Chem Biol Drug Des 2012; **79:** 553–559

Research Letter

doi: 10.1111/j.1747-0285.2011.01289.x

DFT-based QSAR Models to Predict the Antimycobacterial Activity of Chalcones

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In this study, antimycobacterial activity of a set of synthesized chalcone derivatives against *Mycobacterium tuberculosis H37Rv* was investigated by quantitative structure–activity relationship (QSAR) analysis using density functional theory (DFT) and molecular mechanics (MM+)-based descriptors in both gas and solvent phases. The best molecular descriptors identified were hardness, E_{HOMO}, $MR_{A\text{-}4}$ and $MR_{B\text{-}4'}$ that contributed to the antimycobacterial activity of the chalcones as independent factors. The correlation of these four descriptors with their antimycobacterial activity increases with the inclusion of solvent medium, indicating their importance in studying biological activity. QSAR models revealed that in gas phase, lower values of E_{HOMO}, $MR_{A\text{-}4}$ and $MR_{B\text{-}4'}$ increase the antimycobacterial activity of the chalcone molecules. However, in solvent phase, lower values of E_{HOMO} and $MR_{B\text{-}4'}$ and higher values of $MR_{A\text{-}4}$ increase their activity.

Key words: antimycobacterial activity, chalcones, density functional theory, quantitative structure-activity relationships, solvent effect

Received 25 May 2010, revised 15 October 2011 and accepted for publication 29 November 2011

Introduction

The battle between humankind and *Mycobacterium tuberculosis*, the etiological agent of tuberculosis (TB), dates back to antiquity. Although in 1950s, TB incidences were reduced by the introduction of antimycobacterial chemotherapy and the widespread use of BCG vaccine (1), TB still remains a major international health problem, which is likely to become even more alarming in the coming years due partly to TB deaths in HIV-infected patients and partly to the emergence of multidrug resistant strains of the *Mycobacterium tuberculosis* (2). TB was declared as a global emergency by the World Health Organization (WHO) in the year 1993. The prolonged therapy and the significant toxicity of the current TB drugs make patient compliance to therapy very difficult, giving rise to selection for drug-resistant TB bacteria (3). This is also responsible for the emergence of the threats from the phenomena of multidrug resistance and extensive drug resistance against the conventional first line and second line of drugs. The rapid spread of TB worldwide has intensified the need for more efficient antimycobacterial agents to combat this disease.

Chalcones, or 1, 3-diaryl-2-propen-1-ones (Figure 1), are a group of natural or synthetic compounds (4), consisting of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system (5). Chalcones are important precursors of flavonoids and isoflavonoids (6) and, recently, have been subjected to great interest for their valuable pharmacological activities, including antioxidant (7), antibacterial (8), antitrypanosomal (9), antileishmanial (10), anticancer, cytotoxic (11), antidiabetic (12) and anti-inflammatory (13) activities. The presence of a reactive α, β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of the substituent on the aromatic rings (8).

In silico virtual screening is fast emerging to be a potentially useful tool in search of targets of natural products. This approach is inexpensive as it is effective and fast. *In silico* methods are being increasingly applied in generating hypothesis relating to the possible mechanism of drug target interactions. This approach implicates databases, quantitative structure-activity relationships (QSAR), similarity searching, pharmocophores, homology models and other molecular modeling, machine learning, data mining, network analysis tools, and data analysis tools. *In silico* methods have been frequently used in the discovery and optimization of novel molecules with affinity toward a target, the clarification of absorption and in studying the distribution, metabolism, excretion, and toxicity properties as well as physicochemical characterization of the potential drug molecules (14). QSAR is fast emerging as a useful tool in modern chemistry, biology, and drug discovery (15,16). A QSAR model is a mathematical equation that correlates the biological, chemical, or physical activity of a molecular system to its geometric and chemical characteristics. The molecular descriptors are used to define the electronic properties of a molecule owing to the presence of limitations of fundamental physical and chemical laws in direct quantification of biological activity. The quantum chemical descriptors computed by density functional theory (DFT) and semi-empirical methods have found increasing use in modern QSAR analysis (16).

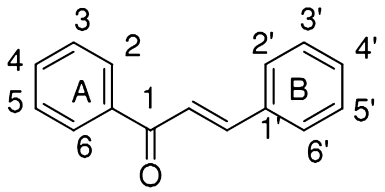

Figure 1: Basic structure of chalcone.

In this study, we have found that DFT-derived descriptors chemical hardness (η), E_{HOMO} and MM+ descriptor, namely molar refractivity (MR), correlates with the antituberculosis activity of the chalcone molecules remarkably in both gas and solvent phases.

Methods

Theoretical background

In theoretical chemistry, the chemical potential (μ) is identified as the negative of the electronegativity (χ) by Iczkowski and Margrave (17) and defined as:

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \tag{1}$$

The quantitative definition of hardness (η) of an N-electron system with total energy E and external potential $v(r)$ using DFT can be expressed as:

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{2}$$

and the global electrophilicity index (ω) is expressed in terms of chemical potential and hardness as:

$$\omega = \frac{\mu^2}{2\eta} \tag{3}$$

According to the finite difference approach, global hardness and chemical potential can be approximated as:

$$\mu = -\left(\frac{\mathrm{IP} + \mathrm{EA}}{2}\right) \tag{4}$$

$$\eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{5}$$

where IP and EA are the first vertical ionization potential and electron affinity, respectively, of the chemical system.

Further approximation using Koopmans' theorem (18), the above parameters can be expressed by taking IP and EA as negative of the HOMO and LUMO energies, respectively.

$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \tag{6}$$

and

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \tag{7}$$

where E_{LUMO} is the energy of the lowest unoccupied molecular orbital and E_{HOMO} is the energy of the highest occupied molecular orbital.

Computational details

Structures of all chalcone molecules are presented in Figure 2. Full unconstrained geometry optimizations of these compounds were carried out using DMol^3 program (19). The most widely used exchange-correlation functional suggested exchange potential by Becke (20) with gradient-corrected correlation provided by Lee, Yang and Parr (21) (BLYP) was used in combination with double numerical with polarization (DNP) basis set to study chalcones derivatives. DNP is the double numerical with polarization basis set, size of which is comparable with 6-31G** basis of Hehre *et al.* (22). However, it is believed to be much more accurate than a Gaussian basis set of the same size. Optimized geometries were verified by frequency calculations and characterized as minima (no imaginary frequency) in their potential energy surface. The reactivity descriptors electrophilicity index (ω), chemical potential (μ), and global hardness (η) were calculated for all systems using eqns 3, 6 and 7, respectively. The conductor-like screening model (COSMO) (23) as incorporated into the DMol^3 program with dielectric constant of 78.4 was adopted to study the solvent (water) effect. In addition, the MR, van der Waals surface area (SA), volume (V), mass (M), and lipophilicity index (logP) for whole molecule were calculated from the MM+ computations with Hyperchem software ([a]).

QSAR modeling

Quantitative structure-activity relationship (QSAR) analysis using multiple linear regression has been attempted to relate the structural features of these chalcone molecules that may have an influence on their observed antimycobacterial activity.

The analysis was performed selecting different descriptors such as, energy of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), energy of the next lowest unoccupied molecular orbital (E_{NL}), energy difference between LUMO and HOMO ($\Delta_{L\text{-}H}$), dipole moments, electrophilicity (ω), and hardness (η). Molecular mechanics (MM) parameters such as van der Waals surface area (SA), molecular volume (V), hydrophobicity, polarizibility, and MR were also calculated. Subdivision of the flavonoid molecules into submolecular fragments has been suggested (24) for a more informative approach in QSAR modeling based on the reports that different moieties of flavonoid scaffold being responsible for antioxidant activity and inhibition of reactive oxygen species production in enzymatic and whole cell system (25,26). Therefore, we also subdivided the chalcone molecules into Ring A and Ring B to calculate the MR of the groups at the carbon position 4 and carbon position 4′ of Ring A and Ring B, respectively.

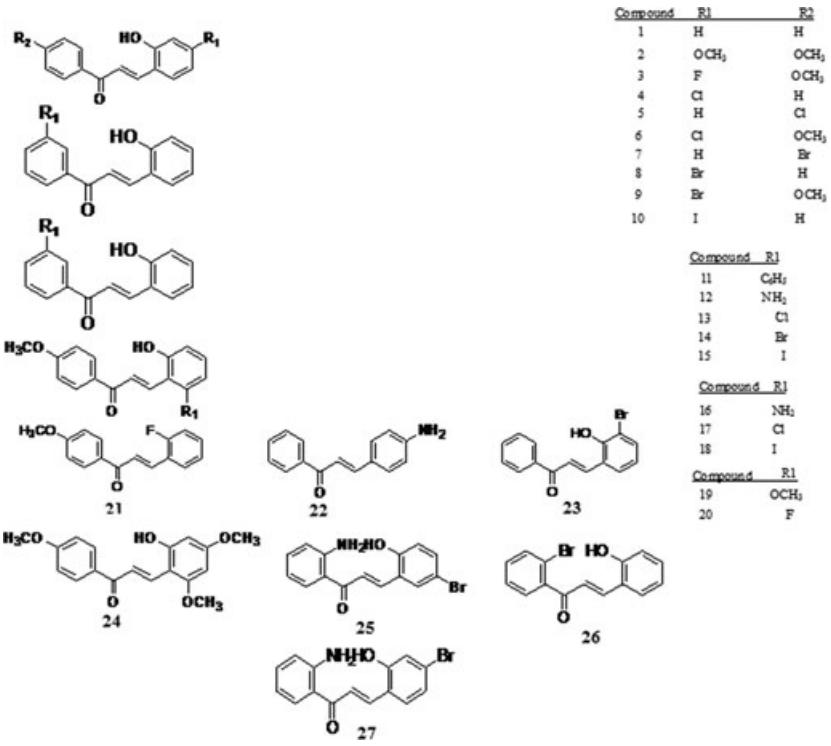

Figure 2: Sketch of the chalcones used to build quantitative structure–activity relationship model.

The antimycobacterial activity data of the chalcone molecules 1–27 against *Mycobacterium tuberculosis H37Rv* determined by BACTEC method were taken from the results reported by Lin *et al.* (27). We have randomly selected these 27 molecules of the reported 47 chalcones (27). However, we have excluded some molecules for this study as they are ineffective with inhibitory activity value zero. The analyses of the 27 molecules were performed in both gas phase and solvent phase. Multi-linear regression was performed by those descriptors which showed greater correlation to the percentage of inhibition of *M. tuberculosis H37Rv* at a concentration of 12.5 μg/mL and smaller autocorrelation were selected out. Four-parameter QSAR was performed using the least square error estimation (28) to calculate and compare bioactivity of the molecules. The quality and predictability of the QSAR models were determined using the 'leave one out' (LOO) cross-validation method.

Results and Discussion

We analyzed all the calculated DFT-based parameters such as ω, E_{NL}, E_{LUMO} for the derivation of the QSAR models and found that the equations derived by considering the percentage of inhibition at 12.5 μg/mL as a dependent variable and hardness (η), energy of the HOMO orbital (E_{HOMO}), MR of the group at position 4 of Ring A ($MR_{A\text{-}4}$), and MR of the position 4′ of Ring B ($MR_{B\text{-}4'}$) as independent variables gave the best correlation in the gas phase and the solvent phase. The gas-phase and solvent-phase models are presented as eqns 8 and 9. The descriptors used to build the QSAR model for both gas and solvent phases are presented in Table 1.

Gas phase:

$$\begin{aligned}\text{Activity} = &-321.01(\pm64.301) + 181.42(\pm69.929)\eta \\ &- 31.07(\pm18.748)E_{HOMO} - 1.104(\pm1.429)MR_{A-4} \\ &- 3.94(\pm0.937)MR_{B-4'}\end{aligned} \quad (8)$$

$n = 27$, $r^2 = 0.73$, $F = 14.86$, $p < 0.05$, $r^2_{cv} = 0.56$

Solvent phase:

$$\begin{aligned}\text{Activity} = &-416.87(\pm61.492) - 7.03(\pm21.689)\eta \\ &- 89.47(\pm13.624)E_{HOMO} + 0.21(\pm0.931)MR_{A-4} \\ &- 3.02(\pm0.778)MR_{B-4'}\end{aligned} \quad (9)$$

$n = 27$, $r^2 = 0.81$, $F = 22.73$, $p < 0.05$, $r^2_{cv} = 0.50$

In the QSAR equations, n is the number of data points, r^2 is square of the correlation coefficient and represents the goodness of fit, r^2_{cv} is the LOO cross-validated r^2 (a measure of the quality of the QSAR model). F is the overall F-statistics for the addition of each successive term, and p is the p values using the F statistics. We have found that the gas-phase r^2 value (0.73) increases (0.81) when calculated in the solvent phase; however, the r^2_{cv} value is 0.56 in the gas phase and decreases to 0.50 in the solvent phase. The errors of regression coefficients are also found to be less in solvent phase than that of gas phase.

These regression models are significant as depicted by the p value <0.05 using the F statistics (29). The QSAR models had to be

Table 1: Parameters used to build the quantitative structure–activity relationship models with the jackknife results for gas and solvent phases against *M. tuberculosis*

	Gas phase						Solvent phase				
Compounds	Percentage of inhibition at 12.5 mg/mL	η	E_{HOMO}	$MR_{A\text{-}4}$	$MR_{B\text{-}4'}$	r_j^2	η	E_{HOMO}	$MR_{A\text{-}4}$	$MR_{B\text{-}4'}$	r_j^2
1	61	1.255	−5.665	0.89	0.89	0.7459	1.203	−5.593	0.89	0.89	0.8116
2	32	1.22	−5.205	7.32	7.32	0.7264	1.161	−5.25	7.32	7.32	0.8043
3	63	1.3	−5.635	7.32	0.8	0.7424	1.258	−5.569	7.32	0.8	0.8084
4	89	1.249	−5.782	0.89	5.39	**0.7508**	1.226	−5.676	0.89	5.39	**0.8222**
5	67	1.231	−5.746	5.39	0.89	0.7285	1.187	−5.599	5.39	0.89	0.8112
6	57	1.278	−5.648	7.32	5.39	0.7297	1.236	−5.572	7.32	5.39	0.8051
7	70	1.224	−5.754	8.21	0.89	0.7267	1.202	−5.588	8.21	0.89	0.8033
8	57	1.252	−5.799	0.89	8.21	0.7306	1.219	−5.644	0.89	8.21	0.8053
9	25	1.275	−5.655	7.32	8.21	0.7449	1.242	−5.545	7.32	8.21	**0.8271**
10	21	1.227	−5.752	0.89	12.99	0.7194	1.178	−5.558	0.89	12.99	0.807
11	68	1.128	−5.422	0.89	0.89	**0.7488**	1.085	−5.366	0.89	0.89	0.8147
12	6	0.905	−4.842	0.89	0.89	0.7309	0.817	−4.754	0.89	0.89	0.7834
13	67	1.192	−5.705	0.89	0.89	0.7275	1.161	−5.582	0.89	0.89	0.8046
14	68	1.18	−5.693	0.89	0.89	0.7274	1.165	−5.546	0.89	0.89	0.8031
15	51	1.142	−5.614	0.89	0.89	0.7312	1.106	−5.437	0.89	0.89	0.8086
16	11	1.074	−5.189	0.89	0.89	0.7267	0.978	−5.078	0.89	0.89	0.8039
17	90	1.222	−5.762	0.89	0.89	0.7231	1.192	−5.631	0.89	0.89	0.8024
18	92	1.225	−5.771	0.89	0.89	0.723	1.207	−5.652	0.89	0.89	0.8013
19	75	1.282	−5.365	7.32	0.89	0.7278	1.201	−5.415	7.32	0.89	0.8169
20	66	1.291	−5.642	7.32	0.89	0.7344	1.252	−5.630	7.32	0.89	0.8102
21	5	1.141	−4.948	0.89	4.22	0.7208	0.990	−4.868	0.89	4.22	0.7819
22	82	1.271	−5.487	7.32	0.89	0.7291	1.267	−5.639	7.32	0.89	0.7981
23	79	1.255	−5.824	0.89	0.89	0.7219	1.245	−5.745	0.89	0.89	0.8013
24	40	1.222	−5.081	7.32	7.32	**0.7499**	1.154	−5.210	7.32	7.32	**0.8258**
25	8	1.103	−5.402	0.89	0.89	**0.7692**	1.027	−5.144	0.89	0.89	**0.8225**
26	83	1.234	−5.645	0.89	0.89	0.7225	1.195	−5.626	0.89	0.89	0.7994
27	12	1.11	−5.383	0.89	8.21	0.705	1.038	−5.147	0.89	8.21	0.787

MR, molar refractivity.
The bold values in Table were selected and subjected to the LOO method with an intention to increase the correlation coefficient.

further improved as general statistical standards requires $r^2 > 0.80$ (30) and $r_{cv}^2 > 0.60$ (31) for a regression model to be acceptable. Therefore, to improve the overall quality of the regression models, we applied the scheme suggested by Dietrich *et al.* (32) and Cornish-Bowden and Wang (33) as we have applied in our recent paper (34,35). In this scheme, a compound is considered as an outlier if its corresponding r^2, called jackknife r^2 (r_{cv}^2) value obtained from the regression analysis after deleting the compound, is comparatively higher than the other r_{cv}^2 values. Table 1 presents the r_{cv}^2 values calculated in gas phase and solvent phase. Although the independent variables are same in both gas and solvent phases, the r_{cv}^2 values differed in case of each molecule. In gas phase, it was observed that molecules 4, 11, 24, and 25 possessed higher r_{cv}^2 values (0.751, 0.749, 0.750, and 0.769, respectively), whereas in solvent phase, molecules 4, 9, 24, and 25 exhibited high r_{cv}^2 values (0.822, 0.827, 0.826, and 0.823, respectively). These molecules were considered as outliers, and it was observed that deleting these molecules from the data set lead to the improvement of the statistical parameters in the QSAR models.

The QSAR equations after deleting these outliers (4, 11, 24, and 25 in gas phase) and (4, 9, 24, and 25 in solvent phase) are as follows:

Gas phase:

$$\begin{aligned}\text{Activity} = &-323.24(\pm54.0887) + 131.53(\pm56.246)\eta \\ &- 42.08(\pm15.610)E_{HOMO} - 0.63(\pm1.127)MR_{A-4} \\ &- 4.46(\pm0.752)MR_{B-4'}\end{aligned} \quad (10)$$

$n = 23$, $r^2 = 0.84$, $F = 23.46$, $p < 0.05$, $r_{cv}^2 = 0.70$

Solvent phase:

$$\begin{aligned}\text{Activity} = &-391.63(\pm50.827) - 8.85(\pm16.737)\eta \\ &- 85.38(\pm11.055)E_{HOMO} + 0.31(\pm0.788)MR_{A-4} \\ &- 3.35(\pm0.666)MR_{B-4'}\end{aligned} \quad (11)$$

$n = 23$, $r^2 = 0.88$, $F = 33.0$, $p < 0.05$, $r_{cv}^2 = 0.67$

We have observed that the r^2 value increased from 0.73 to 0.84 and 0.81 to 0.88 in gas phase and solvent phase, respectively. The r_{cv}^2 value increased from 0.56 to 0.70 in the gas phase and 0.50 to 0.67 in the solvent phase; however, the r_{cv}^2 value remained lower in solvent phase as compared to the gas phase. We have found that the error of regression coefficient decreases for both gas- and

solvent-phase model calculated using jackknife scheme. However, the error of regression coefficient significantly decreases for independent variable, E_{HOMO}, in solvent phase. We have also calculated the *t*- and p-values for all the regression coefficients for all the equations and provided in Table 2. Although both the QSAR models are significant, we found solvent phase to be better than the gas phase–derived model based on the r^2 values. The correlation plots between the experimental and calculated bioactivity values of the chalcones molecules derived from the two QSAR models are shown in Figure 3. The plots indicate that these descriptors can be effectively used in the prediction of the bioactivity of the chalcone molecules.

The QSAR models predict that in both gas phase and solvent phase, lower values of E_{HOMO} and $MR_{B\text{-}4'}$ relate to greater inhibition of *M. tuberculosis*. However, difference was observed in the dependence of antimycobacterial activity of the chalcone molecules on hardness and $MR_{A\text{-}4}$ when calculated in gas and solvent phases. In gas phase, the antimycobacterial activity increased with the higher values of hardness and lower values of $MR_{A\text{-}4}$ of the molecules as shown by the eqs 8 and 10. The eqs 9 and 11 depicting the antimycobacterial activity of the chalcone molecules in solvent phase, however, predict that decrease in the hardness and increase in $MR_{A\text{-}4}$ of these molecules increase their antimycobacterial activity.

The frontier orbital theory states that the energy of the HOMO and LUMO is the important factors that determine the reactivity of a molecule. The QSAR models generated in both gas and solvent phase predict that decrease in the energy of HOMO increased the inhibition activity of the chalcone molecules. It was observed that the presence of a halogen in one of the two rings, irrespective of the position, increased the antimycobacterial activity of the chalcones. This could be attributed to the electronegativity of the halogens which decrease the energy of HOMO by removing the electron density from the σ space of the benzene rings (36). The very low values of antimycobacterial inhibitions can be similarly explained by the presence of an electron donating group such as an amino group($-NH_2$). The lone pair of electrons of nitrogen atom delocalize into the π space of the benzene ring and increase the E_{HOMO} of the molecule (35). Table 1 shows that in both gas and solvent phases, the presence of the amino group in the B ring of the chalcone molecules increases the E_{HOMO} more as compared to the presence of the amino group in Ring A. However, no such discrete increase in E_{HOMO} was observed owing to the presence of halogens in Ring A or Ring B. Sivakumar *et al.* (37) reported the QSAR study of 33 chalcones using robust statistical technique such as genetic function approximation. Their analysis also indicates the importance of hydrogen bond donor and HOMO in the determination of antituberculosis activity of chalcones.

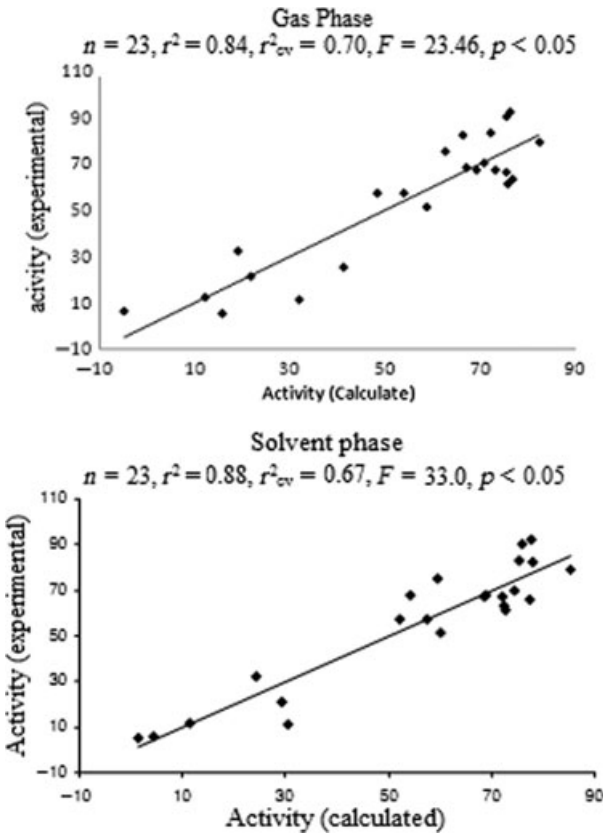

Figure 3: Plot of experimental versus calculated values of bioactivity for the two models.

The correlation plots between experimental and calculated activity values in gas and solvent media presented in Figure 3 indicated that the selected parameters can predict the antimycobacterial activity of the set chalcone molecules with greater predictability in the solvent phase. Thus, designing new chalcone molecules with electron withdrawing substituent on the ring may increase the antimycobacterial activity.

Table 2: Statistical *t*- and p-values for all the regression coefficients for all the equations

		η		E_{HOMO}		$MR_{A\text{-}4}$		$MR_{B\text{-}4'}$	
n	Phase	*t*-Value	p-Value	*t*-Value	p-Value	*t*-Value	p-Value	*t*-Value	p-Value
27	Gas phase	2.5943	0.0166	−1.6574	0.11164	−0.7729	0.4478	−4.2062	0.0004
27	Solvent phase	−0.3242	0.7489	−6.5668	1.32E−06	0.2236	0.8251	−3.8779	0.0008
23	Gas phase	2.3386	0.0311	−2.6958	0.01478	−0.5618	0.5812	−5.9341	1.00E−05
23	Solvent phase	−0.5285	0.6036	−7.7234	4E−07	0.4053	0.6900	−5.0311	9.00E−05

MR, molar refractivity.

Conclusions

The QSAR equations developed with the four parameters hardness (η), E_{HOMO}, $MR_{A\text{-}4}$ and $MR_{B\text{-}4'}$ provide regression models to predict the activity of the set of chalcone molecules against *Mycobacterium tuberculosis H37Rv*. The statistical quality of the regression models in both gas and solvent phases was improved by applying the jackknife test. Increase in correlation coefficient (r^2 = 0.88) by the inclusion of solvent medium depicts the importance of the solvent effect and the selected parameters. These regression models reveal that in gas phase, higher values of hardness and lower values of E_{HOMO}, $MR_{A\text{-}4}$ and $MR_{B\text{-}4'}$ of chalcones increase their inhibitory activities against *M. tuberculosis H37Rv*. In solvent phase, lower values of hardness, E_{HOMO} and MRB-4′ and higher value of MRA-4 increase the antimycobacterial activity of the chalcones. The QSAR models also show that the descriptors derived from DFT and MM+ methods can successfully be utilized to predict the antimycobacterial activity of the chalcone molecules.

Acknowledgment

The authors thank the Department of Science and Technology (DST), New Delhi, for financial support.

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Note

[a]HyperChem; Release 7; Hypercube; http://www.hyper.com/, 2002.