RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.2, No.2 (2009), 456-463
ISSN: 0974-1496
CODEN: RJCABP

QSAR STUDY OF TRISUBSTITUTED THIAZOLIDINONES AS CCR4 ANTAGONISTS

V. Shanthi[1], Satya Parmeshwar[2] and T. Parthasarathy[1*]
[1]Department of Chemistry, Nizam College,
Osmania University, Hyderabad, Andhra Pradesh, India.
[2]A.P. State Council of Higher Education, Hyderabad Andhra Pradesh, India.
*E-mail: sarathychem@gmail.com

ABSTRACT

CCR4 is selectively expressed on Th2-type CD4+ T-cells, which play a pivotal role in driving the allergic inflammation response . CCR4 antagonists are used for the treatment of allergic inflammation .Substituted thiazolidinones were identified as CCR4 antagonists from high throughput screening ,The lead optimization has been carried out by Quantitative Structure Activity Relationship(QSAR) studies .The biological activity is found to be linearly related to QlogP and σ_I.

Keywords: Allergic inflammation diseases; Antihistamines; Bronchodilators; CCR4; T-Cell migration; Biological activity; Combinatorial & Parallel synthesis.

INTRODUCTION

Allergic inflammation diseases, such as asthma, atopic dermatitis and allergic rhinitis are increasing in prevalence in the world and represent significant health care expenses. Asthma affects greater than 15 million people in the US[1] and although less serious, approximately 15 million people are affected by atopic dermatitis and allergic rhinitis[2]. Current treatments for allergic inflammation include antihistamines and bronchodilators, which control symptoms but not disease progression, in addition to corticosteroids which specifically target the disease but present certain safety concerns. There is a need for novel therapies that provide safe and effective treatments for these diseases. CCR4 belongs to a family of CC chemokine receptors which act through G-protein-coupled receptors with a characteristic seven-transmembrane structure. CCR4 is selectively expressed on Th2-type $CD4^+$ T-cells, which play a pivotal role in driving the allergic inflammation response. There are two ligands which bind CCR4 exclusively[3] with high affinity: Macrophage Derived Chemokine (MDC; MW=8081 Daltons; K_d=120pM), Thymus and Activation Regulated Chemokine (TARC; MW=8083 Daltons; K_d=400pM). It has been demonstrated that antagonism of MDC or TARC can reduce the migration of T-cells into sites of inflammation, positioning that CCR4 antagonists may be effective therapeutics for the treatment of allergic inflammation[4].

The use of small heterocyclic rings has become very important to medicinal chemists since they act as rigid cores which can be readily prepared and functionalized to serve as peptidomimetics and thus exhibit wide ranging biological activity. Thiazolidinones exhibit interesting biological activity profile as anti-inflammatories[5], anti-bacterials[6] and anti-histamines[7].

This report focuses to discover novel, selective, small molecule CCR4 antagonists, subsequent validation and such antagonists half T-cell migration by QSAR studies.

EXPERIMENTAL

Computational Methods

(a) Molecular 2D Structure Building

The data set consists of a series of Trisubstituted thiazolidnones analogues (Table-1 to Table-3) which were demonstrated to be as specific inhibitors of CCR4 receptor. The IC_{50} for inhibition of CCR4 inhibitors[8] were converted to activity, (log $1/IC_{50}$) values and used as dependent variable in the QSAR analysis. The program of Window ChemSoftware Inc was used for molecular studies. The molecules were generated and energy was minimized using Molecular Modeling Pro. The windows version software[9]SPSS 10.0 was used in Regression Analysis.

(b) Building of QSAR models

The aim of QSAR studies is to best correlate the physicochemical properties and structural features of a set of the congeners with observed biological responses. QSAR technique was applied to a series of Trisubstituted thiazolidinones analogues obtained by introducing structural modifications in the benzene ring (Fig-1). Appropriate descriptors or parameters for the compounds, QLogP and MR were correlated to the observed immunomodulatory activity and were used as explanatory variables in the multiple regression analysis. The regression models are the QSAR molecular models that are used to predict and design a compound with the best possible immunomodulator activity.

(c) Chemical descriptors

(i) Lipophilic Parameter (QlogP):

The lipophilic factor P is the most used property where P is defined by 1-Octonol/water partition coefficient. All the QLogP values used were calculated as per Bodor and Buchwald method[10] ChemSW.

(ii) Steric Parameter (MR):

The Molar Refractivity (MR) is the molar volume corrected by the refractive index. It represents size and polarisability of a fragment or molecule. These values were generated using ChemSW software.

iii) Electronic Parameter (σ):

The electronic substituent constants were calculated. The electronic effect, σ provides a clue to the substituent effects as correlated to the maximal activity on the basis of electron releasing or electron withdrawing property of the substituents. Positive values correspond to electron withdrawals and negative to the electron release by the substituents .Electronic effects of substitution at meta and para are σ_m, σ_p respectively. Taft's polar substituent, σ_s , is exclusively applicable for aliphatic substituents and σ_i describes the only the polar effects of the substituents.

(d) Correlation Analysis:

Relationship between immunomodulatory activity, expressed as $-\log 1/IC_{50}$ and physicochemical parameters Xi, (QLogP and MR) were analyzed statistically by fitting the data to correlation equations consisting of various combinations of these parameters.

Table-1: Activity and Physico-chemical Parameters of Trisubstituted Thiazolidinone analogues

Compd. No.	R	Activity ($-\log IC_{50}$ (iM)	MR	QLogP	σ_i
*1	4-Cl-Phenyl	3.0809	162.3719	3.2512	0.2880
7	4-F-Phenil	2.3979	157.7835	2.9864	0.2880
8	2-Cl-Phenyl	1.9586	162.3719	3.2662	0.3130
9	3-Cl-Phenyl	2.1549	162.3719	3.2662	0.2850
10	3-CF3-Phenyl	1.9207	163.5408	3.7445	0.2850
11	3,4-di-Cl-Phenyl	1.6030	167.1767	3.7040	0.3050
12	3,5-di-Cl-Phenyl	2.0458	167.1767	3.6992	0.3020
13	2,3-di-Cl-Phenyl	1.7443	167.1767	3.7049	0.3300
14	2,5-di-Cl-Phenyl	1.9207	167.1767	3.7058	0.3300
15	2,6-di-Cl-Phenyl	2.0970	167.1767	3.6978	0.3580
*16	2,4-di-Cl-Phenyl	3.1610	167.1767	3.6956	0.3330
17	2,4-di-MeO-Phenyl	1.4815	170.4935	2.8742	0.2730
*18	2,4-di-CF3-Phenyl	1.0000	169.5145	4.6536	0.3330
*19	2,4-di-F-Phenyl	3.0000	157.9999	3.1435	0.3520
20	2,4-di-Me-Phenyl	1.9586	167.6495	3.7938	0.2820
*21	2-Cl, 4-F-Phenyl	3.0000	162.5883	3.4341	0.3330
22	2-Thienyl	1.4815	155.5102	2.6066	0.3770

23	3-Thienyl	1.1805	156.4487	2.6097	0.3050
24	2-Furyl	1.5366	149.0669	1.6036	0.2970
25	3-Furyl	1.0000	150.0054	1.6062	0.3050
26	4-Pyridyl	1.4685	155.1970	1.2626	0.2880
27	Benzyl	1.0000	166.5711	3.3151	0.1280
28	Phenethyl	1.0000	167.0335	3.7798	0.0190
29	Cyclohexyl	1.0000	158.7547	3.2084	0.0370

*Indicates outliers (which are removed in regression analysis)

$$\textbf{-Log } IC_{50} = aiXi + constant$$

Where, **ai** is the correlation coefficient

Xi is the physicochemical parameter

The statistical optimization is used to propose the best correlation model. The correlation coefficient, σi for each term was determined by least square method. The pharmacophore with best possible inhibitory activity was predicted using the modeled equations.

Table-2: Correlation matrix between activity and physico-chemical parameters
(For 24 analogues)

		ACTIVITY	MR	QLOGP	σi
ACTIVITY	Pearson Correlation	1.000	0.112	0.198	0473*
	Sig. (2-tailed		0.601	0.353	0.020
	N	24	24	24	24
MR	Pearson Correlation	0.112	1.000	.844**	-0.083
	Sig. (2-tailed	0.601		0.000	0.698
	N	24	24	24	24
QLOGP	Pearson Correlation	0.198	.844**	1.000	-0.057
	Sig. (2-tailed	0.353	0.000		0.792
	N	24	24	24	24
σi	Pearson Correlation	473*	-0.083	-0.057	1.000
	Sig. (2-tailed	0.020	0.698	0.792	
	N	24	24	24	24

***** Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-taile

Table-3: Correlation matrix between activity and physico-chemical parameters
(For 19 analogues)

		ACTIVITY	MR	QLOGP	σi
ACTIVITY	Pearson Correlation	1.000	0.272	0.359	0586**
	Sig. (2-tailed		0.259	0.132	0.008
	N	19	19	19	19
MR	Pearson Correlation	0.272	1.000	.846**	-.128
	Sig. (2-tailed	0.259		0.000	.602
	N	19	19	19	19
QLOGP	Pearson Correlation	0.359	.846**	1.000	-.164
	Sig. (2-tailed	0.132	0.000		0.503
	N	19	19	19	19
σi	Pearson Correlation	586**	-.128	-0.164	1.000
	Sig. (2-tailed	0.008	0.602	0.503	
	N	19	19	19	19

** Correlation is significant at the 0.01 level (2-tailed)

RESULTS AND DISCUSSIONS

The biological activity data and the physicochemical properties QlogP and σi of trisubstituted thiazolidinones analogues are given in Table.1. The data from Table 1 were subjected to regression analysis. Correlation matrix was generated with 24 analogues. The correlation terms involved in the correlation matrix (Table 2) indicate the extent of co-linearity. The term close to 1 indicates high co-linearity, while the value below 0.5 indicates that no co-linearity exists between the two parameters. The perusal of correlation matrix (Table 3) indicates that QlogP and sigma induction (σi) are the predicted parameters.

In the initial stage, mono-parametric QSAR equations were generated with QlogP, MR and σi individually. It is interesting to record that R^2_A (adjusted) values take into account the adjustment of % EV. Therefore, if a variable is added which does not contribute its fair share, and then the R^2_A value will actually decline. It is observed that the equation with MR and σi and the equation with QlogP and σi both are giving better results. By the addition of σi with QlogP, R^2_A increased which also supports the bivariant dependence of biological activity. Hence, multiple regressions have been sought[11]. The regression technique was applied through the origin using these explainable parameters. The resulted modeled equations explain the biological activity as a function of QlogP and σi. Hence, on carrying out regression with QlogP and σi, the correlation equation was obtained as:

Act = 0.229 (0.098) QLogP + 3.932 (1.087) σi (5)
N = 24; R = 0.956; %EV = 91.3; SEE = 0.604568; F = 115.433

Where N is the number of data points, R is the regression constant, %EV is the percentage of explained variance, SEE is the standard error estimation, and F is the F ratio. Eq. 5 shows that the value of %EV is 91.3 and to improve its value, outliers were sought and eliminated. In addition, the plot of observed activity versus predicted activity was not found satisfactory. Hence, the predictive ability of the model was not good. After the elimination of outliers (Compounds 1, 16, 18, 19 and 21), a final model was developed.

Act = 0.264 (0.050) QLogP + 3.040 (0.560) σi (6)
N = 19; R = 0.985; %EV = 97.1; SEE = 0.303509; F = 284.275

It is found to be improved model since it explains the biological activity to the extent of 97.1%. In this way, the predictive molecular descriptors QlogP and ó$_i$ were taken as variables and different regression models (Table 4) were generated in a phased manner after eliminating outliers. Overall, there is an increase in R (0.956-0.985) and %EV (91.3-97.1) values, and a decrease in SEE (0.604568-0.303509) and the F value increases from 115.433 to 284.275. These trends support the statistic validity[11] of Eq. 6 (Table 4). In an attempt to investigate the predictive potential of proposed models, the cross-validation parameters (q^2_{cv} and PRESS) were calculated and used. The predictive power of the equations was confirmed by leave-one-out (LOO) cross-validation method[12] where, compounds are deleted one after another and prediction of the activity of the deleted compounds is made based on the QSAR model. Cross-validation evaluates the validity of a model by how well it fits the data. The cross-validation parameter, q^2_{cv}, is mentioned in the respective equation.

$$\mathbf{q^2_{cv} = (SD\text{-}PRESS) / SD,}$$

Where the PRESS (predictive residual sum of squares) and SD (standard deviation) values are obtained as

$$\mathbf{PRESS = (property_{observed} - property_{predicted})^2,}$$
$$\mathbf{SD = (property_{observed} - property_{mean})^2,}$$

Eq. 6 gives a good q^2_{cv} value, which should be always smaller than %EV. A model is considered to be significant when $q^2_{cv} > 0.3$. Another cross-validation parameter, PRESS which is the sum of the

squared differences between the actual and that predicted when the compound is omitted from the fitting process, also supports the predictive ability of Eq. 6 and its value decreases from Eq. 5 to Eq. 6 (8.0412 – 1.5662).

The quality factor Q, is defined as the ratio of regression constant to the standard error estimation (SEE), that is, Q = R/SEE. This indicates that the higher the value of R, and lower the value of SEE, the higher is the magnitude of Q and the better will be the correlation. In present case, Q increases from 1.58129 to 3.2453 (Table 4).

Table-4: Modeled equations generated for the Trisubstituted Thiazolidinone analogues

Eq.	Modeled Equation	n	R	%EV	SEE	F
1	Act=6.286 (0.458) $ó_i$ Q=1.42782; PRESS=10.0537; q^2_{cv}=0.09030	24	0.944	0.891	0.661146	188.440
	Act=0.554 (0.0.046) QLogP Q=1.2429; PRESS=12.8205; q^2_{cv}=0.16004	24	0.928	0.861	0.746600	142.808
	Act=1.134*10^{-2} (0.001) MR Q=1.36314; PRESS=10.9136; q^2_{cv}=0.01249	24	0.939	0.882	0.688848	171.776
	Act=5.199*10^{-3} (0.003) MR+3.556(1.406) $ó_i$ Q=1.53732; PRESS=8.3889; q^2_{cv}=0.23502	24	0.953	0.909	0.619909	109.253
	Act=0.229(0.098) QLogP+3.932(1.087) $ó_i$ Q=1.58129; PRESS=8.0412; q^2_{cv}=0.27240	24	0.956	0.913	0.604568	115.433
	Act=0.264(0.050) QLogP+3.040(0.560) $ó_i$ Q=3.2453; PRESS=1.5662; q^2_{cv}=0.555473	**19**	**0.985**	**0.971**	**0.303509**	**284.275**

n=Number of data points; SEE = standard error estimate; Q=Quality factor;
R = Regression coefficient; %EV=percentage of explained variance;
PRESS =Predictive sum of squares; q^2_{cv} = cross-validated.

The predictive ability of the modeled Eq. 6 is reflected in the low residual values (Table 5). The excellent agreement between the observed activity versus predicted activity is shown in the Figure 4. The linear relationship between activity and Qlog p is shown in fig 2.It indicates that as Qlog p increases ,the activity also increases which is evident from the data (Table 1).This implies that as the hydrophobicity of substituent (R) increases the activity also increases. So, the compound with high lipophilic nature is expected to exhibit high activity. The compounds 11 – 15,with high lipophilicity showed more efficacy .The electronic parameter, σi is similarly enhancing trisubstituted thiazolidinones activity as is evidenced from the fig 3. Small electron withdrawing groups are generally well tolerated , particularly halogens ,whereas the introduction of electron donating group led to much lower potencies even with the preferred substitution pattern. Incorporation of heterocycles (compounds 22 – 26) were detrimental to affinity while removal of aromaticity (compound 29) or homologation (compounds 27,28) led to a complete loss of activity.

Table-5: Observed and Predicted activity values of Trisubstituted Thiazolidinone analogues. (Model equation-6)

Compd. No.	Observed	Predicted Activity	Residual value
7	2.3979	1.6639	.7340
8	1.9586	1.8138	.1448
9	2.1549	1.7287	.4262
10	1.9207	1.8550	.0657
11	1.6030	1.9051	-.3021

12	2.0458	1.8947	.1511
13	1.7443	1.9813	-.2370
14	1.9207	1.9815	-.0609
15	2.0970	2.0645	.0325
17	1.4815	1.5887	-.1072
20	1.9586	1.8588	.0998
22	1.4815	1.8342	-.3527
23	1.1805	1.6162	-.4357
24	1.5366	1.3262	.2104
25	1.0000	1.3512	.3512
26	1.4685	1.2088	.2597
27	1.0000	1.2643	-.2643
28	1.0000	1.0556	-.0556
29	1.0000	.9595	.0405

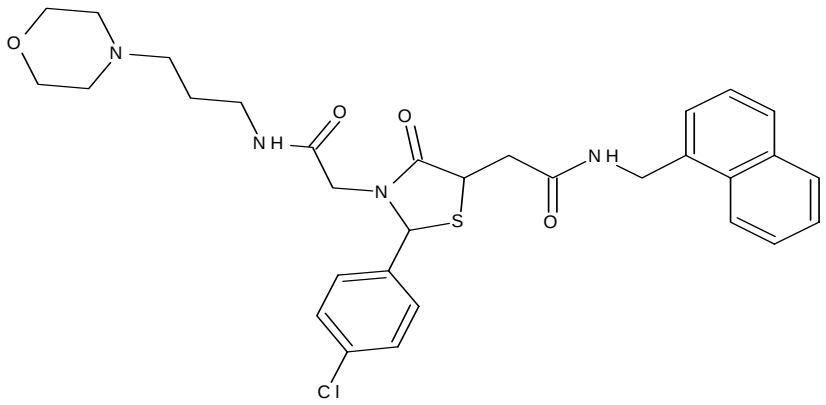

Fig.-1: CCR4 antagonist screening hit

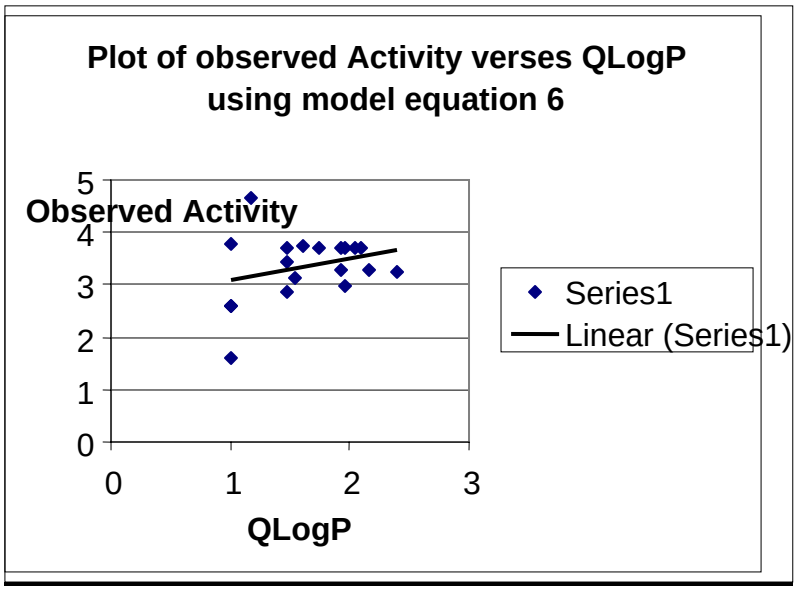

Fig.-2

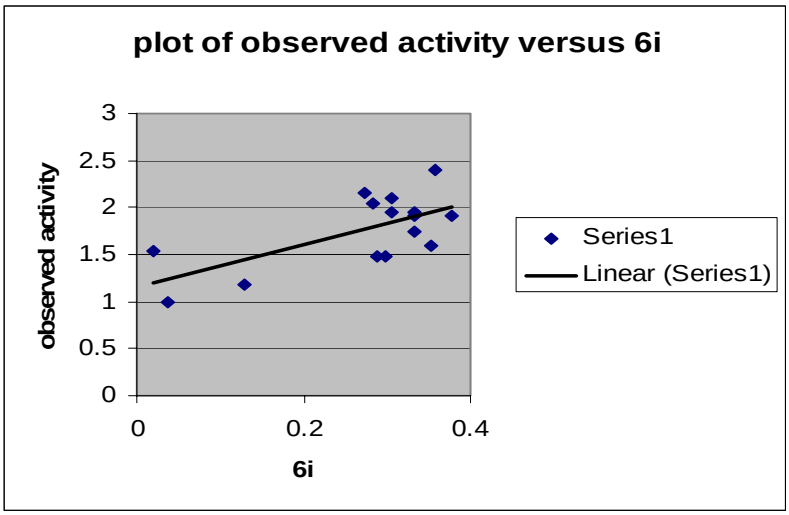

Fig.-3

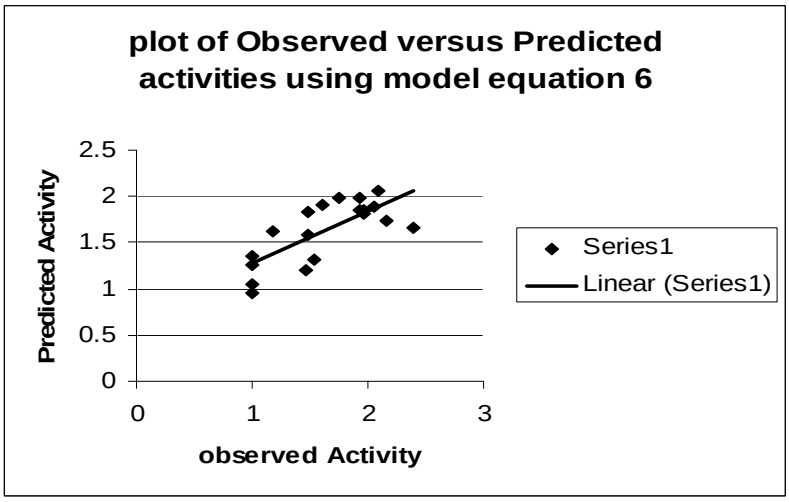

Fig.- 4

ACKNOWLEDGEMENTS

One of the authors (V.S.) is thankful to The Head, Department of Chemistry, Nizam College, Osmania University, for providing the facilities for the research work.

REFERENCES

1. P.J. Barnes, B. Jonsson and J.B. Klim. J.B. *Eurf. Respir. J.*, **9**, 636, (1996).
2. R. Beasley. *Lancer,* **351**, 1225, (1998).
3. Y. Chvatchko, A.J. Hoogewerf, A. Meyer, S. Alouani, P. Juillard, R. Buser, F. Conquet, A.E. Proudfoot, T.N. Wells and C.A. Power. *U. Exp. Med.,* **191**, 1755, (2000).
4. (a) R. Godiska, D. Cantry, C.J. Raport, S. Sozzani, P. Allavena et al. *Exp. Med.,* **185**, 1595, (1997); (b) D. Chantry, A.J. DeMaggio, H. Brammer, C.J. Raport, C.L. Wood, V.L. Schweickart et al. *J. Leukoe, Biol,* **64**, 49, (1998); (c) T. Imai, D. Chantry, C.J. Raport et al. *U. Biol, Chem.,* **273**, 1764, (1998); (d) M. Wakugawa, K. Nakamura, T. Kakinuma, K. Tamaki. *Drug News Perspect,* **15**, 175, (2002).
5. G.C. Look, J.R. Schuflek, C.P. Holmes, J.P. Chinn, E.M. Gordon and M.A. Gallop. *Bioorg. Med. Chem. Lett.*, 707, (1996).

6. S.G. Kucukguzel, E.E. Oruc, S. Rollas, F. Sahin and F. Ozbek. A. *Eur. J. Med. Chem*, **37**, 197, (2002).
7. M.V. Diurno, O. Mazzoni, E. Piscopo, A. Calignano, F. Giordano and A. Bolognese. A. *J. Med. Chem.*, **35**, 2910, (1992).
8. S. Allen et al. *Bioorg. Med. Chem. Lett.*, **14**, 1619, (2004).
9. SPSS software.consult http://www.spss.com
10. N. Bodor and P. Buchwald. P.*J.Phys.Chem*., **101**, 3404, (1997).
11. N. Rameshwar, K. Krishna, B. Ashok Kumar and T. Parthasarathy. *Bioorg. Med. Chem. Lett.* **14**, 319, (2006).
12. S. Chatterjee, A.S. Hadi and B. Price. *Regression Analysis by Examples*, 3rd Ed; Wiley: New York, (2000).

(Received: 16 March 2009 Accepted: 3 April 2009 RJC-348)

RJC will widely cover all branches of **CHEMISTRY** including: Organic, Inorganic, Physical, Analytical, Biological, Pharmaceutical, Industrial, Environmental, Agricultural & Soil, Petroleum, Polymers, Nanotechnology, Green Chemistry, Forensic, Phytochemistry, Synthetic Drugs, Computational, as well as Chemical Physics and Chemical Engineering.
Manuscript Categories: Full-length paper,Review Articles, Short/Rapid Communications.

Manuscripts should be addressed to:

Prof. (Dr.) Sanjay K. Sharma
Editor-in-Chief
23, 'Anukampa',Janakpuri, Opp. Heerapura Power Station,
Ajmer Road, Jaipur-302024 (India)
E-mail: rasayanjournal@gmail.com, drsanjay1973@gmail.com
Mobile: 09414202678, 09887050628

Adopt **GREEN CHEMISTRY**
Save Our Planet.
We publish papers of Green Chemistry on priority.

If you think that you may be a potential reviewer in field of your interest, write us at rasayanjournal@gmail.com with your detailed resume and recent color photograph.