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QSAR studies on thieno[2, 3-b] pyrrolizin-8-ones substituted derivative: A new series of Antitubulin agents

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Abstract : Thieno [2,3-b] pyrrolizine-8-ones series were subjected to quantitative structure activity relationship with an attempt to derive and understand a correlation between biological activity as dependent variable and structure parameter such as equalized electronegativity 'Xeq', molecular connectivity ' $^{I}X^{b}$ ' and hydrophobicity 'logP' descriptors as independent variables. The results have shown that anticancer activity of these compounds in cancer cells L1210 is found to correlate well with hydrophobicity 'logP' and steric parameter ' $^{I}X^{b}$ '. The presence of "3-hydroxy-4-methoxy phenyl group" is found to be important for activity.
Keyword: corelation matrix, antitubulin agents, QSAR, multiple regression analysis.

Introduction

Cancer is one of the major causes of death worldwide. Among the first agent used to treat cancer were member of mustard family. The first clinical trial with nitrogen mustard began in 1942, initiating the era of cancer chemotherapy1. Cancer cells differ from their normal counterparts in a number of biochemical processes, particularly during the control of cell growth and division. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents.

As research develops, treatments are becoming more specific for different varieties of cancer. There has been significant progress in the development of targeted therapy drugs that act specifically on detectable molecular abnormalities in certain tumors, and which minimize damage to normal cells. The prognosis of cancer patients is most influenced by the type of cancer, as well as the stage, or extent of the disease. Despite more than 2000 drugs / candidates are being in the development pipeline or launched, continued innovation is no less important today than it has ever been. The quantitative structure activity relationship (QSAR) study is useful tool for rational search of bioactive compounds. QSAR study describes a definite role in a quantitative term of a structural feature in molecule with a definite contribution to the activity of a particular physico-chemical property of the

structural feature. These QSAR studies have predictive ability and simultaneously provide deeper insight into the mechanism of drug receptor interaction2.We there fore report here a QSAR study on series of anticancer 'thieno[2,3-b] pyrrolizin -8-ones'substituted derivatives, a new series of antitubulin agents3.Many natural and synthetic substances are known to interfere with the dynamic assembly of tubulin and prevent the formation of microtubules which are essential for cellular integrity and cell division4.Currently , the most useful members of these antitubulin agent5 are natural product such as paclitaxel6, vinca alkaloids[7], colchicine and combretastatin8.

The present study was under taken to determine the physico-chemical properties, which govern the anticancer activity, which help in rational drug design and synthesis of new selective 'thieno [2, 3-b] pyrrolizine-8-ones' substituted derivatives with predermind activity.

Material and methods

A data set of 16 molecules have been taken from the reputed published results[3]. Anticancer activity was expressed as IC50 values. It is essential to assess the predictive power of the models by using a test set of compounds. The structures and anticancer activity data of compounds are listed in Table 1.

Experimental

Thieno[2,3-b]pyrrolizine-8-ones(Figure1) were prepared from isovanillin[3]. The electronic parameter i.e. equalized electronegativity 'Xeq' was evaluated using Pauling formula [9]. The steric parameter first order molecular connectivity $^{I}X^{b}$ was calculated as defend by Kupchik[10, 11, 12] and the partition coefficient 'logP' was calculated by the fragmental method developed by Nys and Rekker[13].

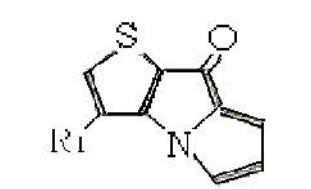


Figure 1 - Thieno [2, 3-b] pyrrolizine-8-ones

Results and discussion

All the compound of this series with calculated physico-chemical parameters and their biological activity are listed in Table 1. In this table $\log(1/IC_{50})$ i.e. $P(I_1)$ represent the antiproliferative activity against cancer cells L1210. IC_{50} (concentration of the drug to reduce the cell number 50%). Before studying the correlation we checked the correlation matrix of the parameters from Table 2, it is clear that there exists autocorrelation between $^{I}X^{b}$ and Xeq as well as logP and $^{I}X^{b}$.

The linear regression analysis of $\log(1/IC_{50})$ with the physico-chemical parameter gave following significant correlation:

$P(I_1) = 0.092(\pm0.160)\ \log P + 4.95$
$n = 16,\ r^2 = 0.566,\ S = 0.991,\ F_{(1,14)} = 0.322$ **…(1)**

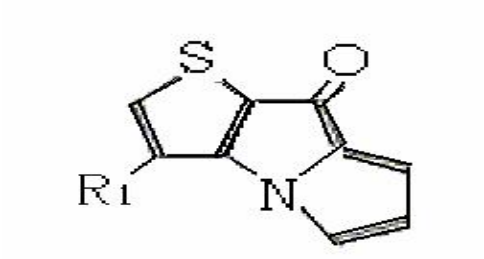
Where n is the number of data points, r = correlation Coefficient, F = the variance ratio between the calculated and observed activities. S= is standard error ..
Introduction of an indicator parameter 'Ind' whose value was taken 1 for the presence of "3-hydroxy -4-methoxy phenyl" at R_1 and zero otherwise. Multiple regression analysis gave the correlation equation:

$P(I_1) = 0.015(\pm0.121)\log P + 2.805(\pm0.773)Ind + 5.082$
$n = 16,\ r^2 = 0.681,\ S = 0.574,\ F_{(1,13)} = 7.956$**…….(2)**

$P(I_1) = -0.096(\pm0.306)^{I}X^{b} + 2.773(\pm0.747)Ind + 5.692$
$n = 16,\ r^2 = 0.621,\ S = 0.554,\ F_{(1,13)} = 7.656$ **……(3)**

After inclusion of the indicator parameter (Ind), correlation of logP with activity has improved significantly, its significance is 68.1% and F ratio value is also 95% significant $F_{(1,13)} = 7.956$ as suggested by F test.
It is noteworthy that in equation (2) and (3) indicator parameter (Ind) has positive regression coefficient and therefore "3-hydroxy-4-methoxy phenyl group" will be beneficial for increasing the activity of the drug.

Table 1. Biological activities and physico-chemical data for 'Thieno (2, 3-b) pyrrolizines -8-ones', substituted derivative.



S.N.	R_1	$^1X^b$	Xeq	logP	log1/IC_{50}	
					observe	calculated[a]
1.	3, 4, 5-Trimethoxyphenyl	2.526	7.575	-4.940	4.444	3.315
2.	4--Hydroxyphenyl	2.415	6.128	-2.908	4.529	4.00
3.	4--Butoxytphenyl	2.353	8.104	1.050	4.528	4.821
4.	3- Hydroxyphenyl	2.415	6.127	-2.070	4.528	4.21
5.	4--Propoxyphenyl	2.415	7.601	-1.740	4.552	2.815
6.	Phenyl	2.365	7.601	1.740	4.552	2.618
7.	2-Methoxyphenyl	2.415	5.992	-1.730	4.574	3.618
8.	3,4--Dimethoxyphenyl	2.400	7.045	-2.780	4.931	5.181
9.	3-Methoxythenyl	2.395	6.516	-3.580	5.284	4.205
10.	3,4--Methylenedioxy - phenyl	2.419	6.806	-4.160	5.368	3.100
11.	2- Hydroxyphenyl	2.371	6.133	-2.600	5.432	3.812
12.	4--Ethoxyphenyl	2.378	7.104	-1.280	6.366	5.816
13.	3,4- Dihydroxythenyl	2.512	6.268	- 5.180	4.552	3.081
14.	4-Methoxyphenyl	2.549	6.516	-2.580	6.721	7.150
15.	3-Hydroxy-4-methoxyphenyl	2.419	6.656	-4.260	7.823	5.162
16.	4-Hyderoxy-Methoxyphenyl	2.419	6.657	-4.260	5.096	4.602

[a] = is the activity calculated from Eq - (2)

Table 2. Correlation matrix of 16 compounds set with activity [log(1/c)]

Physico-chemical parameters	Xeq	$^1X^b$	logP
Xeq	1.00		
$^1X^b$	0.638	10.0	
logP	0.312	0.813	1.00

Conclusions

In summary, from the derived QSAR model it can be concluded that steric parameter play negative role in determining the activity of this series of antiproliferative agents against L1210 cancer cells. It can be therefore being suggested for future designing of more potent drugs in this class, one may look for the compounds with higher hydrophobic and small substituent groups will be preferred in future in order to designing of improve activity of the given series of drug compounds.

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