Structure–Activity Studies of 3-Benzoylpropionic Acid Derivatives Suppressing Adjuvant Arthritis[1)]

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3-Benzoylpropionic acid derivatives possess an immunomodulative activity and suppress adjuvant arthritis. To understand how substituents affect the biological activity, the quantitative structure–activity relationships of 30 compounds were analyzed by the adaptive least-squares method. For the suppressing activity in rats, the electronic effects and the structural feature of the substituent on benzene ring were suggested to be important. To reinforce and confirm the correlation, 4 additional compounds of phenoxybutyric acid derivatives were synthesized and tested with the rat adjuvant-induced arthritis. These compounds were found to have potent suppressing activity.

Keywords 3-benzoylpropionic acid; phenoxybutyric acid; adjuvant-induced arthritis; structure–activity relationship; adaptive least-squares method; immunomodulative activity

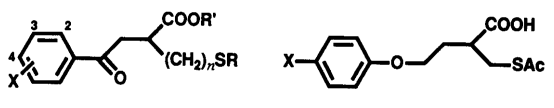
In a previous paper we reported the synthesis and inhibitory activity against rat adjuvant arthritis of 3-benzoylpropionic acid derivatives.[2)] When structure–activity relationships of the derivatives were considered, it appeared that the suppressing activity of ester derivatives was weaker than that of the free carboxylic acids, and *p*-substituents of benzene moiety of 3-benzoylpropionic acids would have good activity. This consideration prompted us to attempt a quantitative-structure activity analysis to develop more potent compounds.

This paper describs the quantitative-structure activity relationship (QSAR) of these derivatives for the suppressing activity using the adaptive least-squares (ALS) method.[3-5)] As an extrapolation of the obtained QSAR models, 4 additional compounds of phenoxybutyric acid derivatives were synthesized and tested against the rat adjuvant-induced arthritis.

Results and Discussion

QSAR of 3-Benzoylpropionic Acids (30 Compounds) The compounds[6)] analyzed in this study are listed in Table Ia along with the descriptors and activity rating. In the parametrization of structural features for the ALS study, we investigated physicochemical parameters[7)] generally used in QSAR studies and several indicator variables. The good discriminant function derived with 3 or 4 descriptors is expressed by Eqs. 1—3 (Table II), which were generated within 20 iterations.

In Eqs. 1—3, R_X is the Swain–Lupton resonance constant of substituent X, and a $\sigma_{R'}$ is the Taft polar constant of substituent R′. The indicator variables $D_{4\text{-Me}}$ and $D_{4\text{-Br}}$ are assigned a value of 1 corresponding to the presence of methyl group or bromo group, respectively, at the *p*-position of benzene moiety. The figure in parentheses under the coefficient is the contribution index (=|coefficient|×S.D. of descriptor), which is a measure of contribution of the descriptor to discriminant score (L). The cross-correlation matrix of the descriptors used in Eqs. 1—3 is shown in Table III. There seems to be no problem due to collinearity between descriptors in these equations.



I VI

Fig. 1

On the basis of Eqs. 1—3 for suppressing activity, the positive coefficient for a $\sigma_{R'}$ may indicate that inductive effect of substituent R′ is important; σ-electron-attracting groups enhance the activity. Further, from the positive coefficient for R_X, π-electron-donating groups of substituent X are not favorable to the activity. As for indicator variables, the positive coefficients for D_1 and D_2 may indicate that the presence of methyl group and bromo group at the *p*-position of benzene moiety enhances the activity.

On the other hand, the effects of substituent R and the presence of methylene ($n=1$) were not clear.

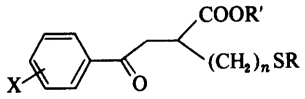
Chemical Synthesis and Assay As an extrapolation of the obtained QSAR models, phenoxybutyric acid derivatives replacing benzoyl moiety of 3-benzoylpropionic acid by phenoxymethyl moiety were synthesized and tested in rat adjuvant-induced arthritis.

For the substituent X at the *p*-position of benzene moiety, H, Me, Cl, and Br groups were chosen. The substituents R′ and R were decided as the fixed to be hydrogen and acetyl group, respectively. The general synthetic route for preparing the phenoxybutyric acid derivatives is shown in Chart 1.

Phenols (II) were reacted with 2-bromoethyl alcohol using sodium hydroxide in ethanol to give the phenoxyethylalcohols, which were treated with thionyl chloride to give chloride derivatives (III). Compounds (III) were reacted with diethyl malonate using sodium hydride, then the diethyl esters were hydrolyzed to the half esters (IV). Compounds (IV) were heated with paraformaldehyde in pyridine in the presence of piperidine at 50 °C to give the ethyl 2-methylene-4-phenoxybutyrate derivatives (V). After hydrolysis of (V), the acid derivatives were treated with thioacetic acid in *N*,*N*-dimethylformamide (DMF) in the presence of 0.1 eq of aqueous potassium carbonate solution to give the 2-acetylthiomethyl-4-phenoxybutyric acid derivatives (VI).

Inhibitory activity of the newly synthesized compounds was tested against rat adjuvant arthritis.[8)] The biological data are shown in Table Ib. Most of the designed compounds showed strong or moderate potency.

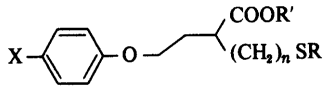
TABLE Ia. Structure–Activity and Descriptors for 3-Benzoylpropionic Acid Derivatives



No.	X	R′	R	n	Activity				$\sigma_{R'}^{*d)}$	$R_X^{d)}$	$D_{4\text{-Br}}$	$D_{4\text{-Me}}$
					Obs.[a)]	Rating	Recog.[b)]	Pred.[c)]				
1	H	Et	Ac	1	0	1	1	1	−0.10	0	0	0
2	4-Br	Me	Ac	1	0	1	1	2	0	−0.17	1	0
3	4-Br	Et	Ac	1	0	1	1	1	−0.10	−0.17	1	0
4	4-Br	iso-Pr	Ac	1	0	1	1	1	−0.19	−0.17	1	0
5	4-F	H	Ac	1	0	1	1	1	0.49	−0.34	0	0
6	4-MeO	H	Ac	1	0	1	1	1	0.49	−0.51	0	0
7	4-F	H	Ac	0	0	1	1	1	0.49	−0.34	0	0
8	3-CF_3	H	Ac	0	0	1	2	2	0.49	0.05	0	0
9	4-MeO	H	Ac	0	0	1	1	1	0.49	−0.51	0	0
10	4-Br	CH_2Ph	Ac	1	1	2	2	2	0.22	−0.17	1	0
11	2,4-diMe	H	Ac	1	1	2	2	3	0.49	−0.26	0	1
12	4-Et	H	Ac	1	1	2	2	2	0.49	−0.10	0	0
13	4-PhO	H	Ac	1	1	2	1	1	0.49	−0.35	0	0
14	H	H	COPh	1	1	2	2	2	0.49	0	0	0
15	4-Br	H	COPh	1	1	2	3	3	0.49	−0.17	1	0
16	H	H	Ac	0	1	2	2	2	0.49	0	0	0
17	2-Br	H	Ac	0	1	2	2	2	0.49	−0.17	0	0
18	4-Cyclohexyl	H	Ac	0	1	2	2	2	0.49	0.02	0	0
19	H	H	H	0	1	2	2	2	0.49	0	0	0
20	H	H	Et	0	1	2	2	2	0.49	0	0	0
21	3-Br	H	Ac	0	2	2	2	2	0.49	−0.05	0	0
22	4-Cl	H	Ac	0	2	2	2	2	0.49	−0.15	0	0
23	H	H	Ac	1	3	3	2	2	0.49	0	0	0
24	4-Br	H	Ac	1	3	3	3	3	0.49	−0.17	1	0
25	3,4-diMe	H	Ac	1	3	3	3	3	0.49	−0.17	0	1
26	4-Br	H	COPh	0	3	3	3	3	0.49	−0.17	1	0
27	4-Br	H	Ac	0	3	3	3	3	0.49	−0.17	1	0
28	3,4-diBr	H	Ac	0	3	3	3	3	0.49	−0.22	1	0
29	4-Br	H	COEt	0	3	3	3	3	0.49	−0.17	1	0
30	4-Me	H	Ac	1	4	3	3	3	0.49	−0.13	0	1

a) Edema suppression rates were calculated as percentages with respect to the control value; less than 10% suppression = 0, 10—25% suppression = 1, 26—40% suppression = 2, 41—55% suppression = 3, more than 55% suppression = 4. *b*) From Eq. 4. *c*) Using the leave-one-out technique. *d*) Ref. 7.

TABLE Ib. Structure–Activity and Descriptors for 4-Phenoxybutyric Acid Derivatives



No.	X	R′	R	n	Activity				$\sigma_{R'}^{*d)}$	$R_X^{d)}$	$D_{4\text{-Br}}$	$D_{4\text{-Me}}$
					Obs.[a)]	Rating	Recog.[b)]	Pred.[c)]				
31	H	H	Ac	1	2	2	2	2	0.49	0	0	0
32	4-Cl	H	Ac	1	2	2	2	2	0.49	−0.15	0	0
33	4-Br	H	Ac	1	3	3	3	3	0.49	−0.17	1	0
34	4-Me	H	Ac	1	4	3	3	3	0.49	−0.13	0	1

a)—*d*) See Table Ia.

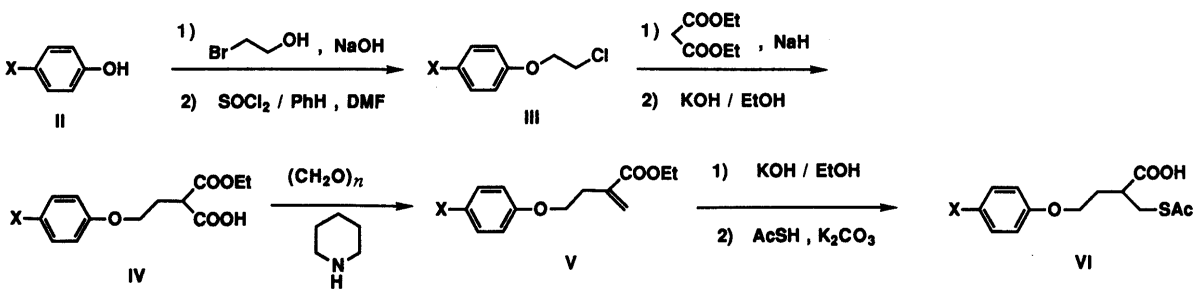


Chart 1

TABLE II. ALS Discriminant Functions and Their Recognition and Prediction Results

Eq. No.	$n^{a)}$	Recognition		Prediction[b]	
		n_{mis}[c]	R_S[d]	n_{mis}[c]	R_S[d]
3-Benzoylpropionic acid derivatives					
(1) $L=3.58\sigma_R^*+1.30D_{4\text{-Br}}+1.24D_{4\text{-Me}}-1.20$ (CI=0.73)[f] (0.61) (0.37)	30	8 (0)[e]	0.78	9 (0)	0.76
(2) $L=3.87\sigma_R^*+3.16R_X+1.21D_{4\text{-Br}}-1.49$ (CI=0.79) (0.45) (0.57)	30	6 (0)	0.82	8 (1)	0.65
(3) $L=3.80\sigma_R^*+2.89R_X+1.38D_{4\text{-Br}}+1.14D_{4\text{-Me}}-1.66$ (CI=0.77) (0.41) (0.65) (0.34)	30	4 (0)	0.88	6 (0)	0.83
3-Benzoylpropionic acid and 4-phenoxybutyric acid derivatives					
(4) $L=3.83\sigma_R^*+2.75R_X+1.39D_{4\text{-Br}}+1.16D_{4\text{-Me}}-1.76$ (CI=0.74) (0.38) (0.65) (0.37)	34	4 (0)	0.89	6 (0)	0.84

a) Number of points used for calculations. *b*) Using the leave-one-out technique. *c*) Number of misclassified compounds. *d*) Spearman rank correlation coefficient with a correction of many ties; the values are all significant at $p<0.01$. *e*) Number of compounds misclassified by two grades. *f*) Contribution index (CI).

TABLE III. Cross-Correlation Matrix of Descriptors for Eqs. 1—3

	σ_R^*	R_X	$D_{4\text{-Br}}$	$D_{4\text{-Me}}$
σ_R^*	1.00			
R_X	−0.08	1.00		
$D_{4\text{-Br}}$	−0.40	−0.08	1.00	
$D_{4\text{-Me}}$	0.14	−0.06	−0.24	1.00

TABLE IV. Cross-Correlation Matrix of Descriptors for Eq. 4

	σ_R^*	R_X	$D_{4\text{-Br}}$	$D_{4\text{-Me}}$
σ_R^*	1.00			
R_X	−0.06	1.00		
$D_{4\text{-Br}}$	−0.39	−0.11	1.00	
$D_{4\text{-Me}}$	0.15	−0.05	−0.25	1.00

QSAR of 3-Benzoylpropionic Acids and 4-Phenoxybutyric Acids (34 Compounds) The QSAR of 34 compounds was analyzed using ALS method. The descriptors and activity ratings for the newly synthesized compounds are listed in Table Ib. The best discriminant function for the suppression activity is expressed by Eq. 4, which was derived within 20 iterations. This model was substantially identical to Eq. 3 obtained for the 30 3-benzoylpropionic acid derivatives. Using this model, the resulting recognition and leave-one-out prediction of newly synthesized compounds were fairly good.

The cross-correlation matrix of the descriptors appearing in Eq. 4 is listed in Table IV. It is almost equal to the matrix for Eqs. 1—3 (Table III), thus allaying no fear of chance correlation.

It can therefore be concluded that the obtained QSAR models for suppressing adjuvant arthritis are fairly reliable and robust, even for extrapolative uses. Among the benzoylpropionic acid and phenoxybutyric acid derivatives, 2-acetylthio-3-(4-methylbenzoyl)propionic acid showed pronounced biological activities. This compound is being further studied.

Experimental

All the melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken in $CDCl_3$ at 200 MHz with tetramethylsilane (TMS) as an internal standard on a Varian XL-200 spectrometer. The chemical shifts are expressed as ppm downfield from TMS. The following abbreviations are used: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet and br=broad. For column chromatography, silica gel (Wako gel, C-200) was used.

Typical examples are given to illustrate the general procedure.

2-(4-Methylphenoxy)ethanol[9] (II) A mixed solution of *p*-cresol (20.0 g) and NaOH (7.4 g) in EtOH (70 ml) was stirred at 70 °C for 30 min, then a solution of 2-bromoethanol (23.0 g) in EtOH (20 ml) was added dropwise at the same temperature. The reaction mixture was heated under reflux with stirring for 4 h. After concentration, the residue was diluted with AcOEt. The whole was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give colorless oil (22.7 g, 74.6%). NMR ($CDCl_3$) δ: 1.05 (1H, s), 2.29 (3H, s), 3.93 (2H, td, J=6, 1 Hz), 4.09 (2H, td, J=6, 1 Hz), 6.82 (2H, d, J=8 Hz), 7.09 (2H, d, J=8 Hz). IR ν_{max}^{neat} cm^{-1}: 3307, 1610, 1511.

2-(4-Methylphenoxy)ethyl Chloride[10] (III) To an ice-cooled stirred solution of 2-(4-methylphenoxy)ethanol (35.3 g) in toluene (40 ml) was added thionyl chloride (18.8 ml), and the stirring was continued for 1 h at 90 °C. The reaction mixture was diluted with hexane and the whole was washed with H_2O, 10% NaOH, H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue was recrystallized from hexane to give colorless needles (28.2 g, 76.8%), mp 43—44 °C. NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.79 (2H, t, J=6 Hz), 4.20 (2H, t, J=6 Hz), 6.82 (2H, d, J=8 Hz), 7.09 (2H, d, J=8 Hz). IR ν_{max}^{KBr} cm^{-1}: 1611, 1511.

2-Ethoxycarbonyl-4-(4-methylphenoxy)butyric Acid (IV) A 60% NaH (6.6 g) was added to a stirred solution of diethyl malonate (32 g) in DMF (70 ml) and the stirring was continued for 30 min at 80 °C. A solution of 2-(4-methylphenoxy)ethylchloride (28.2 g) in DMF (50 ml) was added dropwise to the stirred mixture at 80 °C, and the stirring was continued for 4 h at 100 °C. The reaction mixture was poured into ice-water, then the whole was acidified with 10% HCl and extracted with hexane. The extract was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue (46.4 g) was dissolved in EtOH (150 ml), and a solution of KOH (8.85 g) in H_2O (10 ml)–EtOH (50 ml) was added with stirring. The stirring was continued for 3 h at room temperature, then EtOH was evaporated under reduced pressure. The residue was dissolved in H_2O and the whole was washed with AcOEt. The aqueous layer was acidified with 10% HCl, then the whole was extracted with AcOEt. The extract was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give colorless oil (29.0 g, 66.0%). NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 2.25 (3H, s), 2.40 (2H, q, J=7, 1 Hz), 6.76 (2H, d, J=8 Hz), 7.05 (2H, d, J=8 Hz), 8.35 (1H, br s). IR ν_{max}^{neat} cm^{-1}: 2983, 1736, 1614, 1511.

Ethyl 2-Methylene-4-(4-methylphenoxy)butyrate (V) To a stirred suspension of ethyl 2-ethoxycarbonyl-4-(4-methylphenoxy)butyric acid (29.0 g) and paraformaldehyde (3.9 g) in pyridine (70 ml) was added piperidine (1.2 ml) at 50 °C, then the stirring was continued for 4 h at 65 °C. The mixture was poured into diluted HCl under ice cooling and the whole was extracted with AcOEt. The extract was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue (19.9 g) was dissolved in a solution of KOH (5.7 g) in H_2O (59 ml)–EtOH (100 ml), and the mixture was stirred at room temperature for 8 h. After con-

centration under reduced pressure, the residue was dissolved in H_2O and the whole was washed with AcOEt. The aqueous layer was acidified with 10% HCl and the whole was extracted with AcOEt. The extract was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue was recrystallized from Et_2O–hexane to give colorless needles (10.9 g, 52.9%) mp 90—92 °C. NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.79 (2H, t, J=7 Hz), 4.10 (2H, t, J=7 Hz), 5.84 (1H, d, J=1 Hz), 6.93 (1H, d, J=1 Hz), 6.80 (2H, d, J=8 Hz), 7.02 (2H, d, J=8 Hz), 7.70 (1H, br s). IR ν_{max}^{KBr} cm^{-1}: 2945, 1685, 1628, 1515.

2-Acetylthiomethyl-4-(4-methylphenoxy)butyric Acid (VI) 2-Methylene-4-(4-methylphenoxy)butyric acid (10.9 g) and thioacetic acid (4.5 ml) was dissolved in DMF (50 ml), then a solution of K_2CO_3 (1.5 g) in H_2O (10 ml) was added dropwise with stirring at 30 °C for 30 min. The stirring was continued for 2 h at the same temperature, and the reaction mixture was suspended in H_2O and acidified with 10% HCl. The whole was extracted with AcOEt, and the extract was washed with H_2O and satd. NaCl, then dried ($MgSO_4$) and concentrated. The residue was recrystallized from Et_2O–hexane to give colorless needles (13.0 g, 87.3%) mp 62—63 °C. NMR ($CDCl_3$) δ: 2.20 (2H, m), 2.28 (3H, s), 2.34 (3H, s), 2.95 (1H, m), 3.23 (2H, d, J=6 Hz), 4.05 (2H, d, J=6 Hz), 6.80 (2H, d, J=8 Hz), 7.08 (2H, d, J=8 Hz), 10.80 (1H, br s). IR ν_{max}^{KBr} cm^{-1}: 2850, 2500, 1700, 1640. *Anal.* Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.78; H, 6.42. The following compounds were similarly prepared:

2-Acetylthiomethyl-4-phenoxybutyric Acid Oil. NMR ($CDCl_3$) δ: 2.18 (2H, m), 2.34 (3H, s), 2.95 (1H, m), 3.22 (2H, d, J=7 Hz), 4.07 (2H, t, J=7 Hz), 6.91 (2H, t, J=8 Hz), 6.93 (1H, t, J=8 Hz), 10.50 (1H, br s). IR ν_{max}^{neat} cm^{-1}: 3000, 2500, 1700, 1600. *Anal.* Calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 58.22; H, 6.29.

2-Acetylthiomethyl-4-(4-bromophenoxy)butyric Acid Oil. NMR ($CDCl_3$) δ: 2.00—2.30 (2H, m), 2.36 (3H, s), 3.84—4.01 (1H, m), 3.22 (2H, d, J=7 Hz), 4.04 (2H, t, J=7 Hz), 6.78 (2H, d, J=8 Hz), 8.20 (1H, br s). IR ν_{max}^{neat} cm^{-1}: 2500, 1710, 1690. *Anal.* Calcd for $C_{13}H_{15}BrO_4S$: C, 44.97; H, 4.35. Found: C, 45.16; H, 4.34.

2-Acetylthiomethyl-4-(4-bromophenoxy)butyric Acid mp 53—55 °C (from Et_2O–hexane). NMR ($CDCl_3$) δ: 2.00—2.31 (2H, m), 2.35 (3H, s), 2.91 (1H, m), 3.21 (2H, d, J=6 Hz), 4.04 (2H, t, J=6 Hz), 6.82 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz), 9.00 (1H, br s). IR ν_{max}^{KBr} cm^{-1}: 2900, 2500, 1700. *Anal.* Calcd for $C_{13}H_{15}ClO_4S$: C, 51.57; H, 4.99. Found: C, 51.55; H, 4.87.

ALS Method The ALS system,[3-5] which is a nonparametric pattern classifier, categorized multidimensional structural patterns into multiple ordered classes by means of a single equation. The equation (discriminant function) is formulated by a feedback adaptation procedure in a linear form, as in Eq. 5:

$$L = w_0 + w_1x_1 + w_2x_2 + \cdots + w_px_p \quad (5)$$

where L in the discriminant score for the classification, x_k (k=1, 2, ..., p) is the k-th descriptor for the structure, and w_k (k=0, 1, ..., p) is the weight coefficient. The value of w_k is determined by the least-squares adaptation using the starting score, a_j (j=1, 2, ..., m in the m-group case) and the correction term, $C_i(t)$. In this study, the version of 1981 (ALS 81)[5] was used. The correction term C_i (t) for misclassified compound i at the t-th iteration is given by Eq. 6:

$$C_i(t) = 0.1/[\delta_i(t) + 0.45]^2 + 0.1 \quad (6)$$

where

$$\delta_i(t) = L_i(t) - b_k$$

In this equation, $L_i(t)$ is the discriminant score, and b_k is the cutting point (nearer to $L_i(t)$) of the observed class for compound i. ALS iteration was performed a maximum of 20 times. The best discriminant function was selected according to the reported criteria.[4,5]

Biological Method[8] Eight-week-old female Sprague-Dawley rats (ten rats per group) were used. Rats of each group were administered subcutaneously in the tail a suspension of 0.6 mg of thermally killed Mycobacterium butyricum in liquid paraffin. The test compounds, which were prepared as a suspension in 5% gum arabic solution, were orally administered to the rats at a daily dose of 100 mg/kg for 20 d. The 5% gum arabic solution was orally administered to rats after sensitization in the control group. Twenty-one days later, the edema volume of the hind paw of rats in the test compound-treated groups and the control was measured to evaluate edema-suppressing activity.

References and Notes

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