A polyoxometalate-functionalised amino acid for automated solid-phase peptide synthesis of sidechain-metallo-peptides

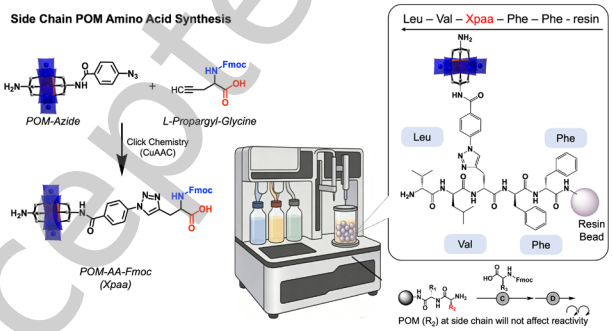
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Abstract: The Fmoc-protected precursor of an unnatural polyoxometalate amino acid (POM-AA, X_{paa}), in which an Anderson–Evans (AE)-type POM cluster is carried on the side chain, has been synthesised and used directly as a building block in standard automated solid-phase peptide synthesis. A tris(hydroxymethyl)azidobenzamide ligand was first grafted onto an AE-POM, and its azide handle was then linked to Fmoc-protected propargylglycine by a click reaction. Because the POM cluster is confined to the side chain, the amino-acid backbone retains its native reactivity: chain assembly proceeds by routine in situ coupling, without the pre-formed Fmoc amino-acid anhydrides required in our previous main-chain POM-peptide synthesis. Four positional isomers of X_{paa}LVFF were assembled on a commercial automated synthesiser. This work provides a practical route to peptides bearing POM side chains and points towards a new class of artificial metalloproteins, the polyoxometalloproteins.



Keywords: polyoxometalate, automated solid-phase peptide synthesis, sidechain-peptide, click reaction, Fmoc-protection

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1 Introduction

The function of a peptide or protein is defined by its amino acid sequence. Every residue shares the same α-amino acid core and is distinguished by its side chain, which determines its role in the folded structure – as a catalytic group in an enzyme active site, for example, or as a structural element of a large protein such as titin.[1-2] Side chains can be decisive: replacing a single residue in haemoglobin causes sickle cell anaemia.[3] The twenty natural amino acids thus constitute the alphabet of protein synthesis, but their side chains are limited to organic functional groups.

Unnatural amino acids (UAAs) with tailored side chains extend this alphabet far beyond nature's repertoire.[4-5] Side-chain engineering is now a mainstream tool in peptide and protein science, underpinning antiviral peptides,[6] bioorthogonal therapeutics,[7] antibody–drug conjugates,[8-14] imaging agents,[15-18] localisation markers,[19-20] antimicrobial peptides,[21-24] catalytic systems[25-26] and conformational probes.[27] Inorganic units – metal clusters,[28-30] coordination complexes[30-32] and polyhedral oligomeric silsesquioxanes[33] – have also been introduced into peptides, yielding valuable probes and diagnostic agents,[28-33] but these constructs are typically assembled by manual synthesis, which limits sequence control and automation.

Polyoxometalates (POMs) are discrete anionic metal-oxide clusters whose redox, catalytic and photochemical properties make them attractive both for interactions with biological systems[34-37] and for incorporation into proteinogenic molecules.[38-40] A common obstacle to their use is hydrolytic instability, but the Anderson–Evans (AE) cluster is an exception: it is comparatively robust and can be functionalised through condensation of tris(hydroxymethyl)aminomethane (Tris)-derived ligands with its six μ_3-bridging hydroxyl groups – chemistry that our group has explored extensively.[41-48] Often termed the "Bio-POM", the AE cluster also carries a tuneable transition-metal heteroatom at its centre.[36] Building on these features, we previously incorporated AE-POMs into peptide main chains via amide bonds, generating a series of POM-peptides.[39] In that system, however, the POM sat inside the backbone: its steric bulk and electron-withdrawing character strongly suppressed chain reactivity, so every residue added after the POM amino acid had to be coupled as a pre-formed fluorenylmethoxycarbonyl group (Fmoc) protected amino-acid anhydride rather than by standard in situ activation.[39] Here, we take a complementary approach: an AE-POM is clicked onto the side chain of propargylglycine, furnishing an Fmoc-protected POM amino acid (POM-AA, X_{paa}, Figure 1) that behaves like a conventional building block in automated solid-phase peptide synthesis (SPPS).

Just as natural amino acids serve as building blocks for everything from enzymes to small-molecule drugs, an Fmoc-protected POM amino acid based on the AE scaffold can serve as a general reagent for introducing metal-oxide clusters into peptides and proteins, opening routes to artificial metalloproteins, peptidomimetic drug candidates and specialised labelling agents. Rather than designing a single-purpose construct, our aim is a modular building block that works with established synthetic methodology and expands the accessible chemical space in three directions: (i) an unnatural amino acid bearing an inorganic side chain; (ii) a general strategy for constructing metalloproteins with metal-oxide clusters on side chains; and (iii) an adaptable SPPS reagent whose scope surpasses that of most UAAs reported to date.

The novelty of this work is as follows. First, in contrast to our

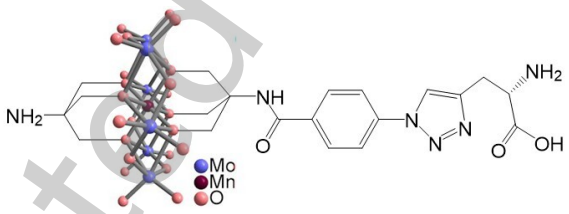


Figure 1. Structure of POM-AA. The POM cluster shown in the structure is a manganese centred Anderson-Evans polyoxometalate $\{MnMo_6O_{24}\}$.

previous POM-peptides, in which the AE-POM units were embedded in the peptide backbone,[39] this is the first synthesis of peptides bearing AE-POM clusters on side chains; because the α-amino and α-carboxyl groups of the residue remain unperturbed, all subsequent residues couple by routine in situ activation, without the pre-formed Fmoc amino-acid anhydrides that were indispensable in the backbone system. Second, click chemistry[49-53] and Fmoc protection – previously used in separate systems – are combined here in a single POM-AA-Fmoc precursor (**3**) (Scheme 1) that closely resembles a standard amino acid and enters SPPS directly with residue-specific precision. Third, we determined the single-crystal X-ray structure of the large POM-AA-Fmoc (**3**) molecule, a rare structural characterisation of such a complex hybrid. Finally, the four positional isomers of the X_{paa}LVFF series provide a first platform for probing how the position of a POM side chain modulates the properties of a biologically relevant sequence.

2 Results and discussion

2.1 Ligand synthesis

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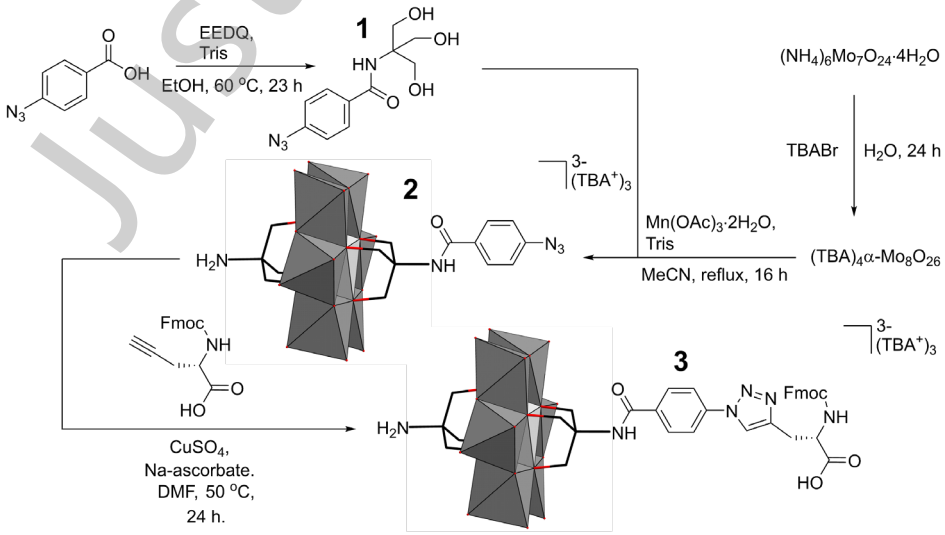
The first step in preparing the POM-AA-Fmoc building block (**3**) was the synthesis of the 4-azidobenzamide-Tris ligand (**1**), which serves as the key linker between the AE-POM and the amino-acid unit (structure shown in Scheme 1). The synthetic route to **1** was adapted from our previous work,[51, 53] with notable improvements in both practicality and yield. In earlier studies, a solution of 4-azidobenzoic acid, N-methylmorpholine, and ethyl chloroformate in THF was cooled to 0 °C and added directly to a solution of Tris and triethylamine in DMF, followed by stirring for 16 hours. We found that ligand **1** could instead be obtained simply by heating 4-azidobenzoic acid, Tris, and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline at 60 °C in ethanol for 23 hours, affording a higher yield with substantially reduced experimental effort and avoiding more hazardous reagents. Ligand **1** was fully characterised by ^{1}H NMR spectroscopy and single-crystal X-ray diffraction (Table S5 and Figure S11).

2.2 POM-Azide synthesis

The POM-Azide **2** was next obtained following another procedure from the established literature.[51] $(TBA)_4[Mo_8O_{26}]$ and $Mn(OAc)_3$ was refluxed in acetonitrile with an excess of **1**, transitioning from a deep red to bright orange solution over the course of 16 hours. At this point, the POM-Azide **2** had been successfully synthesized but further purification was necessary as **2** is one of three compounds formed as part of a statistical product distribution consisting of two symmetric products (AA: 25%, BB: 25%) and the target asymmetric (AB: 50%) form (Figure S2). Reverse phase chromatography with acetonitrile and 10 mM TBA·Br solution on a C-18 column was used to isolate the desired product **2**. Once isolated, the product was concentrated into a precipitate and recrystallized from DMF by Et_2O diffusion giving a pure product (yield 42% based on Mo). The recrystallization served a dual purpose of ensuring sufficient purity for further synthesis steps and providing single crystals for X-ray diffraction structure determination which allowed further characterisation. The ^{1}H NMR spectrum of **2** can be broadly described as a lower resolution form of **1** with a significant broadening and lack of definition observed in multiplets which stem from H's directly attached to the ligand system; 7.14 (m, 2H, CH), 7.83 (bs, 2H, CH). Finally, the indicative tris-functionalised AE-POM peak can be observed at 62.3 (br, 12H, CH_2). Regarding ESI-MS we consider the molecular ion peak of **2** to be $(MHTBA)^-$ which was observed at m/z 1543 (Figure S4). Crystal structure results of **2** from x-ray diffraction are shown in Table S6 and Figure S12.

2.3 POM-AA-Fmoc synthesis

The last step in the building block synthesis is the preparation of the POM-AA-Fmoc 3 by a Cu-catalysed click reaction. Similar click reaction of AE-POM derivative was documented in literature.[53] It was previously thought that a $CuSO_4$/Na-ascorbate catalytic mixture would not be compatible with the Mn-centred AE POM due to the ease with which it is reduced, causing "rapid formation of a bright blue precipitate",[51] indicative of Mo-blue formation from $Mo^{VI} \rightarrow Mo^{V}$ reduction. We found that the click reaction between POM-Azide (**2**) and Fmoc-L-Propargyl-Glycine using $CuSO_4$/Na-Ascorbate proceeded as intended without uncontrolled reduction of Mo centres. Precipitate did form in solution during the reaction, but this is attributed to displacement of counter-cation tetrabutylammonium (TBA) with Cu^{2+} ions making the POM-based structure insoluble in the organic solvent, rather than reduction of Mo^{VI}. In fact, we found that addition of excess TBA-Br resolubilized the precipitate back into solution, causing no additional complications to the synthesis. This finding overturns the previous assumption that redox-active Mn-Anderson clusters are incompatible with the Cu-catalyzed azide–alkyne cycloaddition conditions and considerably simplifies the preparation of clicked POM architectures. Reaction progress was monitored by FTIR spectroscopy through the disappearance of the characteristic azide band at 2124 cm^{-1}. After completion, the POM-AA-Fmoc



Scheme 1 Complete synthetic procedure for the POM-AA-Fmoc (**3**) from commercially available starting reagents.

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(**3**) was isolated in moderate yield (65%) and characterized by ^{1}H NMR, ESI-MS (Figure 2, Table S1) and FTIR analysis. The ^{1}H NMR spectrum of **3** (Figure S9) is comparable to that of **2** but with significantly more peaks in the aryl region owing to the introduction of the Fmoc moiety (δ = 7.26 (bs, 2H, CH), 7.32 (bs, 2H, CH), 7.65 (bs, 2H, CH), 7.87 (bs, 4H, CH), 7.96 (s, 2H, CH)). Two diagnostic signals confirm successful production of **3**: a triazole ring proton at δ = 8.58 (s, H), indicating completion of the click reaction, and a broad resonance at δ = 62.7 (12H, CH_2), demonstrating that the AE-POM framework remains intact. The ESI-MS spectrum (Figure 2) further supports the identity of **3**, with all major m/z peaks corresponding to the POM-AA-Fmoc ion (M^{-3}) bearing either H^+ or TBA^+ counter-cations. FTIR analysis provides additional structural confirmation. Loss of the azide band at 2124 cm^{-1} and emergence of the triazole-associated features corroborate the click transformation, while the C–O vibration at 1028 cm^{-1} verifies retention of the tris-based triols on the POM. The shoulder around 3300 cm^{-1} indicates the continued presence of the free -NH_2 group on the non-functionalized face of the AE-POM (Figure S7). The structure of POM-AA-Fmoc (**3**) was further confirmed by crystal structure determinations (Table S7 and Figure 2 and S13) which clearly establishes the presences of the tris-modified AE-POM cluster, triazole ring, and the Fmoc group connected through benzamide linker. The successful crystallographic characterisation of such a large and intricate hybrid molecule represents a rare example within this class of POM–organic conjugates.

2.4 Automated SPPS of POM-Peptides

After obtaining the POM-AA-Fmoc (**3**), we selected the tetrameric residue (LVFF) from the cationic domain (Aβ$_{13\text{-}20}$, HHQKLVFF) of the amyloid beta (Aβ) aggregation core as a model sequence. Aβ is one of the main components of amyloid plaques which play a key role in the pathogenesis of Alzheimer's disease.[54] It was reported that highly negative POMs can inhibit Aβ aggregation into fibrils due to strong electrostatic interaction between POM anions and the cationic domain of the core.[55-56] Additionally, we reasoned that incorporation of the POM-AA (X_{paa}) into multiple different positions within the LVFF chain (X_{paa}LVFF, LX_{paa}VFF, LVX_{paa}FF and LVFX_{paa}F) would serve as a significant challenge with which to measure the synthetic versatility of the reagent within a commercial SPPS platform. For the reasons outlined above, synthesis of these compounds would represent a proof of concept for the utility of the POM-AA as a practical UAA reagent, as well as showcasing unique functional molecules which are made possible by introduction of AE-POMs into proteinogenic molecules.

The POM-Peptide positional isomer series (X_{paa}LVFF, LX_{paa}VFF, LVX_{paa}FF and LVFX_{paa}F) (Figure 3) were prepared by standard DIC/HOBt double coupling, using a DMF solution of the POM-AA-Fmoc (**3**) alongside commercially available Fmoc-protected amino acid solutions. The unprotected N-terminus of POM-AA is unreactive towards DIC/HOBt coupling: rationalised as a result of a mixture of steric hindrance and electronic withdrawing effects of the POM, making the probability that the Tris amine will be incorporated into the peptide chain overwhelmingly unfavourable, and ensuring only the amino acid amine site is involved in the amide coupling.[45] Equally importantly, because the POM cluster is appended on the side chain, its steric bulk and electron-withdrawing influence are diverted away from the growing chain terminus: all four positional isomers were assembled using the same DIC/HOBt double-coupling protocol applied to the flanking natural residues, and no pre-activation of subsequent amino acids was required at any stage. This contrasts sharply with our previous main-chain POM-peptide chemistry, in which incorporation of the POM amino acid into the backbone drastically suppressed chain reactivity, and every residue installed after the POM unit

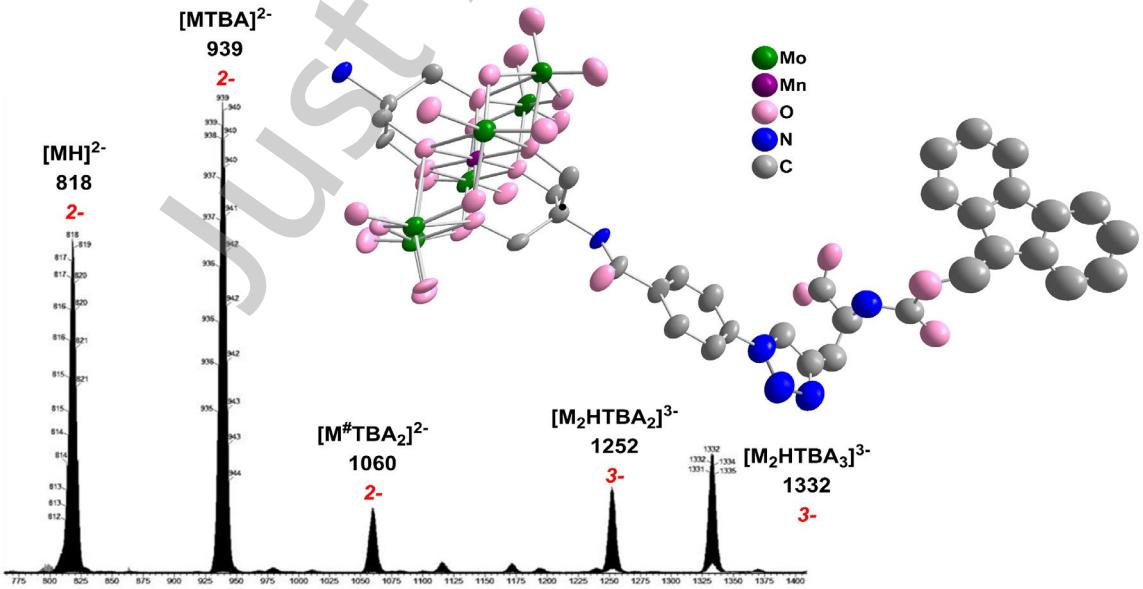


Figure 2. ESI-MS spectrum and crystal structure (thermal ellipsoids drawn at 30%) of POM-AA-Fmoc (**3**). M = $[MnMo_6O_{24}(C_{31}H_{28}N_5O_5)(C_4H_8N)]^{3-}$; TBA = $C_{16}H_{36}N^+$; #deprotonated at carboxylic group

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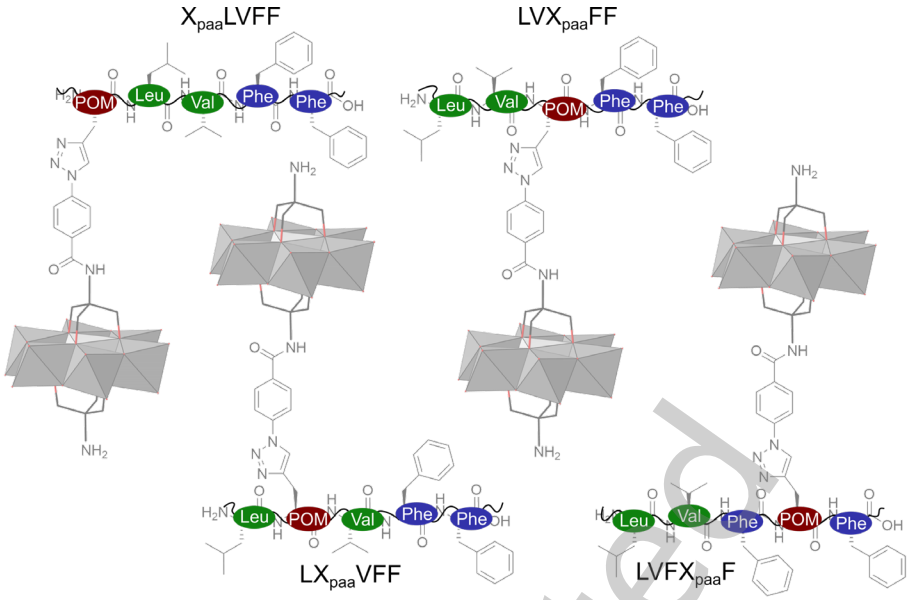


Figure 3. POM-Peptides represented in abstract form with amino acids assigned by three letter codes, superimposed over the skeletal structure of the compounds. X_{paa} and POM represent the single and three letter codes of POM-AA respectively.

had to be coupled as a pre-formed Fmoc amino-acid anhydride.[39] The peptide chains were constructed using a conventional automated SPPS process using a Biotage® Initiator+ Alstra™ Microwave Peptide Synthesizer, following the classical peptide synthesis procedure (as shown in Supporting information). Successful synthesis of the target peptides was confirmed by ESI-MS (Figure S10 and Table S4). Additional information and further detail about the SPPS process can be found in the ESI.

The synthesis of the POM-Peptides demonstrates that the POM-AA-Fmoc (**3**) is a versatile reagent and flexible in terms of positional control with a commercial SPPS. We have found that not only is it possible to incorporate a POM-AA residue into a peptide chain, but that it is effectively facile to produce a POM-Peptide on a SPPS platform, appearing to have no synthetic complexity beyond what would be expected of conventional SPPS: once the POM-AA-Fmoc (**3**) is available, standard SPPS protocols can be used to incorporate it at multiple positions using unmodified protocols, standard solvents and standard coupling agents. Moreover, the availability of all four positional isomers provides a systematic handle on how the position and spacing of an anionic POM side chain modulate peptide properties – an aspect that is inaccessible in backbone-POM constructs.

3 Conclusions

To summarise, we have detailed a synthetic protocol for the preparation of an artificial amino acid which allows residue-specific placement of a chemically complex polyoxometalate cluster in a peptide chain. Using well established click chemistry procedures that were thought to be incompatible with AE POM clusters, it was possible to link the cluster to a commercially available propargylglycine. Once the amino acid functionality had been paired with the POM, we found that the POM-AA-Fmoc (**3**) was readily used as an SPPS reagent in an automated platform. Critically, because the POM cluster is confined to the side chain, the amino-acid backbone of the residue retains its native reactivity: residues installed after the POM-AA couple under standard in situ DIC/HOBt activation, in sharp contrast to our earlier main-chain POM-peptides, in which incorporation of the POM into the backbone drastically diminished chain reactivity and made pre-formed Fmoc amino-acid anhydrides indispensable for every residue following the POM unit. In this sense, the present building block behaves far more like a natural amino acid, and its availability opens a new direction for the fully automated synthesis of POM-peptides – one in which the influence of the POM as a peptide side chain, including its charge, intrinsic catalytic activity and tunability through the central heteroatom, can be explored at any position of a peptide sequence. Fundamentally, this work provides a highly accessible route for precise covalent attachment of reactive polyoxometalate species to proteinogenic structures.

Electronic Supplementary Material: Supplementary material (synthesis, flash chromatography, NMR spectroscopy, electrospray ionization mass spectrometry, and X-ray single crystal structure description) is available in the online version of this article at https://doi.org/10.26599/POM.2026.9140173.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be obtained from the corresponding author upon request.

The X-ray crystallographic data have been deposited at the Crystallographic Data Center with codes CCDC 2346968-2346970, which can be obtained free of charge via

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Declaration of competing interest

There are no conflicts to declare. Author De-Liang Long is the advisory board member of this journal, but he is not involved in the peer-review or decision of this article.

Author contribution statement

S. S. and Z. G.: Data curation, validation, writing and editing manuscript. J. A.: Data validation. P. K.: Data validation, editing manuscript, project team leader. D.-L. L.: Data curation, validation, writing and editing manuscript, project team leader. L.C.: Project administration, funding acquisition, supervision. All the authors have approved the final manuscript.

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None.

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