IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

QSAR STUDY OF PURINE-SCAFFOLD NOVEL CLASS OF HSP90 BINDERS THAT INHIBIT THE PROLIFERATION OF CANCER CELLS

[1]Sukhendra singh patel, [2]Shailja sachan, [1]Priyanka dahiya
[1]Research scholar, [2]Associate professor, [1]Research scholar
[1]Department of Chemistry , Awadesh Pratap Singh University , Rewa (M.P.) 486003 , India
[2]Department of Chemistry , Govt. M.S.Golvalkar College , Rewa (M.P.) 486001 , India

Abstract: The chaperone heat shock protein 90 (Hsp90) is an emerging target for designing anticancer agent due to its important roles in maintaining transformation and modulating the survival and growth potential of cancer cells. Quantitative structure–activity relationship (QSAR) studies have been carried out in a series of purine derivatives with Hsp90 inhibitory activities. The best QSAR model with good correlation coefficient (r^2 = 0.8519), of high statistical significance and well explained the variance in activity.

Key words **- QSAR modeling, Anticancer activity, ETA indices, Burden eigenvalues.**

I. INTRODUCTION

It is estimated that during the next few years, cancer will overtake cardiovascular disease as the main cause of mortality, making it a disease of considerable concern. In most developed nations, cancer is already the second greatest cause of death. Cancer cells may invade nearby tissues and spread through the blood stream and lymphatic system to other parts of the body.[1-2] Targeting only one anomaly might not be enough to undo the changed phenotype because many malignancies are the result of several transformation-specific regulatory alterations. Therefore strategies which can affect multiple targets are being envisioned, for example chaperones, which are the proteins that allow cancer cells to tolerate the components of dysregulated pathways that would otherwise be lethal, the inactivation of which would effect multiple molecular alterations.[3] The heat shock protein 90 is one such chaperone that plays crucial roles in preserving cell-specific transformation (Hsp90). Eukaryotes require the cytoplasmic Hsp90 for viability in all circumstances. . The ATPase binding region of Hsp90 is currently under intensive study, because of its role in cancer and protein maintenance.[4-6] Adenosine triphosphate (ATP) is bound and hydrolyzed by a pocket in the protein's N-terminal region, controlling how it functions. High-affinity ligands that occupy this pocket stop Hsp90 client proteins from separating from the chaperone complex. As a result, the bound proteins are destroyed by the proteasome before they can reach their full functional shape. When these proteins are broken down by Hsp90 inhibitors, cancer cells in culture experience cell-specific growth arrest, apoptosis, and tumour growth suppression. A class of purine derivatives with Hsp90 inhibitory activities has been designed using peculiar bent Hsp90 inhibitors and existent Hsp90 crystal data.[7] The first derivatives of this class to be developed and synthesised (PU3) displayed a modest affinity and had cellular effects. Many of its analogues with modifications to PU3's C-2 and 9-N have been created, and their anticancer effectiveness against Hsp90 has been tested.[8-9]

QSAR experiments were conducted and are presented here to discover the critical physiochemical and structural factors for anticancer action.

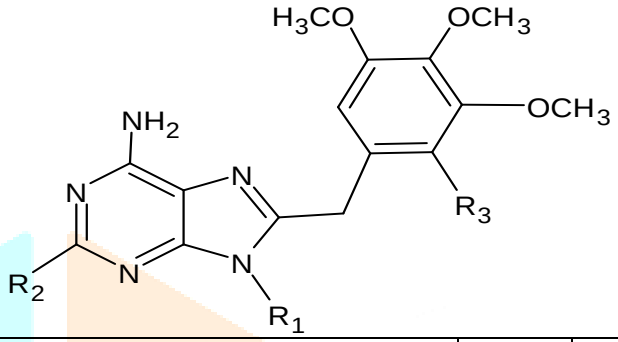
Ⅱ. RESEARCH METHODOLOGY

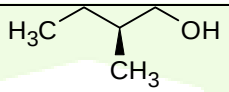
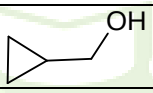
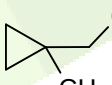
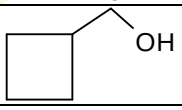
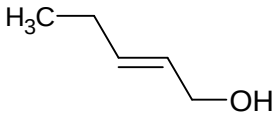
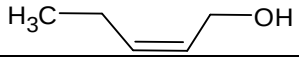
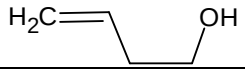
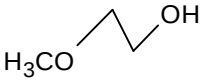
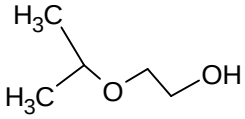
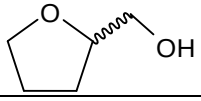
The QSAR analysis was carried out on the set of 35 compounds (Chiosis *et al*., 2002) as shown in table 1, taking the anticancer activity (logBA) as dependant and different physiochemical parameters (Hansch and Leo, 1979; Hansch *et al*., 1995) such as ETA indices (Eta_epsi_A) and Burden eigenvalues (SpMax1_Bh_v_, SpMax6_Bh_m_, SpMin4_Bh_p_, SpMin4_Bh_m_).The values for the physiochemical parameters were taken from the literature (Hansch and Leo, 1979). The multiple linear regression analysis was executed on a personal computer using NCSS version 2007. The pearson correlation matrix (Table 3) was constructed to determine the intercorrelation between the physiochemical parameters used in QSAR analysis.

Ⅲ. RESULTS AND DISCUSSION

Different combinations of (independent) physiochemical parameters showing some acceptable correlation with the (dependent) anticancer activity were carried out using stepwise multiple regression analysis to develop meaningful QSAR equation. The equation were of statistical significance with a correlation coefficient value of more than 0.9.

Table 1. Structural features and anticancer activity of the compound



S. No.	R_1	R_2	R_3	logBA
1	CH_2CH_2OH	H	H	-0.653
2	$CH_2CH_2CH_2OH$	H	H	-1.033
3	$CH_2CH_2CH_2CH_2OH$	H	H	-1.114
4	$CH_2CH_2CH_2CH_2CH_2OH$	H	H	-1.071
5	$CH_2CH(CH_3)CH_2OH$	H	H	-1.309
6	$CH_2CH(CH_3)CH_2CH_2CH_2OH$	H	H	-2.057
7	$CH_2CH_2CH(CH_2CH_3)CH_2OH$	H	H	-1.717
8		H	H	-1.196
9		H	H	-1.209
10		H	H	-1.679
11		H	H	-1.505
12		H	H	-0.978
13		H	H	-0.875
14		H	H	-1.025
15		H	H	-0.176
16		H	H	-0.74
17		H	H	-0.23
18		H	H	-0.531

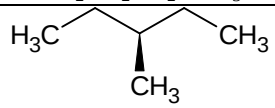
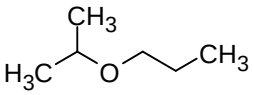
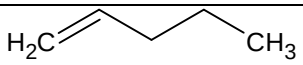
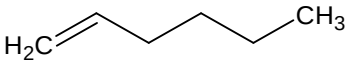
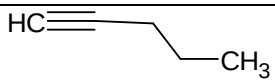
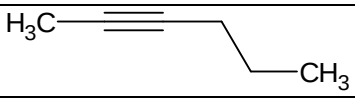
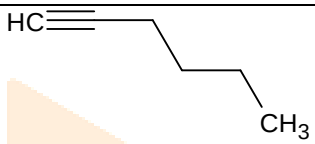
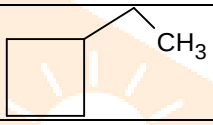
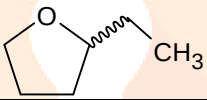
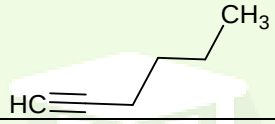
19	$CH_2CH_2CH_2CH_3$	F	H	-0.732
20	$CH_2CH_2CH_2CH_2CH_3$	F	H	-0.544
21	$CH_2CH_2CH_2CH_2CH_2CH_3$	F	H	-0.949
22	$CH_2CH_2CH_2OCH_3$	F	H	-1.139
23		F	H	-1.176
24		F	H	-0.114
25		F	H	-0.991
26		F	H	-1.255
27		F	H	-0.544
28		F	H	-1.02
29		F	H	0.155
30		F	H	-0.964
31		F	H	-0.833
32		H	Cl	-0.633
33		H	Br	-1.06
34		F	Cl	0.346
35	$CH_2CH_2CH_2OCH(CH_3)_2$	F	Cl	0.283

Table 2. Calculated ETA indices, Burden eigenvalues and anticancer activity used in the regression analysis

log BA	Eta_epsi_A	SpMax1_Bh_v_	SpMax6_Bh_m_	SpMin4_Bh_p_	SpMin4_Bh_m_
-0.653	0.852	3.919	2.82	1.085	0.999
-1.033	0.847	3.919	2.829	1.085	1.001
-1.114	0.842	3.919	2.844	1.085	1.003
-1.071	0.838	3.919	2.863	1.085	1.004
-1.309	0.842	3.921	2.891	1.109	1.024
-2.057	0.833	3.921	2.901	1.107	1.035
-1.717	0.833	3.92	2.916	1.115	1.043
-1.196	0.842	3.921	2.891	1.109	1.024
-1.209	0.842	3.916	2.924	1.107	0.994
-1.679	0.838	3.916	2.926	1.127	1.015
-1.505	0.838	3.916	2.925	1.196	1.156
-0.978	0.842	3.921	2.907	1.123	1.046
-0.875	0.842	3.921	2.907	1.123	1.046
-1.025	0.842	3.928	2.884	1.12	1.038
-0.176	0.847	3.889	2.833	1.135	1.028
-0.74	0.868	3.915	2.878	1.115	0.994
-0.23	0.857	3.915	2.927	1.17	0.998
-0.531	0.857	3.916	2.926	1.143	1.002
-0.732	0.873	3.921	2.893	1.087	0.971

-0.544	0.867	3.921	2.9	1.088	0.972
-0.949	0.862	3.921	2.906	1.088	0.972
-1.139	0.893	3.921	2.918	1.093	0.971
-1.176	0.867	3.923	2.926	1.106	0.989
-0.114	0.886	3.929	2.926	1.144	0.98
-0.991	0.873	3.922	2.925	1.095	0.981
-1.255	0.867	3.921	2.927	1.092	0.985
-0.544	0.873	3.891	2.896	1.136	0.995
-1.02	0.867	3.942	2.927	1.179	1.052
0.155	0.867	3.891	2.898	1.137	0.997
-0.964	0.867	3.923	2.927	1.163	1.101
-0.833	0.881	3.922	2.927	1.118	0.979
-0.633	0.858	3.921	2.832	1.07	1.001
-1.06	0.837	3.922	2.848	1.069	1.001
0.346	0.903	3.893	2.913	1.125	0.917
0.283	0.915	3.923	2.928	1.158	0.938

Model No.1 logBA = -16.0608, 17.6945(±3.4650)Eta_epsi_A
N= 35, MSE= 0.1684, R^2= 0.4414, AR^2= 0.4245, Q-VALUE= 3.9453
Model No.2 logBA = 60.6557, 16.7209(±3.0275)Eta_epsi_A, -19.3687(±5.6831)SpMax1_Bh_v_
N= 35, MSE= 0.1274 , R^2= 0.5902 , AR^2= 0.5646, Q-VALUE= 6.0302
Model No.3 logBA = 18.0971, -8.8648(±1.8827)SpMax6_Bh_m_, 16.7024(±2.2898)SpMin4_Bh_p_, -11.8446(±1.3925) SpMin4_Bh_m_
N= 35, MSE= 0.0868 , R^2= 0.7296 , AR^2= 0.7035, Q-VALUE= 9.8406
Model No.4 logBA = 11.6663, 9.1629(±3.9458)Eta_epsi_A, -9.4945(±1.7827)SpMax6_Bh_m_, 13.7078(±2.5011) SpMin4_Bh_p_, -8.1408(±2.0597)SpMin4_Bh_m_
N= 35, MSE= 0.0761, R^2= 0.7708, AR^2= 0.7403, Q-VALUE= 11.5368
Model No.5 logBA = 37.9639, 10.0885(±3.9034)Eta_epsi_A, -7.5332(±4.8695)SpMax1_Bh_v_, -8.4078(±1.8790) SpMax6_Bh_m_, 12.0113(±2.6796)SpMin4_Bh_p_, -6.9826(±2.1481)SpMin4_Bh_m_
N= 35, MSE= 0.0726, R^2= 0.7883, AR^2= 0.7518, Q-VALUE= 12.2295

After deleting outlier compound no. 12, 13, 20 and 29 the final model become ;

Model No.6 logBA = 24.5706, 10.3679(±3.3110)Eta_epsi_A, -3.5028(±4.4985)SpMax1_Bh_v_, -9.4862(±1.6113) SpMax6_Bh_m_, 13.0144(±2.2892)SpMin4_Bh_p_, -7.6663(±1.8254)SpMin4_Bh_m_
N= 31, MSE= 0.0518, R^2= 0.8519, AR^2= 0.8223, Q-VALUE= 17.8182

Here N is the number of compounds used in the study, MSE is the mean square error of estimation, R^2 is the regression coefficient, AR^2 is the adjusted regression coefficient and Q-value is the Quality factor.
The generated equations showed the importance of the physiochemical paramaters, especially ETA indices (Eta_epsi_A) and Burden eigenvalues (SpMax1_Bh_v_, SpMax6_Bh_m_, SpMin4_Bh_p_, SpMin4_Bh_m_). Among these equations, Eq. 6 with the highest correlation coefficient (r = 0.9229) with r^2_{cv} = 0.8262 was considered to be the best model, explaining 85.1% variance in activity. The low standard error of estimate (s) and high F value suggest that the model is highly statistically significant. The correlation between the observed and predicted activities of all the compounds using Eq. 6 (the best result) is represented graphically in fig. 1, fig. 2 and fig. 3.

Table 3. Correlation Matrix

	log_BA	Eta_epsi_A	SpMax1_Bh_v_	SpMax6_Bh_m_	SpMin4_Bh_p_	SpMin4_Bh_m_
log_BA	1.0000					
Eta_epsi_A	0.6644	1.0000				
SpMax1_Bh_v_	-0.4467	-0.0944	1.0000			
SpMax6_Bh_m_	-0.0547	0.3603	0.1959	1.0000		
SpMin4_Bh_p_	0.2286	0.1727	-0.083	0.5483	1.0000	
SpMin4_Bh_m_	-0.5139	-0.6176	0.1829	0.0319	0.4578	1.0000

Table 4. Result of cross validation

Model No.	N	PRESS	SSY	PRESS/SSY	R^2	R^2cv	PSE	S_{press}
1	35	5.5587	4.3925	1.2655	0.4414	-0.2655	0.0674	0.4104
2	35	4.0783	5.8729	0.6944	0.5902	0.3056	0.0577	0.3570
3	35	2.6906	7.2606	0.3706	0.7296	0.6294	0.0468	0.2946
4	35	2.2807	7.6706	0.2973	0.7708	0.7027	0.0432	0.2757
5	35	2.1068	7.8445	0.2686	0.7883	0.7314	0.0415	0.2695
6	31	1.2954	7.4522	0.1738	0.8519	0.8262	0.0367	0.2276

Table 5. Residual report

Com. No.	Obs. logBA	Pred. logBA	Residual
1	-0.653	-0.613	-0.040
2	-1.033	-0.765	-0.268
3	-1.114	-0.975	-0.139
4	-1.071	-1.204	0.133
5	-1.309	-1.276	-0.033
6	-2.057	-1.575	-0.482
7	-1.717	-1.671	-0.046
8	-1.196	-1.276	0.080
9	-1.209	-1.368	0.159
10	-1.679	-1.329	-0.350
11	-1.505	-1.502	-0.003
12	-1.025	-1.198	0.173
13	-0.176	-0.254	0.078
14	-0.740	-0.554	-0.186
15	-0.230	-0.448	0.218
16	-0.531	-0.824	0.293
17	-0.732	-0.854	0.122
18	-0.949	-1.086	0.137
19	-1.139	-0.805	-0.334
20	-1.176	-1.127	-0.049
21	-0.114	-0.387	0.273
22	-0.991	-1.133	0.142
23	-1.255	-1.281	0.026
24	-0.544	-0.323	-0.221
25	-1.020	-0.736	-0.284
26	-0.964	-1.253	0.289
27	-0.833	-0.755	-0.078
28	-0.633	-0.882	0.249
29	-1.060	-1.268	0.208
30	0.346	0.274	0.072
31	0.283	0.420	-0.137

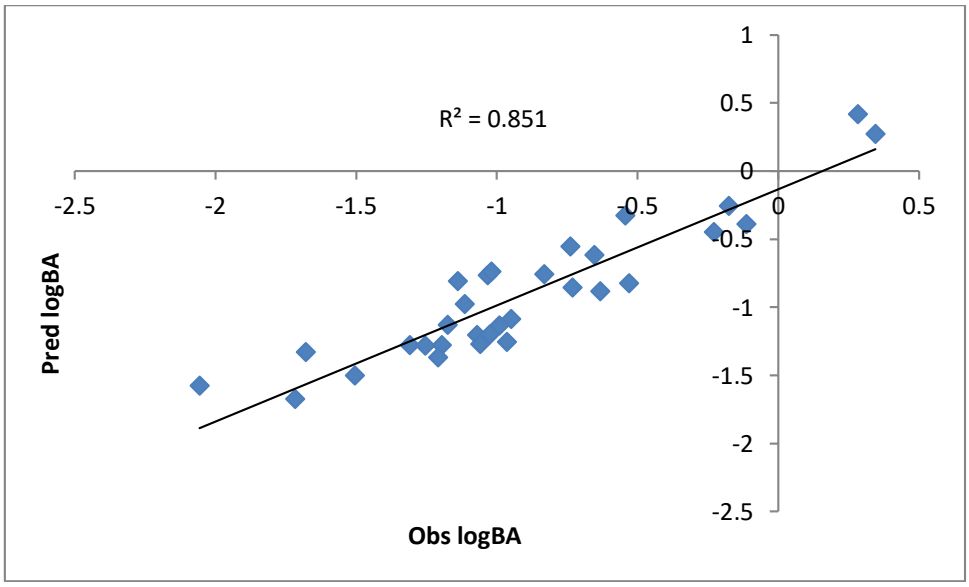


Fig. 1 plot of Observed logBA versus Predicted logBA

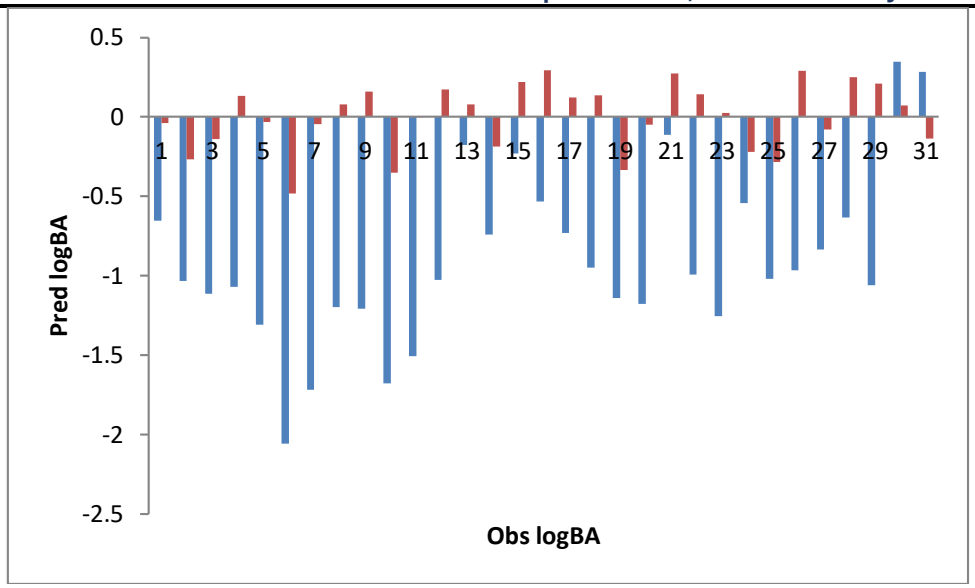


Fig. 2 plot of Observed logBA versus Residual

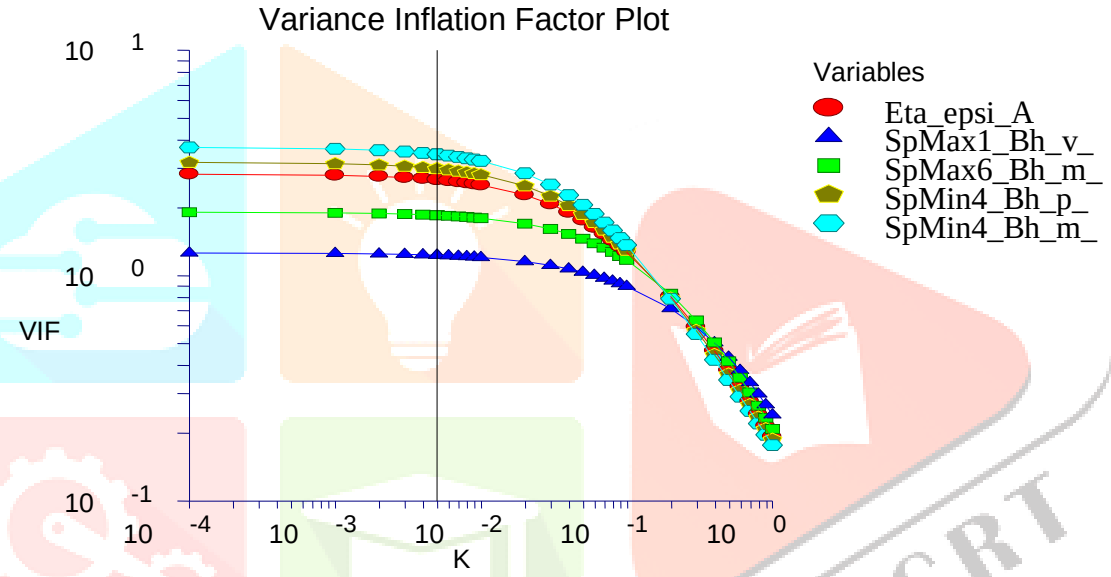


Fig. 3 Plot between VIF and K

Ⅳ.Conclusion:

The described QSAR analysis led to the identification of important physiochemical parameters in explaining the variation in activity in a set of 35 compounds. Hence the model can be useful in the optimization of activity in this class of molecules, leading to improved Hsp90 inhibitors for assessment as anticancer therapeutics.

Ⅴ. Acknowledgment

WE ARE THANKFUL TO DR. V.K.AGRAWAL, FOR HIS VALUABLE AND INSPIRATION FOR DOING THIS WORK. ONE OF THE AUTHORS DR.SHAILJA SACHAN IS PARTICULARLY THANKFUL TO UGC BHOPAL FOR FINANCIAL SUPPORT TO PURCHASE NCSS AND E-DRAGON SOFTWARE USED IN THIS WORK, WITHOUT WHICH THIS WOULD NOT HAVE BEEN POSSIBLE.

References

[1] Callery P, Gannett P (2002) Cancer and Cancer Chemotherapy, In Foye's Principles of Medicinal Chemistry, Lippincott Williams and Wilkins Philadelphia: pp 925.

[2] Pearson OH, Eliel LP (1949) Adrenocorticotropic hormone- and cortisone-induced regression of lymphoid tumors in man: a preliminary report. Cancer 2:943–945.

[3] Mosser DD, Morimoto RI (2004) Molecular chaperones and the stress of oncogenesis. Oncogene 23:2907–2918.

[4] Immormino RM, Kang Y, Chiosis G, Gewirth DT (2006) Structural and quantum chemical studies of 8-aryl-sulfanyl adenine class Hsp90 inhibitors. J Med Chem 49:4953–4960.

[5] Llauger L, He H,Kim J, Aguirre J, Rosen N, Peters U, Davies P, Chiosis G (2005) Evaluation of 8-arylsulfanyl, 8-arylsulfoxyl and 8-arylsulfonyl adenine derivatives as inhibitors of the heat shock protein 90. J Med Chem 48:2892–2905.

[6] Wright L, Barril X, Dymock B, Surgenor A, Hubbard RE (2004) Structure–activity relationships in purine based inhibitor binding to Hsp90 isoforms. Chem Biol 11:775–785.

[7] Chiosis G,Lucas B, Shtil A, Huezo H, Rosen N (2002) Development of a Purine Scaffold Novel Class of Hsp90 Binders that inhibit the proliferation of cancer cells and induce the degradation of Her2 Tyrosine Kinase. Bioorg Med Chem 10:3555–3564.

[8] Hansch C, Leo A (1979) Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley Interscience, New York, p. 48.

[9] Hansch C,Leo A, Hoekman D (1995) Exploring QSAR: Hydrophobic, Electronic and Steric Constants. Am Chem Soc 2:1.