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QSAR Study of Anticancer Agents: 1,8-Naphthyridine Derivatives

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In a persevering effort to develop better anticancer drugs, a quantitative structure-activity relationship analysis using a set of 2-D descriptors was performed on a series of 1,8-naphthyridine derivatives acting by the inhibition of tubulin polymerization. QSAR models that were derived from the study were found to be statistically significant with a good predicting ability. The results obtained from the study justify the use of 2-D descriptors for exploring the requirements of binding of 1,8-naphthyridines to the heterodimer, tubulin. An attempt has been made to explore the structural and/or physico-chemical requirements of the compounds, responsible for the action against tumour cells. The physico-chemical descriptors and indicator variables were correlated with the biological activity.

Key Words: QSAR, Hammett's substituent constant, Tubulin, Chemotherapy, Antitumor, Cytotoxic.

INTRODUCTION

Cancer is the most frequent cause of deaths reported worldwide, next only to CVS disorders. Despite continual research on anticancer agents, the disease is yet to be cured. The effectiveness of anticancer chemotherapeutic agents is mainly limited due to lack of selectivity of these agents, the acquired resistance against the existing agents and the metastatic nature of the tumour cells[1]. In the recent decade, with the help of tumour markers and various screening programs, detection of cancer has been possible at the early stages of the disease.

Response to chemotherapy in cancer is greatly dependent on the performance status of the patient and the disease stage[2]. Tumour response is conventionally the indication of an effective chemotherapy, but occurs late during treatment and may be obscured by diagnostic uncertainties. The primary goal of treatment should therefore be the stabilization of the disease.

The research on anticancer agents has been oriented mainly to the cell cycle specific agents and more recently towards certain enzymes. The inhibition of cell division by interfering with the mitotic spindle has been an attractive target for research worldwide[3–5]. The cytotoxic effects of the agents interfering with the mitotic assembly functioning are due to the inhibition of polymerization of the heterodimer tubulin present in the microtubule of the mitotic spindle. A series of substituted-2-aryl-1, 8-naphthyridine-4(1*H*)-ones (Fig. 1) have shown significant cytotoxic effects against a variety of human tumour cell lines. The naphthyridine derivatives were subjected to quantitative structure activity relationship (QSAR) study using physico-chemical descriptors and the indicator variables. The present

work describes the QSAR analysis of 1,8-naphthyridine derivatives, to explore the structural and physico-chemical requirements for the compounds to be active against the various tumour cells.

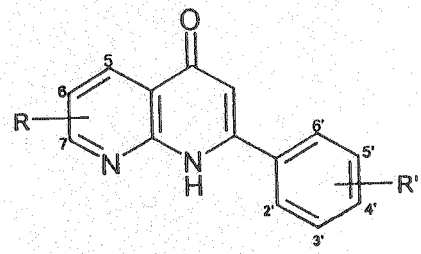

Fig. 1. Parent structure of substituted-2-aryl-1,8-naphthyridine-4(1*H*)-ones.

The series of substituted-2-aryl-1,8-naphthyridin-4(1*H*)-one derivatives as potent antitumour agents acting by tubulin inhibition has been reported by Chen *et* al.[6]

EXPERIMENTAL

QSAR with physico-chemical descriptors and indicator variables: A detailed QSAR study of the efficacy of 1,8-naphthyridine derivatives for antitumour action and inhibition of tubulin polymerization was attempted using free energy related model of Hansch, additivity model of Free Wilson and the mixed approach of Hansch and the Free Wilson models, to explore the structural and/or physico-chemical requirements of the substituents responsible for the action[7]. The efficacy data (Table-2) were then subjected to multiple regression analysis with different physico-chemical descriptors and indicator variables to generate QSAR equations for individual cancer cell lines and *in vitro* inhibition of tubulin polymerization.

The knowledge of the important parameters contributing to efficacy against various cancer cell lines can be used to design new antitumour agents of the series. The congeneric series presented six regions of structural variations: R_5, R_6, R_7, R_2', R_3' and R_4' (Table-1). The variations in all the six regions were represented by different physico-chemical descriptors (Table-3) and indicator variables (Table-4). The values of physico-chemical parameters of the substituents were obtained from literature.

Multiple regression analysis: The stepwise multiple regression analyses were carried out using the statistical software Openstat2, version 6.5.1, designed and standardized by Bill Miller and Stat Val. Correlation matrix was obtained to justify the use of more than one variable in the study. The variables used were with maximum correlation to activity and minimum intercorrelation with each other. From the statistical viewpoint the ratio of the number of sample (N) to the number of variables used (M) should not be very low; usually it is recommended that N/M ≥ 5.

Out of the 24 compounds in the series, 23 for ITP, 19 for HL-60 (TB), 22 for NCI-H460, 19 for HCT-116, 22 for U-251, 21 for SK-MEL 19 for OVCAR-3, 23 for CAKI-1, 21 for PC-3 and 16 for MDA-N were taken for the QSAR study. The remaining compounds in each cell line study were rejected due to lack of discrete biological activity values.

The QSAR equations were constructed for efficacy data of each cell line with the physico-chemical descriptors and indicator variables. The statistical quality of the equations[8] was judged by the parameters like correlation coefficient (r), explained

variance (r^2), standard error of estimate (s) and the variance ratio or overall significance value (F). All the accepted equations have the Fischer value corresponding to more than 95% of overall significance value.

TABLE-1
REGIONS OF STRUCTURAL VARIATION IN THE CONGENERIC SERIES WITH SUBSTITUENTS

S.No.	R_5	R_6	R_7	R_2'	R_3'	R_4'
1.	H	CH_3	H	H	F	H
2.	H	H	CH_3	H	F	H
3.	CH_3	H	CH_3	H	F	H
4.	H	H	H	H	Cl	H
5.	CH_3	H	H	H	Cl	H
6.	H	CH_3	H	H	Cl	H
7.	H	H	CH_3	H	Cl	H
8.	CH_3	H	CH_3	H	Cl	H
9.	H	H	H	H	CH_3	H
10.	CH_3	H	H	H	CH_3	H
11.	H	CH_3	H	H	CH3	H
12.	H	H	CH_3	H	CH_3	H
13.	CH_3	H	CH_3	H	CH_3	H
14.	H	H	H	CH=CH—CH=CH		H
15.	CH_3	H	H	CH=CH—CH=CH		H
16.	H	CH_3	H	CH=CH—CH=CH		H
17.	H	H	CH_3	CH=CH—CH=CH		H
18.	CH_3	H	CH_3	CH=CH—CH=CH		H
19.	H	H	H	H	CH=CH—CH=CH	
20.	CH_3	H	H	H	CH=CH—CH=CH	
21.	H	CH_3	H	H	CH=CH—CH=CH	
22.	H	H	CH_3	H	CH=CH—CH=CH	
23.	CH_3	H	CH_3	H	CH=CH—CH=CH	
24.	H	Cl	H	H	CH=CH—CH=CH	

TABLE-2
BIOLOGICAL ACTIVITY DATA OF THE SERIES OF 1,8-NAPHTHYRIDINE DERIVATIVES

				–log IC_{50}						
ITP	HL60(TB)	NCIH460	HCT116	SF295	U251	SKMEL5	OVCAR3	CAKI1	PC3	MDAN
0.2006	7.69	7.41	7.62	7.56	7.39	7.55	7.87	7.55	7.46	7.93
0.2757	7.65	7.48	7.55	7.54	7.42	7.65	7.71	7.34	7.46	7.84
0.1307	7.43	7.27	–	7.48	7.19	7.43	7.74	7.45	7.21	7.89
–0.1761	7.58	7.06	7.54	7.20	6.84	7.28	7.34	7.25	7.65	7.76
0	–	7.41	7.80	7.39	7.28	7.38	7.50	7.48	7.81	7.93
0.1427	7.51	7.30	7.52	7.60	7.16	7.15	7.65	7.37	–	–
–0.0506	7.54	7.38	7.59	7.64	7.19	7.50	–	7.38	–	–
–0.1135	7.13	6.65	6.77	7.32	6.53	6.93	6.77	6.69	7.56	7.72
–0.5185	7.72	7.59	7.65	7.43	7.35	7.59	7.38	7.43	7.37	–
–0.2553	7.74	7.44	7.33	7.52	7.27	7.47	7.65	7.27	7.48	7.96
0.1761	6.76	6.41	6.39	6.38	6.77	6.54	6.60	6.36	6.51	–

	–log IC_{50}									
ITP	HL60(TB)	NCIH460	HCT116	SF295	U251	SKMEL5	OVCAR3	CAKI1	PC3	MDAN
–0.2787	7.57	7.75	6.92	7.22	6.70	6.90	6.31	6.37	6.86	7.50
–0.3617	4.89	4.35	4.75	4.19	4.27	4.46	4.52	4.25	4.50	4.68
–0.0414	–	7.41	–	–	7.99	–	–	7.82	7.75	–
0.0315	–	–	–	7.79	–	–	–	7.92	7.70	–
0.2596	–	–	–	–	–	–	–	–	–	–
0.1804	–	7.76	–	7.62	7.81	7.86	–	5.2	7.52	–
0.1079	6.61	6.20	6.42	6.23	6.43	6.33	6.46	5.02	6.12	6.63
–0.1461	5.74	5.42	5.42	5.04	5.36	5.46	5.08	5.25	4.98	5.78
–0.2553	6.69	5.98	6.37	5.83	6.19	6.36	5.89	5.62	5.86	6.69
–0.3222	6.85	6.40	6.33	6.26	6.33	6.44	6.45	6.21	6.39	6.88
–0.7076	5.75	5.42	5.40	5.42	5.34	5.48	5.44	5.27	5.58	5.71
–	5.46	4.88	4.90	4.83	4.80	5.66	4.70	4.29	5.26	5.49
0.3979	5.75	5.39	5.40	5.26	5.32	5.53	5.58	5.12	5.51	5.81

TABLE-3
PHYSICO-CHEMICAL DESCRIPTOR VALUES OF THE SUBSTITUENTS

S. No.	π	MR	F	R	σ_o	σ_p
1.	0.70	10.69	0.39	–0.5	0.27	–0.11
2.	0.70	10.69	0.39	–0.5	0.27	–0.11
3.	1.26	15.31	0.35	–0.6	0.20	–0.28
4.	0.71	11.18	0.41	–0.2	0.37	0.23
5.	1.27	15.80	0.37	–0.3	0.30	0.06
6.	1.27	15.80	0.37	–0.3	0.30	0.06
7.	1.27	15.80	0.37	–0.3	0.30	0.06
8.	1.83	20.42	0.33	–0.4	0.23	–0.11
9.	0.51	10.80	0.00	–0.1	–0.07	–0.17
10.	1.07	15.42	–0.10	–0.3	–0.14	–0.34
11.	1.07	15.42	–0.10	–0.3	–0.14	–0.34
12.	1.07	15.42	–0.10	–0.3	–0.14	–0.34
13.	1.63	20.04	–0.10	–0.4	–0.21	–0.51
14.	3.28	43.96	0.28	–0.3	0.20	–0.08
15.	3.84	48.58	0.24	–0.5	0.03	–0.25
16.	3.84	48.58	0.24	–0.5	0.13	–0.25
17.	3.84	48.58	0.24	–0.5	0.13	–0.25
18.	4.40	53.20	0.20	–0.6	–0.04	–0.42
19.	3.28	43.96	0.28	–0.2	0.20	–0.08
20.	3.84	48.58	0.24	–0.5	0.03	–0.08
21.	3.84	48.58	0.24	–0.5	0.13	–0.42
22.	3.84	48.58	0.24	–0.5	0.13	–0.25
23.	4.40	53.20	0.20	–0.6	–0.04	–0.42
24.	3.99	48.96	0.69	–0.5	0.57	0.15

Validation of the accepted equations

The accepted equations for activity against all the cancer cell lines are validated for stability and predictive ability using "leave-one-out" technique to obtain the PRESS statistics.

The best equations exploring the physico-chemical and positional requirements from the compounds to be active against cancer cell lines are given below:

ITP: $\log IC_{50} = 0.74(\pm0.381)\sigma_p + 0.336(\pm0.155)I_{R6} - 1.729(\pm0.556)R - 0.54(\pm0.166)I_{R'4} - 0.584(\pm0.203)$

$n = 23, r = 0.913, r^2 = 0.834, F = 22.664, s = 0.160$

HL-60 (TB): $-\log IC_{50} = 1.011(\pm1.473)F - 0.519(\pm 0.235) + 1.017I_{R'2} + 1.334(\pm0.102)$

$n = 19, r = 0.753, r^2 = 0.567, F = 6.541, s = 0.654$

NCI-H460: $-\log IC_{50} = 1.148(\pm1.502)\sigma_m - 0.584(\pm0.235)\pi + 1.677(\pm0.963) + 1.406(\pm0.109)$

$n = 22, r = 0.780, r^2 = 0.608, F = 9.302, s = 0.687$

HCT-116: $-\log IC_{50} = 1.694(\pm1.424)\sigma_p - 0.524(\pm0.217)\pi + 1.499(\pm1.399)I_{R'2} + 1.469(\pm0.099)$

$n = 19, r = 0.832, r^2 = 0.693, F = 11.285, s = 0.618$

SF-295: $-\log IC_{50} = 1.656(\pm 1.593)\sigma_m - 0.649(\pm 0.248)\pi + 2.178I_{R'2} + 1.453(\pm 0.117)$

$n = 22, r = 0.803, r^2 = 0.644, F = 10.866, s = 0.721$

U-251: $-\log IC_{50} = 1.308(\pm1.409)\sigma_m - 0.544(\pm0.220)\pi + 2.015(\pm0.903)I_{R'2} + 1.382(\pm0.103)$

$n = 22, r = 0.802, r^2 = 0.643, F = 10.822, s = 0.645$

SK-MEL-5: $\log IC_{50} = 1.389(\pm 1.466)F - 0.542(\pm0.234)\pi + 1.606(\pm1.108)I_{R'2} + 1.340(\pm0.107)$

$n = 21, r = 0.757, r^2 = 0.573, F = 7.590, s = 0.663$

OVCAR-3: $-\log IC_{50} = 1.964(\pm1.522)F - 0.677(\pm0.243)\pi + 1.563(\pm1.508)I_{R'2} + 1.340(\pm0.109)$

$n = 19, r = 0.826, r^2 = 0.683, F = 10.771, s = 0.672$

CAKI-1: $-\log IC_{50} = 1.989(\pm1.785)F - 0.739(\pm0.279)\pi + 1.444(\pm1.019)I_{R'2} + 1.447(\pm0.138)$

$n = 23, r = 0.778, r^2 = 0.605, F = 9.692, s = 0.797$

PC-3: $-\log IC_{50} = 1.722(\pm1.546)F - 0.630(\pm0.244)\pi + 1.803(\pm0.863)I_{R'2}$

$n = 21, r = 0.803, r^2 = 0.645, F = 10.317, s = 0.675$

MDA-N: $-\log IC_{50} = 1.492(\pm2.033)F - 0.581(\pm0.305)\pi + 1.072(\pm1.803)I_{R'2} + 1.345(\pm0.152)$

$n = 16, r = 0.749, r^2 = 0.561, F = 5.112, s = 0.806$

The 95% confidence intervals of the regression coefficients are shown within parentheses.

The results of QSAR analysis revealed that the electronic descriptors (σ_p and R) along with substituent positions R'_4 and R_6 described the variation in activity of the compounds as inhibition of tubulin polymerization. The electronic descriptor σ_p correlated positively along with substituent at position R'_4 whereas the descriptor R and substituent at position R'_4 correlated negatively to the activity (ITP).

On the other hand, for the compounds to be active as anticancer agents acting by the virtue of inhibition of tubulin polymerization, the electronic descriptors (F, σ_p and σ_m), hydrophobicity (π) and the substituents at position R_2' explained the variations in activity.

The electronic descriptors and substituents at position R_2' correlated positively whereas hydrophobicity of the substituents correlated negatively with the activity. The inductive effect characteristic of substituents (F) correlated to the activity against most of the cancer cell lines, *viz.*, HL-60(TB), SK-MEL-5, OVCAR-3, CAKI-1, PC-3 and MDA-N whereas σ_m correlated to the activity against NCI-H460, SF-295 and U-251. The descriptor σ_p correlated to the activity against only HCT-116.

TABLE-4
INDICATOR VARIABLES REPRESENTING SUBSTITUENTS AT DIFFERENT POSITIONS

S.No.	I_{R_5}	I_{R_6}	I_{R_7}	$I_{R_2'}$	$I_{R_3'}$	$I_{R_4'}$
1.	0	1	0	0	1	0
2.	0	0	1	0	1	0
3.	1	0	1	0	1	0
4.	0	0	0	0	1	0
5.	1	0	0	0	1	0
6.	0	1	0	0	1	0
7.	0	0	1	0	1	0
8.	1	0	1	0	1	0
9.	0	0	0	0	1	0
10.	1	0	0	0	1	0
11.	0	1	0	0	1	0
12.	0	0	1	0	1	0
13.	1	0	1	0	1	0
14.	0	0	0	1	1	0
15.	1	0	0	1	1	0
16.	0	1	0	1	1	0
17.	0	0	1	1	1	0
18.	1	0	1	1	1	0
19.	0	0	0	0	1	1
20.	1	0	0	0	1	1
21.	0	1	0	0	1	1
22.	0	0	1	0	1	1
23.	1	0	1	0	1	1
24.	0	1	0	0	1	1

1 indicates the presence of substituent at particular position.
0 indicates the absence of substituent at particular position.

Conclusion

It was concluded from the study that the inhibition of different types of cancer cells by 1,8-naphthyridine derivatives depends on certain physico-chemical characteristics of the compounds. This leads us to infer that for designing new 1,8-naphthyridine derivatives as anticancer molecules, the substituents selected should be such that in the substituted phenyl ring a substituent at R_2' position, with positive F value should be present and on the naphthyridine nucleus, substituent at R_6 position with positive σ_p value should be present. This would lead to an increased cytotoxicity by virtue of inhibition of tubulin polymerization.

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