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QSAR Studies of Pyridazine Derivatives as Tuberculostatic Agents

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QSAR studies have been done by taking a series of pyrazine derivatives exhibiting tuberculostatic activity against (1) Mycobacterium tuberculosis strain H_{37} Rv, (2) Mycobacterium tuberculosis strain 109, isolated from a patient, resistant to isoniazid, ethambutol and refampcin (3) Mycobacterium tuberculosis strain 193, isolated from a patient fully susceptible to tuberculostatic and by using openstate 4 version 6.5.1 statistical software. The studies were carried out on 15 analogs. These studies produced good predictive models and give statistically significant correlations of hydrophobic and molar refractivity in R1 position of the compounds, which are having significant correlation with all the tubercular strain.

Key Words: QSAR, Antitubercular drug, Pyrazine derivatives, Descriptors.

INTRODUCTION

Tuberculosis is a disease caused by facultative, acid fast, intracellular bacillus called Mycobacterium tuberculosis[1]. Many people think that tuberculosis is a disease of the past. But still, it is a leading killer in the world. In worldwide, tuberculosis kills 8000 people per day *i.e.* 2-3 millions people per year. In India, about 0.5 million people die from tuberculosis every year and more than 1000 people everyday (approx one person every minute). Tuberculosis sends self sustaining families into poverty. One of the major problems with antitubercular drug is that they have lot of side effects and the bacteria develop resistance to them. The duration of therapy with the available drugs for complete cure of tuberculosis is also long. So the research has been focused on developing novel antitubercular drugs, which will not resistant to multi drug resistance strain of the bacteria and should have enhanced potency, less side effect and short duration of therapy. A series of pyrazine derivatives were selected for QSAR analysis using different physico-chemical parameters exhibiting tuberculostatic activity against: (1) Mycobacterium tuberculosis strain

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H_{37} Rv, (2) mycobacterium tuberculosis strain 109, isolated from a patient, resistant to isoniazid, ethambutol and refampcin (3) mycobacterium tuberculosis strain 193, isolated from a patient fully susceptible to tuberculostatic.

EXPERIMENTAL

The biological activity data for the QSAR analysis was obtained from Milczarska *et al.*[2] and MIC (μg/mL) of the compounds in the series was converted in to IC_{50} (μM) by dividing MIC with the molecular weight of the corresponding compounds. The -log IC_{50} was then calculated (Table-1). The physico-chemical parameters and -log IC_{50} values were loaded into the MS Excel worksheet and saved as coma delimited file. Openstate 4 version 6.5.1 software was used to derive by regression equations between physiochemical descriptors and biological activity of the compounds. The statistical parameters that were considered for the analysis are correlation coefficient (r), squared correlation (r^2), F test value and VIF. The selected significant equations were validated by leave one out method (LOO).

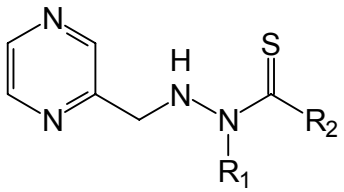


Fig. 1. Structure of 1-[1-(2-pyrazinyl)ethyl]-4-N-substituted thiosemicarbazide derivative

RESULTS AND DISCUSSION

15 Compounds belonging to pyrazine category were taken for study. The biological activities data for pyrazine derivatives were taken from literature[3]. The IC_{50} values for inhibitory action on different tubercular strain were transformed into -log IC_{50}. Stepwise regression analysis was performed by taking -log IC_{50} as dependent variable and descriptors as independent variables. From the analysis significant equations were selected which were validated by leave one out method. The significant regression equations for different strains were:

Strain H37

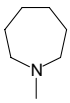
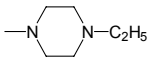
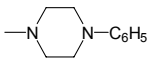
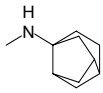
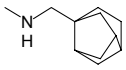
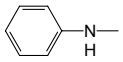
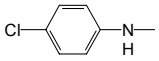
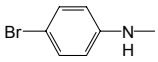
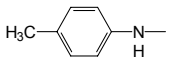
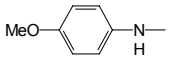
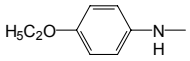
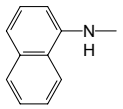
-log IC_{50} = -0.913 (± 0.167) R_1 -1.013

n = 15, r = 0.834, r^2 = 0.696, F = 29.715, VIF = 1.000, PRESS = 3.29, Q^2 = 0.4264, S_{DEP} = 0.4685

-log IC_{50} = -0.198 (± 0.036) MR R_1 +1.216

n = 15, r = 0.834, r^2 = 0.696, F = 29.715, VIF = 1.000, PRESS = 1.976, Q^2 = 0.558, S_{DEP} = 0.3629

TABLE-1
LIST OF SUBSTITUENTS ON PARENT STRUCTURE AND BIOLOGICAL ACTIVITY OF THE PYRAZINE SERIES

Compd. No.	R_1	R_2	Tubercular activity MIC (μgm/cm^3)			Tubercular activity -log IC50 (μmol)		
			$H_{37}RV$†	109‡	193¶	$H_{37}RV$†	109‡	193¶
1	H		8	8	8	1.508	1.508	1.508
2	H		16	16	16	1.229	1.229	1.229
3	H		63	32	63	0.651	0.651	0.651
4	H		63	63	63	0.649	0.649	0.649
5	H		125	63	63	0.437	0.735	0.735
6	H		32	32	32	0.924	0.924	0.924
7	H		16	8	16	1.337	1.638	1.337
8	H		16	8	32	1.356	1.657	1.050
9	CH_3		250	250	250	0.060	0.060	0.060
10	CH_3		250	125	125	0.110	0.471	0.411
11	CH_3		125	125	250	0.467	0.467	0.467
12	CH_3		250	250	250	0.008	0.081	0.081
13	CH_3		500	500	500	-0.197	-0.197	-0.197
14	CH_3		250	250	500	0.122	0.122	0.122
15	CH_3		250	250	250	0.130	0.130	0.130

†Mycobecterium tuberculosis
‡Strain isolated from a patient, resistant to isoniazid
¶Strain, isolated from a patient fully susceptible to tuberculostatic

Rv strain 109

$-\log IC_{50} = -1.000 (\pm 0.176) R1 + 1.161$

$n = 15, r = 0.845, r^2 = 0.714, F = 32.44, VIF = 1.000, PRESS = 3.50, Q^2 = 0.327, S_{DEP} = 0.485$

$-\log IC_{50} = -0.216 (\pm 0.0176) MR\ R_1 + 1.384$

$n = 15, r = 0.834, r^2 = 0.714, F = 27.95, VIF = 1.000, PRESS = 3.09, Q^2 = 0.327, S_{DEP} = 0.46$

Strain 193

$-\log IC_{50} = -0.943 (\pm 0.145) R_1 + 1.010$

$n = 15, r = 0.875, r^2 = 0.765, F = 42.32, VIF = 1.000, PRESS = 2.46, Q^2 = 0.414, S_{DEP} = 0.4051$

$-\log IC_{50} = -0.204 (\pm 0.031) R_1 + 1.221$

$n = 15, r = 0.876, r^2 = 0.767, F = 42.765, VIF = 1.000, PRESS = 2.145, Q^2 = 0.489, S_{DEP} = 0.378$

QSAR study indicates that hydrophobic and molar refractivity in R_1 position of the compounds has significant correlation with all the tubercular strain. All monoparametric regression analysis equations showed that the correlated parameters negatively contributed for the activity, which showed that decrease in the property values responsible for the activity. While performing the multiparameter regression analysis, the t-value is decreased and no significant correlation coefficient results are also obtained. The best equation selected from the monoparametric regression analysis was validated by leave one out method, which possesses significant validation parameters Q2, PRESS and SDEP values.

Conclusion

QSAR study indicates that hydrophobic and molar refractivity in R_1 position of the compounds has significant correlation with all the tubercular strain. This QSAR studies will enable in designing new pyrazine derivatives with enhanced potency towards multi drug resistance strains and less side effects. These studies can be extended to 3D-QSAR analysis and analog based drug design which also give us an idea about the position of the substitution and type of possible interaction.

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