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CC chemokine receptor-3 (CCR3) antagonists: Improving the selectivity of DPC168 by reducing central ring lipophilicity

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Abstract—DPC168, a benzylpiperidine-substituted aryl urea CCR3 antagonist evaluated in clinical trials, was a relatively potent inhibitor of the 2D6 isoform of cytochrome P-450 (CYP2D6). Replacement of the cyclohexyl central ring with saturated heterocycles provided potent CCR3 antagonists with improved selectivity against CYP2D6. The favorable preclinical profile of DPC168 was maintained in an acetylpiperidine derivative, BMS-570520.

CC Chemokine receptor 3 (CCR3) is the dominant chemokine receptor on eosinophils, and is also expressed by mast cells, basophils, and Th2 lymphocytes.[1–3] A growing body of evidence supports a critical role for CCR3 and its cognate ligands (notably eotaxin) in the inflammatory component of diseases such as asthma, allergic rhinitis, and contact dermatitis, all of which are characterized by eosinophil migration into affected tissues.[2–6] The clinical significance of these allergic diseases has prompted research into the discovery of small molecule antagonists of CCR3 as potential new therapeutics.[1,7]

Previous reports from our group detailed the discovery of potent aryl urea antagonists of CCR3, culminating in the identification of DPC168 (**1**, see Table 1).[8–11] Starting with simple lead compounds,[8] incorporation of the (*S*)-3-(4-fluorobenzyl)piperidine moiety imparted single-digit nanomolar CCR3 binding potency and good selectivity,[10] while rigidification of the central linker of the molecule with the (1*R*,2*S*)-disubstituted cyclohexyl core provided compounds with extremely potent activity against eotaxin-induced chemotaxis (double-digit picomolar IC_{50}).[11] DPC168 was advanced into human clinical trials based on good preclinical pharmacokinetics, an acceptable toxicology profile, and robust efficacy in rodent and monkey models of eosinophilia.

While the selectivity of DPC168 with respect to other chemokine receptors, 7-transmembrane G protein-coupled receptors, and biogenic amine transporters was generally high (ranging from 250-fold to greater than 10,000-fold), only 15-fold selectivity was observed for CCR3 binding relative to inhibition of the 2D6 isoform of human cytochrome P-450 (CYP2D6). This was a potential cause of concern, since CYP2D6 contributes to the metabolism of about 20–25% of clinically used drugs, and is also characterized by widespread genetic polymorphism in the general population. Inhibition of this enzyme raised the possibility of unpredictable interactions between DPC168 and other commonly used drugs, including antidepressants, neuroleptics, β-blockers, and antiarrhythmics. In particular, the antitussives dextromethorphan and codeine, both likely to be used by asthmatics, are metabolized by CYP2D6.[15,16]

A likely culprit contributing to the potent CYP2D6 inhibitory activity of DPC168 is the added lipophilicity

Keywords: SAR; Selectivity; CCR3; Chemokine; Cytochrome P-450; CYP2D6.
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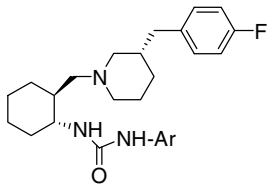
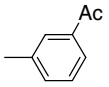
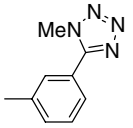
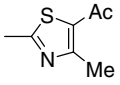
Table 1. In vitro potency and selectivity comparison of DPC168 with two arylurea analogs

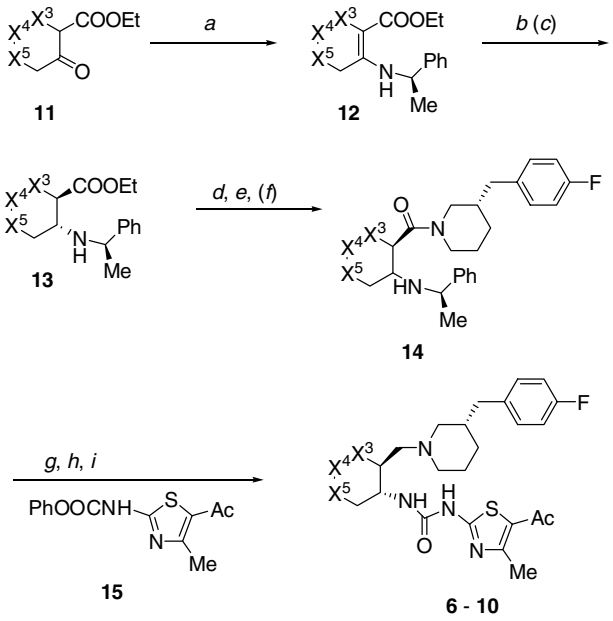


Compound	Ar	CCR3 IC_{50}[a] (nM)	Chemotaxis IC_{50}[b] (nM)	CYP2D6 IC50[c] (nM)
1		2.0	0.034	30
2		0.7	0.010	210
3		0.9	0.030	240

[a] Inhibition of eotaxin binding to CCR3. See Ref. 12.
[b] Inhibition of eosinophil chemotaxis stimulated by eotaxin. See Ref. 13.
[c] Inhibition of oxidative demethylation of a model substrate by CYP2D6. See Ref. 14.

accompanying the incorporation of the cyclohexyl group.[17] Indeed, the analog of DPC168 wherein the 3-(4-fluorobenzyl)piperidine and 3-acetylphenylurea moieties are linked by a simple propylene chain displayed similar CCR3 binding potency (IC_{50} 2.5 nM),[10] yet was much less potent as an inhibitor of CYP2D6 (IC_{50} 680 nM; 270-fold selective). Compounds **2** and **3** (Table 1) demonstrated the possibility of improving the selectivity over CYP2D6 inhibition (300- and 370-fold, respectively) while maintaining or even improving CCR3 antagonism. We sought to improve the selectivity further by replacing the cyclohexyl moiety of DPC168 with less lipophilic heterocyclic rings which would maintain the projection vectors of the benzylpiperidine and arylurea groups.

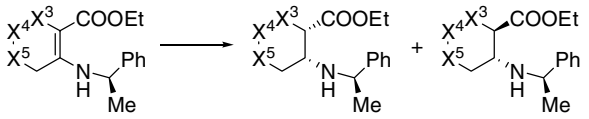
Since 2-amino-4-methyl-5-acetylthiazole (incorporated into **3**) is commercially available, we chose this aromatic group for our SAR exploration of the central region of the molecule. With the exception of **4** and **5**,[18] the compounds were prepared from β-ketoesters **11**, as shown in Scheme 1).[19–21] Condensation of **11** with R-(+)-α-methylbenzylamine provided the corresponding vinylogous carbamates **12**. Reduction to the β-aminoesters **13** proved to be sensitive to the structure of the starting material, as summarized in Table 2. Standard reduction using sodium triacetoxyborohydride (Method A) proceeded with fair to good selectivity in the piperidine cases, providing mostly the expected[22] but undesired *cis* relative stereochemistry, necessitating base-catalyzed equilibration in a subsequent step. However, unexpectedly, the diastereoselectivity of the reduction was much poorer in the case of the tetrahydropyran precursor to **6**. An alternative method, using triethylsilane and trifluoroacetic acid (Method B), was somewhat more diastereoselective and gratifyingly provided the desired *trans* isomer directly. Surprisingly, in the pyrrolidine case leading to **9**, neither Method A nor a modification using



Scheme 1. Reagents and conditions: (a) R-(+)-α-methylbenzylamine, *p*-TsOH, benzene reflux (–H_2O); (b) [see Table 2]; (c) [for **7** and **8**] K_2CO_3, EtOH reflux (7–22% from **11**, with unepimerized material which was separated and recycled); (d) LiOH or NaOH, H_2O–THF, rt; (e) (S)-(+)-3-(4-fluorobenzyl)piperidine, BOP, Et_3N, CH_2Cl_2, rt (60–100% for 2 steps); (f) [for **10**] Oxone, MeOH, H_2O, acetone, rt, 72%; (g) $Pd(OH)_2$ (20% on carbon), H_2 (60 psig), EtOH, rt; (h) BH_3, THF, rt, then HOAc; (i) **15**, acetonitrile, rt (12–42% for 3 steps).

chloroacetic acid in place of acetic acid (Method C) provided the desired product. However, sodium cyanoborohydride in acetonitrile/acetic acid (Method D) provided mostly the desired *trans* aminoester in good yield, but unfortunately with low diastereoselectivity. Both Methods B and C provided the desired *trans* tetrahydrothiophene analog, but with only poor to modest selectivity.

Table 2. Reduction of vinylogous carbamates



Target Compound	X^3	X^4	X^5	Method[a]	Yield[b]	*cis*:*trans*	de[c] (%)
6	CH_2	CH_2	O	A	79%	>9:1	20
6	CH_2	CH_2	O	B	76%	1:3	46
7	CH_2	NBoc	CH_2	A	81%	>9:1	67
8	CH_2	CH_2	NBoc	A	47%	>9:1	50
9	CH_2	NBoc	Bond	C	(nr)		
9	CH_2	NBoc	Bond	D	71%	1:9	26
10	CH_2	S	Bond	A	(nr)		
10	CH_2	S	Bond	B	67%	1:4	36
10	CH_2	S	Bond	C	60%	1:3	56

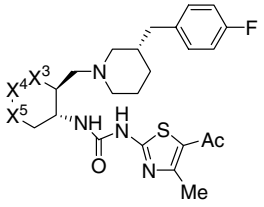
[a] Method A: $NaBH(OAc)_3$, HOAc, acetonitrile, 0 °C. Method B: CF_3COOH, Et_3SiH, rt. Method C: $NaBH(OAc)_3$, $ClCH_2COOH$, acetonitrile, rt. Method D: $NaBH_3CN$, HOAc, acetonitrile, rt.
[b] Overall yield of all isomers; (nr), no reaction.
[c] Diastereomeric excess of major isomer (*cis* or *trans*), based on reverse phase HPLC.

Saponification of the esters and coupling with (S)-(+)-3-(4-fluorobenzyl)piperidine provided the amide intermediates **14**. Reductive removal of the benzylic chiral auxiliary was followed by amide reduction with borane, and urea formation by reaction with the phenoxycarbonylaminothiazole **15**. (In the case of the tetrahydrothiophene derivative, oxidation to the sulfone was performed prior to the reductive debenzylation.) Finally, Boc removal from **7a**, **8a**, **9a**, and **9c**, followed by standard nitrogen derivatization reactions (alkylation, reductive alkylation, acylation), provided the analogs **7c**–**x**, **8c**–**x**, **9b**, and **9d**.

CCR3 binding and CYP2D6 inhibition results for an initial set of different heterocyclic replacements for the cyclohexyl group are shown in Table 3, along with the carbocyclic parent **3**. Calculated log *D* values at pH 7.4 (clog $D_{7.4}$) were determined for the core heterocyclic linkers (lacking the two appendages) and are listed in the table in order to facilitate comparing the relative lipophilicity of the different analogs.[23]

The potencies of the six-membered ring heterocycles (**4**–**8**) varied within a 10-fold range and were similar to that of **3**. The Boc-piperidine analogs (**7a**, **8a**) showed slightly

Table 3. In vitro binding and selectivity data for an initial set of heterocyclic DPC168 analogs



Compound	X^3	X^4	X^5	CCR3 IC_{50}[a] (nM)	CYP2D6 IC_{50}[b] (nM)	linker clog $D_{7.4}$[c]
3	CH_2	CH_2	CH_2	0.9	240	3.39
4	O	CH_2	CH_2	1.7	100	0.89
5	CH_2	O	CH_2	2.0	490	0.89
6	CH_2	CH_2	O	1.0	440	0.89
7a	CH_2	NBoc	CH_2	6.0	570	2.61
7b	CH_2	NH	CH_2	1.9[e]	20,000	−2.10
8a	CH_2	CH_2	NBoc	9.2	160	2.61
8b	CH_2	CH_2	NH	2.1[f]	56,000	−2.10
9a	CH_2	NBoc	Bond	2.6	800	1.39
9b	CH_2	NH	Bond	7.6	28,000	−2.66
9c[d]	CH_2	NBoc	Bond	16.0	1400	1.39
9d[d]	CH_2	NH	Bond	44.0	>100,000	−2.66
10	CH_2	SO_2	Bond	1.2[g]	2100	−0.75

[a] See Ref. 12.
[b] See Ref. 14.
[c] See Ref. 23.
[d] 3,4-*cis*-Disubstituted pyrrolidine.
[e] Chemotaxis IC_{50} 0.10 nM.
[f] Chemotaxis IC_{50} 0.075 nM.
[g] Chemotaxis IC_{50} 0.90 nM.

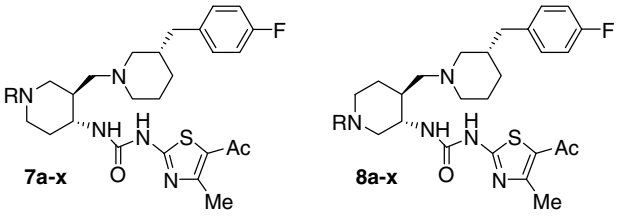
decreased potency, while both *N*-unsubstituted piperidines (**7b**, **8b**) showed excellent binding potency as well as good activity as antagonists of eosinophil chemotaxis. The *trans*-substituted pyrrolidine analogs (**9a**,**b**) showed similar potency, whereas the corresponding *cis* analogs (**9c**, **d**) showed a slightly greater loss in potency. The *trans* compounds in particular can readily adopt a conformation in which the projection of the two substituents approximates that achieved in the six-membered ring cases, although with less rigidity. Interestingly, in the case of **9**, the Boc derivatives were a bit more potent than the unsubstituted analogs, unlike the piperidines **7** and **8**, where the opposite was true. The tetrahydrothiophene sulfone **10**, expected to mimic the six-membered ring more closely due to the larger size of the sulfur atom, was equivalent in binding potency to **3**. However, its potency as an antagonist of chemotaxis was significantly reduced (900 pM vs 30 pM for **3**).[24]

In contrast to the effects on CCR3 binding, the structure of the core ring could have a dramatic effect on CYP2D6 inhibition. Although the three isomeric tetrahydropyran derivatives **4**–**6** would be expected to display greater polarity based on clog $D_{7.4}$, the CYP2D6 inhibition was only slightly impacted. This was also true of the fairly lipophilic Boc derivatives of the nitrogen heterocycles. However, the unsubstituted piperidine and pyrrolidine analogs (**7b**, **8b**, **9b**, **9d**) showed greatly enhanced selectivity for binding over CYP2D6 inhibition. The polar sulfone moiety of **10** also increased the selectivity, although to a lesser extent.

Because both piperidines **7b** and **8b** showed good binding potency and chemotaxis inhibition, as well as a great improvement in selectivity against CYP2D6, a variety of *N*-substituted analogs were evaluated for binding and selectivity. Results of these efforts are shown in Table 4. Interestingly, the potency for CCR3 antagonism of all the analogs shown fell within a 10-fold range, supporting the contention that this region of the molecule has little direct interaction with the receptor. In contrast, dramatic effects were seen on the selectivity toward CYP2D6, where the inhibitory potencies covered a 10,000-fold range.

The compounds in which the piperidine nitrogen was rendered non-basic through acylation or carbamylation tended to display greater selectivity in the '3-aza' series (**8a**,**c**–**n**) than in the '4-aza' series (**7a**,**c**–**n**). The Boc derivatives (**7**/**8a**) were outliers from this gen-

Table 4. In vitro binding and selectivity results for piperidine core analogs



R	Linker clog $D_{7.4}$[a] (nM)	Compound	CCR3 IC_{50}[b] (nM)	CYP2D6 IC_{50}[c] (nM)	Compound	CCR3 IC_{50}[b] (nM)	CYP2D6 IC_{50}[c] (nM)
Boc	2.61	**7a**	6.0	570	**8a**	9.2	160
C(=O)cyclopentyl	2.23	**7c**	2.9	340	**8c**	3.6	910
C(=O)-4-THP[d]	2.23	**7d**	1.2	1200	**8d**	1.5	1800
C(=O)*i*Pr	1.61	**7e**	2.0	50	**8e**	2.1	810
C(=O)OMe	1.38	**7f**	2.3	10	**8f**	4.9	80
C(=O)Et	1.26	**7g**	3.3	140	**8g**	2.1	1500
C(=O)cyclopropyl	1.10	**7h**	3.2	60	**8h**	2.5	80
C(=O)Me	0.73	**7i**	1.3	1400	**8i**	1.9	1300
$C(=O)CH_2OMe$	0.57	**7j**	0.9	1200	**8j**	1.3	1200
C(=O)NHEt	0.35	**7k**	1.5	170	**8k**	1.1	1100
C(=O)NHMe	−0.18	**7m**	0.7	550	**8m**	0.6	1200
$C(=O)CH_2NMe_2$	−0.18	**7n**	1.6	5100	**8n**	1.6	500
CH_2CN	0.80	**7o**	1.3	2000	**8o**	1.2	410
CH_2-2-furyl	0.73	**7p**	0.9	780	**8p**	2.6	170
$CH_2C(=O)Me$	0.72	**7q**	1.3	28,000	**8q**	6.9	3900
CH_2CH_2F	0.58	**7r**	0.9	4300	**8r**	1.2	3300
$CH_2C(=O)NMe_2$	0.03	**7s**	1.8	2800	**8s**	2.0	740
CH_2-cyclopropyl	−0.12	**7t**	4.0	920	**8t**	2.7	2200
1-Ac-4-piperidinyl	−0.35	**7u**	2.2	36,000	**8u**	2.0	1100
1-Me-4-piperidinyl	−0.52	**7v**	2.0	>100,000	**8v**	1.4	12,000
CH_2CH_2OH	−0.58	**7w**	2.3	23,000	**8w**	2.8	12,000
Me	−1.09	**7x**	2.0	2200	**8x**	1.2	7400
H	−2.10	**7b**	1.9	20,000	**8b**	2.1	56,000

[a] See Ref. 23.
[b] See Ref. 12.
[c] See Ref. 14.
[d] THP, tetrahydropyranyl.

eralization, as were the dimethylaminoacetyl derivatives (**7/8n**). However, **7n** and **8n** bear a basic nitrogen on the substituent, and so are more properly considered with other charged analogs (see below). Only some variants provided improved selectivity over the cyclohexyl analog **3**. In neither isomeric series was the correlation between selectivity and the clog $D_{7.4}$ strong, but among structurally similar compounds there was a tendency for more lipophilic analogs to display reduced selectivity (compare **7i**, **7g**, and **7e**). As the substituent became larger (**7d**) the trend was reversed, suggesting a steric clash with the active site. The lack of selectivity of the methyl carbamates (**7/8f**) relative to **3** was quite unexpected. Clearly bulk lipophilicity is unable to completely explain the results observed, suggesting some contribution from specific interactions between the active site of the cytochrome and the substituent on the inhibitor.

In contrast to the results seen with non-basic piperidine derivatives, the alkylated derivatives **7/8o–x** were almost all significantly more selective than **3** for CCR3 over CYP2D6, indicating that the second positive charge present at physiological pH is poorly tolerated by the CYP2D6 active site. The unsubstituted analogs **7/8b** and the dimethylaminoacetamides **7/8n** should be considered with this group as well, since they also bear a second positive change. Unlike the acylated derivatives discussed above, the '4-aza' charged analogs (**7**) usually but not always showed greater selectivity than the '3-aza' series (**8**). As was the case for the acylated compounds, there was little correlation of selectivity with calculated polarity for the doubly charged compounds (compare, for example, **7/8w**, **7/8s**, and **7/8q**). Interestingly, these trends were the same in both isomeric series (**7** and **8**).

While the doubly changed analogs tended, as a group, to demonstrate better selectivity, this advantage was accompanied by a liability not wholly unexpected. Almost without exception, these compounds showed very poor potential for absorption as estimated using the Caco-2 model system (data not shown). The apparent permeability generally fell below 2.5×10^{-6} cm/s, and was in many cases unmeasurable.

The more selective acylated derivatives were expected to be somewhat better absorbed, although the Caco-2 apparent permeability values (2.5×10^{-6}–5.5×10^{-6} cm/s) were still significantly lower than that observed for DPC168, which was well-absorbed (see Table 5). Considering these results, as well as the measured degree of protein binding in human serum and the expected metabolic liability (estimated by incubation with hepatocyte microsomes, data not shown), compound **8i** (BMS-570520) emerged as the analog with the best overall balance of selectivity and predicted pharmacokinetic characteristics. BMS-570520 was compared with DPC168 in a variety of in vitro and in vivo models, with the results shown in Table 5. Very similar CCR3 potency and in vitro efficacy in chemotaxis and calcium mobilization assays were observed for the two compounds. Selectivity was improved or maintained against not only CYP2D6, but also against other 7-transmembrane G protein-coupled receptors, biogenic amine transporters, and the hERG potassium channel. Pharmacokinetic parameters were similar in the mouse and improved in the Cynomolgus monkey, despite the reduced absorption predicted by the smaller Caco-2 permeability. Poorer absorption was, however, consistent with the reduced bioavailability of **8i** in the chimpanzee. Both **1** and **8i** showed good activity in two murine models of CCR3 antagonism. The greater in vitro potency of compound **8i** against mouse CCR3 was reflected in vivo in the mouse intranasal eotaxin challenge model.[25]

Table 5. Comparison of potency, selectivity, pharmacokinetic, and in vivo efficacy results for DPC168 (**1**) and BMS-570520 (**8i**)[a]

Assay or PK parameter	Compound **1**	Compound **8i**
CCR3 IC_{50} (nM)	2.0	1.9
Chemotaxis IC_{50} (nM)	0.034	0.068
Ca^{2+} mobilization IC_{50} (nM)	8.0	2.6
CYP2D6 IC_{50} (nM)	30	1300
$5HT_{2A}$ IC_{50} (nM)	920	5300
D_2 IC_{50} (nM)	1000	640
Serotonin transporter K_i (nM)	2900	29,000
Dopamine transporter K_i (nM)	490	6500
Norepinephrine transporter K_i (nM)	950	7700
hERG IC_{50} (nM)	400	6000
Mouse F (%)	20	25
Mouse $t_{1/2}$ (h)	2.0	1.2
Mouse CL (L/h/kg)	1.8	2.5
Cyno F (%)	8	18
Cyno $t_{1/2}$ (h)	4.0	5.5
Cyno CL (L/h/kg)	2.1	0.87
Chimp F (%)	22	7
Chimp $t_{1/2}$ (h)	5.0	4.5
Chimp CL (L/h/kg)	1.2	1.3
Protein binding (human, %)	96.3	93.1
Caco-2, Papp (cm/s)	11×10^{-6}	2.8×10^{-6}
Intrinsic clearance (L/h/kg)	0.97	0.96
Mouse CCR3 IC_{50} (nM)	54	3.6
Mouse chemotaxis IC_{50} (nM)	41	7.0
Mouse eotaxin challenge EC_{50} (mg/kg)	20	1.5
Mouse OVA challenge (% inhibition at 100 mg/kg bid)	86%	82%

[a] See Refs. 11,25 for descriptions of the assays and tests, the results for compound **1**, and the in vivo results for compound **8i**.

In summary, heterocyclic replacement of the cyclohexyl linker ring of the potent, efficacious CCR3 antagonist DPC168 led to significant improvement in selectivity with respect to CYP2D6 inhibition. Incorporation of a nitrogen in the ring allowed the preparation of analogs which showed dramatic improvement while retaining binding and chemotaxis potency, leading to the discovery of BMS-570520, a more selective compound with a very similar activity profile. Increasing the polarity of the central portion of molecule, while retaining the projection vectors of the 3-benzylpiperidine and arylurea moieties, is a viable approach for improvement of the preclinical profile of this series of antiinflammatory compounds.

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13. The chemotaxis assay was carried out using eotaxin and human eosinophils in 96-well chemotaxis chambers, as described in Ref. 9.
14. Inhibition of CYP2D6 was evaluated using recombinant human enzyme (prepared from baculovirus-infected insect cells) in 96-well plates in the presence of an NADPH generating system. The model substrate 3-[2-(*N*,*N*-diethyl-*N*-methylamino)-ethyl]-7-methoxy-4-methylcoumarin was used at a single concentration (approximately the apparent K_m), with production of 3-[2-(*N*,*N*-diethylamino)ethyl]-7-hydroxy-4-methylcoumarin monitored by fluorescence detection. Multiple concentrations of inhibitor, separated by half-log units, were evaluated in duplicate and the IC_{50} was determined. Quinidine served as a positive control.
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