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NOTE

QSAR Studies of 2-Aroylindole Derivatives: Tubulin Inhibitors in Cancer Therapy

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QSAR study was used to relate the tubulin inhibitory activity of 2-Aroylindole derivatives with various physicochemical descriptors. Stepwise multiple regression analysis was performed to find out the correlation between various physicochemical descriptors and biological activity of the compounds by using Openstat 2 version 6.5.1 and Valstat statistical software.

Out of several equations developed, the best equations having highest significance were selected for further studies, which are mentioned below:

$$-\log IC_{50} = 0.0604(\pm0.222)R_6 - 0.479(\pm0.239)\pi - 0.781(\pm0.455)H_D - 0.163(\pm0.147)H_A - 0.018(\pm0.304)$$
$$n = 25;\ r = 0.812;\ r^2 = 0.659;\ F = 9.707;\ s = 0.2361 \quad (1)$$

$$-\log IC_{50} = 0.565(\pm0.240)R_6 - 0.367(\pm0.217)\pi - 0.723(\pm0.493)H_D - 0.318(\pm0.472)F - 0.138(\pm0.297)$$
$$n = 25;\ r = 0.782;\ r^2 = 0.612;\ F = 7.900;\ s = 0.252 \quad (2)$$

The results obtained from QSAR studies indicate that in both the equations, the hydrogen donor, field effects and hydrophobic descriptors contributed negatively to the biological activity.

In eqn. (1), the indicator variable at R_6 position of the parent nucleus positively contributes to the activity. But in eqn. (2), R_6 positively and field effect negatively contributes along with hydrogen donor. Both the equations have 95% significance and the F value is 9.707 and 7.900 respectively suggests that the equations have very good predictive power.

Key Words: 2D QSAR, Anticancer activity, 2-Aroylindole derivatives.

The chemotherapy of neoplastic disease has become of immense importance in recent years which is already indicated by the introduction of special branch "oncology" in medical science. Recent advances in clinical techniques and interdisclipinary studies have allowed more rapid and reliable evaluation of new drugs[1].

The discovery of various cytotoxic compounds from natural resources acting by interfering with mitotic spindle apparatus has attracted much attention and microtubules have become attractive pharmacological targets for anticancer drug discovery[2–5]. The mitotic spindle is a bipolar, self-organizing microtubule (MT) based machine that uses energy liberated from nucleotide to segregate sister chromatids accurately into daughter cells during cell division.[6]

The tubulin inhibitory and *in vitro* cytotoxic activity of 2-aroylindole derivatives has already been reported. Hence, the 2-aroylindole derivatives were taken

for the QSAR study. The aim of this study was to select the highly significant physicochemical descriptors, which was correlated with biological activity.

EXPERIMENTAL

The biological activity data of various compounds for QSAR studies was obtained from Mahboobi *et al.*[7] The biological activity was converted into –log (biological activity) to decrease the variance and to convert the data into free energy changes related value. The various physicochemical descriptors of the compounds obtained from "substituent constant for correlation analysis in chemistry and biology developed by Corwin Hansch and Albert Leo". Indicator variables of the parent structure, the physicochemical descriptors and the data were entered into Excel Worksheet and saved in Comma Delimited file.

The correlation and intercorrelation matrix between biological activities and various physicochemical descriptors and indicator variables were obtained by using Openstat 2 version 6.5.1 and Valstat statistical software. Multiple regression analysis was performed, which correlated biological activity with physicochemical descriptors.

The best equations were selected with the consideration of statistical parameters[8] such as correlation coefficient (r), squared correlation coefficient (r^2), F_{test} value (F_{test}) and standard deviation.

The minimum intercorrelated descriptors were subjected to stepwise multiple regression analysis. Among the equations obtained from the stepwise multiple regression analysis, the significant equations with high correlation are listed below:

$$-\log IC_{50} = 0.0604(\pm0.222)R_6 - 0.479(\pm0.239)\pi - 0.781(\pm0.445)H_D - 0.163(\pm0.147)H_A - 0.018(\pm0.304)$$
$$n = 25;\ r = 0.812;\ r^2 = 0.659;\ F = 9.707;\ s = 0.2361 \quad (1)$$

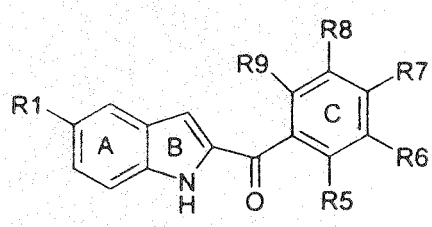
$$-\log IC_{50} = 0.565(\pm0.240)R_6 - 0.367(\pm0.217)\pi - 0.723(\pm0.493)H_D - 0.318(\pm0.472)F - 0.138(\pm0.297)$$
$$n = 25;\ r = 0.782;\ r^2 = 0.612;\ F = 7.900;\ s = 0.252 \quad (2)$$

$$-\log IC_{50} = -0.0237(\pm0.149)R_7 - 0.474(\pm0.219)R_6 - 0.332(\pm0.226)\pi - 0.596(\pm0.496)H_D - 0.285(\pm0.235)$$
$$n = 25;\ r = 0.760;\ r^2 = 0.577;\ F = 6.845;\ s = 0.263 \quad (3)$$

The results obtained from QSAR studies indicate that in all the equations, the hydrogen donor (H_D) and hydrophobic descriptor (π) contribute negatively to the biological activity whereas the indicator variable at R_6 position of the parent nucleus positively contributes to the activity.

In eqn. (1), the hydrogen acceptor (H_A) negatively contributes to the activity. But in eqn. (2), R_6 positively and field effect (F) negatively contribute along with hydrogen donor (H_D). All the equations have 95% significance and the F values 9.707, 7.900 and 6.845, respectively suggest that the equations have very good predictive power. The electronic and hydrophobic descriptors of the equations are collinear with each other.

TABLE-1
TUBULIN INHIBITORY ACTIVITY OF 2-AROYLINDOLE ANALOGS



S.No.	R_1	R_5	R_6	R_7	R_8	R_9	IC_{50} (μM)	$-\log IC_{50}$
1.	OCH_3	H	H	H	H	H	0.53	0.2757
2.	OCH_3	OCH_3	H	H	H	H	1.29	–0.1106
3.	OCH_3	H	OCH_3	H	H	H	0.53	0.2757
4.	OCH_3	OCH_3	H	OCH_3	H	H	5.60	–0.7482
5.	OCH_3	H	OCH_3	OCH_3	H	H	0.81	0.0915
6.	OCH_3	H	OCH_3	H	OCH_3	H	0.81	0.0915
7.	OCH_3	H	OCH_3H	OCH_3	OCH_3	H	0.99	0.0044
8.	OCH_3	CH_3	H	H	H	H	4.80	–0.6812
9.	OCH_3	H	H	CH_3	H	H	1.50	–0.1761
10.	OCH_3	CH_3	H	H	CH_3	H	5.20	–0.7160
11.	OCH_3	H	OH	H	H	H	0.66	0.1805
12.	OCH_3	H	$O(OC)(CH_2)_2CH_3$	H	H	H	0.85	0.0706
13.	OCH_3	H	OCF_3	H	H	H	1.70	–0.2304
14.	OCH_3	H	SCF_2H	H	H	H	2.10	–0.3222
15.	OCH_3	H	CF_3	H	H	H	1.50	–0.1761
16.	OCH_3	NH_2	H	H	H	H	6.70	–0.8207
17.	OCH_3	H	NO_2	H	H	H	0.85	0.0706
18.	OCH_3	H	NH_2	H	H	H	0.99	0.0044
19.	OCH_3	H	H	Cl	H	H	5.00	–0.6990
20.	OCH_3	H	H	Br	H	H	4.30	–0.6335
21.	OCH_3	F	H	H	H	H	1.00	0.0000
22.	OCH_3	H	F	H	H	H	0.39	0.4089
23.	OCH_3	H	Cl	Cl	H	H	2.50	–0.3979
24.	CH_3	OCH_3	H	H	H	H	3.50	–0.5441
25.	CH_3	H	OCH_3	OCH_3	OCH_3	H	0.86	–0.0655

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REFERENCES

1. W.A. Remers, in: J.N. Degaldo and W.A. Remers (Eds.), Wilson and Giswold's Textbook of Organic, Medicinal and Pharmaceutical Chemistry, 10th Edn., Lippincott, Williams & Wilkins Publishers, Philadelphia, p. 343 (1998).
2. M.A. Lordan and L. Wilson, *Curr. Opin. Cell Biol.*, **10**, 123 (1998).
3. Q. Shi, K. Chen, S.L. Morris-Natschke and K.H. Lee, *Curr. Pharm. Des.*, **4**, 219 (1998).
4. Q. Li, H.L. Sham and S.H. Rosenberg, *Ann. Rep. Med. Chem.*, **34**, 139 (1999).
5. http//dtp.nic.nih.gov/docs/compare/examples/antitub.html, N.p.c.t.i.
6. D.J. Sharp, G.C. Rogers and J.M. Scholey, *Nature*, **407**, 41 (2000).
7. S. Mahboobi, H. Pongratz, S. Basner and T. Beckers, *J. Med. Chem.*, **44**, 4535 (2001).
8. C. Hansch, P.G. Sammes and J.B. Taylor, in: Comprehensive Medicinal Chemistry, 4th Edn., Pergamon Press, Great Britain, p. 497 (1990).

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