70.8	66.86 (66.82)	7.59 (7.57)	4.59 (4.55)	20.96 (20.92)
12	$C_{17}H_{22}N_2O_6$	350	66–68	0.48[a]	50.2	58.28 (58.32)	6.33 (6.36)	8.00 (7.95)	27.40 (27.35)
13	$C_{18}H_{26}O_3$	290	78–80	0.30[e]	51.7	74.45 (74.41)	9.02 (9.05)	–	16.53 (16.56)
14	$C_{18}H_{26}O_3$	290	81–83	0.34[d]	46.8	74.45 (74.43)	9.02 (8.97)	–	16.53 (16.59)
15	$C_{18}H_{26}O_3$	290	76–78	0.42[b]	48.9	74.45 (74.39)	9.02 (9.07)	–	16.53 (16.51)
16	$C_{18}H_{26}O_2$	274	73–75	0.35[c]	53.2	78.48 (78.52)	9.55 (9.57)	–	11.66 (11.71)
17	$C_{18}H_{26}O_2$	274	68–70	0.36[d]	54.7	78.48 (78.46)	9.55 (9.53)	–	11.66 (11.61)
18	$C_{18}H_{26}O_2$	274	65–67	0.44[a]	56.9	78.48 (78.50)	9.55 (9.49)	–	11.66 (11.61)
19	$C_{19}H_{26}O_2$	286	37–39	0.52[b]	57.3	79.68 (79.64)	9.15 (9.11)	–	11.17 (11.12)
20	$C_{19}H_{25}NO_4$	331	49–51	0.40[e]	53.7	68.86 (68.81)	7.60 (7.63)	4.23 (4.26)	19.31 (19.27)
21	$C_{19}H_{25}NO_4$	331	84–86	0.45[a]	51.3	68.86 (68.82)	7.60 (7.56)	4.23 (4.25)	19.31 (19.36)
22	$C_{19}H_{25}NO_4$	331	92–94	0.57[a]	56.7	68.86 (68.81)	7.60 (7.62)	4.23 (4.21)	19.31 (19.28)
23	$C_{12}H_{22}O_2$	198	102–104*	0.27[a]	58.5	72.68 (72.61)	11.18 (11.15)	–	16.14 (16.10)
24	$C_{12}H_{21}ClO_2$	233	106–108*	0.31[a]	50.6	61.93 (61.96)	9.09 (9.07)	–	13.75 (13.80)
25	$C_{13}H_{24}O_2$	212	104–106*	0.38[b]	46.2	73.54 (73.54)	11.39 (11.36)	–	15.07 (15.06)
26	$C_{13}H_{23}ClO_2$	247	113–115*	0.44[a]	38.8	63.27 (63.29)	9.39 (9.42)	–	12.97 (12.94)

TLC mobile phase: [a] hexane:ethyl acetate (9:1); [b] hexane:acetone (9:1); [c] chloroform:acetone (8.5:1.5); [d] hexane:ethyl acetate (4:1); [e] toluene:chloroform (7:3)

albicans and *Aspergillus niger*. MIC was determined by serial dilution method (Shadomy and Espinel, 1980).

The results of antimicrobial study are presented in Table 2. The compounds **10**, **11**, **12**, **20**, and **21** showed significant activity against *S. aureus* with $pMIC_{sa}$ values 2.29, 2.29, 2.35, 2.33, and 2.33, respectively. Further the compounds **18**, **19**, and **22** were found to be more active against *B. subtilis* having $pMIC_{bs}$ values more than 2.09 in comparison to other synthesized derivatives. Compounds **9**, **10**, **20**, and **22** were found to be highly active against *E. coli* with $pMIC_{ec}$ value more than 2.28. Further in case of *C. albicans*, compounds **10**, **20**, **21**, and **22** showed highest pMIC value ($pMIC_{ca} = 2.33$) in comparison to other synthesized derivatives. Compounds **10**, **20**, and **21** were found to be more active against *A. niger* having $pMIC_{an}$ more than 2.28.

From the above results the following structure–activity relationship can be deduced:

1. The presence of electron withdrawing group like nitro increases the antimicrobial potential of synthesized compounds which is clearly evident from the high-antimicrobial activity of compounds **10**, **11**, **12**, **20**, **21**, and **22**. The importance of electron withdrawing group in the increasing antimicrobial activity is similar to the results obtained by Sharma *et al*. (2004).
2. The 2-isopropyl-5-methylcyclohexanol esters derived from aromatic carboxylic acids were found to be more active than derivatives obtained from aliphatic carboxylic acids which can be evidenced from low pMIC values of aliphatic esters (**23**, **24**, **25**, and **26**) Table 2. This may be probably due to the involvement of aromatic nucleus with the target binding site which is similar to the results of our previous study (Narasimhan *et al.*, 2007a).
3. The derivative obtained by esterification of cinnamic acid were found to be more active as compared to

Table 2 Antimicrobial activity of synthesized 2-isopropyl-5-methylcyclohexanol derivatives

Comp.	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$
1	1.92	2.01	2.01	1.92	1.92
2	2.04	2.04	1.98	2.04	2.04
3	1.96	1.96	1.88	2.04	2.04
4	1.98	2.04	2.02	1.85	2.04
5	1.97	1.91	2.10	1.97	2.10
6	1.97	1.97	1.88	1.97	1.97
7	1.88	1.97	1.67	1.67	2.05
8	2.02	1.96	2.02	1.72	1.95
9	1.99	2.03	2.29	2.29	2.17
10	2.29	1.99	2.29	2.33	2.29
11	2.29	2.02	1.99	2.29	2.18
12	2.35	2.05	2.35	2.05	2.05
13	2.06	1.98	1.97	1.97	2.07
14	1.97	1.99	1.97	1.97	2.11
15	2.01	2.01	1.98	1.67	2.04
16	1.94	1.94	2.01	1.64	1.94
17	2.05	2.02	1.93	1.94	2.03
18	1.85	2.10	1.90	1.94	2.04
19	1.96	2.26	1.96	1.96	2.01
20	2.33	2.03	2.33	2.33	2.33
21	2.33	2.03	2.14	2.33	2.33
22	2.03	2.33	2.33	2.33	2.18
23	1.50	1.80	1.50	1.80	1.98
24	2.00	1.86	1.79	1.87	2.17
25	1.75	1.88	1.75	1.83	2.13
26	1.60	1.90	1.90	1.90	1.90
SD	0.22	0.11	0.21	0.22	0.12
Std.	2.61*	2.61*	2.61*	2.64**	2.64**

SD standard deviation

* Norfloxacin, ** Fluconazole

derivative obtained by esterification with benzoic acid which may be due to the presence of an extra unsaturation in the molecule containing cinnamic acid derivatives. The above results are summarized in Fig. 1.

In an attempt to determine the role of structural features which appear to influence the antimicrobial activity of

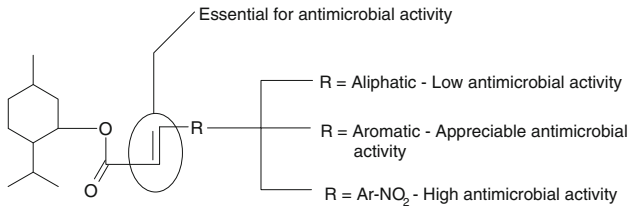


Fig. 1 SAR for antimicrobial activity of synthesized 2-isopropyl methylcyclohexanol derivatives

synthesized compounds, QSAR studies were undertaken using linear free energy relationship (LFER) model of Hansch and Fujita 1964). Biological activity data determined as MIC value were first transformed to pMIC on molar basis, which was used as dependent variable in QSAR studies. These were correlated with different molecular descriptor like log of octanol–water partition coefficient (log P), molar refractivity(MR), Kier's molecular connectivity (χ) and shape (κ_1, $\kappa\alpha_1$) topological indices, Randic topological index (R), Balaban topological index (J), Wiener topological index (W), Total energy (Te), energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), and dipole moment (μ) (Hansch *et al.*, 1973; Kier and Hall, 1976; Randic, 1975, 1993; Balaban, 1982; Wiener, 1947). The values of selected descriptors used in regression analysis are presented in Table 3.

In the present study, a set of 2-isopropyl-5-methylcyclohexanol derivatives (**1**–**26**) were used for linear regression model generation. The reference drugs were not included in model generation as they belong to different structural series. Preliminary analysis was carried out in terms of correlation analysis.

A correlation matrix constructed for antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol derivatives against *C. albicans* is presented in Table 4. In general, the parameters showed high colinearity ($r > 0.700$). The data presented in Table 5 demonstrated the correlation of molecular descriptors of different substituted esters with their corresponding antimicrobial activity. Generally, good correlation was observed with dipole moment (μ) in case of *C. albicans* (Eq. 1).

QSAR model for antifungal activity against *C. Albicans*

$$pMIC_{ca} = 0.121\mu + 1.609 \quad (1)$$

$n = 26$, $r = 0.906$, $r^2 = 0.820$, $q^2 = 0.788$, $F = 109.85$, $s = 0.093$.

Here and thereafter n is the number of data points, r correlation coefficient, r^2 squared correlation, q^2 cross-validated r^2 obtained by LOO method, s standard error of estimation, and F Fischer ratio.

The antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol ester against *C. albicans* is positively correlated to the dipole moment (μ). The coefficient of dipole moment in Eq. 1 is positive which signifies that the activity of synthesized compounds will increase with increase in value of dipole moment. This is evidenced by the antifungal activity data of 2-isopropyl-5-methylcyclohexanol esters (Table 2.) and their μ values (Table 3). Compounds **20** and **21** have highest μ values 6.54 and 6.30 (Table 3.), respectively, and have maximum antifungal

Table 3 Values of selected molecular descriptors used in regression analysis

Comp.	log P	MR	κ_1	κ_2	κ_3	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	Te	μ
1	4.82	76.77	15.39	7.14	4.23	14.26	6.33	3.66	−3149.45	2.16
2	5.61	84.39	16.37	7.32	4.25	15.71	6.86	3.93	−3488.84	2.47
3	5.61	84.39	16.37	7.32	4.50	15.71	6.86	4.16	−3489.03	2.70
4	5.61	84.39	16.37	7.32	4.50	15.71	6.86	4.16	−3489.03	1.65
5	5.34	81.57	16.37	7.32	4.25	15.53	6.73	3.84	−3509.37	2.73
6	5.34	81.57	16.37	7.32	4.50	15.53	6.73	4.07	−3509.52	2.78
7	5.34	81.57	16.37	7.32	4.50	15.53	6.73	4.07	−3509.54	1.63
8	5.86	86.38	17.36	7.51	4.49	16.79	7.13	4.21	−3869.44	2.21
9	4.78	84.09	18.34	8.20	4.75	16.77	7.11	4.00	−3980.03	4.73
10	4.78	84.09	18.34	8.20	5.00	16.77	7.11	4.22	−3980.24	6.74
11	4.78	84.09	18.34	8.20	5.00	16.77	7.11	4.22	−3980.23	4.93
12	4.73	91.42	21.30	9.27	5.49	19.30	7.90	4.53	−4810.65	4.33
13	4.57	83.23	17.36	8.02	4.49	16.19	7.19	3.92	−3625.15	2.69
14	4.57	83.23	17.36	8.02	4.73	16.19	7.19	4.14	−3625.27	3.40
15	4.57	83.23	17.36	8.02	4.73	16.19	7.19	4.14	−3625.34	1.72
16	5.29	81.81	16.37	7.32	4.25	15.24	6.53	3.71	−3305.25	1.68
17	5.29	81.81	16.37	7.32	4.50	15.24	6.53	3.93	−3305.32	2.08
18	5.29	81.81	16.37	7.32	4.50	15.24	6.53	3.93	−3305.33	2.63
19	5.23	87.01	17.36	8.59	5.61	15.97	7.56	4.82	−3432.64	2.02
20	5.18	94.34	20.31	9.63	6.05	18.49	8.31	5.07	−4263.30	6.54
21	5.18	94.34	20.31	9.63	6.35	18.49	8.31	5.34	−4263.45	6.30
22	5.18	94.34	20.31	9.63	6.35	18.49	8.31	5.34	−4263.46	4.94
23	2.91	56.60	12.07	5.19	3.59	11.70	4.92	3.38	−2482.54	1.84
24	3.50	61.35	13.07	5.92	3.81	12.99	5.86	3.76	−2842.52	2.07
25	3.54	61.22	13.07	5.92	3.81	12.70	5.64	3.60	−2638.34	1.65
26	4.04	65.84	14.06	6.07	4.08	13.98	6.02	4.03	−2998.24	2.15

Table 4 Correlation matrix for antifungal activity of 2-isopropyl-5-methylcyclohexanol derivatives against *C. albicans*

	$pMIC_{ca}$	log P	MR	κ_1	κ_2	κ_3	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	Te	μ
$pMIC_{ca}$	1.000										
log P	0.128	1.000									
MR	0.488	0.793	1.000								
κ_1	0.624	0.548	0.931	1.000							
κ_2	0.638	0.520	0.925	0.976	1.000						
κ_3	0.676	0.397	0.815	0.890	0.943	1.000					
$\kappa\alpha_1$	0.592	0.590	0.938	0.991	0.958	0.870	1.000				
$\kappa\alpha_2$	0.593	0.580	0.936	0.958	0.982	0.929	0.963	1.000			
$\kappa\alpha_3$	0.614	0.397	0.752	0.802	0.863	0.966	0.809	0.892	1.000		
Te	−0.611	−0.513	−0.881	−0.977	−0.919	−0.819	−0.983	−0.913	−0.746	1.000	
μ	0.906	0.123	0.553	0.732	0.720	0.736	0.702	0.670	0.658	−0.735	1.000

activity against *C. albicans* having $pMIC_{ca}$ value of 2.33 and 2.33, respectively. Compounds **7** and **16** have minimum μ values 1.63 and 1.68, respectively, and have minimum antifungal activity with $pMIC_{ca}$ 1.67 and 1.64, respectively, which supports the positive correlation of dipole moment (μ) with antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol esters against *C. albicans*.

The importance of dipole moment (μ) in the modulating antifungal activity against *C. albicans* may be due to the

Table 5 Correlation of molecular descriptors with antimicrobial activity of 2-isopropyl-5-methylcyclohexanol derivatives

Parameter	$pMIC_{sa}$	$pMIC_{bs}$	$pMIC_{ec}$	$pMIC_{ca}$	$pMIC_{an}$
log P	0.415	0.502	0.419	0.128	−0.034
MR	0.736	0.707	0.754	0.488	0.355
$^{0}\chi$	0.811	0.650	0.844	0.595	0.466
$^{0}\chi^{v}$	0.712	0.625	0.707	0.395	0.265
$^{1}\chi$	0.790	0.675	0.817	0.567	0.442
$^{1}\chi^{v}$	0.698	0.650	0.697	0.395	0.262
$^{2}\chi$	0.790	0.649	0.820	0.576	0.422
$^{2}\chi^{v}$	0.573	0.546	0.588	0.279	0.089
$^{3}\chi$	0.731	0.464	0.752	0.553	0.383
$^{3}\chi^{v}$	0.192	0.156	0.218	−0.027	−0.250
κ_1	0.816	0.659	0.855	0.624	0.506
κ_2	0.782	0.725	0.821	0.638	0.549
κ_3	0.689	0.756	0.725	0.676	0.592
$\kappa\alpha_1$	0.821	0.642	0.851	0.592	0.478
$\kappa\alpha_2$	0.782	0.722	0.807	0.593	0.520
$\kappa\alpha_3$	0.628	0.731	0.647	0.614	0.553
R	0.790	0.675	0.817	0.567	0.442
B	−0.531	−0.635	−0.492	−0.318	−0.204
W	0.791	0.697	0.823	0.643	0.540
Te	−0.833	−0.560	−0.854	−0.611	−0.491
LUMO	−0.797	−0.617	−0.820	−0.642	−0.452
HOMO	−0.047	0.283	−0.110	−0.340	−0.281
μ	0.716	0.324	0.742	0.906	0.821

presence of carbonyl group (C^{+}–O^{-}) where permanent polarization is seen due to electro negativity difference between the atoms. The carbonyl oxygen of 2-isopropyl-5-methylcyclohexanol esters may involve in making fruitful binding interaction with amino acid present at the target site, through hydrogen bonding. The molecular property dipole moment (μ) thus plays an important role in modulating antifungal profile of synthesized 2-isopropyl-5-methylcyclohexanol esters (Pillai *et al.*, 2005).

The QSAR model expressed by Eq. 1 was cross validated by its high q^2 value ($q^2 = 0.788$) obtained by LOO method (Tetko *et al.*, 2001). It is noteworthy to mention here that the entire data set ($n = 26$) was used for the generation of QSAR models as no outliers were seen in the study. The q^2 value of Eq. 1 ($q^2 = 0.788$; $q^2 > 0.5$) qualifies it to be a valid model according to the recommendation of Golbraikh and Trophsa (2002). In order to confirm our results, we have predicted antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol esters against *C. albicans* using Eq. 1. The comparison of the observed and predicted values (Table 7; Fig. 2) demonstrated that they are close to each other which is evident from their low-residual values.

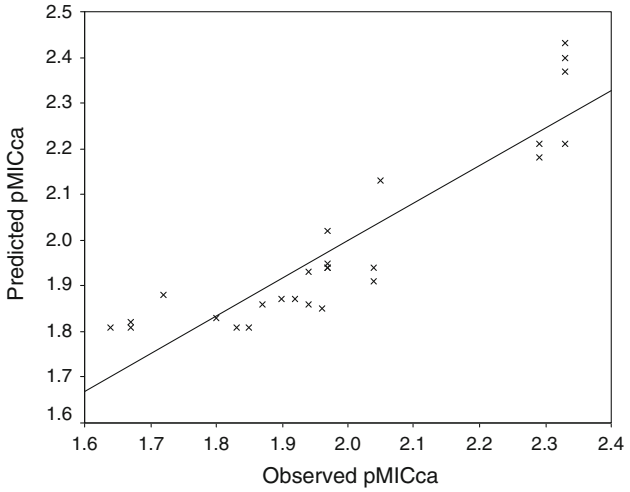


Fig. 2 Plot of predicted $pMIC_{ca}$ activity values against the experimental $pMIC_{ca}$ values for the linear regression developed model by Eq. 1

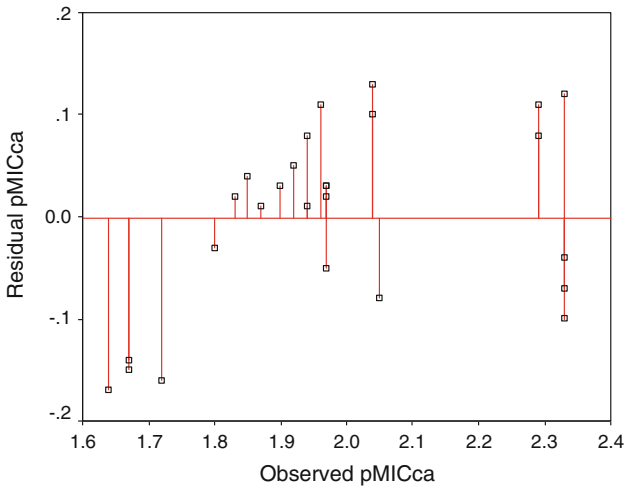


Fig. 3 Plot of residual $pMIC_{ca}$ values against the experimental $pMIC_{ca}$ values

To determine the existence of systemic error in the model development, we have plotted $pMIC_{ca}$ observed against $pMIC_{ca}$ residual values (Fig. 3). The propagation of residuals on both sides of zero indicated that there is no systemic error in development of QSAR models (Heravi and Kyani, 2005). The QSAR models presented in Eqs. 2–5 are developed to predict the antimicrobial activity of 2-isopropyl-5-methylcyclohexanol esters against *A. niger*, *S. aureus*, *B. subtilis*, and *E. coli*, respectively.

QSAR model for antifungal activity against *A. Niger*

$$pMIC_{an} = 0.059\mu + 1.894 \quad (2)$$

$n = 26$, $r = 0.821$, $r^2 = 0.674$, $q^2 = 0.625$, $F = 49.69$, $s = 0.068$.

QSAR model for antifungal activity against *S. Aureus*

$$pMIC_{sa} = -0.003Te + 0.764 \quad (3)$$

$n = 26$, $r = -0.833$, $r^2 = 0.693$, $q^2 = 0.627$, $F = 54.23$, $s = 0.123$.

QSAR model for antifungal activity against *B. Subtilis*

$$pMIC_{bs} = 0.114\kappa_3 + 1.461 \quad (4)$$

$n = 26$, $r = 0.756$, $r^2 = 0.572$, $q^2 = 0.398$, $F = 32.07$, $s = 0.073$.

QSAR model for antifungal activity against *E. Coli*

$$pMIC_{ec} = 0.114\kappa_1 + 0.671 \quad (5)$$

$n = 26$, $r = 0.855$, $r^2 = 0.730$, $q^2 = 0.686$, $F = 65.07$, $s = 0.109$.

The antifungal activity of synthesized 2-isopropyl-5-methylcyclohexanol esters against *A. niger* was correlated with the dipole moment (μ). As in case of *C. albicans*, here also a positive correlation was observed between the molecular descriptor (μ) and antifungal activity against *A. niger* (Eq. 2). In case of antibacterial activity against *S. aureus*, an inverse relationship was observed between antibacterial activity of synthesized 2-isopropyl-5-methylcyclohexanol esters and total energy (Te) of the molecule (Eq. 3). This is evidenced by low Te values (−4263.30 and −4263.45) of compounds **20** and **21** and high $pMIC_{sa}$ values (2.33 and 2.33), respectively.

The total energy calculated by semiempirical methods can be used as a measure of non-specific interaction of drug with its target site, i.e., the total energies of the protonated and neutral forms of molecule can be considered as good measure of the strength of hydrogen bonds (the higher the energy, the stronger the bond) and can be used to determine correct localization of most favorable hydrogen bond acceptor site (Karelson *et al.*, 1996).

The negative correlation of total energy of molecule with antibacterial activity against *S. aureus* indicated that the increase in the total energy of the molecule will decrease the antibacterial activity against *S. aureus* of the synthesized 2-isopropyl-5-methylcyclohexanol esters which is evidenced by antibacterial activity (Table 2) and total energy values (Table 3).

The antibacterial activity against *B. subtilis* and *E. coli* was best correlated with topological parameter κ (Table 5). The positive correlation of κ with antibacterial activity indicated that the antibacterial potential will increase with increase in κ values. The antibacterial model against *B. subtilis* has the q^2 value less than 0.5 ($q^2 = 0.398$) which indicated that the developed model is invalid one as it fails to meet the requirement of $q^2 > 0.5$. However, one should not forget the recommendation of Golbraikh and Trophsa (2002) who have recently reported that the only way to estimate the true predictive power of model is to test their ability to predict accurately the biological activities of compound. As the observed and predicted values are close to each other, the QSAR model for *B. subtilis* (Eq. 4) is valid one. In order to confirm the validity of all the developed QSAR models, we have predicted the antimicrobial activity of all the synthesized compounds using the models expressed by Eqs. 2 to 5 and compared them with observed values (Tables 6, 7; Figs. 4, 5, 6, 7).

Even though the sample size and the "Rule of Thumb" (Narasimhan *et al.*, 2006c) allowed us to go for the development of penta-parametric model in multiple linear regression analysis, the high interrelationship among the parameters restricted us for mono-parametric model. The multi-colinearity occurs when two independent variables are correlated with each other. One should note that the change in signs of the coefficients, a change in the values

Table 6 Observed and predicted antibacterial activities of synthesized 2-isopropyl-5-methylcyclohexanol derivatives using best QSAR models

Comp.	$pMIC_{sa}$			$pMIC_{bs}$			$pMIC_{ec}$		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.92	1.85	0.07	2.01	1.95	−0.06	2.01	1.88	0.13
2	2.04	1.96	0.08	2.04	1.95	0.09	1.98	1.95	0.03
3	1.96	1.96	0.00	1.96	1.98	−0.02	1.88	1.95	−0.07
4	1.98	1.96	0.02	2.04	1.98	0.06	2.02	1.95	0.07
5	1.97	1.97	0.00	1.91	1.95	−0.04	2.10	1.95	0.15
6	1.97	1.97	0.00	1.97	1.98	−0.01	1.88	1.95	−0.07
7	1.88	1.97	−0.09	1.97	1.98	−0.01	1.67	1.95	−0.28
8	2.02	2.09	−0.07	1.96	1.97	−0.01	2.02	2.03	−0.01
9	1.99	2.13	−0.14	2.03	2.00	0.03	2.29	2.11	0.18
10	2.29	2.13	0.16	1.99	2.03	−0.04	2.29	2.11	0.18
11	2.29	2.13	0.16	2.02	2.03	−0.01	1.99	2.11	−0.12
12	2.35	2.42	−0.07	2.05	2.09	−0.04	2.35	2.34	0.01
13	2.06	2.01	0.05	1.98	1.97	0.01	1.97	2.03	−0.06
14	1.97	2.01	−0.04	1.99	2.00	−0.01	1.97	2.03	−0.06
15	2.01	2.01	0.00	2.01	2.00	0.01	1.98	2.03	−0.05
16	1.94	1.90	0.04	1.94	1.95	−0.01	2.01	1.95	0.06
17	2.05	1.90	0.15	2.02	1.98	0.04	1.93	1.95	−0.02
18	1.85	1.90	−0.05	2.10	1.98	0.12	1.90	1.95	−0.05
19	1.96	1.94	0.02	2.26	2.10	0.16	1.96	2.03	−0.07
20	2.33	2.23	0.10	2.03	2.15	−0.12	2.33	2.26	0.07
21	2.33	2.23	0.10	2.03	2.19	−0.16	2.14	2.26	−0.12
22	2.03	2.23	−0.20	2.33	2.19	0.14	2.33	2.26	0.07
23	1.50	1.62	−0.12	1.80	1.87	−0.07	1.50	1.62	−0.12
24	2.00	1.74	0.26	1.86	1.90	−0.04	1.79	1.70	0.10
25	1.75	1.67	0.08	1.88	1.90	−0.02	1.75	1.70	0.06
26	1.60	1.79	−0.19	1.90	1.93	−0.03	1.90	1.77	0.13

Table 7 Observed and predicted antifungal activities of synthesized 2-isopropyl-5-methylcyclohexanol derivatives using best QSAR models

Comp.	$pMIC_{ca}$			$pMIC_{an}$		
	Obs.	Pre.	Res.	Obs.	Pre.	Res.
1	1.92	1.87	0.05	1.92	2.02	−0.10
2	2.04	1.91	0.13	2.04	2.04	0.00
3	2.04	1.94	0.10	2.04	2.06	−0.02
4	1.85	1.81	0.04	2.04	1.99	0.05
5	1.97	1.94	0.03	2.10	2.06	0.04
6	1.97	1.95	0.02	1.97	2.06	−0.09
7	1.67	1.81	−0.14	2.05	1.99	0.06
8	1.72	1.88	−0.16	1.95	2.03	−0.08
9	2.29	2.18	0.11	2.17	2.18	−0.01
10	2.33	2.43	−0.10	2.29	2.30	−0.01
11	2.29	2.21	0.08	2.18	2.19	−0.01
12	2.05	2.13	−0.08	2.05	2.15	−0.10
13	1.97	1.94	0.03	2.07	2.05	0.02
14	1.97	2.02	−0.05	2.11	2.10	0.01
15	1.67	1.82	−0.15	2.04	2.00	0.04
16	1.64	1.81	−0.17	1.94	1.99	−0.05
17	1.94	1.86	0.08	2.03	2.02	0.01
18	1.94	1.93	0.01	2.04	2.05	−0.01
19	1.96	1.85	0.11	2.01	2.01	0.00
20	2.33	2.40	−0.07	2.33	2.28	0.05
21	2.33	2.37	−0.04	2.33	2.27	0.06
22	2.33	2.21	0.12	2.18	2.19	−0.01
23	1.80	1.83	−0.03	1.98	2.00	−0.02
24	1.87	1.86	0.01	2.17	2.02	0.15
25	1.83	1.81	0.02	2.13	1.99	0.14
26	1.90	1.87	0.03	1.90	2.02	−0.12

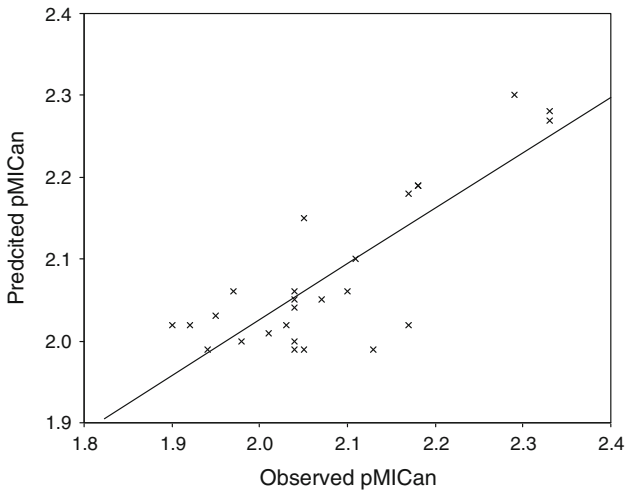


Fig. 4 Plot of predicted $pMIC_{an}$ activity values against the experimental $pMIC_{an}$ values for the linear regression developed model by Eq. 2

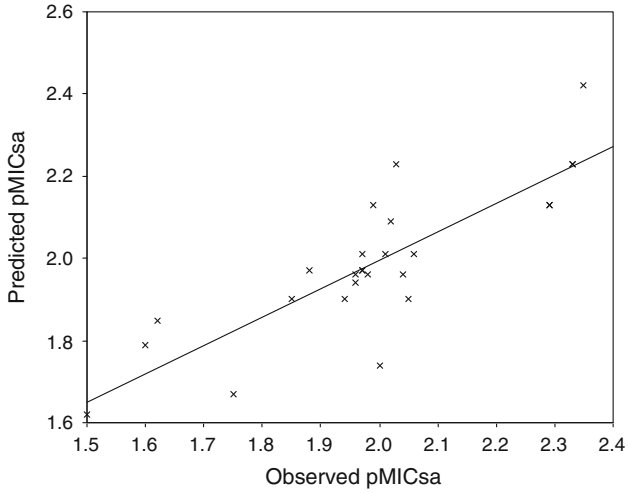


Fig. 5 Plot of predicted $pMIC_{sa}$ activity values against the experimental $pMIC_{sa}$ values for the linear regression developed model by Eq. 3

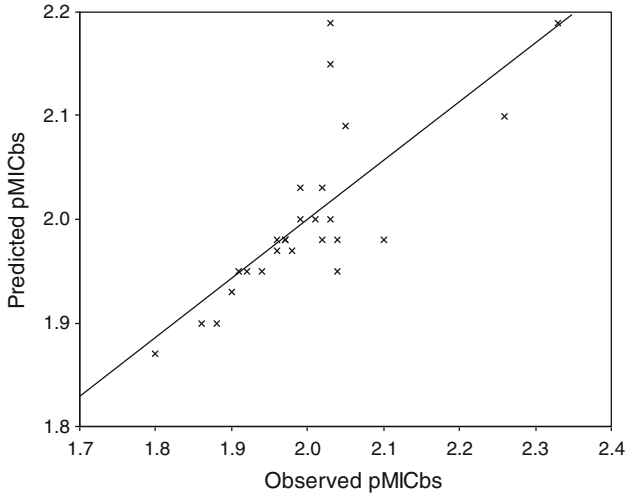


Fig. 6 Plot of predicted $pMIC_{bs}$ activity values against the experimental $pMIC_{bs}$ values for the linear regression developed model by Eq. 4

of previous coefficient, change of significant variable into insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model are indications of high interrelationship among descriptors (Narasimhan *et al.*, 2006c).

Generally for QSAR studies, the biological activities of compounds should span 2–3 orders of magnitude. However, in the present study, the range of antimicrobial activities of the synthesized compounds is within one order of magnitude. However, it is important to note that the predictability of the QSAR models developed in the

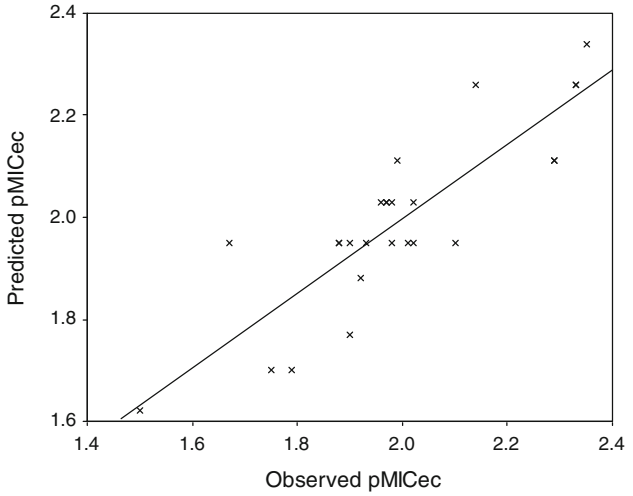


Fig. 7 Plot of predicted $pMIC_{ec}$ activity values against the experimental $pMIC_{ec}$ values for the linear regression developed model by Eq. 5

present study is high, which is evidenced by the low residual values (Tables 6, 7; Figs. 2, 3, 4, 5, 6, 7). This is in accordance with the results suggested by Bajaj *et al.* (2005), who stated that the reliability of the QSAR model lies in its predictive ability even though the activity data are in the narrow range. Further, recent literature reveals that the QSAR has been applied to describe the relationship between the narrow range of biological activity and the physicochemical properties of the molecules (Narasimhan *et al.*, 2007b; Sharma *et al.*, 2006; Hatya *et al.*, 2006; Kumar *et al.*, 2006). Further biological activity data lie in the narrow range, the presence of minimum standard deviation of the biological activity justifies its use in QSAR studies (Narasimhan *et al.*, 2007b; Kumar *et al.*, 2007). The minimum standard deviation (Table 2) observed in the antimicrobial activity data justifies its use in QSAR studies.

Conclusion

In conclusion, a number of 2-isopropyl-5-methylcyclohexanol derivatives have been synthesized in efficient yields. The synthesized compounds exhibited good in vitro antibacterial and antifungal profiles. Moreover, quantitative structure–activity relationship study carried out to determine the relationship between the physicochemical characteristics of synthesized 2-isopropyl-5-methylcyclohexanol derivatives with their antimicrobial activity revealed that the antimicrobial activity is mainly governed by the dipole moment (μ), total energy (Te), and topological parameter (κ_1 and κ_3).

References

Bajaj S, Sambi SS, Madan AK (2005) Prediction of anti-inflammatory activity of N-arylanthranilic acids: computational approach using refined Zagreb indices. Croat Chem Acta 78(2):165–174

Balaban AT (1982) Discriminating distance based topological indices. Chem Phys Lett 89:399–404

Beck B, Bidaux G, Bavencoffe A, Lemonnier L, Thebault S, Shuba Y, Barrit G, Skryma R, Prevarskaya N (2007) Prospects for prostate cancer imaging and therapy using high-affinity TRPM8 activators. Cell Calcium 41:285–294

Dambolena JS, Lopez AG, Canepa MC, Theumer MG, Zygadlo JA, Rubinstein HR (2008) Inhibitory effect of cyclic terpenes (limonene, menthol, menthone and thymol) on *Fusarium verticillioides* MRC 826 growth and fumonisin B1 biosynthesis. Toxicon 51(1):37–44

Desousa DP, Raphael E, Brocksom U, Brocksom TJ (2007) Sedative effect of monoterpene alcohols in mice: a preliminary screening. Z Nat 62(7/8):563–566

Emami S, Foroumadi A, Falahati M, Loffali E, Rajabalian S, Ebrahimi SA, Farahyar S, Shafiee A (2008) 2-Hydroxy phenacyl azoles and related azolium derivative as antifungal agents. Bioorg Med Chem Lett 18:141–146

Galeotti N, Mannelli LDC, Mazzanti G, Bartolini A, Ghelardini C (2002) Menthol: a natural analgesic compound. Neurosci Lett 322:145–148

Garcia DA, Bujons J, Vale C, Sunol C (2006) Allosteric positive interaction of thymol with the GABA-A receptor in primary cultures of mouse cortical neurons. Neuropharmacology 50: 25–35

Garcia-Domenech R, Rios-Santamariana I, Catala A, Calabuig C, Castillo LD, Galvez J (2003) Application of molecular topology to the prediction of antifungal activity for a set of dication-substituted carbazoles, furans and benzimidazoles. J Mol Str (Theochem) 624:97–107

Golbraikh A, Tropsha A (2002) Beware of q^2!. J Mol Graph Model 20(4):269–276

Haeseler G, Maue D, Grosskreutz J, Bufler J, Nentwig B, Piepenbrock S, Dengler R, Leuwer M (2002) Voltage-dependent block of neuronal and skeletal muscle sodium channels by thymol and menthol. Eur J Anaesth 19:571–579

Hansch C, Fujita T (1964) p-σ-π Analysis. A method for the correlation of biological activity and chemical structure. J Am Chem Soc 86:1616–1626

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

Hatya SA, Aki-sener E, Tekiner-Gulbas B, Yildiz I, Temiz-Arpaci O, Yalcin I, Altanlar N (2006) Synthesis, antimicrobial activity and QSARs of new benzoxazine-3-ones. Eur J Med Chem 41: 1398–1404

Hawthorn M, Ferrante J, Luchowski E, Rutledge A, Wei XY, Triggle DJ (1988) The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. Aliment Pharmacol Therap 2:101–118

Heravi JM, Kyani A (2005) A use of computer-assisted methods for the modeling of the retention time of a variety of volatile organic compounds: a PCA-MLR-ANN approach. J Chem Inf Comput Sci 44:1328–1335

Janbaz KH, Gilani AH (2002) Menthol prevents liver damage induced by paracetamol and CCl4. Pak J Biol Sci 5(10):1101–1103

Juergens UR, Stober M, Vetter H (1998) The anti-inflammatory activity of L-menthol compared to mint oil in human monocytes in vitro: a novel perspective for its therapeutic use in inflammatory diseases. Eur J Med Res 3(12):539–545

Karelson M, Lobanov VS, Katritzky AR (1996) Quantum—chemical descriptors in QSAR/QSPR studies. Chem Rev 96(3):1027–1043

Kier LB, Hall LH (1976) Molecular connectivity in chemistry and drug research. Academic Press, New York, pp 79–82

Kim HK, Yun YK, Ahn YJ (2008) Fumigant toxicity of cassia bark and cassia and cinnamon oil compounds to dermatophagoides farinae and dermatophagoides pteronyssinus (*Acari*: *Pyroglyphidae*). Exp Appl Acarol 44(1):1–9

Kotan R, Kordali S, Cakir A (2007) Screening of antibacterial activities of twenty-one oxygenated monoterpenes. Z Nat C 62(7/8):507–513

Kumar A, Sharma P, Gurram VK, Rane N (2006) Studies on synthesis and evaluation of quantitative structure–activity relationship of 10-methyl-6-oxo-5-arylazo-6, 7-dihydro-5H-[1,3]azaphospholo[1,5-d][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides. Bioorg Med Chem Lett 16:2484–2491

Kumar A, Narasimhan B, Kumar D (2007) Synthesis, antimicrobial and QSAR studies of substituted benzamides. Bioorg Med Chem 15:4113–4124

Macpherson LJ, Hwang SW, Miyamoto T, Dubin AE, Patapoutian A, Story GM (2006) More than cool: promiscuous relationships of menthol and other sensory compounds. Mol Cell Neurosci 32:335–343

Mimica-Dukic N, Bozin B, Sokovic M, Mihajlovic B, Matavulj M (2003) Antimicrobial and antioxidant activities of three Mentha species essential oils. Planta Med 69(5):413–419

Miyazawa M, Watanabe H, Kameoka H (1997) Inhibition of acetylcholinesterase activity by monoterpenoids with a p-menthane skeleton. J Agric Food Chem 45:677–679

Narasimhan B, Kothwade UR, Pharande DS, Mourya VK, Dhake AS (2003) Syntheses and QSAR studies of sorbic, cinnamic and ricinoleic acid derivatives as potential antibacterial agents. Indian J Chem 42(B):2828–2834

Narasimhan B, Belsare D, Pharnde P, Mourya V, Dhake AS (2004) Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations. Eur J Med Chem 39(10):827–834

Narasimhan B, Kumari M, Dhake AS, Sundaravelan C (2006a) QSAR studies on structurally similar 2-arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides as anti-inflammatory agents. Arkivoc xiii: 73–82

Narasimhan B, Mourya VK, Dhake AS (2006b) Design, synthesis, antibacterial and QSAR studies of myristic acid derivatives. Bioorg Med Chem Lett 16:3023–3029

Narasimhan B, Kumari M, Jain N, Dhake AS, Sundaravelan C (2006c) Correlation of antibacterial activity of some n-[5-(2-furanyl)-2-methyl-4-oxo-4h-thieno[2,3-d]pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2-furanyl)-2-methyl-3h-thieno[2,3-d]pyrimidin4-ones with topological indices using Hansch analysis. Bioorg Med Chem Lett 16:4951–4958

Narasimhan B, Narang R, Judge V, Ohlan S, Ohlan R (2007a) Synthesis, antimicrobial and QSAR studies of substituted anilides. ARKIVOC xv:112–126

Narasimhan B, Judge V, Narang R, Ohlan S, Ohlan R (2007b) Quantitative structure–activity relationship studies for prediction of antimicrobial activity of synthesized 2,4-hexadienoic acid derivatives. Bioorg Med Chem Lett 17:5836–5845

Narasimhan B, Mourya VK, Dhake AS (2007c) QSAR studies of antibacterial ricinoleic acid derivatives. Pharm Chem J 41(3):133–139

Ohlan R, Ohlan S, Judge V, Narang R, Ahuja M, Narasimhan B (2007) 2-(2,4-Difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol derivatives: synthesis, antifungal evaluation and QSAR studies by Hansch analysis. ARKIVOC xiv:172–184

Pharmacopoeia of India (1996) Ministry of Health Department, Govt. of India, New Delhi, vol II, A-88

Pillai AD, Rani S, Rathod PD, Xavier FP, Vasu KK, Padh H, Sudarsanam V (2005) QSAR studies on some thiophene analogs as anti-inflammatory agents: enhancement of activity by electronic parameters and its utilization for chemical lead optimization. Bioorg Med Chem 13:1275–1283

Randic M (1975) On the characterization of molecular branching. J Am Chem Soc 97:6609–6615

Randic M (1993) Comparative regression analysis. Regressions based on single descriptor. Croat Chem Acta 66:289–312

Schaper KJ (1999) Free-Wilson-type analysis of non-additive substituent effects on THPB dopamine receptor affinity using artificial neural networks. Quant Struct Act Relat 18:354–360

Schelz Z, Molnar J, Hohmann J (2006) Antimicrobial and antiplasmid activities of essential oils. Fitoterapia 77:279–285

Shadomy S, Espinel A (1980) Manual of clinical microbiology. American Society for Microbiology, Washington, DC, 647 pp

Sharma P, Rane N, Gurram VK (2004) Synthesis and QSAR studies of pyrimido[4,5-d]pyrimidine-2,5-dione derivatives as potential antimicrobial agents. Bioorg Med Chem Lett 14:4185–4190

Sharma P, Kumar A, Sharma M (2006) Synthesis and QSAR studies on 5-[2-(2-methylprop1-enyl)-1H-benzimidazol-1yl]-4,6-diphenyl-pyrimidin-2-(5H)-thione derivatives as antibacterial agents. Eur J Med Chem 41:833–840

Sidell N, Taga T, Hirano T, Kishimoto T, Saxom A (1991) Retinoic acid-induced growth inhibition of a human myeloma cell line via down-regulation of IL-6 receptors. J Immunol 146(11):3809–3814

Silva MIG, Neto MR, Neto PFT, Moura BA, Amaral JF, Desousa DP, Vasconcelos SMM, Desousa FCF (2007) Central nervous system activity of acute administration of isopulegol in mice. Pharmacol Biochem Behav 88(2):141–147

Sortino M, Delgado P, Jaurez S, Quiroga J, Abonia R, Insuasey B, Nogueras M, Rodero L, Garibotto FM, Enriz RD, Zacchino SA (2007) Synthesis and antifungal activity of (Z)-5-arylidenerhodanines. Bioorg Med Chem Lett 15:484–494

SPSS Inc. (1999) SPSS for Windows, Version 10.05. SPSS Inc., Bangalore

Tamaoki J, Chiyotani A, Sakai A, Takemura H, Konno K (1995) Effect of menthol vapour on airway hyperresponsiveness in patients with mild asthma. Respir Med 89(7):503–504

Tetko IV, Tanchuk VY, Villa AE (2001) Prediction of n-octanol/water partition coefficients from PHYSPROP database using artificial neural networks and E-state indices. J Chem Inf Comput Sci 41:1407–1421

Trombetta D, Castelli F, Sarpietro MG, Venuti V, Cristini M, Daniele C, Sajja A, Mazzanti G, Bisigano G (2005) Mechanisms of antibacterial action of three monoterpenes. Antimicrob Agents Chemother 49(6):2474–2478

TSAR (2000) TSAR 3D version 3.3. Oxford Molecular Limited

Vasanthanthan P, Lakshmi M, Babu MA, Gupta AK, Koshedikar SG (2006) QSAR study of 3-phenyl-5-acyloxymethyl-2H,5H-furan-2-ones as antifungal agents: the dominant role of electronic parameter. Chem Pharm Bull 54:583–587

Wang XH, Tang Y, Xie Q, Qiu Z (2006) QSAR study of 4-phenylpiperidine derivatives as μ opioid agonists by neural network method. Eur J Med Chem 41:226–232

Wiener H (1947) Structural determination of paraffin boiling points. J Am Chem Soc 69:17–20

Yao XJ, Panye JP, Doucet JP, Zang RS, Chen HF, Lice MC, Hu ZD, Fan BT, Liu MC, Hu ZD (2004) Comparative study of QSAR/QSPR correlations using support vector machines, radial basis function neural networks, and multiple linear regression. J Chem Inf Comput Sci 44:1257–1266