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QSAR modeling of globulin binding affinity of corticosteroids using AM1 calculations

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Abstract—A quantitative structure–activity analysis of binding affinity of a series of 30 steroids for corticosteroid-binding globulin was performed using Wang–Ford charges of the non-hydrogen common atoms obtained from molecular electrostatic potential surface of AM1 optimized energy-minimized geometries of the compounds. Attempts were made to include lipophilicity ($\log P$) and molar refractivity (MR) values of the whole molecules in the multivariate relations. The final relations were subjected to 'leave-one-out' cross-validation to check their predictive potential. It was found from the study that the charges of different atoms of the steroid nucleus [atoms 3, 4, 5 (ring A), 8, 9 (fusion points of rings B and C) and 16 (ring D)] contribute significantly to the binding affinity. This suggests the importance of these atoms/sites for the globulin binding affinity, which is also supported by previous reports on structure–activity relations of corticosteroids. Further, molar refractivity shows parabolic relation with the binding affinity, which indicates the possibility of dispersion interactions. The statistical qualities of the final equations generated in the present study (predicted variance 77–82%; explained variance 83–87%) are better than those of some of the previously reported models.

1. Introduction

The adrenal cortex secretes two major groups of steroids that have been arbitrarily classified as glucocorticoids and mineralocorticoids though carbohydrate metabolism is intimately linked to mineral balance in mammals.[1] The mineralocorticoids have effects on Na^+, K^+ and fluid balance while glucocorticoids have effects on carbohydrate, protein, fat and calcium metabolism, water excretion, cardiovascular system, skeletal muscle, central nervous system, lymphoid and blood cells, inflammatory and immunological phenomena. Anti-inflammatory and immunosuppressive actions of corticosteroids, one of the major 'pharmacological' uses of this class of drugs, provide a protective mechanism in the physiological setting, since many of the immune mediators, which are associated with the inflammatory response, decrease vascular tone and could lead to cardiovascular collapse if unopposed by the adrenal corticosteroids. The pharmacological actions of corticosteroids in different tissues and many of their physiological effects seem to be mediated by the same receptor. Thus, various corticoids used as pharmacological agents have side effects on physiological processes that parallel their therapeutic effectiveness.[2] Corticoid hormones exert their physiological actions by binding to receptors[3,4] that belong to a transcription factor superfamily, which also includes some of the proteins regulating steroid synthesis. Steroids stimulate sodium absorption by the activation and/or de novo synthesis of the ion-gated, amiloride-sensitive sodium channel in the apical membrane and that of Na^+/K^+-ATPase in the basolateral membrane. Corticosteroids exert anti-inflammatory action by a variety of mechanisms: (i) induction of lipocortins in macrophages leading to decreased production of prostaglandins, leukotrienes and platelet activating factor; (ii) negative regulation of genes for cytokines in macrophages, endothelial cells and lymphocytes leading to decreased production of interleukins (IL-1, IL-2, IL-3, IL-6), tumour necrosis factor (TNF-α), etc.; (iii) decrease in products of acute phase reactants from macrophages leading to the interference in the complement functions; (iv) inhibition of immunoglobulin E (IgE) mediated histamine and leukotriene C4 (LTC_4) release from basophils, leading to interference in the antigen-antibody reaction;[5] etc.

Keywords: QSAR; Corticosteroid-binding globulin; Modeling; AM1 calculations.
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Quantitative structure–activity relationship (QSAR) techniques have become indispensable in all aspects of research for the molecular interpretation of biological properties.[6] It has become evident that physical, chemical or biological properties of a compound depend on the three-dimensional (3D) arrangements of the atoms in the molecule. Many different types of models have been developed to predict the binding affinity of corticosteroids with globulin. These corticosteroid-binding globulin models include molecular similarity analysis,[7] hybrid electrotopological state (E state),[8] self-organizing map (SOM),[9] combination QSAR E-state model,[10] quantitative spectrometric data–activity relationship (QSDAR)[11] models, comparative spectra analysis (CoSA)[12] and comparative molecular field analysis (CoMFA).[13] The results of SAR/QSAR studies on corticosteroids have been recently reviewed by Avery and Woolfrey.[14]

The present work explores quantitative structure–activity relationship (QSAR) of the globulin binding affinity (pK_{aff}) of a series of 30 corticosteroids using quantum chemical descriptors along with physicochemical parameters and compares the relations with those of some of the previously reported models.

2. Materials and methods

The globulin binding affinity values (pK_{aff})[10] and structural features of the compounds are presented in Table 1. Quantum mechanical calculations were done according to AM1 (Austin model 1)[15–17] method using Chem 3D Pro[18] package. The non-hydrogen common atoms of the compounds were given same serial numbers in all models (Fig. 1). Energy minimization was done under MOPAC module using RHF (restricted Hartree–Fock: closed shell) wave function. The energy-minimized geometry was used for calculation of Wang–Ford charges (obtained from molecular electrostatic potential surface) of different atoms as described earlier.[19,20] The software Chem Draw Ultra ver 5.0 was used for the calculation of $\log P$ and MR values (Ghose and Crippen's fragmentation method[21]).

The charges (q_x) of different atoms (x) and the physicochemical parameters were subjected to intercorrelation study. The binding affinity data of the compounds were subjected to multiple linear regression (MLR) with different combinations of charges of different atoms and physicochemical parameters (all-possible-subsets regression) to obtain best univariate and multivariate relations (involving one and more than one predictor variables, respectively) using the program AUTOREG[22] developed by one of the authors. For the multivariate relations, predictor variables with lower intercorrelation ($|r| < 0.5$) were only considered. Further, multivariate relations having correlation coefficients higher than those of the best relations involving less number of predictor variables were recorded.

The regression analyses were carried out using a GW-BASIC program RRR98.[22] The statistical quality of the equations[23] was judged by the parameters like explained variance (R^2_a, i.e., adjusted R^2), correlation coefficient (r or R), standard error of estimate (s), average of absolute values of the residuals (AVRES), variance ratio (F) at specified degrees of freedom (df) and 't' values of the regression coefficients. Use of more than one variable in a multivariate equation was justified by intercorrelation study. All the accepted equations have regression constants and F ratios significant at 95% and 99% levels, respectively, if not stated otherwise (marked with *). The stability and predictive capacity of the equations was cross-validated from PRESS statistics [cross-validation $R^2(Q^2)$, predicted residual sum of squares (PRESS), standard deviation based on PRESS (S_{PRESS}), standard deviation of error of prediction (SDEP) and average absolute predicted residual ($Pres_{av}$)] obtained by the leave-one-out technique[24] using KRPRES1 and KRPRES2 programs.[22]

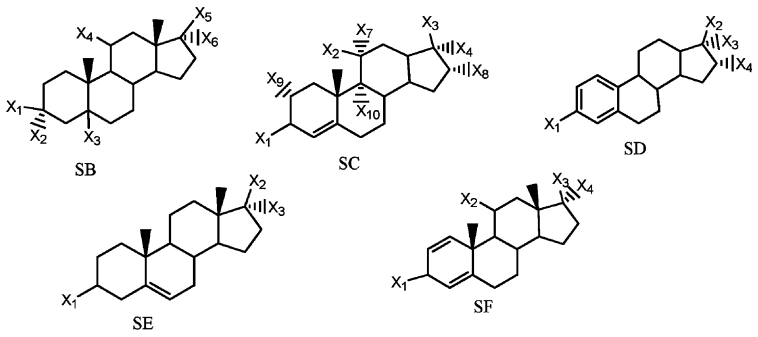
The appropriateness of selection of descriptors in the multivariate equations was also cross-checked using principal component factor analysis[25,26] of the data matrix composed of the binding affinity values, charge parameters and physicochemical variables. Factor analysis displays multidimensional data in a space of lower dimensionality with minimal loss of information and extracts basic features behind the data with ultimate goal of interpretation and/or prediction. The factors were extracted by principal component method and then rotated by VARIMAX rotation to obtain Thurston's simple structure. Factors describing $\geqslant 5\%$ of the total variance were only considered. Variables with nonzero loadings in such factors where the binding affinity also has nonzero loading were considered important in explaining the variance of the affinity. Further, variables with nonzero loadings in different factors were combined in the final regression equations. The factor analysis was carried out using software STATISTICA.[27]

3. Results and discussion

The Wang–Ford charges of different non-hydrogen common atoms of the corticosteroids are given in Table 2 while the values of physicochemical parameters are given in Table 3. The intercorrelations ($|r|$) among the charges and physicochemical parameters are listed in Table 4. Table 5 lists the statistical parameters of univariate and selected multivariate relations of globulin binding affinity of the corticosteroids with Wang–Ford charges of different atoms and/or physicochemical parameters. Figure 2 shows energy-minimized representations of the most active three compounds of the series (compounds **5**, **6** and **10**).

The best univariate relation (Table 5) involves charge of atom 4 (q_4). The equation explains 68.8% of the variance and regression coefficient of q_4 is significant at 95% level.

Table 1. Structural features, and observed, calculated and predicted globulin binding affinity data of corticosteroids



Sl. no	Key	Structural features										Binding affinity for corticosteroid binding globulin (pK_{aff})[a]				
		X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	Obsd[b]	Calcd[c]	Pred[c]	Calcd[d]	Pred[d]
1	SB	OH	H	H[e]	H	OH	H					5.000	4.702	4.619	4.656	4.531
2	SE	OH	OH	H								5.000	4.759	4.716	5.010	5.011
3	SC	=O	H	=O				H	H	H	H	5.763	6.287	6.472	6.218	6.311
4	SB	H	OH	H[e]	H	=O						5.613	5.06	4.921	5.041	4.899
5	SC	=O	OH	$COCH_2OH$	H			H	H	H	H	7.881	7.639	7.576	7.761	7.726
6	SC	=O	OH	$COCH_2OH$	OH			H	H	H	H	7.881	8.021	8.069	7.994	8.031
7	SC	=O	=O	$COCH_2OH$	OH				H	H	H	6.892	7.073	7.103	7.251	7.324
8	SE	OH	=O									5.000	5.369	5.431	5.617	5.680
9	SC	=O	H	$COCH_2OH$	H			H	H	H	H	7.653	7.123	7.091	7.200	7.160
10	SC	=O	H	$COCH_2OH$	OH			H	H	H	H	7.881	7.493	7.433	7.423	7.356
11	SB	=O		H[e]	H	OH	H					5.919	6.274	6.298	6.167	6.187
12	SD	OH	OH	H	H							5.000	5.391	5.413	5.221	5.299
13	SD	OH	OH	H	OH							5.000	5.022	5.025	5.265	5.310
14	SD	OH	=O		H							5.000	5.084	5.100	4.836	4.766
15	SB	H	OH	H[f]	H	=O						5.225	4.680	4.570	4.661	4.550
16	SE	OH	COMe	H								5.225	5.608	5.751	5.570	5.710
17	SE	OH	COMe	OH								5.000	5.415	5.569	5.447	5.622
18	SC	=O	H	COMe	H			H	H	H	H	7.380	6.694	6.617	6.808	6.725
19	SC	=O	H	COMe	OH			H	H	H	H	7.740	7.429	7.297	7.367	7.211
20	SC	=O	H	OH	H			H	H	H	H	6.724	6.646	6.638	6.662	6.651
21	SF	=O	OH	$COCH_2OH$	OH							7.512	7.621	7.634	7.524	7.527
22	SC	=O	OH	$COCH_2OC$-OMe	OH			H	H	H	H	7.553	7.628	7.641	7.227	6.932
23	SC	=O	=O	COMe	H				H	H	H	6.779	6.761	6.759	6.952	6.982
24	SC	=O	H	$COCH_2OH$	H			OH	H	H	H	7.200	7.748	7.906	7.836	8.010
25	SC[g]	=O	H	OH	H			H	H	H	H	6.144	6.163	6.165	6.009	5.962
26	SC	=O	H	COMe	OH			H	OH	H	H	6.247	6.115	6.013	6.704	6.806
27	SC	=O	H	COMe	H			H	Me	H	H	7.120	6.911	6.892	7.031	7.022
28	SC[g]	=O	H	COMe	H			H	H	H	H	6.817	6.594	6.575	6.676	6.660
29	SC	=O	OH	$COCH_2OH$	OH			H	H	Me	H	7.688	7.596	7.591	7.165	7.086
30	SC	=O	OH	$COCH_2OH$	OH			H	H	Me	F	5.797	6.651	6.966	6.330	6.699

[a] pK_{aff} = negative logarithm of affinity constant (K_{aff}), where K_{aff} is the binding affinity of steroids to corticosteroid-binding globulin.
[b] Obsd = observed,[10] Calcd = calculated, Pred = predicted applying leave-one-out technique.
[c] From Eq. 5.
[d] From Eq. 7.
[e] 5-α Steroid series.
[f] 5-β Steroid series.
[g] H (hydrogen) instead of Me at C_{10} of the steroid skeleton.

$$pK_{aff} = -11.110(\pm 2.83)q_4 + 2.576(\pm 1.00),$$
$$n = 30,\ q^2 = 0.66,\ r_a^2 = 0.69,\ r = 0.84,\ s = 0.62,$$
$$F = 64.8\ (\text{df}\ 1, 28),\ \text{AVRES} = 0.47,\ \text{SDEP} = 0.63,$$
$$S_{PRESS} = 0.65,\ \text{Pres}_{av} = 0.50. \quad (1)$$

The 95% confidence intervals of the regression coefficients are given within parentheses. Eq. 1 suggests that the binding affinity increases with increase in negative charge of the atom 4. Again, the statistical quality of the relation ($r = 0.813$) with charge of atom 3 closely follows that of Eq. 1. It is observed from Table 4 that charges of atoms 3 and 4 are highly intercorrelated ($|r| = 0.97$). The charge values of atoms 3 and 4 are largely dependent on the substitution pattern of ring A. It is observed that presence of enone moiety in ring A (SC and SF series of compounds) increases negative charge on atom 4 and such compounds have higher binding affinity.

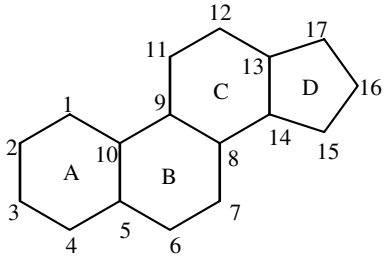


Figure 1. General structure of corticosteroids: the common atoms have been numbered 1 through 17.

On inclusion of the second parameter, charge (q_9) of atom 9, the best bivariate relation (Table 5), explaining 78.0% of the variance of the binding affinity, was obtained.

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = -11.358(\pm 2.38)q_4 - 3.205(\pm 1.84)q_9 \\ &\qquad + 2.168(\pm 0.87), \\ &n = 30,\ Q^2 = 0.75,\ R_{\mathrm{a}}^2 = 0.78,\ R = 0.89,\ s = 0.52, \\ &F = 52.5\ (\mathrm{df}\ 2, 27),\ \mathrm{AVRES} = 0.38,\ \mathrm{SDEP} = 0.54, \\ &S_{\mathrm{PRESS}} = 0.57,\ \mathrm{Pres}_{\mathrm{av}} = 0.42. \end{aligned} \tag{2}$$

The parameters, q_4 and q_9 are not much intercorrelated ($|r| = 0.06$, Table 4).

The best trivariate relation (Table 5) involves charges of atoms 4, 8 and 9. There is a tangible increase in statistical quality in the equation in comparison to the best bivariate equation (Eq. 2).

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = -10.456(\pm 2.16)q_4 - 5.597(\pm 3.74)q_8 \\ &\qquad - 4.191(\pm 1.74)q_9 + 2.000(\pm 0.84), \\ &n = 30,\ Q^2 = 0.80,\ R_{\mathrm{a}}^2 = 0.83,\ R = 0.92,\ s = 0.45, \\ &F = 49.1\ (\mathrm{df}\ 3, 26),\ \mathrm{AVRES} = 0.35,\ \mathrm{SDEP} = 0.49, \\ &S_{\mathrm{PRESS}} = 0.52,\ \mathrm{Pres}_{\mathrm{av}} = 0.41. \end{aligned} \tag{3}$$

All regression coefficients of Eq. 3 are significant at 95% level and the parameters show acceptable intercorrelation (Table 4).

The best tetravariate relation involves charges of atoms 3, 8 and 9 and molar refractivity. However, intercept of this equation is not significant at 95% level. Omitting the intercept, the following relation was obtained:

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = 3.671(\pm 0.81)q_3 - 5.271(\pm 3.53)q_8 \\ &\qquad - 3.399(\pm 1.70)q_9 + 0.453(\pm 0.060)\mathrm{MR}, \\ &n = 30,\ Q^2 = 0.80,\ R_{\mathrm{a}}^2 = 0.85,\ R = 0.93,\ s = 0.42, \\ &F = 1769.0\ (\mathrm{df}\ 4, 26)\ \mathrm{AVRES} = 0.33,\ \mathrm{SDEP} = 0.48, \\ &S_{\mathrm{PRESS}} = 0.52,\ \mathrm{Pres}_{\mathrm{av}} = 0.40. \end{aligned} \tag{4}$$

Eq. 4 suggests that positive charge on atom 3 and negative charges on atoms 8 and 9 are conducive to the binding affinity. Again, molar refractivity of the molecules has positive contribution to the binding affinity. The positive coefficient of charge of atom 3 (Eq. 4) and negative coefficients of charge of atom 4 (Eqs. (1)–(3)) indicate that charge difference between atoms 3 and 4 may be required for optimum binding.

In case of the equations involving five predictor variables, the best one (Table 5) was the following (after setting intercept to zero):

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = 3.827(\pm 0.80)q_3 - 5.202(\pm 3.38)q_8 \\ &\qquad - 3.236(\pm 1.63)q_9 - 1.000(\pm 1.10)^{*}q_{16} \\ &\qquad + 0.426(\pm 0.065)\mathrm{MR}, \\ &n = 30,\ Q^2 = 0.82,\ R_{\mathrm{a}}^2 = 0.87,\ R = 0.94,\ s = 0.40, \\ &F = 1551.1\ (\mathrm{df}\ 5,\ 25),\ \mathrm{AVRES} = 0.30,\ \mathrm{SDEP} = 0.46, \\ &S_{\mathrm{PRESS}} = 0.51,\ \mathrm{Pres}_{\mathrm{av}} = 0.37. \end{aligned} \tag{5}$$

The regression coefficient of the variable q_{16} is significant at 90% level. The negative coefficient of q_{16} suggests that the binding affinity increases on increase of negative charge on atom 16, which should be mostly influenced by the substituents in ring D.

Again, as charges of atoms 3, 4 are 5 are highly intercorrelated (Table 5), a new variable q_{3+4+5} was defined as sum of the charges of atoms 3, 4 and 5. Using q_{3+4+5} instead of q_3 in Eq. 5, the following relation was obtained:

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = 3.560(\pm 0.86)q_{3+4+5} - 4.312(\pm 3.84)q_8 \\ &\qquad - 3.033(\pm 1.84)q_9 - 1.294(\pm 1.26)q_{16} \\ &\qquad + 0.540(\pm 0.058)\mathrm{MR}, \\ &n = 30,\ Q^2 = 0.77,\ R_{\mathrm{a}}^2 = 0.83,\ R = 0.92,\ s = 0.45, \\ &F = 1223.6\ (\mathrm{df}\ 5,\ 25),\ \mathrm{AVRES} = 0.34,\ \mathrm{SDEP} = 0.52, \\ &S_{\mathrm{PRESS}} = 0.58,\ \mathrm{Pres}_{\mathrm{av}} = 0.42. \end{aligned} \tag{6}$$

The statistical quality of Eq. 6 is slightly inferior to that of Eq. 5.

Again, using MR^2 term instead of q_{16} in Eq. 6, a slightly better equation was obtained:

$$\begin{aligned} &\mathrm{p}K_{\mathrm{aff}} = 3.694(\pm 0.81)q_{3+4+5} - 4.376(\pm 3.69)q_8 \\ &\qquad - 3.654(\pm 1.77)q_9 + 5.118(\pm 4.86)\mathrm{MR} \\ &\qquad - 0.276(\pm 0.28)^{*}\mathrm{MR}^2 - 18.593(\pm 21.19)^{*}, \\ &n = 30,\ Q^2 = 0.80,\ R_{\mathrm{a}}^2 = 0.85,\ R = 0.94,\ s = 0.42, \\ &F = 34.7\ (\mathrm{df}\ 5,\ 25),\ \mathrm{AVRES} = 0.33,\ \mathrm{SDEP} = 0.48, \\ &S_{\mathrm{PRESS}} = 0.54,\ \mathrm{Pres}_{\mathrm{av}} = 0.42. \end{aligned} \tag{7}$$

The regression coefficient of MR^2 term and the intercept of Eq. 7 are significant at 90% level. Leave-one-out

Table 2. Wang–Ford charges (q_x) of the non-hydrogen common atoms of corticosteroids obtained from molecular electrostatic potential surface of energy-minimized geometry: (Panel a) Part I, (Panel b) Part II

Compd no	Wang–Ford charges (q_x)								
	q_1	q_2	q_3	q_4	q_5	q_6	q_7	q_8	
Panel a									
1	−0.08042	−0.23639	0.15161	−0.23060	−0.10155	−0.13745	−0.20365	0.03665	
2	−0.11346	−0.21203	0.09025	−0.21281	−0.01077	−0.15918	−0.17759	−0.06516	
3	−0.01431	−0.34348	0.60841	−0.39677	0.18920	−0.19801	−0.15145	−0.04808	
4	−0.10235	−0.23542	0.14623	−0.21411	−0.07448	−0.15483	−0.20150	0.01740	
5	−0.06446	−0.33846	0.60604	−0.40775	0.16398	−0.14774	−0.12032	−0.02828	
6	−0.06448	−0.34421	0.60682	−0.41015	0.17360	−0.15103	−0.10030	−0.06601	
7	−0.09711	−0.32415	0.59161	−0.37425	0.12933	−0.13900	−0.20800	−0.00215	
8	−0.06373	−0.24848	0.16802	−0.20714	0.02385	−0.17672	−0.16187	−0.06985	
9	−0.03275	−0.33102	0.60553	−0.40538	0.17798	−0.15153	−0.14884	−0.09338	
10	−0.03643	−0.33621	0.60458	−0.40302	0.17155	−0.14988	−0.13650	−0.14661	
11	−0.09225	−0.24995	0.53140	−0.27347	−0.02715	−0.16023	−0.16701	−0.04481	
12	−0.06923	−0.25924	0.31551	−0.27893	0.02254	−0.13848	−0.16792	−0.08841	
13	−0.06568	−0.26151	0.31751	−0.28055	0.03258	−0.16182	−0.16691	−0.05931	
14	−0.03169	−0.27235	0.32054	−0.28000	0.02613	−0.13292	−0.20041	0.01255	
15	−0.12946	−0.23965	0.12618	−0.21771	−0.05588	−0.15914	−0.15342	−0.02448	
16	−0.11332	−0.21700	0.09619	−0.21925	−0.03586	−0.13935	−0.18962	−0.12836	
17	−0.11197	−0.22270	0.08887	−0.22340	0.00639	−0.16721	−0.15038	−0.12591	
18	−0.02394	−0.34625	0.61001	−0.39276	0.14780	−0.14925	−0.16523	−0.11256	
19	−0.00747	−0.34841	0.60925	−0.39910	0.16977	−0.15924	−0.10992	−0.20703	
20	−0.03334	−0.32363	0.60520	−0.40025	0.17184	−0.14161	−0.14872	−0.10887	
21	0.12291	−0.40874	0.65489	−0.43719	0.23980	−0.24492	−0.11061	−0.08204	
22	−0.05872	−0.33911	0.60255	−0.40169	0.17829	−0.17114	−0.13597	−0.02973	
23	−0.12751	−0.31173	0.59459	−0.37367	0.14049	−0.17243	−0.15624	−0.01765	
24	−0.08341	−0.33748	0.60405	−0.40292	0.14000	−0.13880	−0.11340	−0.08388	
25	−0.04355	−0.33277	0.60858	−0.40558	0.17430	−0.17703	−0.14140	−0.07792	
26	−0.04869	−0.32695	0.59721	−0.39228	0.17749	−0.17700	−0.18361	−0.04525	
27	−0.03509	−0.32321	0.60623	−0.40330	0.17258	−0.14931	−0.16124	−0.08921	
28	−0.06876	−0.33152	0.60822	−0.40376	0.15110	−0.16792	−0.13186	−0.10462	
29	−0.10876	−0.18868	0.61601	−0.42292	0.14983	−0.13848	−0.12034	−0.07792	
30	−0.10931	−0.20186	0.62187	−0.42153	0.18514	−0.17487	−0.12744	−0.06532	
	q_9	q_{10}	q_{11}	q_{12}	q_{13}	q_{14}	q_{15}	q_{16}	q_{17}
Panel b									
1	−0.15379	0.03238	−0.08600	−0.18302	−0.00859	−0.17887	−0.14704	−0.23375	0.16157
2	−0.07086	−0.01629	−0.12436	−0.18831	−0.08334	−0.06441	−0.14482	−0.22946	0.19147
3	0.01773	−0.22393	−0.15679	−0.11052	−0.27524	−0.18760	−0.02719	−0.41162	0.60142
4	−0.21036	0.06407	−0.04375	−0.20754	−0.07730	−0.26036	−0.06690	−0.36972	0.57347
5	−0.32265	−0.09482	0.11253	−0.21723	−0.14944	−0.11975	−0.04549	−0.22236	−0.02436
6	−0.33276	−0.10643	0.13541	−0.21245	−0.21744	−0.03993	0.00575	−0.31407	0.23396
7	−0.22993	−0.11006	0.54764	−0.21044	−0.15821	−0.09181	−0.15286	−0.13519	0.20304
8	−0.12397	−0.01048	−0.06201	−0.24435	−0.07800	−0.22344	−0.05033	−0.38569	0.58420
9	−0.07849	−0.21295	−0.17363	−0.15001	−0.16375	−0.12001	−0.02374	−0.22158	−0.02325
10	−0.07760	−0.20157	−0.15663	−0.15037	−0.25042	0.00900	−0.01540	−0.26388	0.21863
11	−0.07109	−0.10127	−0.12114	−0.14381	−0.02516	−0.15123	−0.13450	−0.24821	0.14747
12	−0.08119	−0.04068	−0.14392	−0.19881	−0.14274	−0.08370	−0.11637	−0.24229	0.14015
13	−0.08160	−0.04896	−0.13427	−0.21886	−0.10948	−0.17461	−0.17316	0.04623	0.03886
14	−0.11808	−0.06680	−0.13975	−0.13647	−0.21235	−0.22782	−0.07733	−0.36869	0.56706
15	−0.06139	−0.06013	−0.09919	−0.17556	−0.10406	−0.16809	−0.07769	−0.33077	0.54977
16	−0.12952	0.06715	−0.15604	−0.12800	0.13182	−0.03656	−0.10180	−0.19029	−0.25690
17	−0.07006	−0.02652	−0.13591	−0.10172	−0.12377	−0.00023	−0.13652	−0.17017	0.17607
18	0.02622	−0.17618	−0.15354	−0.17788	0.06635	−0.06084	−0.24923	−0.11233	−0.24903
19	0.00995	−0.19088	−0.15450	−0.21249	−0.03523	0.00135	−0.08852	−0.24475	−0.02080
20	−0.03330	−0.23672	−0.10752	−0.17492	−0.18145	−0.05979	−0.07968	−0.25559	0.17066
21	−0.13041	−0.20085	0.27800	−0.27934	−0.19760	0.01299	−0.28250	−0.03615	−0.07806
22	−0.22968	−0.16335	0.15410	−0.27662	−0.13321	−0.15282	−0.34731	−0.06181	−0.03827
23	−0.12789	−0.13391	0.53255	−0.24946	0.07562	−0.24188	−0.06902	−0.21661	−0.14319
24	−0.29795	−0.04429	0.00451	−0.12807	−0.01715	−0.00742	−0.10218	−0.12950	−0.27469
25	0.00912	−0.30282	−0.12559	−0.15203	−0.18765	−0.09445	−0.06262	−0.24452	0.16677
26	0.00562	−0.24439	−0.15134	−0.16704	−0.03114	−0.20240	−0.39181	0.25829	−0.15455
27	−0.03588	−0.22184	−0.18504	−0.10644	−0.17623	−0.11236	−0.06771	−0.06016	−0.14584
28	−0.00208	−0.24035	−0.20430	−0.08975	−0.16514	−0.06630	−0.06746	−0.15575	−0.14038
29	−0.14077	−0.14028	0.09576	−0.27726	−0.01721	−0.09580	−0.08632	−0.20445	−0.01696
30	0.11723	−0.18757	0.07175	−0.22828	−0.08548	−0.10497	−0.10662	−0.14668	−0.03140

Table 3. Physicochemical parameter values of 30 steroids

Compd no	Log*P*	MR[a]
1	3.69	8.414
2	3.22	8.496
3	2.80	7.881
4	4.18	8.320
5	0.79	9.178
6	−0.04	9.314
7	0.28	9.206
8	3.71	8.402
9	1.95	9.032
10	1.12	9.168
11	3.85	8.291
12	3.37	7.562
13	2.42	7.708
14	3.69	7.453
15	4.18	8.320
16	3.98	9.311
17	2.56	9.454
18	3.31	8.804
19	1.82	8.948
20	2.48	7.990
21	0.48	9.939
22	0.19	10.249
23	2.47	8.842
24	0.79	9.178
25	2.01	7.550
26	0.86	9.094
27	3.64	9.282
28	2.84	8.365
29	0.52	9.806
30	0.37	9.784

[a] MR values are scaled to a factor of 0.1 as usual.

cross-validation applied on Eqs. 6 and 7 shows predicted variances of 77.0% and 80.0%, respectively. This shows that the models have significant predictive potential. The calculated and predicted binding affinity values according to Eqs. 5 and 7 are given in Table 1.

Table 6 shows the results of factor analysis of the data matrix composed of the binding affinity and the descriptors. It can be observed that 10 factors can explain 96% of the variance of the data matrix. The binding affinity is highly loaded with factor 1 (which is in turn highly loaded in q_2, q_3, q_4, q_5 and q_{10}), moderately loaded with factor 2 (highly loaded in MR and MR^2) and factor 9 (highly loaded in q_9), and slightly loaded with factor 3 (highly loaded in q_8). The best formulated equation based on the results of factor analysis is same as Eq. 5. This shows that the variables in the multivariate equations have been appropriately chosen.

To further validate the obtained models, leave-many-out cross-validation was applied on Eqs. 5 and 7. Both leave-25%-out and leave-50%-out tests were performed where 25% and 50%, respectively, of the compounds were deleted in each cycle (as shown in Table 7) and the models were developed from rest of the compounds, which were then used to predict the binding affinities of the deleted compounds in each cycle. Based on these tests, predicted variance (Q^2) and predicted residual sum of squares (PRESS) values were noted (Table 7). Q^2 values for Eq. 5 are 0.822 and 0.864, respectively, based on the leave-25%-out and leave-50%-out tests, while

Table 4. Intercorrelation ($|r|$) among Wang–Ford charges (q_x) of different non-hydrogen common atoms of corticosteroids and physicochemical parameters

	q_1	q_2	q_3	q_4	q_5	q_6	q_7	q_8	q_9	q_{10}	q_{11}	q_{12}	q_{13}	q_{14}	q_{15}	q_{16}	q_{17}	log *P*	MR
q_1	1.00	0.73	0.46	0.48	0.55	0.55	0.31	0.28	0.14	0.51	0.08	0.23	0.44	0.28	0.23	0.17	0.09	0.23	0.05
q_2		1.00	0.71	0.70	0.73	0.36	0.41	0.21	0.11	0.63	0.19	0.35	0.39	0.27	0.14	0.22	0.26	0.42	0.13
q_3			1.00	0.97	0.91	0.21	0.57	0.22	0.07	0.83	0.30	0.07	0.26	0.24	0.06	0.29	0.44	0.66	0.31
q_4				1.00	0.96	0.22	0.64	0.28	0.06	0.83	0.28	0.12	0.30	0.34	0.05	0.32	0.48	0.73	0.40
q_5					1.00	0.36	0.65	0.37	0.12	0.84	0.27	0.02	0.37	0.35	0.08	0.32	0.42	0.73	0.41
q_6						1.00	0.32	0.06	0.27	0.37	0.18	0.32	0.23	0.01	0.33	0.20	0.02	0.20	0.18
q_7							1.00	0.51	0.08	0.46	0.10	0.10	0.24	0.54	0.18	0.01	0.30	0.59	0.43
q_8								1.00	0.38	0.34	0.38	0.16	0.02	0.75	0.12	0.10	0.40	0.11	0.20
q_9									1.00	0.48	0.48	0.09	0.01	0.02	0.10	0.13	0.04	0.29	0.26
q_{10}										1.00	0.02	0.08	0.42	0.21	0.09	0.28	0.27	0.43	0.10
q_{11}											1.00	0.22	0.08	0.08	0.12	0.08	0.12	0.53	0.43
q_{12}												1.00	0.09	0.12	0.22	0.06	0.08	0.07	0.08
q_{13}													1.00	0.10	0.27	0.22	0.47	0.24	0.18
q_{14}														1.00	0.03	0.14	0.45	0.38	0.39
q_{15}															1.00	0.76	0.38	0.22	0.31
q_{16}																1.00	0.70	0.39	0.39
q_{17}																	1.00	0.37	0.51
Log*P*																		1.00	0.63
MR																			1.00

Table 5. Statistical quality of univariate and selected[a] multivariate relations (all-possible-subsets regression) of the globulin binding affinity of corticosteroids with Wang–Ford charges (q_x) of different non-hydrogen common atoms and/or physicochemical parameters

Combination of variables	R	R^2_a	F^b	s	Combination of variables	R	R^2_a	F^b	s
q_1	0.39	0.12	5.0	1.03	q_2	0.68	0.44	24.1	0.82
q_3	0.81	0.65	54.6	0.65	q_4	0.84	0.69	64.8	0.62
q_5	0.78	0.59	42.2	0.71	q_6	0.04	−0.03	0.06	1.12
q_7	0.64	0.39	19.6	0.86	q_8	0.33	0.08	3.4	1.06
q_9	0.26	0.03	2.0	1.08	q_{10}	0.57	0.30	13.4	0.92
q_{11}	0.33	0.07	3.3	1.06	q_{12}	0.11	−0.02	0.3	1.11
q_{13}	0.15	−0.01	0.7	1.11	q_{14}	0.42	0.15	6.0	1.02
q_{15}	0.01	−0.04	0.05	1.12	q_{16}	0.19	0.10	1.0	1.10
q_{17}	0.47	0.19	8.0	0.99	$\log P$	0.67	0.42	22.4	0.83
MR	0.57	0.30	13.5	0.92					
q_1, q_4	0.84	0.68	31.3	0.63	q_2, MR	0.84	0.68	31.6	0.62
q_3, q_9	0.87	0.74	43.2	0.56	q_3, q_{14}	0.85	0.69	33.8	0.61
q_3, MR	0.88	0.76	45.7	0.54	q_4, q_6	0.85	0.70	34.6	0.60
q_4, q_8	0.84	0.69	32.7	0.62	q_4, q_9	0.89	0.78	52.5	0.52
q_4, q_{11}	0.84	0.69	32.7	0.62	q_4, q_{12}	0.84	0.68	31.3	0.63
q_4, q_{13}	0.84	0.69	32.9	0.62	q_4, q_{14}	0.85	0.70	34.6	0.60
q_4, q_{15}	0.84	0.68	31.8	0.62	q_4, q_{16}	0.84	0.68	32.3	0.62
q_4, q_{17}	0.84	0.68	32.2	0.62	q_4, MR	0.87	0.75	43.8	0.55
q_5, q_9	0.85	0.71	35.7	0.60					
q_1, q_4, q_9	0.89	0.77	33.8	0.53	q_2, q_{12}, MR	0.89	0.77	33.5	0.53
q_3, q_6, MR	0.90	0.78	35.2	0.52	q_3, q_8, q_9	0.92	0.83	48.1	0.45
q_3, q_9, q_{14}	0.90	0.79	38.3	0.50	q_3, q_9, MR	0.91	0.80	40.7	0.49
q_3, q_{15}, MR	0.90	0.78	35.4	0.52	q_3, q_{16}, MR	0.90	0.78	34.9	0.52
q_4, q_6, q_9	0.89	0.78	34.6	0.52	q_4, q_6, MR	0.89	0.77	33.5	0.53
q_4, q_8, q_9	0.92	0.83	49.1	0.45	q_4, q_9, q_{11}	0.90	0.78	34.9	0.52
q_4, q_9, q_{12}	0.89	0.77	34.0	0.52	q_4, q_9, q_{13}	0.90	0.79	36.5	0.51
q_4, q_9, q_{14}	0.90	0.79	38.4	0.50	q_4, q_9, q_{15}	0.89	0.77	33.9	0.52
q_4, q_9, q_{16}	0.89	0.77	34.1	0.52	q_4, q_9, q_{17}	0.90	0.78	35.2	0.52
q_4, q_9, MR	0.91	0.80	40.5	0.49	q_4, q_{16}, MR	0.89	0.77	33.2	0.53
q_9, q_{10}, MR	0.89	0.77	33.4	0.53					
q_1, q_3, q_8, q_9	0.92	0.82	34.7	0.46	q_1, q_4, q_8, q_9	0.92	0.83	35.4	0.46
q_2, q_6, q_7, MR	0.93	0.83	37.4	0.45	q_3, q_6, q_8, q_9	0.92	0.82	34.8	0.46
q_3, q_8, q_9, q_{11}	0.92	0.82	34.8	0.46	q_3, q_8, q_9, q_{12}	0.92	0.82	35.1	0.46
q_3, q_8, q_9, q_{13}	0.92	0.83	35.4	0.46	q_3, q_8, q_9, q_{15}	0.92	0.82	34.7	0.46
q_3, q_8, q_9, q_{16}	0.92	0.82	34.8	0.46	q_3, q_8, q_9, q_{17}	0.92	0.82	34.8	0.46
q_3, q_8, q_9, MR	0.94	0.86	45.0	0.41	q_3, q_9, q_{11}, MR	0.92	0.83	35.8	0.46
q_3, q_9, q_{14}, MR	0.92	0.82	34.7	0.46	q_4, q_6, q_8, q_9	0.92	0.83	35.8	0.46
q_4, q_8, q_9, q_{11}	0.92	0.83	35.5	0.46	q_4, q_8, q_9, q_{12}	0.92	0.83	35.5	0.46
q_4, q_8, q_9, q_{13}	0.93	0.83	37.6	0.45	q_4, q_8, q_9, q_{15}	0.92	0.83	35.5	0.46
q_4, q_8, q_9, q_{16}	0.93	0.83	35.8	0.46	q_4, q_8, q_9, q_{17}	0.92	0.83	35.4	0.46
q_4, q_8, q_9, MR	0.93	0.84	39.5	0.44	q_8, q_9, q_{10}, MR	0.92	0.82	34.9	0.46
q_1, q_3, q_8, q_9, MR	0.94	0.85	34.9	0.42	q_2, q_6, q_7, q_{12}, MR	0.94	0.86	37.1	0.41
q_3, q_6, q_8, q_9, MR	0.94	0.86	36.1	0.41	q_3, q_8, q_9, q_{11}, MR	0.94	0.86	35.8	0.42
q_3, q_8, q_9, q_{12}, MR	0.94	0.85	34.8	0.42	q_3, q_8, q_9, q_{13}, MR	0.94	0.85	34.5	0.42
q_3, q_8, q_9, q_{15}, MR	0.94	0.86	35.9	0.42	q_3, q_8, q_9, q_{16}, MR	0.94	0.86	37.3	0.41

[a] Selected multivariate relations involving charges of atoms and/or physicochemical variables that are not much intercorrelated ($|r| < 0.5$) and having correlation coefficients higher than those of the best relations involving less number of variables are shown.
[b] df = np, n − np − 1; n = no of data points (=30); np = no of predictor variables.

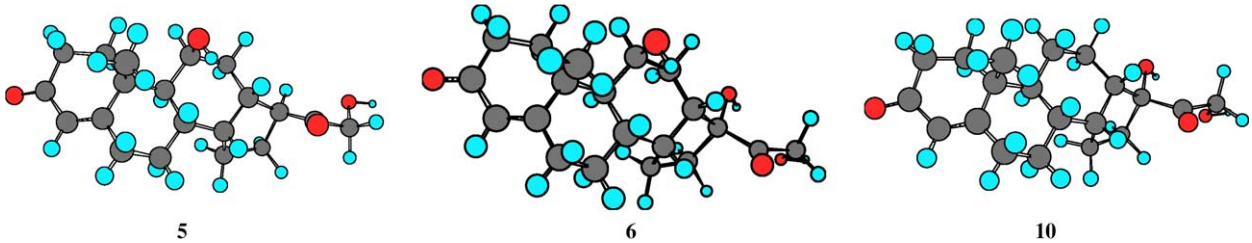


Figure 2. Energy-minimized representations of the most active compounds of the series (**5**, **6**, **10**).

Table 6. Factor loadings of the variables (after VARIMAX rotation)

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7	Factor 8	Factor 9	Factor 10	Communalities
pC	0.823	0.393	0.199	0.059	0.312	−0.031	0.082	0.025	0.268	0.002	0.955
q_1	0.491	−0.092	0.251	−0.165	−0.122	0.620	−0.261	0.291	0.104	−0.169	0.930
q_2	**−0.784**	0.077	−0.155	0.100	0.350	−0.276	0.100	−0.171	−0.240	0.039	0.952
q_3	**0.961**	0.091	0.033	−0.068	0.050	0.040	0.024	−0.067	−0.046	0.112	0.961
q_4	**−0.946**	−0.171	−0.119	0.090	−0.085	−0.045	0.035	0.113	0.036	−0.104	0.982
q_5	**0.897**	0.194	0.171	−0.092	−0.010	0.156	−0.112	−0.135	−0.111	0.107	0.960
q_6	−0.144	−0.123	0.048	0.134	0.183	**−0.883**	0.095	0.148	0.232	−0.111	0.966
q_7	0.520	0.273	0.388	0.218	0.054	0.282	0.031	−0.564	0.121	−0.083	0.966
q_8	−0.211	−0.086	**−0.838**	−0.068	−0.030	−0.047	−0.132	0.084	0.269	0.264	0.928
q_9	0.051	−0.209	0.118	−0.093	0.067	0.148	0.036	0.059	**−0.917**	−0.201	0.982
q_{10}	**−0.845**	0.031	−0.063	0.097	−0.050	−0.152	0.157	0.031	0.426	0.062	0.964
q_{11}	0.211	0.307	−0.230	0.014	−0.147	0.067	0.119	−0.004	0.257	**0.824**	0.977
q_{12}	0.047	0.059	0.072	0.093	**0.965**	−0.166	0.050	−0.015	−0.053	−0.090	0.992
q_{13}	−0.324	0.122	−0.019	−0.198	0.065	−0.136	**0.870**	0.044	−0.023	0.067	0.946
q_{14}	0.177	0.206	**0.931**	−0.047	0.050	0.000	−0.058	−0.032	0.062	0.050	0.956
q_{15}	0.029	−0.178	0.103	**0.880**	0.101	−0.238	−0.080	−0.113	0.030	−0.039	0.905
q_{16}	0.221	0.159	0.053	**−0.907**	−0.028	−0.012	0.149	−0.086	−0.082	−0.011	0.937
q_{17}	−0.382	−0.228	−0.353	0.494	−0.017	0.141	−0.578	0.066	−0.016	0.006	0.926
$\log P$	−0.564	−0.408	−0.145	0.265	−0.026	0.021	0.234	0.394	−0.192	−0.388	0.973
$\log P^2$	−0.623	−0.287	−0.219	0.276	−0.032	0.014	0.213	0.419	−0.110	−0.366	0.962
MR	0.197	**0.918**	0.160	−0.198	0.038	0.043	0.113	−0.067	0.106	0.137	0.997
MR^2	0.200	**0.916**	0.156	−0.209	0.045	0.055	0.096	−0.074	0.106	0.142	0.997
% Variance	0.290	0.117	0.101	0.103	0.053	0.069	0.064	0.040	0.067	0.055	0.960

those for Eq. 7 are 0.782 and 0.856, respectively. This shows that Eq. 5 is statistically more robust than Eq. 7.

Eqs. 6 and 7 signify the importance of atoms 3, 4 and 5 (ring A), 8 and 9 (fusion points between rings B and C) and atom 16 (ring D). The importance of the charge parameters implies possible involvement of electronic interactions of the compounds with the binding site. The relations also signify the importance of different substituents at these positions. The importance of the different atoms of ring A as evidenced from this study corroborates the previous report[2] that the 4, 5 double bond and 3-keto group on ring A are essential for both glucocorticoid and mineralocorticoid activities. Introduction of an additional double bond in the 1,2-positions of ring A selectively increases glucocorticoid action. Further, it is found from the literature[14] that the conformation of the A ring has a pronounced effect on the binding of the steroid to the receptor. The importance of the atoms 8 and 9 in the regression equations is also corroborated by the report[2] that fluorination at the 9α-position of ring B enhances both glucocorticoid and mineralocorticoid activities. Presence of q_{16} in Eqs. 5 and 6 indicates the importance of substituents at ring D. It is found from the literature[14] that 16α-hydroxyl group decreases while 16α-methyl or 16α-fluoro group enhances the corticosteroid activity. Thus, previous SAR studies corroborate the present finding of importance of different atoms or sites of the corticosteroid nucleus for globulin binding affinity. Again, Eq. 7 shows parabolic relation of molar refractivity with an optimum value of 9.272. This is justified from Table 3, where it can be found that the most active three compounds (**5**, **6** and **10**) have MR values near 9.2. This implies that the binding affinity increases with increase in volume of the compounds until a critical value reaches after which the affinity decreases. Involvement of molar refractivity in the final equations suggests possible involvement of dispersion interactions of the corticosteroids with the binding site.

It may be noted here that de Gregorio et al.[10] have modeled the same data set with E-state index and they have found importance of E-state values of atom 4 (ring A), atom 16 (ring D) and atom 10. The best relation (involving three predictor variables) developed by them had squared correlation coefficient of 0.82 ($q^2 = 0.78$). Further, globulin binding affinity of corticosteroids was also modeled by self-organizing map ($r^2 = 0.85$),[9] comparative structurally assigned spectral analysis ($r^2 = 0.80$, $q^2 = 0.73$)[11] and comparative spectral analysis ($r^2 = 0.80$, $q^2 = 0.78$).[11] In our present work, the best model (Eq. 5) could explain and predict to the extent of 87.0% and 82.0%, respectively. This implies that, in the present study, on use of charge parameters, better relations have been obtained (vide Eqs. (3–7) for comparison). Thus, it appears that Wang–Ford charges along with hydrophobicity and/or molar refractivity may be suitable for modeling biological activity values of other classes of steroidal compounds also.

4. Conclusion

MLR models developed in the present study using quantum chemical and physicochemical descriptors indicate the importance of ring A (particularly atoms 3, 4, 5) and ring D (atom 16 in particular) and atoms 8 and 9 of the corticosteroid nucleus for globulin binding affinity. These observations are supported by previous reports on structure–activity relations of corticosteroids. Dispersion interaction appears to be of significant importance for the globulin binding affinity.

Table 7. Results of leave-many-out cross-validation

Sl. no	Globulin binding affinity of corticosteroids				
	Obsd[a]	Predicted from leave-25%-out cross-validation test[b]		Predicted from leave-50%-out cross-validation test[c]	
		Eq. 5[d]	Eq. 7[e]	Eq. 5[f]	Eq. 7[g]
1	5.000	4.661	4.601	4.636	4.624
2	5.000	4.764	5.055	4.873	5.133
3	5.763	6.471	6.384	6.338	6.321
4	5.613	5.081	5.097	5.236	5.071
5	7.881	7.486	7.581	7.569	7.757
6	7.881	7.842	7.689	8.293	8.039
7	6.892	7.184	7.474	7.018	7.254
8	5.000	5.507	5.781	5.562	5.704
9	7.653	7.076	7.123	7.105	7.144
10	7.881	7.362	7.346	7.602	7.553
11	5.919	6.369	6.274	6.268	6.184
12	5.000	5.516	5.443	5.504	5.153
13	5.000	5.081	5.306	4.951	5.313
14	5.000	5.193	4.761	5.145	4.668
15	5.225	4.682	4.644	4.637	4.597
16	5.225	5.933	5.893	5.835	5.779
17	5.000	5.593	5.576	5.314	5.215
18	7.380	6.727	6.952	6.627	6.914
19	7.740	7.320	7.171	7.417	7.229
20	6.724	6.691	6.773	6.675	6.648
21	7.512	7.593	7.447	7.566	7.452
22	7.553	7.655	7.244	7.690	7.201
23	6.779	6.895	7.165	6.744	6.967
24	7.200	7.977	8.087	7.964	7.901
25	6.144	6.090	6.008	6.188	6.136
26	6.247	6.304	7.019	5.900	6.777
27	7.120	6.909	7.069	6.882	6.957
28	6.817	6.617	6.725	6.560	6.729
29	7.688	7.535	7.106	7.557	7.073
30	5.797	6.887	6.850	6.438	6.420

[a] Observed; Ref. 10.
[b] Compounds were deleted in 4 cycles in the following manner: **1**, **5**, **9**, ..., **29**; **2**, **6**, **10**, ..., **30**; ...; **8**, **12**, **16**, ..., **28**.
[c] Compounds were deleted in 2 cycles in the following manner: **1**, **3**, **5**, ..., **29**; **2**, **4**, **6**, ..., **30**.
[d] $Q^2 = 0.822$, PRESS = 6.3.
[e] $Q^2 = 0.782$, PRESS = 7.7.
[f] $Q^2 = 0.864$, PRESS = 4.8.
[g] $Q^2 = 0.856$, PRESS = 5.1.

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