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NOTE

QSAR Studies of Benzylidene-9(10H) Anthracenone Derivatives: Tubulin Inhibitor in Cancer Therapy

SURYA PRAKASH B.N GUPTA* and N.S. HARI NARAYANA MOORTHY†
Department of Pharmaceutical Chemistry, Oriental College of Pharmacy
Thakral Nagar, Raisen Road, Bhopal, India

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

$$-\log IC_{50} = 0.396R_2(\pm 0.129) + 0.333R_4(\pm 0.212) + 0.236H_D(\pm 0.105) - 0.273(\pm 0.176)$$
$$n = 17; r = 0.746; r^2 = 0.556; F = 5.103 \quad (1)$$

$$-\log IC_{50} = 0.273R_2(\pm 0.179) + 0.408H_D(\pm 0.239) + 0.186\pi(\pm 0.069) - 0.624(\pm 0.234)$$
$$n = 17; r = 0.615; r^2 = 0.378; F = 4.641 \quad (2)$$

The results obtained from QSAR studies indicate that in both the equations, the HD, π and indicator variables R_2 and R_4 contributed positively to the biological activity.

In eqn. (1), the indicator variables at R_2 and R_4 position of the parent nucleus positively contribute to the activity. But in eqn. (2), R_2, HD and π contribute positively. Both the equations have 85% significance and the F values are F = 5.103 and F = 4.641, respectively suggesting that the equations have very good predictive power.

Key Words: QSAR, Benzylidene-9(10H) anthracenone derivatives.

Attacking the microtubule system is a common strategy to inhibit tumour cell proliferation. The importance of microtubule for cellular life, mitosis, induction and progression makes them one of the most prominent targets for the development of anticancer agents[1–3].

Novel compounds provide new perspective for the inhibition of tumour cell growth and suppression of cancer by interfering with tubulin assembly like inhibiting polymerization or causing depolymerization upon binding to tubulin. Numerous antimitotic agents displaying a wide structural diversity have been found to affect microtubule dynamics.

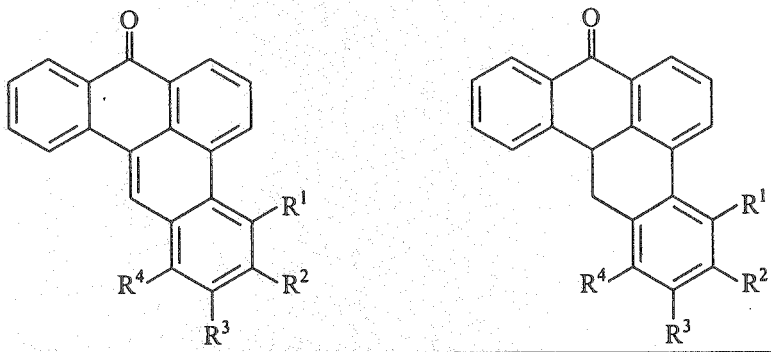
A series benzylidene 9(10H) anthracenones bearing alkylidene and alkyl linked aromatic substituents were taken for the QSAR study. The aim of this study was

†Department of Pharmaceutical Chemistty, School of Pharmaceutical Sciences, UTD, Rajiv Gandhi Nagar, Bhopal, India.

to select the highest significant physicochemical descriptors, which was correlated with biological activity.

The biological activity data of various compounds for QSAR studies was obtained from Helge Priz *et al.*[4] The biological activity was converted to –log (biological activity) to decrease the variance and to convert the data into free energy changes related value (Table-1). The various physicochemical descriptors of the compounds obtained "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 fed into the Excel Worksheet and saved in Comma delimited file.

TABLE-1
TUBULIN INHIBITORY ACTIVITY OF BENZYLIDENE-9(10H) ANTHRACENONE DERIVATIVES



S.No.	R_1	R_2	R_3	R_4	IC_{50} (μ/m)	–log IC_{50}
1.	H	H	H	H	4.40	–0.6434
2.	H	OCH_3	H	H	0.76	0.1191
3.	OCH_3	OCH_3	H	H	1.70	–0.2304
4.	OH	OH	H	H	1.80	–0.2552
5.	OCH_3	OCH_3	OCH_3	H	10.00	–1.0000
6.	H	OCH_3	H	OH	1.20	–0.0791
7.	OH	OCH_3	H	H	0.67	0.1739
8.	OCH_3	OH	H	H	0.63	0.2006
9.	H	H	OCH_3	OH	0.91	0.0409
10.	OCH_3	OH	OCH_3	H	0.63	0.2006
11.	H	OCH_3	OH	OCH_3	0.43	0.3665
12.	CH_3	OH	CH_3	H	0.91	0.0409
13.	Br	OH	Br	H	0.48	0.3187
14.	H	OH	H	H	2.50	–0.3979
15.	H	OCH_3	H	H	2.60	–0.4149
16.	OCH_3	H	OCH_3	H	10.00	–1.0000
17.	OH	OCH_3	H	H	2.30	–0.3617

The correlation and intercorrelation matrices between biological activities and various physicochemical descriptors and indicator variables were obtained using Openstat 2 version 6.5.1 and Valstat statistical software. Multiple regression analysis was performed, which correlates biological activity with physicochemical descriptors. The best equations were selected with the consideration of statistical parameters[5] such as correlation coefficient (r), squared correlation coefficient (r^2) and F_{test} value (F_{test}).

Conclusion drawn and achievements

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

$$-\log IC_{50} = 0.396R_2(\pm 0.129) + 0.333R_4(\pm 0.212) + 0.236H_D(\pm 0.105) - 0.273(\pm 0.176)$$
$$7n = 17; r = 0.746; r^2 = 0.556; F = 5.103 \quad (1)$$

$$-\log IC_{50} = 0.273R_2(\pm 0.179) + 0.408H_D(\pm 0.239) + 0.186\pi(\pm 0.069) - 0.624(\pm 0.234)$$
$$n = 17; r = 0.615; r^2 = 0.378; F = 4.641 \quad (2)$$

The results obtained from QSAR studies indicate that in both the equations, the hydrogen donor H_D, hydrophobic descriptor π and indicator variables R_2 and R_4 contributed positively to the biological activity.

In eqn. (1), the indicator variables at R_2 and R_4 position of the parent nucleus positively contribute to the activity. But in eqn. (2), R_2, H_D and π contribute positively. Both the equations have 85% significance and the F value is F = 5.103 and F = 4.641, respectively suggesting that the equations have very good predictive power.

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