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Topological Descriptors in Modeling Tumor Necrosis Factor alpha Inhibitory Activity of Xanthines, Pteridinediones and Related Compounds

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Abstract

Motivation. Inhibition of tumor necrosis factor alpha (TNF–α) is an important strategy for the treatment of various inflammatory, infectious, immunological, or malignant diseases such as Crohn's disease, rheumatoid arthritis and psoriasis. Therefore, the TNF–α inhibitory activity of xanthines, pteridinediones and related compounds has been analyzed with different topostructural and topochemical indices.

Method. The quantitative structure–activity relationships (QSAR) study was performed using derivatives of xanthines, pteridinediones and related compounds with Dragon 3.0 structural descriptors. The relationship between inhibitory activity and various descriptors is established by step–wise multiple regression analysis using Systat 10.2 and Valstat.

Results. The analyses have generated significant and predictive QSAR models. The values of statistical indices for QSAR with simple topological descriptors is $R = 0.91$, $F = 19.92$, $SEE = 24$ and $R^2_{CV} = 0.68$; for QSAR with more complex topological descriptors is $R = 0.90$, $F = 25.74$, $SEE = 0.23$ and $R^2_{CV} = 0.67$ and for QSAR with mixed classes of descriptors is $R = 0.93$, $F = 25.93$, $SEE = 0.21$ and $R^2_{CV} = 0.73$.

Conclusions. These models suggest that Lopping centric index, fourth order bond information content of neighbourhood symmetry, polarizability and electronegativity weighted Geary graph spatial autocorrelation coefficient of the first lag, atomic masses weighted Moran graph spatial autocorrelation coefficient of the third lag, and average connectivity index χ^1 have a direct correlation with the biological activity. The average valence connectivity index χ^3, electronegativity weighted Geary graph spatial autocorrelation coefficient of the seventh lag, electronegativity weighted Moran graph spatial autocorrelation coefficient of the fifth lag and number of substituted aromatic sp^2 carbon have an inverse correlation with the biological activity.

Keywords. QSAR; tumor necrosis factor alpha; TNF–alpha inhibitor; xanthines; pteridinediones; topological indices.

Abbreviations and notations

IC_{50}, inhibition concentration that reduces the effect by 50%	HMGB1, high morbidity group B1
pIC_{50}, negative logarithmic value of inhibitory concentration (IC_{50})	PLS, partial least squares
QSAR, quantitative structure–activity relationships	TNF–α, Tumor necrosis factor alpha

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1 INTRODUCTION

Tumor necrosis factor alpha (TNF–α) is a proinflammatory cytokine secreted mainly by monocytes and/or macrophages, in response to pathogens or external cellular stress [1–2]. It amplifies and prolongs the inflammatory response by activating other cells to release cytokine such as interleukin–1 (IL–1) and high morbidity group B1 (HMGB1), and mediators such as eicosanoids, nitric oxide, and reactive oxygen species which promote further inflammation and tissue injury [3]. TNF promotes its actions by binding to TNF receptor (TNFR) type 1 and 2 and initiates a series of parallel protein/threonine kinase cascade, which lead to activation of members of the MAP kinase superfamily. It also causes activation of transcriptional factor NFκB that in turn regulates the production of many proinflammatory cytokines and related proteins that are elevated in immunoinflammatory diseases [4]. TNF–α overproduction mediates or exacerbates various diseases (like cachexia and sepsis). Therefore, decreasing TNF–α levels constitute important therapeutic strategies for the treatment of many inflammatory, infectious, immunological, or malignant diseases such as Crohn's disease, rheumatoid arthritis, psoriasis, and inflammatory bowel disease [5–8].

Some novel biological products such as the chimeric tumor necrosis factor–α (TNF–α) antibody infliximab [9], the soluble TNF–α receptor etanercept [10] and interleukin–1 (IL–1)–receptor antagonist anakinra [11], modify proinflammatory cytokines have gained clinical approval. A variety of QSAR approaches have been used in drug design [12–14]. Since there is no quantitative structure activity relationship (QSAR) study reported for xanthines, pteridinediones and related compounds, we have performed the QSAR studies to design powerful TNF–alpha inhibitors.

2 MATERIALS AND METHODS

2.1 Biological Data

The TNF–α inhibition of xanthines, pteriridinediones and thiadiazolo [3,4–*d*] pyrimidines have been reported in terms of inhibitory concentration 50% of enzyme (IC_{50} in μM). The enzyme inhibition data have been converted to negative logarithmic value (concentration in M) and used for subsequent QSAR analyses as response variable. Structures of all compounds studied with their descriptors and TNF–α inhibitory activities have been presented in Table 1 [15].

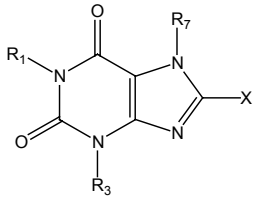
2.2 Molecular Modeling Softwares

All of the Molecular Modeling studies, reported herein were performed running on a Pentium 4 processor (CPU 3.00 GHz HT) using CS Chem Office 6.0.1 (Cambridge soft) [16] and DRAGON 3.0 (Milano Chemometrics) [17].

2.3 Structural Descriptors

Structures of all molecules were constructed in ChemDraw Ultra 6.0 software. Energy of these molecules was minimized CS Chem3D Ultra using molecular mechanics (MM2), then by MOPAC–AM1 (Austin model–1) [18]. The energy minimized molecules obtained from CS Chem3D Ultra, were saved as MDL MolFiles to enable them to be portable to Dragon for computing various classes of molecular descriptors [19–20]. The constitutional, functional groups, atom centered fragments, empirical, molecular walk counts, BCUT descriptors, Galvez topological charge indices, 2D autocorrelations properties, topological descriptors [21] were computed and variable exclusion was done for constant variable and near–constant variable at paired correlation (r = 0.98). As the total number of descriptors involved in the study is about 215 for each set of compounds, only significant descriptors have been given in the discussion. The descriptors present in the model along with definition and class are presented in Table 2 and values of these descriptors for each compound are presented in Table 3.

Table 1. Structural features of all of the compounds studied and their TNF–α inhibitory activity



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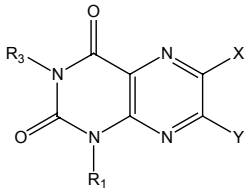

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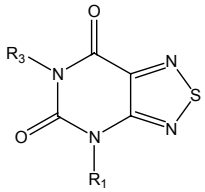

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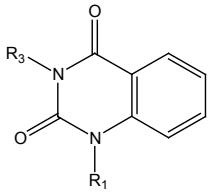

IV

No	Class	R_1	R_3	R_7	X	Y	IC_{50} [a]	pIC_{50} [b]
1	**I**	5–oxohexyl	CH_3	CH_3	H		85	4.071
2	**I**	$CH_2COOC_2H_5$	CH_3	CH_3	H		200	3.699
3	**I**	$(CH_2)_2COOC_2H_5$	CH_3	CH_3	H		10	5.000
4	**I**	$(CH_2)_3COOC_2H_5$	CH_3	CH_3	H		6	5.222
5	**I**	$(CH_2)_4COOC_2H_5$	CH_3	CH_3	H		11	4.959
6	**I**	$(CH_2)_3COOC_2H_5$	CH_3	CH_3	Br		60	4.222
7	**I**	$(CH_2)_3COOC_2H_5$	CH_3	CH_3	SH		100	4.000
8	**I**	n–hexyl	CH_3	H	OH		50	4.301
9	**I**	$(CH_2)_3COOC_2H_5$	n–propyl	CH_3	H		5	5.301
10	**II**	CH_3	$CH_2CH=CHCOOCH_3$		H	H	25	4.602
11	**II**	CH_3	$(CH_2)_3COOC_2H_5$		H	H	12	4.921
12	**II**	n–propyl	$(CH_2)_3COOC_2H_5$		H	H	5	5.301
13	**II**	n–butyl	$(CH_2)_3COOC_2H_5$		H	H	15	4.824
14	**II**	n–pentyl	$(CH_2)_3COOC_2H_5$		H	H	16	4.796
15	**II**	isobutyl	$(CH_2)_3COOC_2H_5$		H	H	20	4.699
16	**II**	THF	$(CH_2)_3COOC_2H_5$		H	H	19	4.721
17	**II**	Benzyl	$(CH_2)_3COOC_2H_5$		H	H	175	3.757
18	**II**	CH_3	$(CH_2)_3COOC_2H_5$		C_2H_5	C_2H_5	130	3.886
19	**III**	CH_3	$(CH_2)_3COOC_2H_5$				25	4.602
20	**III**	n–propyl	$(CH_2)_3COOC_2H_5$				18	4.745
21	**III**	CH_3	n–heptyl				75	4.125
22	**IV**	CH_3	$(CH_2)_3COOC_2H_5$				55	4.260

[a] IC_{50} in μM [Reference 15].
[b] Negative logarithmic value of IC_{50} (in moles) [$pIC_{50} = -\log_{10}IC_{50}$]

Table 2. Definitions and Class of the Molecular Descriptors Used in the QSAR Models

Descriptors	Definition	Class (notation)
Lop	Lopping centric index	Topological descriptors (TOPO)
X3Av	Average valence connectivity index chi–3	Topological descriptors (TOPO)
Jhetv	Balaban–type index from van der Waals weighted distance matrix	Topological descriptors (TOPO)
MATS5e	Moran autocorrelation – lag 5 / weighted by atomic Sanderson electronegativities	2D autocorrelations (2D AUTO)
nCaR	number of substituted aromatic C(sp2)	Functional groups (FUN)
GATS1e	Geary autocorrelation – lag 1 / weighted by atomic Sanderson electronegativities	2D autocorrelations (2D AUTO)
X1A	Average connectivity index chi–1	Topological descriptors (TOPO)
GATS1p	Geary autocorrelation – lag 1 / weighted by atomic polarizabilities	2D Autocorrelations (2D AUTO)
MATS3m	Moran autocorrelation – lag 3 / weighted by atomic masses	2D autocorrelations (2D AUTO)
GATS7e	Geary autocorrelation – lag 7 / weighted by atomic Sanderson electronegativities	2D autocorrelations (2D AUTO)
BIC4	Bond information content (neighborhood symmetry of 4–order)	Topological descriptors (TOPO)
Jhetp	Balaban–type index from polarizability weighted distance matrix	Topological descriptors (TOPO)
D/Dr05	Distance/detour ring index of order 5	Topological descriptors (TOPO)

Table 3. Descriptors of the Compounds from the Statistically Significant Models

No	GATS1p	MATS3m	GATS7e	Lop	X3Av	BIC4	D/Dr05	Jhetp	MATS5e	nCaR	GATS1e	X1A
1	1.481	0.970	1.039	1.818	0.084	0.854	45.706	1.582	–0.282	3	0.669	0.449
2	1.581	0.964	1.465	1.643	0.070	0.850	41.582	1.529	0.145	3	0.763	0.448
3	1.571	0.969	0.698	1.958	0.074	0.854	45.461	1.500	–0.328	3	0.749	0.451
4	1.563	0.974	0.482	1.980	0.078	0.858	49.408	1.471	–0.280	3	0.738	0.453
5	1.556	0.977	0.862	2.133	0.082	0.862	53.415	1.444	–0.333	3	0.73	0.455
6	1.154	0.982	0.319	1.945	0.089	0.858	51.602	1.514	–0.217	4	0.742	0.451
7	1.360	0.977	0.539	1.945	0.095	0.863	51.602	1.514	–0.224	4	0.753	0.451
8	1.414	0.988	1.173	1.848	0.084	0.868	41.935	1.564	0.064	4	0.831	0.453
9	1.551	0.980	0.595	2.102	0.080	0.865	54.413	1.526	–0.296	3	0.723	0.459
10	1.409	0.971	0.478	1.797	0.069	0.869	0.000	1.642	–0.127	3	0.756	0.455
11	1.475	0.982	0.431	1.957	0.076	0.865	0.000	1.508	–0.198	3	0.727	0.457
12	1.473	0.988	0.558	2.075	0.078	0.871	0.000	1.559	–0.229	3	0.709	0.462
13	1.473	0.989	0.775	2.132	0.083	0.873	0.000	1.569	–0.211	3	0.703	0.464
14	1.473	0.991	0.745	2.188	0.087	0.875	0.000	1.570	–0.172	3	0.698	0.465
15	1.473	0.981	0.568	2.053	0.079	0.840	0.000	1.586	–0.185	3	0.703	0.458
16	1.454	0.989	0.716	1.723	0.081	0.884	55.068	1.294	–0.151	3	0.748	0.449
17	1.261	0.986	0.714	1.641	0.079	0.864	0.000	1.344	–0.156	4	0.695	0.452
18	1.473	0.975	0.856	1.996	0.083	0.814	0.000	1.673	–0.141	5	0.698	0.459
19	1.351	0.995	0.419	2.013	0.086	0.859	47.160	1.465	–0.173	3	0.706	0.455
20	1.363	1.000	0.604	2.128	0.087	0.866	52.165	1.513	–0.210	3	0.683	0.461
21	1.318	1.003	1.099	2.038	0.102	0.858	43.554	1.565	–0.044	3	0.621	0.458
22	1.331	0.979	0.319	1.957	0.083	0.873	0.000	1.566	–0.185	3	0.675	0.457

2.4 Multivariate Regression Analysis and Model Development

The relationship between response variable (pC as dependent variables for TNF–α inhibition) and various molecular descriptors (as independent variables) is established by step–wise linear multiple regression analysis using Systat and Valstat [22–23]. Significant descriptors were chosen on the basis of statistical data of analysis. Inter–correlation between these descriptors was checked for independence of the variables. The predictive power of equations were validated by leave one out (*LOO*) cross–validation method, standard deviation based on predicted residual sum of squares (S_{PRESS}) and standard deviation of error of prediction (S_{DEP}).

3 RESULTS AND DISCUSSION

The statistical quality of the developed equations was judged by the parameters like explained variance (*%EV*), correlation coefficient (*r*), standard error of estimate (*s*), *F* test, *LOO* cross–validation r^2 (R^2_{CV}), S_{PRESS} and S_{DEP}. The number of developed equations was high, so further analysis was based on statistical significant parameters, namely *r*, *s*, R^2_{CV}, *F* and maximum limit of inter–correlation among parameters (|*ICAP*|) used in the generation of the QSAR equation. Among several generated models, some statistically significant QSAR models were selected for discussion and summarized in Table 4. Calculated and predicted values of TNF–α inhibitory activities using these models are presented in Table 5.

Table 4. The Data for the Statistically Significant Models [a]

S. No.	*r*	*s*	*F*	R^2_{CV}	S_{PRESS}	S_{DEP}	/*ICAP*/ [b]	Outliers
1	0.91	0.23	19.92	0.68	0.31	0.27	≤0.38	Zero
2	0.90	0.24	18.66	0.66	0.32	0.28	≤0.38	Zero
3	0.90	0.23	25.74	0.67	0.31	0.28	≤0.47	Zero
4	0.93	0.21	25.93	0.73	0.29	0.25	≤0.42	Zero

[a] *Chance* < 0.001, [b] Maximum limit of intercorrelation among the parameters used in the generation of equation

Table 5. Observed, calculated and predicted values of TNF α inhibitory activity

No	Obs. [a]	Cal. [b]	Pred. [c]	Cal. [d]	Pred. [e]	Cal. [f]	Pred. [g]	Cal. [h]	Pred. [i]
1	4.071	4.086	4.088	3.915	3.885	4.044	4.038	4.259	4.356
2	3.699	4.155	4.393	4.012	4.157	3.816	3.928	3.823	3.973
3	5.000	4.907	4.884	4.843	4.815	4.812	4.775	4.967	4.958
4	5.222	4.862	4.806	4.830	4.779	5.158	5.143	4.890	4.842
5	4.959	5.173	5.227	5.192	5.266	4.747	4.722	5.062	5.081
6	4.222	4.293	4.302	4.227	4.228	3.797	3.431	4.220	4.220
7	4.000	4.092	4.118	4.036	4.046	4.294	4.332	4.305	4.378
8	4.301	4.327	4.330	4.159	4.132	4.036	3.965	4.238	4.166
9	5.301	5.221	5.200	5.081	5.051	5.118	5.089	5.136	5.110
10	4.602	4.645	4.659	4.492	4.398	4.430	4.397	4.754	4.774
11	4.921	4.719	4.689	4.850	4.843	5.037	5.052	4.836	4.829
12	5.301	5.029	4.970	5.085	5.048	5.023	4.989	5.046	5.004
13	4.824	4.989	5.031	5.055	5.100	4.789	4.785	5.069	5.130
14	4.796	4.990	5.062	5.075	5.150	4.873	4.884	4.999	5.063
15	4.699	4.528	4.478	4.654	4.643	4.841	4.851	4.706	4.706
16	4.721	4.393	4.243	4.490	4.319	4.778	4.783	4.456	4.406
17	3.757	3.715	3.691	4.070	4.249	3.881	3.911	3.837	3.858
18	3.886	3.863	3.825	3.955	4.050	4.350	4.391	3.726	3.476
19	4.602	4.599	4.599	4.628	4.631	4.838	4.881	4.546	4.542
20	4.745	4.984	5.028	4.908	4.930	4.791	4.802	4.789	4.795
21	4.125	3.930	3.797	3.901	3.741	4.080	4.051	3.869	3.638
22	4.260	4.513	4.563	4.556	4.602	4.481	4.528	4.480	4.506

[a] Observed activity (Obs.) [pC], [b] Calculated (Cal.) and [c] Predicted (Pred.) activity with Eq. (1), [d] Calculated (Cal.) and [e] Predicted activity (Pred.) with Eq. (2), [f] Calculated (Cal.) and [g] Predicted activity (Pred.) with Eq. (3), [h] Calculated (Cal.) and [i] Predicted activity (Pred.) with Eq. (4).

No significant QSAR model was formed out of constitutional, atom centered fragments, empirical, properties, molecular walk counts, BCUT, Galvez topological charge indices class of descriptors. One model was generated from functional groups class of descriptors that showed good

correlation but this model also was not accepted due to poor internal predictivity. Statistically significant and good predictive QSAR models were obtained from simple topological (TOPO) and general index of spatial autocorrelation (2D AUTO) classes of molecular descriptors.

The topological descriptors are molecular descriptors obtained from usually H–depleted molecular graph. These are conformationally independent. Two statistically significant models 1 and 2 were generated that are as follows. Model 1 contains Lop, X3Av, BIC4 and D/Dr05 that is capable to predict 68.2% and explain 90.8% of variance of TNF–α inhibition. The parameters used in this equation are almost independent (Table 6) and the calculated activity using this equation shows a linear relationship with observed activity (Figure 1).

$$\begin{gathered} pIC_{50} = -8.330\ (\pm 6.634) + 2.719\ (\pm 0.749)\ Lop - 44.134\ (\pm 16.435)\ X3Av \\ + 12.813\ (\pm 7.520)\ BIC4 + 0.0052\ (\pm 0.004)\ D/Dr05 \\ n = 22 \quad R = 0.908 \quad \%EV = 82.4 \quad p<0.001 \quad s = 0.229 \quad F = 19.917 \quad R^2_{CV} = 0.682 \\ S_{PRESS} = 0.308 \quad S_{DEP} = 0.271 \quad |ICAP| \leq 0.38 \end{gathered} \tag{1}$$

Table 6. Pearson correlation matrix of parameters used in model 1

	Lop	X3Av	BIC4	D/Dr05
Lop	1.00			
X3Av	0.38	1.00		
BIC4	0.00	0.03	1.00	
D/Dr05	0.06	0.30	0.07	1.00

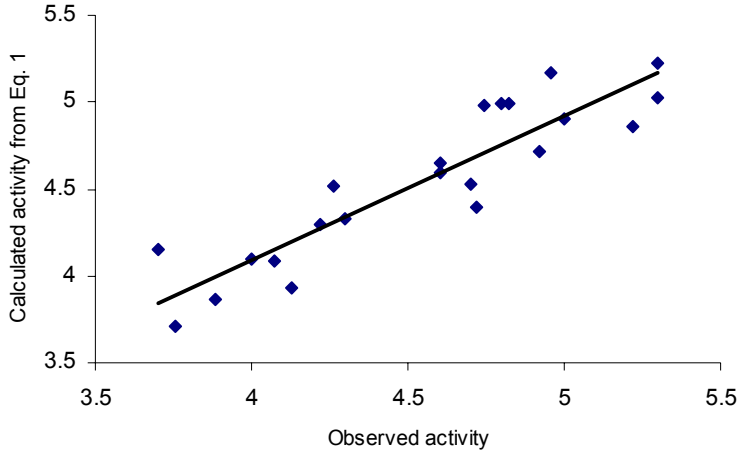

Figure 1. Observed versus Calculated TNF–α inhibitory activity from Eq 1.

The coefficient of the descriptor X3Av bears a negative sign in model 1 which indicates that it is inverse correlated with the activity and the coefficient of the descriptor Lop, BIC4 and D/Dr05 bears a positive sign in model 1 which indicates that it has a direct correlation with the activity.

Model 2 contains Lop, X3Av, BIC4 and Jhetp that is capable to predict 66.4% and explain 90.3% of variance of TNF–α inhibition. The parameters used in this equation are almost independent (Table 7) and the calculated activity using this equation shows a linear relationship

with observed activity (Figure 2).

$$pIC_{50} = -3.393\ (\pm 8.684) + 2.878\ (\pm 0.820)\ Lop - 39.529\ (\pm 15.932)\ X3Av + 9.230\ (\pm 8.727)\ BIC4 - 1.571\ (\pm 1.549)\ Jhetp$$
$$n = 22 \quad R = 0.903 \quad \%EV = 81.5 \quad p<0.001 \quad s = 0.235 \quad F = 18.663 \quad R^2_{CV} = 0.664 \qquad (2)$$
$$S_{PRESS} = 0.317 \quad S_{DEP} = 0.279 \quad /ICAP/ \leq 0.38$$

Table 7. Pearson correlation matrix of parameters used in model 2

	Lop	X3Av	BIC4	Jhetp
Lop	1.00			
X3Av	0.38	1.00		
BIC4	0.00	0.03	1.00	
Jhetp	0.34	0.03	0.44	1.00

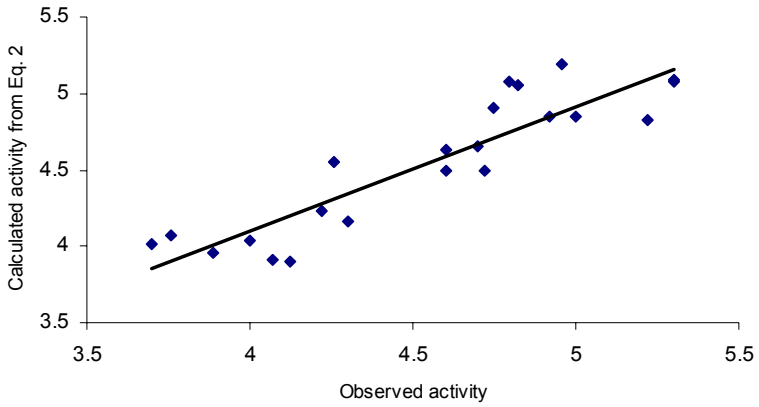

Figure 2. Observed versus Calculated TNF–α inhibitory activity from Eq 2.

The coefficient of the descriptor X3Av and Jhetp bears a negative sign in model 2 which indicates that it is inverse correlated with the activity and the coefficient of the descriptor Lop and BIC4 bears a positive sign in model 2 which indicates that it has a direct correlation with the activity.

The Lop is derived from the pruning partition of a graph, Valence connectivity indices are calculated in a unique manner from the valence vertex degree δ^v of the atoms in the H depleted molecular graph. The bonding information content BIC4 accounts the number of the 4 bonds and their multiplicity. D/Dr05 (distance/detour ring index of order 5) is calculation of some local and graph invariants that is related to cyclicity of the molecule. Another topological descriptor is the Balaban–type index from polarizability weighted distance matrix in order to account for both bond multiplicity and heteroatoms.

The 2DAUTO are molecular descriptors calculated from molecular graph by summing the products of atom weights of the terminal atoms of all the paths of the considered path length (the lag). In 2DAUTO class, MATS is Moran Autocorrelation of Topological Structure and GATS is Geary Autocorrelation of Topological Structure. In these descriptors k indicates the path length

(lag) in the graph, and the w corresponds to atomic property used to weight the graph. [24] Here graph lengths 3, 7, and 1 in association with atomic properties namely masses (m), Sanderson electronegativities (e) and polarizabilities (p), respectively, have shown significance in correlating the activity in model 3.

General index of spatial autocorrelation by Moran (MATS) and Geary (GATS) algorithms are calculated from lag 1 to lag 8 for 4 different weighting atomic properties masses (m), van der Waals volumes (v), polarizabilities (p) and Sanderson electronegativities (e).

$$\begin{gathered} pIC_{50} = -24.738\ (\pm 12.606) + 4.280\ (\pm 1.177)\ GATS1p + 24.416\ (\pm 11.973)\ MATS3m \\ - 1.194\ (\pm\ 0.392)\ GATS7e \\ n = 22 \quad R = 0.901 \quad \%EV = 81.1 \quad p<0.001 \quad s = 0.231 \quad F = 25.742 \quad R^2_{CV} = 0.667 \\ S_{PRESS} = 0.306 \quad S_{DEP} = 0.277 \quad /ICAP/ \leq 0.47 \end{gathered} \tag{3}$$

Eq 3 is capable to predict 66.7% and explain 90.1% of variance of TNF α inhibition. Calculated activity using this equation shows a linear relationship with observed activity (Figure 3). The parameters used in the equation are almost independent (Table 8). The coefficient of the descriptors GATS1p and MATS3m have positive signs in model 3 which indicates that it has a direct correlation with the activity and coefficient of the descriptors GATS7e bears a negative sign in model 3 which indicates that it has an inverse correlation with the activity.

Table 8. Pearson correlation matrix of parameters used in model 3

	GATS1p	MATS3m	GATS7e
GATS1p	1.00		
MATS3m	0.47	1.00	
GATS7e	0.35	0.12	1.00

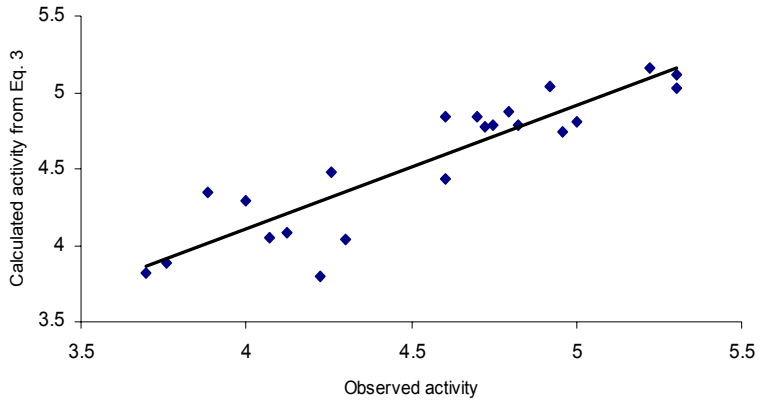

Figure 3. Observed versus Calculated TNF–α inhibitory activity from Eq 3.

When other relationships were searched with the descriptors obtained from all classes, a highly significant equation containing MATS5e, nCaR, GATS1e and X1A was found which is able to explain 92.7% of variance of TNF–α inhibition. The activity calculated using this equation shows a linear relationship with the experimental activity (Figure 4).

$$pIC_{50} = -21.941\ (\pm\ 10.671) - 2.286\ (\pm\ 0.866)\ MATS5e - 0.449\ (\pm 0.178)\ nCaR + 6.275\ (\pm\ 2.560)\ GATS1e + 50.564\ (\pm\ 21.485)\ X1A$$
$$n = 22 \quad R = 0.927 \quad \%EV = 85.9 \quad p<0.001 \quad s = 0.205 \quad F = 25.930 \quad R^2_{CV} = 0.727$$
$$S_{PRESS} = 0.285 \quad S_{DEP} = 0.251 \quad |ICAP| \leq 0.42 \qquad (4)$$

Table 9. Pearson correlation matrix of parameters used in model 4

	MATS5e	nCaR	GATS1e	X1A
MATS5e	1.00			
nCaR	0.19	1.00		
GATS1e	0.25	0.21	1.00	
X1A	0.17	0.15	0.42	1.00

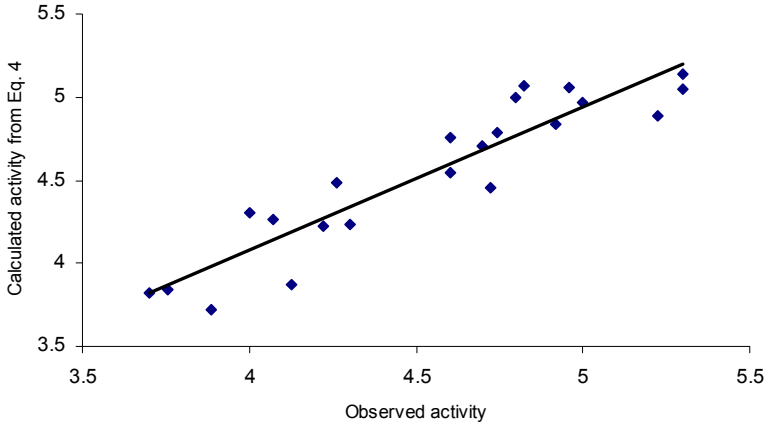

Figure 4. Observed versus Calculated TNF–α inhibitory activity from Eq 4.

MATS5e is the electronegativities–weighted Geary graph spatial autocorrelation coefficient of the fifth lag and GATS1e is the electronegativities–weighted Geary graph spatial autocorrelation coefficient of the first lag, nCaR is number of substituted aromatic carbon in the molecule, and X1A is first order chi in terms of average connectivity index.

This equation is having high internal predictivity as shown by good R^2_{CV} value of 0.727. The parameters used in the equation are almost independent (Table 9). The coefficient of the descriptor MATS5e and nCaR bears a negative sign in model 4 which indicates that it has an inverse correlation with the activity, and the coefficient of the descriptor GATS1e and X1A bears a positive sign in model 4 which indicates that it has a direct correlation with the biological activity.

4 CONCLUSIONS

In the present investigation, QSAR study was performed using derivatives of xanthines, pteridinediones and related compounds using Dragon 3.0. The relationship between inhibitory activity and various descriptors is established by step–wise multiple regression analysis using Systat

10.2 and Valstat.

The analyses have generated significant and predictive QSAR models. The values of statistical data with simple topological descriptors is R = 0.91, F = 19.92, SEE = 24 and R^2_{CV} = 0.68; with more complex topological descriptors is R = 0.90, F = 25.74, SEE = 0.23 and R^2_{CV} = 0.67 and mixed classes of descriptors is R = 0.93, F = 25.93, SEE = 0.21 and R^2_{CV} = 0.73.

The regression analysis of activity with simple topological (TOPO), more complex topological (2D AUTO) and mixed classes of descriptors produced statistically significant and good predictive QSAR models. These QSAR models suggest that Lopping centric index, fourth order bond information content of neighbourhood symmetry, polarizability and electronegativity weighted Geary graph spatial autocorrelation coefficient of the first lag, atomic masses weighted Moran graph spatial autocorrelation coefficient of the third lag, and average connectivity index χ^1 have a direct correlation with the biological activity. The average valence connectivity index χ^3, electronegativity weighted Geary graph spatial autocorrelation coefficient of the seventh lag, electronegativity weighted Moran graph spatial autocorrelation coefficient of the fifth lag and number of substituted aromatic sp^2 carbon have an inverse correlation with the biological activity. Thus these studies bring a structural insight to aid design of potent TNF–α inhibitors.

Supplementary Material

The molecular files for all compounds used in QSAR models can be found in the supplementary material.

5 REFERENCES

[1] J. Vilcek, and T. H. Lee, Tumor Necrosis Factor, new insights into the molecular mechanisms of its multiple action, *J. Biol. Chem*. **1991**, *266*, 7313–7316.
[2] R. M. Locksley, N. Killeen, and M. J. Lenardo, The TNF and TNF Receptor Review Superfamilies: Integrating Mammalian Biology, *Cell* **2001**, *104*, 487–501.
[3] K. J. Tarcey, The inflammatory reflex, *Nature*, **2002**, *420*, 853–859.
[4] J. F. Cheng, M. Chen, D. Wallace, S. Tith,; T. Arrhenius, H. Kashiwagi, Y. Ono, A. Ishikawa, H. Sato, T. Kozono, H. Sato, and A.M. Nadzan, Discovery and structure–activity relationship of coumarin derivatives as TNF–α inhibitors *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2411–2515.
[5] H. M. Van Dulleman, S. J. H. Van Deventer, D. W. Hommes, H. A. Bijl, J. Jansen, G. N. Tytget, and J. Woody, Treatment of Crohn's Disease with Antitumor Necrosis Factor Chimeric Monoclonal Antibody (cA2), *Gastroenterology* **1995**, *109*, 129–135.
[6] S. Miwatashi, Y. Arikawa, E. Kotani, M. Miyamoto, K. Naruo, H. Kimura, T. Tanaka, S. Asahi, and S. Ohkawa, Novel Inhibitor of p38 MAP Kinase as an Anti–TNF–α Drug: Discovery of N–[4–[2–Ethyl–4–(3–methylphenyl)–1,3–thiazol–5–yl]–2–pyridyl]benzamide (TAK–715) as a Potent and Orally Active Anti–Rheumatoid Arthritis Agent *J. Med. Chem*. **2005**, *48*, 5966–5979.
[7] L. Kincaid, Psoriasis:TNF–α inhibitors and beyond, *Drug Discov. Today* **2005**, *10*, 884–886.
[8] D. A. van Heel, I. A. Udalova, A. P. De Silva, D. P. McGovern, Y. Kinouchi, J. Hull, N. J. Lench, L. R. Cardon, A. H. Carey, D. P. Jewell and D. Kwiatkowski, Inflammatory bowel disease is associated with a TNF polymorphism that affects an interaction between the OCT1 and NF–B transcription factors, *Human Molecular Genetics*, **2002**, *11*, 1281–1289.
[9] M. J. Elliott, R. N. Maini, M. Feldmann, J. R. Kalden, C. Antoni, J. S. Smolen, B. Leeb, F. C. Breedveld, J. D. Macfarlane, H. Bijl, and J. N. Woody, Randomised Double–Blind Comparison of Chimeric Monoclonal Antibody to Tumour Necrosis Factor R (cA2) versus Placebo in Rheumatoid Arthritis. *Lancet* **1994**, *344*, 1105–1110.
[10] L. W. Moreland, S. W. Baumgartner, M. H. Schiff, E. A. Tindall, R. M. Fleischmann, A. L. Weaver, R. E. Ettlinger, S. Cohen, W. J. Koopman, K. Mohler, M. B. Widmer, and C. M. Blosch, Treatment of Rheumatoid

Arthritis with a Recombinant Human Tumor Necrosis Factor Receptor (p75)–Fc Fusion Protein, *N. Engl. J. Med.* **1997**, *337*, 141–147.
[11] B. Bresnihan, The Prospect of Treating Rheumatoid Arthritis with Recombinant Human Interleukin–1 Receptor Antagonist, *BioDrugs BioDrugs* **2001**, *15*, 87–97.
[12] M. Vracko and J. Gasteiger, A. QSAR Study on a Set of 105 Flavonoid Derivatives Using Descriptors Derived From 3D Structures, *Internet Electron. J. Mol. Des.* **2002**, *1*, 527–544, http://www.biochempress.com.
[13] A. V. Raichurkar and V. M. Kulkarni, 3D–QSAR of Cyclooxygenase–2 Inhibitors by Genetic Function Approximation, *Internet Electron. J. Mol. Des.* **2003**, *2*, 242–261, http://www.biochempress.com.
[14] S. M. Vadlamudi and V. M. Kulkarni, 3D–QSAR of Protein Tyrosine Phosphatase 1B Inhibitors by Genetic Function Approximation, *Internet Electron. J. Mol. Des.* **2004**, *3*, 586–609, http://www.biochempress.com.
[15] H. B. Cottam, H. Shih, L. R. Tehrani, D. B. Wasson, and D. A. Carson, Substituted xanthines, pteridinediones, and related compounds as potential antiinflammatory agents. Synthesis and biological evaluation of inhibitors of tumor necrosis factor alpha, *J. Med. Chem.* **1996**, *39*, 02–09.
[16] CS Chem Office, Version 6.0, Cambridge Soft Corporation, Washington D.C. USA.
[17] DRAGON Software (Version 3.0 – 2003), by R. Todeschini, V. Consonni, A. Mauri and M. Pawan, Milano Chemometrics, Italy.
[18] L. B. Kier, Molecular Orbital Theory in Drug Research, Academic Press, New York, 1971, pp 1–62.
[19] H. K. Jain and R. K. Agrawal, QSAR analysis of indomethacin derivatives as selective COX–2 inhibitors, *Internet Electron. J. Mol. Des.* **2006**, *5*, 224–236, http://www.biochempress.com.
[20] H. K. Jain and R. K. Agrawal, Inhibitory mode of 2–acetoxyphenyl alkyl sulfides against COX–1 and COX–2: QSAR analyses, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5280–5284.
[21] R. Todeschini and V. Consonni, Handbook of molecular descriptors, Wiley–VCH Verlag GmbH, Weinheim, Germany.
[22] SYSTAT, Instruction Manual, University of Waterloo, Department of Statistics and Actuarial Science, September 1, 1998.
[23] A. K. Gupta, M. A. Babu and S. G. Kaskhedikar, VALSTAT: Validation program for Quantitative Structure Activity Relationships Studies, *Indian J. Pharm. Sci.* **2004**, *66*, 396–402.
[24] M. K. Gupta and Y. S. Prabhakar, Topological descriptors in modeling the antimalarial activity of 4–(3',5'–disubstituted anilino)quinolines, *J. Chem. Inf. Model.* **2006**, *46*, 93–102.

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