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Original Article

QSAR Study on Arylthioquinoline Derivatives as Anti-tubercular Agents

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ABSTRACT

Aim: The major issue for many anti-tubercular agents is the resistance of *Mycobacterium tuberculosis* strains. Quinoline compounds serve as anti-mycobacterial agents with encouraging anti-tubercular activity. The main aim of this study is to develop 2D QSAR models for a series of arylthioquinoline to predict their ideal characteristics as potential anti-tubercular agents. **Materials and Methods:** Used CS Chem Office 2004 and Molecular Modeling Pro 6.1.0 software for modeling and models development. Some of the statistical parameters were calculated by using QSARINS (HYPERLINK "http://www.qsar.it/"www.qsar.it). We have used MLR techniques to develop QSAR models. The developed QSAR models were found to be statistically significant based on internal and external validation parameters. **Results:** The significance and predictive ability of the developed QSAR model was confirmed as it satisfied the following conditions: r^2=0.817>0.6; CCC_{tr}=0.899>0.85; q^2LOO=0.729>0.5; pred_r^2=0.922>0.6; pred_r^2se=0.186; CCC_{pred}=0.907>0.85; r^2m=0.753>0.5; r'^2m=0.714>0.5; Δ r^2m=0.039<0.2k'=0.966; k=1.014 (0.85<k or k'<1.15); r^2-r^2_0/r^2=0.064; r^2-r'^2_0/r^2=0.086 (r^2-r^2_0/r^2 or r^2- r'^2_0/r^2<0.1); r^2p=0.775>0.5; q^2LMO=0.650>0.5. The major outcome of this study is that the density of the molecules significantly influences the anti-tubercular activity of novel arylthioquinoline derivatives. **Conclusion:** It can be concluded that the proposed models explained the relationship of the density of arylthioquinolines with their anti-tubercular activity and these can be used as guidance for synthesis of new anti-tubercular agents.

Key words: Anti-tubercular agents, 3-heteroarylthioquinolinederivatives, Quantitative structure activity relationship, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is the most common mycobacterial chronic communicable disease as stated by WHO. The major issue for many anti-mycobacterial agents is its resistance of *Mycobacterium tuberculosis* strains. In the last forty years there is no effective new anti-TB drugs have been identified with new mechanism of action. However isoniazid show severe toxicity on repeated dosing, still it is considered as the drug of choice for TB. The literature reports suggest that nearly 8 million people develop active TB every year and approximately 5,500 people die every day (www.who.int/mediacentre/factsheets/ fs104/ en//).[1,2]

It was also noticed that single drug regimen resulted in rapid development of resistance and lack of efficiency in management hence, TB has been therapeutically managed by combination therapy for more than last five decades.[1] The rationale for combination therapy to treat TB is purely based on simple probability. The risk factors such as HIV infection, previous incarceration, failed TB treatment, failure to respond to standard TB treatment, and relapse following standard TB treatment adds to the complications of Multi Drug Resistant (MDR) –TB.[2] People with HIV and latent TB infection need to be treated at the earliest to prevent active tubercular infection. People with HIV and latent TB infection are more susceptible to develop active tubercular infection than people without HIV. It was also reported that one in five people with tubercular infection are unaware of their HIV status. Center for Disease Control (CDC) recommends the screening for HIV in TB patients.[3]

Recent advances in TB genome sequence like, a gene probe for *rpoB*, *katG*,[4] and *mabA-inhA*[5] have provided a platform for development of novel targets for drug deevelopment.[6] However no new specific and effective drug has been launched for TB in the last 40 years.[7] It is imminent to discover new structural classes of anti-tuberculosis agents.

The contribution of computational chemistry in rational drug design is an important factor to note. Quantitative structure activity rela-

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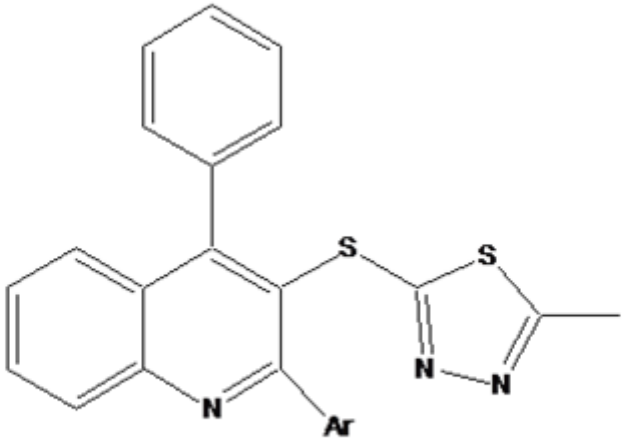

The key output of this study is that the density of the molecules significantly influences the anti-tubercular activity of novel 3-heteroarylthioquinoline derivatives.

Graphical Abstract

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tionship (QSAR) is able to identify the relationship between a molecule and its structure and how the structure influences the activity of the molecule.[8] Several QSAR models have been reported for the designing of potent anti-tubercular agents.[9-20] As a part of our investigation, for further optimizing the quinolone anti-bacterial against *Mycobacterium tuberculosis*, the QSAR studies were performed on twenty 3-heteroarylthioquinoline derivatives to assess their anti-tubercular activity based on their physico-chemical property.

MATERIALS AND METHODS

We used Chem. Office 2004 (Cambridge Soft Corp., Cambridge, USA, http://www.cambridgesoft.com) and Molecular Modeling Pro 6.1.0 (Trial version, ChemSW, Inc., www.chemsw.com) to perform molecular modeling studies and SPSS 11.5 to develop and validate QSAR models.

Biological data

We used the biological and chemical data of twenty 3-heteroarylthioquinoline derivatives reported by Chitra *et al.* (2011)[21] (Table 1) for the present study. High structural diversity was observed in the selected series of 3-heteroarylthioquinoline derivatives and also high range of the biological activity. Anti-tubercular activity was expressed as – log MIC, where MIC is the micro molar concentration of the compounds producing minimum inhibition against *Mycobacterium tuberculosis* and considered as the mean of at least two experiments. The selected series was used as such for the model development since the selected series of 3-heteroarylthioquinolines contained less number of compounds.

Molecular structure optimization

Chem Office 2004 software was used for structure building and for entire modeling works. Physico-chemical descriptors were calculated by using Chem Office 2004 and Molecular Modeling Pro 6.1.0 software.

Calculation of descriptors

The various physico-chemical descriptors [ClogP (calculated partition coefficient in octanol/water), CMR (calculated molar refractivity of the whole molecule), HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), B1 (measure of the width of the first atom of a substituent), B5 (overall volume of a substituent), L (substituent length), density] were calculated using the sketched molecules. (Physico-chemical parameter involved in model is given in Table 1)

QSAR model-development and validation

Descriptors were selected based on permutation and correlation matrices to prevent co-linearity problems. Stepwise multiple linear regression analysis was used to optimize the best model. The following parameters like n-number of data points, r^2-squared correlation coefficient, F-test (Fischer value) for statistical significance, se-standard error, q^2-cross validated correlation coefficient and correlation matrix are used in QSAR equations.[22]

Leave one out - cross validation (LOO-CV) method was used for internal validation. The cross validated correlation coefficient q^2 was calculated by the given formula

$$q^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{mean})^2}$$

Where yi, and ŷi are the actual and predicted activity of the i^{th} molecule in the training set, respectively and ymean is the average activity of all molecules in the training set. However, a high q^2 value does not necessarily give a suitable representation of the real predictive power of the model. The predictive ability of the selected model was also confirmed by r^2-r_0^2/r^2 r^2-$r'_0{}^2/r^2$, k, k', r^2m, r'^2m r'^2m and Concordance Correlation Coefficient (CCC) using LOO predicted values since we did not have separate external data set.[23-25]

$$r_m^2 = r^2\left(1 - \sqrt{|r^2 - r_0^2|}\right)$$

$$r_m'^2 = r^2\left(1 - \sqrt{|r^2 - r_0'^2|}\right)$$

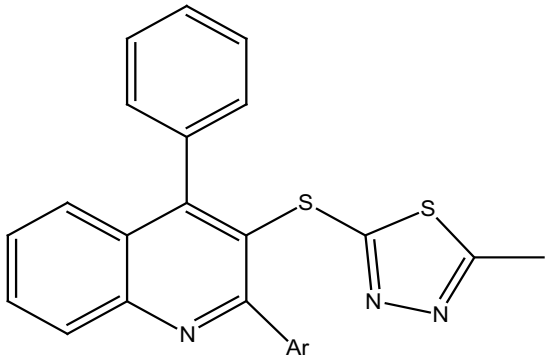
$$\overline{r_m^2} = \frac{r_m^2 + r_m'^2}{2}$$

Where r^2 is squared correlation coefficient between observed and predicted values and r_0^2 is squared correlation coefficient between observed and predicted values with intercept value set to zero. A value of r^2m is greater than 0.5 indicates good external predictability.

$$CCC = \frac{2\sum(y_i - \bar{y})(\hat{y}_i - \bar{\hat{y}})}{\sum(y_i - \bar{y})^2 + \sum(\hat{y}_i - \bar{\hat{y}})^2 + n_{EXT}(\bar{y} - \bar{\hat{y}})^2}$$

Where y is mental data and ŷ is predicted data.

Table 1: Structures, selected physico-chemical parameter, calculated and predicted anti-tubercular activity of the 3-heteroarylthioquinolines



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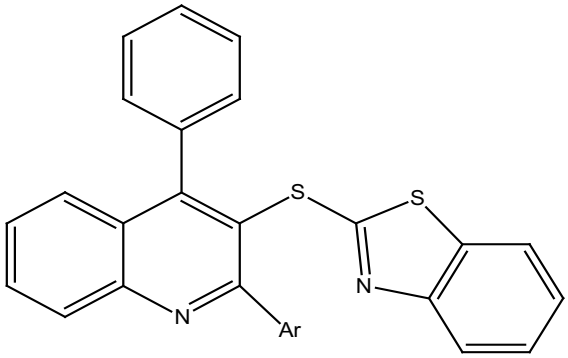

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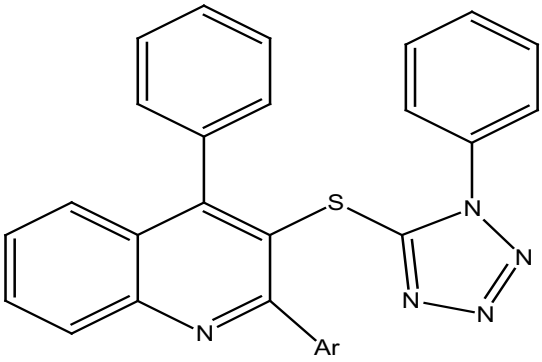

15-20

Compd. No.	Ar	-logMIC (μM)	Density	Calculated -logMIC	Predicted -logMIC
1	C_6H_5	-1.483	2.055	-1.429	-1.417
2	4-MeC_6H_4	-1.468	2.006	-1.566	-1.56
3a	4-ClC_6H_4	-0.505	2.272	-0.822	--
4	4-BrC_6H_4	-1.452	2.276	-0.811	-0.962
5	4-MeOC6H4	-1.747	2.025	-1.513	-1.506
6a	2-Naphthyl	-1.735	2.199	-1.026	--
7a	4-PhC_6H_4	-1.111	2.273	-0.819	--
8	C_6H_5	-0.771	2.018	-1.532	-1.506
9	4-MeC_6H_4	-1.674	1.989	-1.613	-1.589
10	4-ClC_6H_4	-1.737	2.127	-1.228	-1.238
11	4-BrC_6H_4	-1.724	2.29	-0.772	-0.787
12a	2-Naphthyl	-1.706	2.003	-1.574	--
13	4-PhC_6H_4	-1.367	2.001	-1.58	-1.56
14	C_6H_5	-1.709	1.91	-1.834	-1.827
15	4-MeC_6H_4	-1.692	1.887	-1.899	-1.908
16	4-ClC_6H_4	-1.670	2.013	-1.546	-1.523
17	4-BrC_6H_4	-1.483	2.165	-1.122	-1.087
18	4-$MeOC_6H_4$	-1.468	1.883	-1.91	-1.926
19	2-Naphthyl	-0.505	2.015	-1.541	-1.518
20	4-PhC_6H_4	-1.452	1.974	-1.655	-1.638

a- test set compounds

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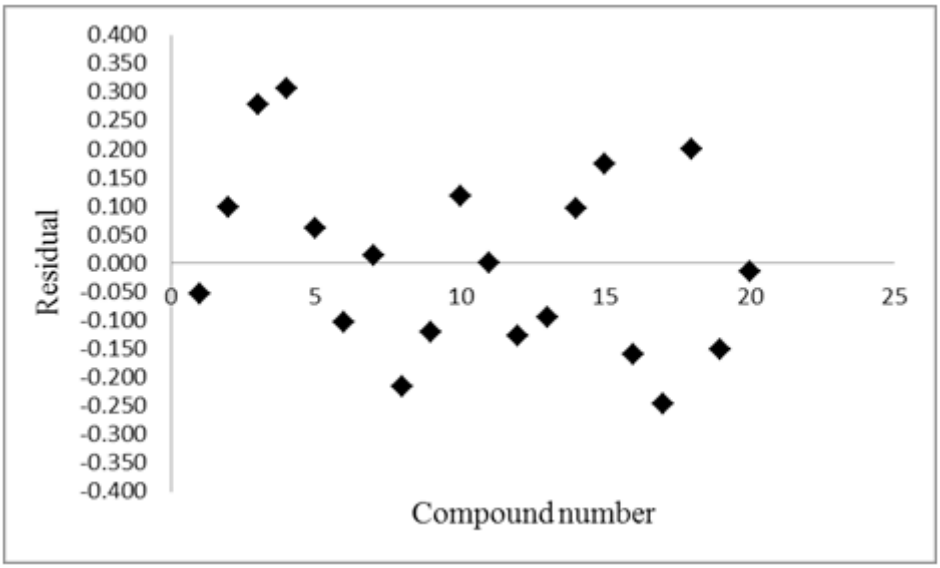

Figure 1: Residual plot between experimental and calculated anti-tubercular activities of both training and test set 3- heteroarylthioquinolines

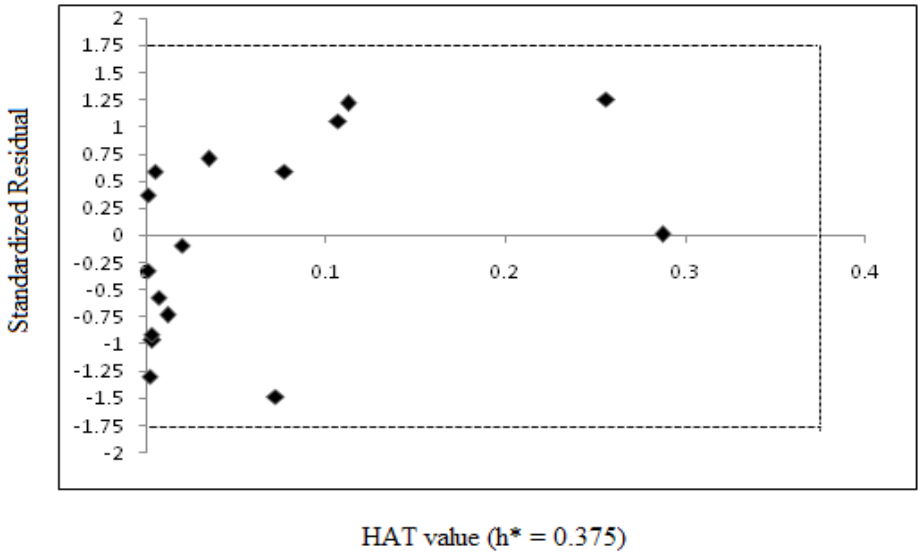

Figure 2: Williams plot: plot of standardized residuals (Y-axis) versus leverages (hat values (X-axis) for each compund

Y-Randomization test was used to assess the robustness of a QSAR model. A new model was developed using the original independent variable matrix and the dependent variable vector randomly shuffled in this technique. The random number simulation showed that the probability of chance correlation and the degree of inflation of internal figures of merit is considerable in small data sets and in the case of low object-to-variable ratios.[26] Hence Y-randomization test has become a common practice in QSAR studies. The new QSAR models (after several repetitions) are expected to provide low R^2 and Q^2values, otherwise an acceptable QSAR model cannot be obtained for the specific modeling method.[27-29]

RESULTS AND DISCUSSION

The best model generated by stepwise multiple linear regression analysis is identified as Model-1.

Model-1:

-logMIC=-7.172 (± 0.723) + 2.795 (± 0.354) Density

n=16, r^2=0.817, r^2adj=0.804, r^2se=0.165, q^2=0.729, q^2se=0.201, F1,14=62.42, CCC_{tr}=0.899, VIF: Density=1.000

Based on high q^2 and r^2 values Model-1 was chosen as the significant model. The values given in the parentheses are within 95% confidence intervals of the regression coefficients. 81.7% variance in biological activity was explained by square of correlation coefficient (r^2) of 0.817. Statistical significance of the model was indicated by >99.0% with F1, 14=62.42. Cross-validated Square of correlation coefficient of 0.729 indicated the good internal prediction power of model. The observed VIF value of the selected descriptor was 1.000. The selected physico-chemical parameter, calculated and predicted anti-tubercular activity of the 3-heteroarylthioquinolines are given in Table 1. The residual plot between experimental and calculated anti-tubercular activities of 3-heteroarylthioquinoline derivatives is given in Figure 1.

The significance and predictive ability of the proposed Model-1 was confirmed as it satisfied the following conditions:

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r^2=0.817>0.6; CCC_{tr}=0.899>0.85; q^2LOO=0.729>0.5; pred_r^2se=0.922>0.6; pred_r^2se=0.186; CCCpred=0.907>0.85; q1-F1=0.929>0.5; q1-F2=0.860>0.5; q1-F3=0.799>0.5; r^2m=0.753>0.5; r'^2m=0.714>0.5; Δ r^2m=0.039<0.2; r^2m average=0.733>0.5; k'=0.966; k=1.014 (0.85<k or k'<1.15); r^2-r^2_0/r^2 =0.064; r^2-r'^2_0/r^2= 0.086 (r^2-r^2_0/r^2 or r^2- r'^2_0/ r^2 <0.1); r^2p=0.775>0.5; r^2m(overall)=0.941>0.5; r'^2m(overall)=0.745>0.5; r^2m average (overall)=0.841>0.5; Δ r^2m (overall)=0.196<0.2; q^2LMO=0.650>0.5.

The proposed 2D QSAR model is predictive as it satisfied the conditions pred_r^2>

0.6 (pred_r^2=0.922). The applicability domain for Model-1 was established by determining the leverage values for each compound. William's plot of standardized residuals (*y*-axis) *versus* leverages (*x*-axis) for each compound of the training set was shown in Figure 2. The applicability domain was established inside a squared area within ± 1.75 standard deviations and a leverage threshold h^*=0.375 (h^*=3p'/n, being p' the number of model parameters + 1, and n the number of compounds). All compounds of training set and test set were seen inside of the square area.

For future investigations, the predicted anti-tubercular activity data must be considered only if the molecules fall within the applicability domain on which the model was constructed.

Moreover the reported QSAR models are not used to predict the activity of any type of molecules *vs.* anti-tubercular activity. However, it is very important to highlight the eventual QSAR models disappointments: activity cliffs.[30] It is possible because similar molecules can exhibit different biological activity. Activities are often mispredicted for these molecules, even though the overall prediction of these models is high.

The positive contribution of density to anti-mycobacterium activity indicates that highly dense (more volume) groups are advantageous for anti-mycobacterium activity. The molecules may not fit into the binding site when they have less volume. The presence of *bromo* or *chloro* substituted benzene at "Ar" could provide potent anti-mycobacterium compounds which is evident from the data of the compounds 3, 4, 7 and 11. Our study findings support the reports of Chitra *et al.* (2011)[19] which indicated that the presence of halogens in the aryl ring (compounds 3, 4 and 11) enhances the anti-mycobacterium activity.

CONCLUSION

We had developed a QSAR model for a set of twenty3- heteroarylthioquinoline derivatives having *Mycobacterium tuberculosis* inhibitory activity. The LOO cross-validation methods and Y-randomization technique suggested that the model was significant, robust and possess good internal predictability. The result findings can be utilized in the development and optimization of novel anti-tubercular agents. The reported QSAR models in the manuscript might be used for predicting the anti- tubercular activity of 3- heteroarylthioquinoline derivatives only. We also suggest to performing 3D QSAR and docking studies to understand the mechanisms of chemical–biological interactions of 3-heteroarylthioquinolines against *Mycobacterium tuberculosis*.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGMENT

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ABBREVIATION

WHO: World Health Organization
QSAR: Quantitative Structure Activity Relationship
LOO: Leave One Out
LMO: Leave Many Out

Highlights of Paper

- *2D QSAR models were developed for arylthioquinolines.*
- Developed QSAR models were validated internally and externally.
- Density plays a significant role in the anti-tubercular activity of *arylthioquinolines*.

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