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QSAR STUDY ON 3-SUBSTITUTED INDOLE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

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ABSTRACT

Anti-inflammatory agents have attracted much attention in recent years in the design of non-steroidal anti-inflammatory agents (NSAIDs), which are devoid of the common side effects of classical NSAIDs. QSAR studies have been performed on a series of 3-substituted indole derivatives with a hope to design compounds with better anti-inflammatory activity and lesser side effects. Various physicochemical parameters were calculated and good predictive QSAR models were generated for anti-inflammatory activity using stepwise multiple regression analysis. Statistically significant models were obtained that gave r-value (correlation coefficient) as <0.80 which depicts a good correlation between anti-inflammatory activity with physicochemical properties, connectivity and conformation of molecule. The indicator variables like presence of aromatic ring and lipophilic groups play an important role in anti-inflammatory activity. Cross validation was performed using the leave one-out method. The results obtained along with validated models bring important structural insight in designing novel 3-substituted indole derivatives as anti-inflammatory agents.

KEYWORDS: Quantitative structure–activity relationship, 3-substituted indole, lipophilicity and Anti-inflammatory activity.

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INTRODUCTION

Inflammation is a diseased condition in which body tissues are affected by heat, redness, swelling and pain [1]. There is a plethora of reviews and textbooks outlining the pathology of inflammation, including the sequence of events, network of mediators, such as prostaglandins (PGs), leukotrienes and cytokines along with complex molecular mechanisms that are involved [2]. Inflammation is a key feature of a number of diseases and the clinical features of these diseases are described extensively [3]. The therapeutic effects of non-steroidal anti-inflammatory drugs (NSAIDs) are well known regarding different diseases [4] and understood especially of those that do not have steroidal nucleus. These drugs have three important effects; anti–inflammatory, analgesic and antipyretic. Non-steroidal anti-inflammatory agents are of current interest [5] because there are no drugs of choice for the treatment of most of the diseases like rheumatoid arthritis [6], psoriasis [7, 8], ulcerative colitis and asthma [9]. In continuation of our search to find new potent anti-inflammatory agents [10, 11], it was thought to study the QSAR of some anti-inflammatory 3-substituted indole derivatives reported by Kumar et al [12]. The objective of QSAR study is to develop a relationship between the structure of selected set of compounds and the biological activity (BA) of interest [13]. The relationship can be defined as BA = *f* (molecular structure) = *f* (descriptors) The ultimate objective of QSAR is prediction of hypothesis on the mechanism of action for new analogs with high potency [14]. The nature of descriptors used and the extent to which they encode the structural feature of the molecules that influence biological activity of drugs, depend on the types and magnitude of reaction between the receptor and drug molecules. The descriptors may be physicochemical parameters (hydrophobic, steric or electronic), structural descriptors, topological indices and geometric parameters calculated from quantum mechanical method [13]. These are also the determining factors regulating the drug-receptor interactions [15]. QSAR study enables the investigators to establish a reliable quantitative structure–activity and structure–property relationship to derive an in silico QSAR model to predict the activity of novel molecules prior to their synthesis. The overall process of QSAR model development can be divided into three stages namely, the data preparation, data analysis and model validation. In this research, an attempt has been made to describe and deduce a correlation between structure and anti-inflammatory activity of indole derivatives.

MATERIALS AND METHODS

A training set of 30 3-substituted indole derivatives exhibiting potent anti-inflammatory activity was taken from the reported work of Kumar et al [12]. The activity data have been given as IC_{50} values, where IC_{50} refers to the experimentally determined molar concentration of the indoles required to inhibit carrageenan-induced rat paw oedema by 50%. The biological activity values IC_{50} (μM) reported in the literature were converted to molar units and then further to -log scale and subsequently used as the response variable for the QSAR analysis. The -log values of IC_{50} along with the structure of compounds in the series are presented in (Table 1) and (Fig 1).

Table 1
Anti-inflammatory activity data for indole derivatives

Comp. No.	R	IC_{50}	pIC_{50}
1	m-OCH_3, p-OH	0.12	6.93
2	p-OH	0.14	6.84
3	-H	0.13	6.88
4	p-N $(CH_3)_2$	0.08	7.11
5	p-O CH_3	0.06	7.25
6	-CH_3	0.22	6.5
7	-Cl	0.43	6.35
8	-F	0.37	6.43
9	-NO_2	0.26	6.55
10	p, m-$(OCH_3)_2$	0.28	6.59
11	m-OCH_3p-OH	0.14	6.85
12	p-OH	0.17	6.71
13	-H	0.15	6.82
14	p-N $(CH_3)_2$	0.11	6.97
15	p-OCH_3	0.10	7
16	-CH_3	0.20	6.69
17	-Cl	0.13	6.88
18	-F	0.16	6.79
19	-NO_2	0.15	6.82
20	p, m-$(OCH_3)_2$	0.18	6.74
21	m-OCH_3p-OH	0.34	6.45
22	p-OH	0.47	6.32
23	-H	0.38	6.42
24	p-N$(CH_3)_2$	0.62	6.6
25	p-OCH_3	0.33	6.49
26	-CH_3	0.22	6.63
27	-Cl	0.28	6.58
28	-F	0.24	6.61
29	-NO_2	0.15	6.85
30	p, m-$(OCH_3)_2$	0.19	6.72

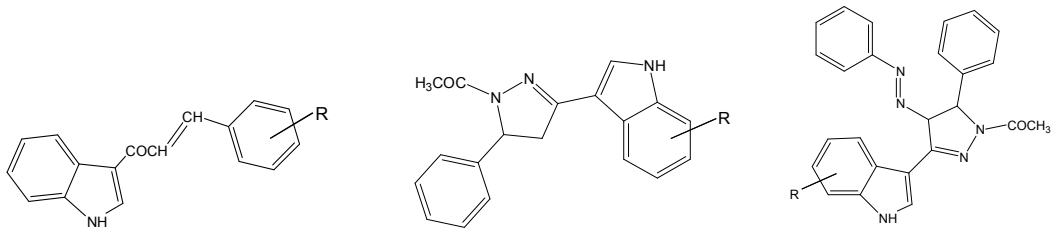

Figure 1
General structure of substituted Indoles

All the computations in the present study were performed on PIV workstation. The molecular structures of the training set were sketched using Chem. Draw Ultra module of CS Chem. Office 2004 molecular modeling software ver. 6.0 [16], supplied by Cambridge Software Company. The sketched structures were exported to Chem3D module in order to create its 3D model. Each model was "cleaned up" and energy minimization was performed using Allinger's MM2 force field by fixing Root Mean Square Gradient (RMS) to 0.1 Kcal/mol Aº. Further geometry optimization was done using semiemperical AM1 (Austin Model) Hamiltonian method, closed shell restricted wave function available in the MOPAC module until the RMS

value becomes smaller than 0.001 Kcal/mol Aº. The low energy conformers obtained from the aforementioned procedure were used for the calculation of the ChemSAR descriptors. The ChemSAR descriptors include physicochemical, thermodynamic, electronic and spatial descriptors available in the 'Analyze' option of the Chem3D package (Table 2). The descriptors calculated for the present study accounts four important properties of the molecules viz., physicochemical, thermodynamic, electronic and steric, as they represent the possible molecular interactions between the receptor and indole nucleus. The values of only those descriptors occurring in different equations are given (Table 3).

Table 2
Descriptors calculated for QSAR study

Sr. No.	Descriptor	Type
1	Heat of Formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
7	Henry's Law Constant (HLC)	Thermodynamic
8	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
9	Log P	Thermodynamic
10	Melting Point (MP)	Thermodynamic
11	Molar Refractivity (MR)	Thermodynamic
12	Standard Gibbs Free Energy (SGFE)	Thermodynamic
13	Connolly Accessible Area (CAA)	Steric
14	Connolly Molecular Area (CMA)	Steric
15	Connolly Solvent–Excluded Volume (CSEV)	Steric
16	Ovality (OVA)	Steric
17	Principle Moment of Inertia – X (PMI–X)	Steric
18	Principle Moment of Inertia – Y (PMI–Y)	Steric
19	Principle Moment of Inertia – Z (PMI–Z)	Steric
20	Dipole Moment (D)	Electronic
21	Dipole Moment –X Axis (DX)	Electronic
22	Dipole Moment –Y Axis (DY)	Electronic
23	Dipole Moment –Y Axis (DZ)	Electronic
24	Electronic Energy (EE)	Electronic
25	HOMO Energy (HOMO)	Electronic
26	LUMO Energy (LUMO)	Electronic
27	Repulsion Energy (RE)	Electronic
28	Bend Energy (E_b)	Thermodynamic
29	Charge–Charge Energy (CCE)	Thermodynamic
30	Charge–Dipole Energy (CDE)	Thermodynamic
31	Dipole–Dipole Energy (DDE)	Thermodynamic
32	Non–1, 4 VDW Energy (E_v)	Thermodynamic
33	Stretch Energy (SE)	Thermodynamic
34	Stretch–Bend Energy (SBE)	Thermodynamic
35	Torsion Energy (E_t)	Thermodynamic
36	Total Energy (E)	Thermodynamic
37	Van der Waals e 1,4 Energy (VDWE)	Thermodynamic
38	VDW 1,4 Energy (VDWE)	Thermodynamic
39	Partition coefficient	Thermodynamic

Table 3
Calculated descriptor values for the given series of compounds

Comp. No.	MR	SBE	DX	PMI-Y	PC
1	83.0362	-0.5258	3.3907	2545.3	4.521
2	78.2114	6.64E-02	4.643	4173.56	4.165
3	82.7998	5.06E-02	-2.6659	4796.89	15.6377
4	82.7998	0.68059	9.1853	2552.87	3.765
5	90.9214	-0.5649	4.0051	3155.1	4.03
6	94.8628	-1.5707	3.8154	3792.67	3.646
7	90.038	-1.539	5.6189	3861.98	3.29
8	94.6264	-1.4975	3.5405	4403.69	3.86
9	94.6264	-1.4937	9.3818	4600.48	2.89
10	102.748	-1.5619	4.6918	5366.88	2.805
11	128.539	-1.6046	3.6306	5000.86	5.9
12	123.714	-1.5673	3.9219	5114.28	5.544
13	128.303	-0.622	3.11	5706.12	6.114
14	128.303	-1.5368	8.0075	5950.53	5.144
15	136.424	-1.6593	3.6714	6470.86	5.059
16	86.1523	0.14377	3.7917	5687.58	3.2042
17	79.6891	6.94E-02	4.6902	4078.14	3.355
18	77.995	5.30E-02	5.1305	3276.38	4.022
19	92.4236	-0.4498	4.2031	3659.48	4.187
20	84.4582	-0.3516	4.359	2743.45	3.941
21	97.9789	-1.5137	2.9269	4885.69	2.3292
22	91.5157	-1.4924	4.0415	3819.21	2.48
23	89.8216	-1.4706	3.7078	3369.8	3.147
24	104.25	-1.3729	5.0229	4823.03	3.312
25	102.3	-1.5688	3.5803	4297.8	3.066
26	131.655	-1.8533	0.8025	5175.29	4.5832
27	125.192	-1.5782	4.4524	5137.88	4.734
28	123.498	-1.5647	3.7516	4339.81	5.401
29	137.927	-1.4957	3.7102	6741.53	5.566
30	127.02	-1.6206	3.3635	5787.59	5.32

To establish the correlation between physicochemical parameters as independent variable and anti-inflammatory activity as dependent variable, the data were transferred to statistical program VALSTAT [17]. Sequential multiple linear regression analysis method, a program which searches for all permutations and combinations sequentially for the data set was applied for the same. The best model was selected on the basis of statistical parameters viz., observed squared correlation coefficient (r^2), standard error of estimate (s), and sequential Fischer test (F). Z score (absolute difference between values of model and activity field, divided by the square root of mean square error of data set) was taken as a measure of outlier detection. To assess the self-consistency of derived models, they were validated using leave-one-out (LOO) and the predictive ability was checked using cross-validated squared correlation coefficient (r^2_{cv} or q^2), bootstrapping squared correlation coefficient (r^2_{bs}), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation) and outliers (on the basis of Z-score value). The ±data within parentheses are the standard deviation, associated with the coefficient of descriptors in regression equations. Each of the statistical parameters mentioned above were used for assessing the statistical significance of QSAR. Additionally, the developed QSAR models were also checked for significance of the regression coefficients in the model and for multicolinearity problem by the calculation of Student's t-test values (t-value) using statistical software SYSTAT [18]. The generated QSAR models were validated for predictive ability inside the model (LOO) by using VALSTAT. The statistical program which is tailored specifically for QSAR statistics estimates the predictive potential of model by calculating the validation parameters squared cross-correlation coefficient (q^2), standard deviation of sum of square of

difference between predicted and observed values (S_{PRESS}) and standard deviation of error of prediction (S_{DEP}).

RESULTS

Biological activity data and various physicochemical parameters were taken as dependent and independent variables; respectively and correlations were established using sequential multiple regression analysis. Among the many correlations generated, two best quadratic and triparametric models were selected on the basis of statistical significance. The best models obtained are given below along with their statistical measures.

Model-I

pIC_{50} = 5.881(± 0.256) + 0.008(± 0.002) MR + 0.024(± 0.022) PC + 0.265(± 0.074) SBE - 0.029(± 0.022) DX n=28, r = 0.905, r^2 = 0.819, SE = 0.075, F = 26.115

Model-II

pIC_{50} = 6.120(± 0.263) + 0.009(± 0.004) MR - 2.456(± 6.375) PMI-Y + 0.308(± 0.080) SBE n= 29, r = 0.847, r^2 = 0.717, SE = 0.115, F = 21.161

Model-I

It shows good correlation (r = 0.905) between descriptors (MR, PC, SBE, DX) and the biological activity. MR, thermodynamic descriptors has been corrected from of the molar volume; it reflects the effect of size, polarizalibility and steric bulk of molecules, as indicated in Model-I, suggesting that MR plays a significant role in influencing the expressed biological activities, which is probably due to steric interaction occurring in the polar spaces. It has generally been assumed that a positive coefficient with an MR term in a correlation equation suggests a binding action via dispersion forces. Such binding could produce a concomitant conformational change in a macromolecular binding site; however, if the conformations are detrimental, a negative coefficient could result for the MR term. Negative coefficient with MR has also been assumed to reflect steric hindrance of one kind or another. PC has been calculated using atom-based approach and represents the hydrophobicity of the molecules [19]. By looking at the structures of the molecules, it is evident that they are lipophilic, which suggests good contribution of PC in altering activity. PC is correlated positively, as anti-inflammatory active site is hydrophobic in nature and molecules with proper lipophilicity and bulkiness as that of most active compound may have same or enhanced enzyme inhibition property. It appears that an increase in the bulkiness of functional group(s) on aromatic ring(s) may lead to less active compound, as bulkiness may disorient the aromatic ring away from favorable interactions with active site residues. In case of compounds 4, 9 and 14 which have a dimethyamine group, bulkier than most active compound, are less active because they may not be accommodated in the active site properly to have favorable interactions.

SBE, a thermodynamic parameter, deals with energy required to stretch the two bonds involved in a bond angle when that bond is severely compressed. The positive coefficient of the descriptor in model suggests that an increase in the SBE of the molecule is conducive for activity. Dipole X, an electronic parameter indicates the dipole moment in X–axis. This term was negatively correlated and indicates that the compounds having dipole moment in X-axis may show less activity. Compounds 4, 9 and 14 (Table 1) with functional groups orienting toward X-axis showed less activity. Thus, model-I suggests that partition coefficient is of significance having high value of t-test indicating statistical significance of calculated regression coefficient. To confirm these results, the value of pIC_{50} was estimated using leave one-out and correlated with observed value of pIC_{50}. The value of r^2_{bs},

chance and q^2 in randomized biological activity indicates the statistical significance of the model as given below.

r^2_{bs} = 0.86, Chance = < 0.001, q^2 = 0.74, S_{PRESS} = 0.11, S_{DEP} = 0.10

The predicted activity data of model-I is shown in Table 4. A plot of observed versus predicted (LOO) pIC_{50} for anti-inflammatory activity using model-I is shown in (Fig 2).

Table 4
Predicted activity data of Model-I

Comp. No.	Observed pIC_{50}	Predicted pIC_{50}	Calculated pIC_{50}
1	6.93	-	-
2	6.84	6.7689	6.77827
3	6.88	6.83597	6.87779
4	7.11	7.09917	7.10376
5	7.25	-	-
6	6.5	6.43545	6.4423
7	6.35	6.4754	6.45607
8	6.43	6.45988	6.45693
9	6.55	6.64345	6.60742
10	6.59	6.50838	6.5143
11	6.85	6.74867	6.75852
12	6.71	6.73046	6.72888
13	6.82	7.06125	7.00724
14	6.97	6.84737	6.88586
15	7	6.75563	6.78884
16	6.69	6.85197	6.81467
17	6.88	6.7529	6.77254
18	6.79	6.78298	6.78389
19	6.82	6.73925	6.74481
20	6.74	6.70111	6.70438
21	6.45	6.41951	6.42402
22	6.32	6.42668	6.41368
23	6.42	6.41109	6.4122
24	6.6	6.59903	6.59908
25	6.49	6.48154	6.48226
26	6.63	6.59261	6.60148
27	6.58	6.74685	6.73379
28	6.61	6.72778	6.71919
29	6.85	6.85974	6.85821
30	6.72	6.71956	6.7196

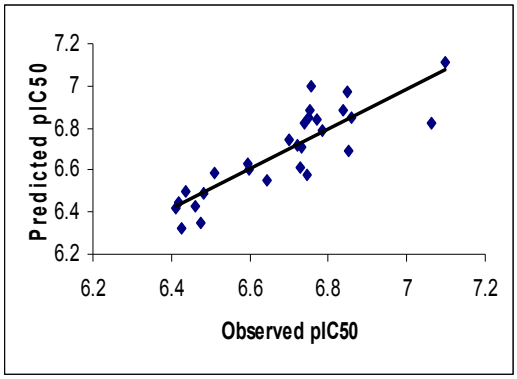

Figure 2
Observed versus predicted (LOO) pIC_{50} for anti-inflammatory activity using model-I

Model-II

It shows good correlation (r =0.84) between descriptors (MR, PMI-Y, SBE) and the biological activity. MR, thermodynamic parameters that contribute positively to the model means the groups which increases molar volume, may cause increase in biological activity. PMI-Y depends on the total mass of the molecule, the distribution within the molecule and position of axis rotation of the molecule. It is a spatial descriptor which explains the significance of orientation and conformational rigidity of biological activity. The positive coefficient of PMI-Y suggests the presence of bulky substituent's oriented towards Y-axis of the molecule which will give better activity. SBE, a thermodynamic parameter, deals with energy required to stretch the two bonds involved in a bond angle when that bond is severely compressed. The positive coefficient of this descriptor in Model- II suggests that an increase in the stretch bend energy of the molecule is conducive for activity. Thus, Model-II suggests that MR has high value in t-test indicating statistical significance of calculated regression coefficient. To confirm these results, the value of pIC_{50} was estimated using LOO and correlated with observed value of pIC_{50}. The value of r^2_{bs}, chance and q^2 in randomized biological activity indicates the statistical significance of the model as follows.

r^2_{bs} = 0.74, Chance=0.01, q^2 = 0.58, S_{PRESS} = 0.13, S_{DEP} = 0.12

The predicted activity data of Model-II is shown as below (Table 5). A plot of observed versus predicted (LOO) pIC_{50} for anti-inflammatory activity using Model-II is shown in (Fig 3).

Table 5
Predicted activity data of Model-II

Comp. No.	Observed pIC_{50}	Predicted pIC_{50}	Calculated pIC_{50}
1	6.93	6.66024	6.70557
2	6.84	6.79469	6.80119
3	6.88	6.81346	6.82573
4	7.11	7.055	7.07514
5	7.25	-	-
6	6.5	6.46409	6.46794
7	6.35	6.44029	6.42899
8	6.43	6.47789	6.47322
9	6.55	6.45978	6.46957
10	6.59	6.49718	6.50886
11	6.85	6.74384	6.75611
12	6.71	6.71843	6.71779
13	6.82	7.09719	7.03951
14	6.97	6.72753	6.75139
15	7	6.74036	6.77999
16	6.69	6.95629	6.86527
17	6.88	6.80974	6.81886
18	6.79	6.82078	6.81698
19	6.82	6.791	6.79316
20	6.74	6.77337	6.7683
21	6.45	6.49375	6.48908
22	6.32	6.47576	6.45882
23	6.42	6.46623	6.46007
24	6.6	6.59489	6.59515
25	6.49	6.66024	6.52864
26	6.63	6.79469	6.70549
27	6.58	6.81346	6.72824
28	6.61	7.055	6.73548
29	6.85	6.46409	6.83844
30	6.72	6.44029	6.71702

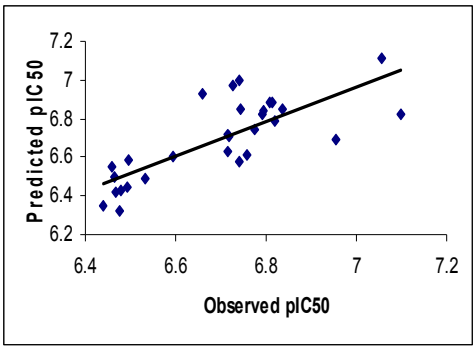

Figure 3
Observed versus predicted (LOO) pIC_{50} for anti-inflammatory activity using model-II

The intercorrelation between the descriptors is within the acceptable range (< 0.8) [20]. The t-statistics at 95% significance level for the regression coefficients is given (Table 6) for Model-I and Model-II. Furthermore, the models were tested for autocorrelation problem by evaluation of Durbin Watson Statistics, which is 1.85 and 1.92 for Model-I and for Model-II; respectively. Durbin Watson statistics confirm the absence of autocorrelation among residuals, as their values are between the acceptable ranges from 1.5 to 2.5 [21, 22] (Table 6).

Table 6
t-Statistics and Durbin Watson statistic values for the descriptors in selected models

Model No.	Constant/Descriptor	t–value	Durbin Watson Statistics
Model-I	Constant	41.473	1.853
	MR	2.634	
	DX	-1.872	
	PC	4.386	
	SBE	4.436	
Model-II	Constant	62.859	1.927
	MR	3.958	
	PMI-Y	-1.627	
	SBE	5.311	

DISCUSSIONS

Comparison of Model-I and Model-II reveals that the former shows better correlation (r = 0.905) between descriptors and biological activity than later one (r = 0.847). The bootstrapping r^2 (r^2_{bs} = 0.86) results reflect the significance of the Model-I as compared to Model-II. The cross validation (q^2) values reflect predictive power of the Model-I. Low standard error of estimation (<0.4) suggests a high degree of confidence in the analysis. Moreover, the descriptors used to construct the model are not correlated with each other as suggested by their correlation matrix values; respectively (Table 7 and Table 8). However, the model manifests moderate predictive potential as indicated by cross-validated correlation coefficient values.

Table 7
Correlation matrix for parameters in model-I

Parameters	MR	PC	SBE	DM
MR	1.000000			
PC	0.136743	1.000000		
SBE	0.649661	0.208053	1.000000	
DM	0.121941	0.611803	0.064278	1.000000

Table 8
Correlation matrix for parameters in model II

Parameters	MR	PMIY	SBE
MR	1.000000		
PMIY	0.761484	1.000000	
SBE	0.657646	0.444331	1.000000

CONCLUSION

QSAR analysis was performed on a series of anti-inflammatory indole derivatives using molecular modeling program Chemoffice 2004. QSAR models were proposed for the same using ChemSAR descriptors employing sequential multiple regression analysis method. The selected models were checked for multicolinearity and autocorrelation with Durbin Watson statistics values. The predictive power of each model was estimated with bootstrapping r^2 method and LOO cross validation method. The results of the study suggest involvement of MR and PC in anti-inflammatory activity of indole derivatives and also increase in molar volume and lipophilicity is conducive for this activity. Thus, the discussed models could be explored further to design potent anti-inflammatory agents.

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