CHAPTER-1

INTRODUCTION AND OBJECTIVE

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INTRODUCTION

Waisser and his associates investigated[1-3] thiobenzmides (Fig.-1) on various mycobacteria and related the activity of the thioamides with various physico chemical techniques. Several derivatives of thiomides were studied against M. avium, M. tuberculosis, M. fortuitum, M. kansasii. The QSAR derivatives of thiobenzamide were developed using electronic parameters and the results obtained indicated the correlation coefficient above 0.88. QSAR models with quantum mechanical parameters are fast developing and in recent years valuable papers have been published.[4-9]

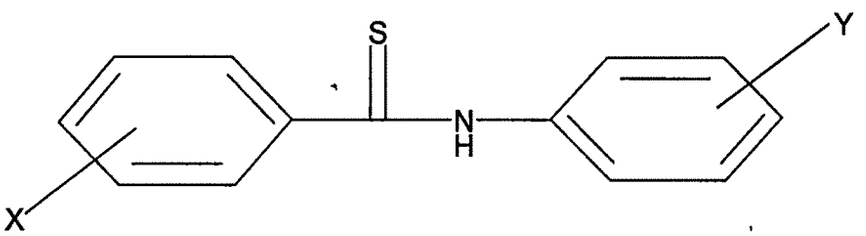


Fig-1: Thiobenzmide

QSAR is a process whereby the structures of a set of compounds are quantified and then compared to the numerical values of a biological activity or a physical property. The challenge here has been to find some numerical code for a molecule or a fragment that is information-rich. This structure information and the measured property or activity is then processed into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity.

The laws necessary for mathematical treatment of large part of physics and chemistry are though known but the difficulty has been only in the fact that applications of these laws were too complex to be solved. The works of Kohn & Pople have made it possible to make use of these laws in the study of complex molecules. The semiemperical calculation such as AMI, PM3, PM5 and DFT calculations. Several physicist & chemist in the recent years have made number of approaches for study of molecular electronic structure and the reactivity of compounds.

Computational chemistry represents molecular structures as a numerical model and simulates their behavior with the equations of quantum and classical physics. Available programs enable scientists to easily generate and present molecular data including geometries, energies and associated properties (electronic, spectroscopic and bulk). The usual paradigm for displaying and manipulating these data is a table in which compounds are defined by individual rows and molecular properties (or descriptors) are defined by the associated columns. A QSAR attempts to find consistent relationships between the variations in the values of molecular properties and the biological activity for a series of compounds so that these "rules" can be used to evaluate new chemical entities.

A QSAR generally takes the form of a linear equation

$$\text{Biological Activity} = \text{Const} + (C_1 P_1) + (C_2 P_2) + (C_3 P_3) + \ldots$$

where the parameters P_1 through P_n are computed for each molecule in the series and the coefficients C_1 through C_n are calculated by fitting variations in the parameters and the biological activity.[10-15]

OBJECTIVE

The first approach to developing quantitative relationships, which described activity as a function of chemical structure, relied on the principles of thermodynamics, which could be derived for a given molecule.[16-24]

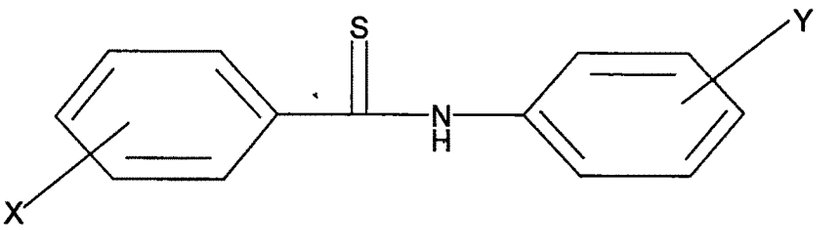
Electronic effects such as electron donating and withdrawing tendencies, partial atomic charges and electrostatic field densities were defined by Hammett sigma values, resonance parameters, inductive parameters and Taft substituent values. Steric effects such as molecular volume and surface area were represented by values calculated for Molar Refractivity and the Taft steric parameter.[25-28] Enthalpic effects were calculated using partition coefficients (LogP) or the hydrophobic parameter, which was derived from the partition coefficient. In addition, assortments of structural indices were used to describe the presence of specific functional groups at positions within the molecule. The linear equation, which described the relationship between activity and this parameter set, was the Hansch equation

$$\log 1/[C] = A(\log P) - B(\log P)^2 + C(E_s) + D() + E + \ldots$$

Multiple linear regression analysis was used to derive the values of the coefficients. In general, Hansch type studies were performed on compounds, which contained a common template (usually a rigid one such as an aromatic ring) with structural variation limited to functional group changes at specific sites. In accordance with the above principles, we have used the following quantum mechanical parameters for QSAR study.[29-43]

1. Heat of Formation
2. Molecular Weight
3. Total Energy
4. HOMO Energy
5. LUMO Energy
6. Absolute Hardness
7. Electronegativity

In view of the importance of thiobenzamides as a potent inhibitor of mycobacteria, we have chosen to make QSAR study of the derivatives of thioamides described in Tables-1-4.



Thiobenzamides

Table-1: MIC of thiobenzamides with *M. Avium*[1]

Compound	Substituents		Log 1/C obsd
	X	Y	
T1C1	H	3-F	3.3
T1C2	3-Cl	3-F	3.9
T1C3	4-Cl	3-F	3.6
T1C4	4-NO2	3-F	3.9
T1C5	4-Me	3-F	3.3
T1C6	4-OMe	3-F	3.3
T1C7	3-Br	3-F	4.22
T1C8	H	4-F	3.6
T1C9	3-Cl	4-F	3.6
T1C10	4-Cl	4-F	3.3
T1C11	4-NO2	4-F	3.9
T1C12	4-Me	4-F	2.7
T1C13	4-OMe	4-F	2.7
T1C14	3-Br	4-F	3.6

Table-2: MIC of thiobenzamides with *M. Tuberculosis* [1]

Compound	Substituents		Log 1/C Obsd.
	X	Y	
T2C1	H	3-F	4.22
T2C2	3-Cl	3-F	4.22
T2C3	4-Cl	3-F	4.22
T2C4	4-NO2	3-F	4.52
T2C5	4-Me	3-F	3.6
T2C6	4-OMe	3-F	3.3
T2C7	3-Br	3-F	4.52
T2C8	H	4-F	3.6
T2C9	3-Cl	4-F	3.9
T2C10	4-Cl	4-F	3.9
T2C11	4-NO2	4-F	4.22
T2C12	4-Me	4-F	2.7
T2C13	4-OMe	4-F	2.7
T2C14	3-Br	4-F	3.9

Table-3: MIC of thiobenzamides with *M. fortuitum*[1]

Compound	Substituents		Log 1/C Obsd.
	X	Y	
T3C1	H	3-F	3.6
T3C2	3-Cl	3-F	3.9
T3C3	4-Cl	3-F	3.3
T3C4	4-NO2	3-F	3.9
T3C5	4-Me	3-F	3.3
T3C6	4-OMe	3-F	3.3
T3C7	3-Br	3-F	4.22
T3C8	H	4-F	3.6
T3C9	3-Cl	4-F	3.6
T3C10	4-Cl	4-F	3.3
T3C11	4-NO2	4-F	3.9
T3C12	4-Me	4-F	2.7
T3C13	4-OMe	4-F	2.7
T3C14	3-Br	4-F	3

Table-4: MIC of *M. kansasii* with thiobenzamides[1]

Compound.	Substituents		Log 1/C Obsd.
	X	Y	
T4C1	H	3-F	3.9
T4C2	3-Cl	3-F	4.22
T4C3	4-Cl	3-F	4.22
T4C4	4-NO2	3-Fa	4.22
T4C5	4-Me	3-F	3.3
T4C6	4-OMe	3-F	3.3
T4C7	3-Br	3-F	4.22
T4C8	H	4-F	3.6
T4C9	3-Cl	4-F	3.6
T4C10	4-Cl	4-F	3.6
T4C11	4-NO2	4-F	4.22
T4C12	4-Me	4-F	2.7
T4C13	4-OMe	4-F	2.7
T4C14	3-Br	4-F	3.9

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