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Der Pharmacia Lettre, 2010, 2(6):208-211
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Prediction of some heterocyclic compounds as antifungal agent

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ABSTRACT

Prediction of the antifungicidal activity of few heterocyclic compounds having antituberculastic moieties has been made by using openstate 4 version 6.5.1 statistical software. The studies were carried out on nine analogs. These studies produced good predictive models and give statistically significant correlations of hydrophobic and molar refractivity in R position of the compounds, which having significant correlation with all the fungi strains.

Key Words: QSAR, Antifungal agent, Oxadiazole derivatives, Descriptors.

INTRODUCTION

Many heterocyclic compounds like thiazole, oxadiazole, pyrimidine pyrazine, azetidinone play pivotal role for biological properties [1,2]. Many of them have good antifungal activity. Some of the organic compounds having drug activity have been studied by Qualitative Structure Activity Relative group (QSAR) [3-9]. Such a computation study predicts the pharmaceutical activities of organic compounds [3-9]. The compounds i.e. oxadiazole derivatives containing tuberculostic moieties like isoniazide and p-amino salicylic acid (PAS) have been studied recently for their antifungal activities [10]. Such a series of oxadiazole derivatives have been selected. Thus the present paper comprises the QSAR studies of these compounds using different physico-chemical parameters [11-13] with antifungal activity against: fungi (i.e. plant pathogens) Botrydepladia thiobromine, Nigrospora Sp., and Trichothesium Sp.

MATERIALS AND METHODS

The biological activity data for the QSAR analysis was obtained from literature [10] 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 selected for the analysis are correlation coefficient (r), squared correlation (r^2), F test value and VIF the statistical significance. The selected significant equations were performed using the leave one out (LOO) method, in which compound is remove from the dataset and it's activity is predicted using the model derived from the rest of the dataset. Q^2 cross validated squared correlating coefficient, S_{PRESS}: Standard devotional predictivity, S_{DEP}: Standard devotional of error of predictivity

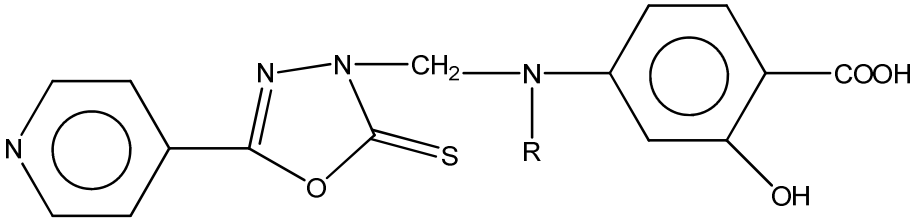


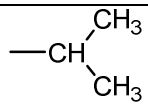
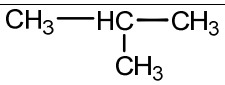
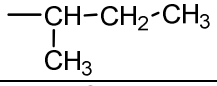
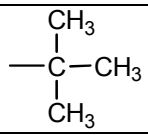
Fig.1 structure of 2-hydroxy-4-(R)-((5-pyridin-4-yl)-2-thioxo-1, 3, 4- Oxadiazole-3(2H)-yl) methyl) amino) benzoic acid derivatives

RESULTS AND DISCUSSION

Nine compounds of oxadiazole moiety were selected for study. The biological activity data for oxadiazole derivatives were obtained from literature [10]. The IC_{50} values for inhibitory action on three various fungal strains were transformed into -log IC_{50}. Stepwise regression analysis was performed by puting -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 [LOO] method. The significant regression equations for all three fungal strains were:

Botrydepladia thiobromine:
-log IC_{50} = -0.923 (± 0.169) R -1.023
n=9, r = 0.844, r^2 = 0.698, F = 29.815, VIF = 1.000, S_{PRESS} = 3.38, Q^2 = 0.4364, S_{DEP} = 0.4765
-log IC_{50} = -0.188 (±0.036) MR R +1.216
n=9, r = 0.844, r^2 = 0.698, F = 29.815, VIF = 1.000, S_{PRESS} = 1.986, Q^2 = 0.526, S_{DEP} = 0.3428
Nigrospora Sp.:
-log IC_{50} = -1.015 (± 0.179) R +1.163
n=9, r = 0.854, r^2 = 0.703, F =34.815, VIF = 1.000, S_{PRESS} = 3.50, Q^2 = 0.3764, S_{DEP} = 0.485
-log IC_{50} = -0.228 (±0.026) MR R +1.394
n=9, r = 0.844, r^2 = 0.714, F = 29.635, VIF = 1.000, S_{PRESS} =3.03, Q^2 = 0.3764, S_{DEP} = 0.490
Trichothesium Sp.
-log IC_{50} = -0.953 (± 0.157) R +1.015
n=9, r = 0.878, r^2 = 0.768, F =42.38, VIF = 1.000, S_{PRESS} =2.47, Q^2 = 0.417, S_{DEP} = 0.4113
-log IC_{50} = -0.208 (±0.034) MR R +1.225
n=9, r = 0.882, r^2 = 0.769, F = 42.766, VIF = 1.000, S_{PRESS} =2.175, Q^2 = 0.493, S_{DEP} = 0.38

Table 1: List of substituents on parent structure and biological activity of the oxadiazole series

Comp. No.	R	Antifungal activity MIC (µgm/cm^3)			Antifungal activity -log IC_{50} (µmol)		
		Botrydepladia thiobromine	*Nigrospora Sp.*	*Trichothesium Sp.*	*Botrydepladia thiobromine*	*Nigrospora Sp.*	*Trichothesium Sp.*
1.	$-H$	9	9	9	1.503	1.503	1.503
2.	$-CH_3$	17	17	17	1.223	1.223	1.223
3.	$-CH_2CH_3$	61	34	61	0.658	0.658	0.658
4.	$-CH_2CH_2CH_3$	61	61	61	0.656	0.656	0.656
5.		122	61	61	0.437	0.737	0.737
6.	$-CH_2CH_2CH_2CH_3$	34	34	34	0.934	0.934	0.934
7.		17	9	17	1.348	1.648	1.348
8.		17	9	34	1.359	1.661	1.078
9.		242	238	243	0.070	0.070	0.070

QSAR study indicates that hydrophobic and molar refractivity in R position of the compounds has significant correlation with all the three fungi. 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 Q^2, S_{PRESS}, S_{DEP} values.

CONCLUSION

QSAR study indicates that hydrophobic and molar refractivity in R position of the compounds has significant correlation with all the three fungi. This QSAR studies will enable in designing new oxadiazole derivatives with enhanced potency towards multi fungal against with good toxicity In general the presence of alkyl substituent on amine nitrogen improve the activity. The alkyl group increases the lipophilicity. These studies can be explore to 3D-QSAR analysis and more particular analog based antituberculosis drug design which also give us an idea about the position of the substitution and type of possible interaction. This work is in progress.

Acknowledgement
Thanks to Dr. B. C. Dixit, Head Department of chemistry, V. P. and R. P. T. P. Science collage, V. V. Nagar, 388120, Gujarat, INDIA for assisting in chemistry part.

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