Enhanced Antimalarial Activity of Novel Synthetic Aculeatin Derivatives

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Abstract: We report the design, synthesis, and in vitro evaluation of novel polyspirocyclic structures, inspired by the antimalarial natural products, the aculeatins. A divergent synthetic strategy was conceived for the practical supply and has allowed the discovery of two novel and more potent analogues active on the *Plasmodium falciparum* 3D7 strain. Moreover, these compounds proved to be potent against *Toxoplasma gondii*. A number of features that govern these inhibitions were identified.

Malaria is the most widespread parasitic disease in tropical and subtropical regions, and its burden steadily increases, infecting 300-500 million people and killing 1-3 million people a year.^{1,2} This major disease is caused by blood protozoan parasites of Plasmodium genus classified in the Apicomplexa phylum, of which the most deadly species is Plasmodium *falciparum*. The rise of malaria death toll is notably due to the spread of resistance to all currently used antimalarial drugs, artemisinin derivatives still remaining an exception, although forerunners of resistant forms have recently given cause for concern.³ There is thus a constant need for the search for novel antimalarial molecules. Priority should be given to approaches with novel mechanisms of action and whose compounds are structurally unrelated to existing antimalarial agents. These new compounds would keep a therapeutic rampart in controlling malaria.4

Natural products extracted from traditional medicines (e.g., quinine and more recently artemisinin) have provided the starting point for the discovery of the most efficient antimalarial drugs.^{4–8} In 2000, a novel type of polyspirocyclic natural products, the aculeatins (Figure 1), was isolated from the rhizome of *Amomun aculeatum* by Heilmann and co-workers.⁹ This plant has been used in the folk medicine of Papua New Guinea to treat fever and malaria.¹⁰ Very recently, Kinghorn and co-workers have isolated from the leaves and rachis of *Amomun aculeatum* new members of this family, the aculeatols, the amomols, and novel analogues of aculeatin having a shorter lipophilic side chain.^{11,12} Some of these compounds showed interesting antimalarial activities with inhibitory effects in the submicromolar range, and especially against *P. falciparum* strain



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Figure 1. Antimalarial activity of aculeatins.

Scheme 1. Synthesis of **2** as Key Precursor for Accessing to New Analogues $\mathbf{1}^a$



^{*a*} Reagents and conditions: (a) BnBr, NaOH, Bu₄NHSO₄ cat., THF, 99%; (b) (COCl)₂, CH₂Cl₂, 4 h, then Meldrum's acid, pyridine, CH₂Cl₂, 0°C; (c) EtOH, reflux (72% from 4); (d) H₂, Pd/C, AcOEt, 99%; (e) 1,3-propanedithiol, BF₃·Et₂O, CH₂Cl₂, 79%; (f) DIBAL-H, toluene, -78° C, 73%.

K1 (Figure 1), with a low cytotoxicity against human cell lines in vitro.^{9,12} A selectivity for MCF-7 cells in an in vivo hollow fiber assays has been reported for aculeatin A.¹²

A few years ago, we selected the aculeatins to start a program aiming to develop new antiprotozoal agents inspired by natural products. Interestingly, aculeatin A was described to be 5-fold more efficient than aculeatin D (Figure 1) based on in vitro proliferation assays of P. falciparum strain K1, suggesting that a biological selectivity could arise from a proper spatial arrangement of the polyspiro structure and their appendage orientations. Moreover, this unexplored biologically active scaffold represents a family of new probes, with the prospect that new antimalarial biological targets, directly or indirectly interacting with this scaffold, could be identified in the future.¹³ We report here the evaluation of new aculeatin analogues and the discovery of improved antimalarial compounds, with the identification of features contributing to their biological activity. Recently, we were keen to develop novel diastereodivergent and tandem one-pot synthetic approaches giving rise to desired molecules within few steps.^{14,15} Although quite complex polyspirocylic structures are targeted, the synthesis of new aculeatin analogues 1 (Scheme 1) is designed in a practical manner that allows a specific structural variability, mainly located at the R tail position. All these new derivatives are conveniently derived from a common precursor 2.

An approach allowing large amounts of products to be handled was desired to synthesize the key precursor 2. Starting from the acid 3 protected as a benzylated derivative 4, the corresponding acyl chloride was condensed with Meldrum's acid to afford 5, which was then refluxed in ethanol to give the



^{*a*} Reagents and conditions: (a) THF, -78° C, 80%; (b) toluene, 110° C; (c) Et₃B, NaBH₄, THF/MeOH (4:1), -78° C; (d) (CH₃)₄NBH(OAc)₃, CH₃CN/AcOH (4:1), 0°C; (e) NaBH₄, MeOH/CH₂Cl₂, 0°C; (f) PIFA, acetone/H₂O, 15 min.

 β -ketoester **6** (71% overall yield from **3**). Hydrogenation of **6** gave the phenol β -ketoester **7**, which was next transformed into the dithiane ester **8**. Finally, reduction with DIBAL-H gave the corresponding aldehyde **2** in good yield.

To introduce different lipophilic side chains, the dioxinone (\pm) -10 was prepared by condensing the aldehyde 2 with the lithiated dioxanone dienol ether 9 (Scheme 2). The dioxinone functional group of (\pm) -10 allows the facile addition of various nucleophiles 11a-e by simply heating both reactants in toluene, giving rise to a series of β -ketoesters (\pm) -12a-e.¹⁶ Although the yields range from 35% to 64%, it is noteworthy that neither the secondary alcohol nor the phenol group of (\pm) -10 needs to be protected.¹⁷

Hydroxyl-directed selective reductions of (\pm) -**12a**–**d** were successfully applied to obtain syn diols (\pm) -**13a**–**d**¹⁸ or anti diols (\pm) -**14b,c**.¹⁹ Same conditions were applied to the β -ketoamide (\pm) -**12e** but failed to run the reactions until completion resulting in poor yields. The β -ketoamide (\pm) -**12e** was finally reduced by NaBH₄, yielding an inseparable mixture of diastereomers (\pm) -**13e**/**14e** (76%).

According to our previous work,¹⁴ the diols (\pm) -**13a**-**d** and (\pm) -14b,c were treated by phenyliodine(III) bis(trifluoroacetate) reagent (PIFA) in acetone/H₂O to promote a tandem phenolic oxidation/dithiane deprotection sequence leading to the formation of aculeatins polyspirocyclic structures. Hence, the transformation of syn diols (\pm) -13a-d gave two separable aculeatin derivatives (\pm) -15a-d (12-19%) and (\pm) -16a-d (11-21%), as analogue of aculeatins A and B, respectively, whereas the anti diols (\pm)-14b,c led to two separable products (\pm)-17b,c (16%) and (\pm) -18b,c (16–17%), as analogues of aculeatins D and 6-epi-D, respectively. The mixture of syn/anti diols (±)-13e/14e gave with PIFA a mixture of stereoisomers of which only (\pm) -15e (9%) could be isolated from the other products by flash chromatography. Comparisons of the NMR data of (\pm) -15a-e, $(\pm)-16a-d$, $(\pm)-17b$, c, and $(\pm)-18b$, c with those arising from previous configurational NMR studies of natural products^{12,14c,15b,c} allow the assignment of their structures.

Scheme 3. Synthesis of (\pm) -20, (\pm) -21, and 22 (with Representative NOE Signals) and Further Derivations To form (\pm) -25a-c and 26a,b^{*a*}



 a Reagents and conditions: (a) (i) BF_3.OEt_2, $-78^\circ C,$ CH_2Cl_2; (ii) TBAF, THF; (b) PIFA, acetone/H_2O, 18 h; (c) DMAP, Et_3N, CH_2Cl_2; (d) THF, reflux, 6 h.

To explore the biological effect of cyclohexadienone ring, we suspected that introducing twice this moiety on the same molecule, while keeping a polyspirocyclic structure, would amplify the putative pharmacophoric feature. Within the context of our oxidative spiroannulation strategy, we envisioned that the diphenolic product 20 should be the precursor of choice (Scheme 3). Compound 20 in racemic form was easily obtained in good yield (84%) by the reaction of the aldehyde 2 with the enoisslane $19^{14\mathrm{b}}$ according to the Mukaiyama coupling reaction, followed by a treatment with TBAF to remove all silvl groups. When treating this linear precursor (\pm) -20 with PIFA in acetone/ H₂O, we were pleased to mainly obtain in one step two novel and complex structures (\pm)-21 (19%) and 22 (11%) having five successive spirocyclic rings in junction. As evidenced by the NMR spectroscopy, product 22 has a symmetric structure and NOE measurements assigned the configuration, notably with the NOE signals observed between the axial proton at geminal position of the hydroxyl group and the protons of both cyclohexadienone rings. For product (\pm) -21, representative NOE signals also confirm the configuration. No NOE signal between the proton at geminal position of the hydroxyl and the proton of cyclohexadienone ring has been observed, suggesting that the hydroxyl group is at axial position.

To restore the hydrophobic part of aculeatins, different lipophilic chains were grafted on the remaining hydroxyl group, either with the acyl chlorides **23a**,**b** or by heating with **24** to give either the polyspirocyclic esters (\pm) -**25a**,**b** and **26a**,**b** or the polyspirocyclic β -ketoester (\pm) -**25c**, respectively.

Finally, to verify the plausible role of the cyclohexadienone ring on the biological activity, (\pm) -aculeatin A^{14a} was converted into the cyclohexanone derivative (\pm) -**27** by catalytic hydrogenation with palladium (Scheme 4). A dramatic decrease in activity should confirm that the cyclohexadienone ring plays a crucial role.

Considering that another pathogenic member of the Apicomplexa phylum includes *Toxoplasma* species, the series of natural and non-natural aculeatins A, B, D and 6-*epi* D^{14b} and the new synthesized analogues were evaluated for their potency against both *P. falciparum* 3D7 and *Toxoplasma gondii* RH- β 1 (Table 1). We also tested our compounds for their toxicity against mammalian cells using the human erythroblasts K562 to

Table 1. In Vitro Activity of the Compounds against the Parasites *Plasmodium falciparum (P.f.)* and *Toxoplasma gondii (T.g.)* and against the Human Erythroblasts (h.e.) $K-562^a$



IC50 (µM) compd substituent CC50 (µM), h.e. K-562 P.f. 3D7 T.g. RH- $\beta 1$ 0.008 chloroquine 9.7 (-)-aculeatin A^b 25.5 0.288 0.309 27.5 (+)-aculeatin B^{*b*} 0.454 0.365 (+)-aculeatin D^b 28.0 0.478 0.640 (+)-aculeatin 6-epi-D⁶ 30.2 0.451 0.377 25.8 0.436 (+)-aculeatin A⁴ 0.335 (-)-aculeatin B^c 22.1 0.329 0.627 (-)-aculeatin D^a 26.70.220 0.436 (-)-aculeatin 6-epi-D⁶ 30.8 0.366 0.400 $X = O; R^3 = (CH_2)_2 CH_3$ 1.840 109.3 0.500 $(\pm)-15a$ $X = O; R^3 = (CH_2)_9 CH_3$ $(\pm)-15b$ 28.20.654 0.341 $X = O; R^3 = (CH_2)_{17}CH_3$ 13.9 0.770 (±)-15c 2.40 $X = O; R^3 = CH[(CH_2)_9]CH_3]_2$ $(\pm)-15d$ 22.1 1.151 4.45 $(\pm)-15e$ $X = N(CH_2)_5CH_3; R^3 = (CH_2)_5CH_3$ 0.39 0.899 ND 41.2 1.364 1.63 (\pm) -16b 17.5 3.54 $(\pm)-17c$ 1.031 (±)-18c 15.6 1.133 3.52 Z = H0.39 $(\pm)-21$ 0.414 0.173 $(\pm)-25a$ $Z = CO(CH_2)_5CH_3$ < 0.38 0.343 ND $Z = CO(CH_2)_{12}CH_3$ 0.081 0.346 $(\pm)-25b$ 8.75 $(\pm)-25c$ $Z = COCH_2CO(CH_2)_{12}CH_3$ < 0.38 0.120 ND 22 1.50 Z = H0.584 cytot. 26a $Z = CO(CH_2)_5CH_3$ < 0.38 0.331 ND $Z = CO(CH_2)_{12}CH_3$ 26b 11.3 0.092 0.636 $(\pm)-27$ 25.6 >5 11 (+)-2817.6 4.80 ND (-)-29 34.5 > 10ND

^{*a*} All IC₅₀ values were calculated from experiment carried out in triplicate on *T.g.* and from two independent experiments carried out in duplicate on *P.f.* ^{*b*} Natural product. ^{*c*} Non-natural product.

Scheme 4. Reduction of (±)-Aculeatin A to the Cyclohexanone (±)-27^{*a*}



^a Reagents and conditions: (a) H₂/Pd, EtOH, 16 h, 71%.

establish an in vitro selectivity index (SI, the ratio of the IC_{50} for in vitro cytotoxicity on K-562 to the IC_{50} of inhibition on parasite).

First, we confirmed the submicromolar antimalarial activity of natural aculeatins, with their corresponding non-natural enantiomers displaying the same level of inhibition (IC₅₀ = $0.22-0.48 \ \mu$ M). Interestingly, these compounds similarly inhibited the growth of *T. gondii* RH- β 1 at submicromolar concentration (IC₅₀ = $0.31-0.64 \ \mu$ M). Moreover, these molecules showed a good to excellent SI, which ranges from 35 to 121 for both parasites. For the new aculeatin A ester analogues (\pm)-**15a**-**d**, the SI was in general lower, mainly because of a less pronounced antiparasitic potency. A remarkable exception was the low cytotoxicity (IC₅₀ = $109 \ \mu$ M) together with a good antitoxoplasmal activity (IC₅₀ = $0.50 \ \mu$ M) of (\pm)-**15a** which gave a SI of 219. Furthermore, a comparison of the ester analogues (\pm) -15 revealed that the length of the lipophilic chain can impact the selectivity between P. falciparum 3D7 and T. gondii RH- β 1. When this alkyl chain is short ((±)-15a, R³ = (CH₂)₂CH₃), a better inhibitory effect was observed for T. gondii $(IC_{50} = 0.50 \ \mu M)$ compared with P. falciparum $(IC_{50} = 1.84)$ μ M). A much longer chain ((±)-15c, R³ = (CH₂)₁₇CH₃) resulted in a reversal of affinity in favor of P. falciparum (0.77 μ M versus 2.40 μ M with T. gondii). An intermediate chain length ((±)-**15b**, $R^3 = (CH_2)_9 CH_3$ in turn proved adequate to have a similar effect on both parasites at submicromolar concentrations (IC50 = 0.65 and 0.34 μ M). To extend the study of the lipophilic effect, we tested the ester analogue (\pm) -15d (R³ = $CH[(CH_2)_9CH_3]_2$) and the amide analogue (\pm) -15e (X = $N(CH_2)_5CH_3$, $R^3 = (CH_2)_5CH_3$), which have an extra side chain. We observed no improvement on the inhibition of P. falciparum, while the amide analogue (\pm) -15e was shown to be too toxic.

We next focused on the impact of aculeatin configurations on the biological activities. Considering the most potent ester analogue (\pm)-**15b** for *P. falciparum* and *T. gondii*, we tested the corresponding stereoisomer (\pm)-**16b** of aculeatin B type. This aculeatin B configuration proved to be less efficient over (\pm)-**15b** for both parasites (IC₅₀ = 1.36 and 1.63 μ M). We also evaluated the stereoisomers of aculeatins D and 6-*epi* D types, i.e., (\pm)-**17c** and (\pm)-**18c**, respectively, which hold the proper alkyl length to be selective for *P. falciparum* (R³ =

We also evaluated the compounds (\pm) -21, 22, (\pm) -25a-c, and 26a,b, obtained in only one or two steps from (\pm) -20 (Scheme 3). Essentially, these molecules feature two cyclohexadienone rings and a more complex polyspirocyclic structure. The unsubstituted derivatives (\pm) -21 and 22 (with the free secondary alcohol) and the ester-substituted derivatives (\pm) -25a and 26a with a relatively short chain length (Z =CO(CH₂)₅CH₃) exhibited a high cytotoxicity against mammalian cell that resulted in a poor SI. However, when the lipophilic chain was longer ($Z = CO(CH_2)_{12}CH_3$), the corresponding products (\pm) -25b and 26b showed a high antimalarial activity (81 and 92 nM, respectively) with a decreased cytotoxicity compared to the former products. The SI is about 109 and 123, respectively. This enhancement of antimalarial activity seems to be due to the presence of the two cyclohexadienones ring combined with a proper hydrophilic chain length. The role of the configuration from the products seems to be less important in this case.

Finally, tests using reduced analogues of aculeatins confirmed the crucial role of cyclohexadienone ring on the antimalarial activity. The cyclohexanone (\pm)-**27**, derived from aculeatin A, and (+)-**28** and (-)-**29**, the phenolic precursors of aculeatins,^{14b} were weakly active against *P. falciparum*.

In conclusion, we have developed a divergent approach to obtain in practical manner novel aculeatins derived from a common precursor 2. From this study, we have identified two novel polyspirocyclic products, (\pm) -25b and 26b, whose antiparasitic activities against the two widespread Apicomplexa occur at very low concentration (e.g., $IC_{50} = 81$ and 92 nM, respectively, against P. falciparum 3D7 strain). Very interestingly, their toxicities against mammalian cells occur at much higher concentration, resulting in a SI higher than 100 for P. falciparum. The cyclohexadienone moiety, in association with a well-defined aliphatic chain length, has been characterized as important functions for antimalarial and antitoxoplasmal activities. As many other analogues can be easily produced, these valuable candidates clearly deserve further structural optimizations to improve their antiparasitic activities and to decrease their cytotoxicity. Future prospects include additional tests, synthetic efforts, and the complementary development of probes derived of the best analogues described here to fish out and study the still unknown biological target(s) in Apicomplexan parasites.

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Supporting Information Available: Details of biological assays and synthetic procedures of new compounds tested and precursors, product characterization, ¹H and ¹³C NMR spectra, and HPLC purity results for (\pm) -25b and 26b. This material is available free of charge via the Internet at http://pubs.acs.org.

References

- Guerra, C. A.; Snow, R. W.; Hay, S. I. Mapping the global extent of malaria in 2005. *Trends Parasitol.* 2006, 22, 353–358.
- (2) Greenwood, B. M.; Bojang, K.; Whitty, C. J. M.; Targett, G. A. T. Malaria. *Lancet* 2005, 365, 1487–1498.
- (3) (a) Hyde, J. E. Drug-resistant malaria. *Trends Parasitol.* 2005, 21, 494–498. (b) Hyde, J. E. Drug-resistant malarial—an insight. *FEBS J.* 2007, 274, 4688–4698.
- (4) Gelb, M. H. Drug discovery for malaria: a very challenging and timely endeavour. *Curr. Opin. Chem. Biol.* **2007**, *11*, 440–445.
- (5) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. New antimalarial drugs. Angew. Chem., Int. Ed. 2003, 42, 5274–5293.
- (6) Biagini, G. A.; O'Neill, P. M.; Bray, P. G.; Ward, S. A. Current drug development portfolio for antimalarial therapies. *Curr. Opin. Pharmacol.* 2005, *5*, 473–478.
- (7) Schlitzer, M. Antimalarial drugs—what is in use and what is in the pipeline. Arch. Pharm. Chem. Life Sci. 2008, 341, 149–163.
- (8) Kapoor, V. K.; Kumar, K. Recent Advances in the Search of Newer Antimalarial Agents. In *Progress in Medical Chemistry*; King, F. D., Lawton, G. Ed.; Elsevier: Amsterdam, 2005; pp 189–237.
- (9) (a) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. Antiprotozoal activity and cytotoxicity of novel 1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one derivatives from *Amomum aculeatum. Helv. Chim. Acta* **2000**, *83*, 2939–2945. (b) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. Minor cytotoxic and antibacterial compounds from the rhizomes of *Amomum aculeatum. Phytochemistry* **2001**, *57*, 1281– 1285.
- (10) Holdsworth, D. K.; Mahana, P. Traditional medicinal plants of Huon Peninsula, Morobe province, Papua New Guinea. *Inter. J. Crude Drug Res.* **1983**, *21*, 121–133.
- (11) Salim, A. A.; Su, B.-N.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. Dioxadispiroketal compounds and a potential acyclic precursor from *Amomum aculeatum. Tetrahedron Lett.* **2007**, *48*, 1849–1853.
- (12) Chin, Y.-W.; Salim, A. A.; Su, B.-N.; Mi, Q.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. Potential anticancer activity of naturally occurring and semisynthetic derivatives of aculeatin A and B from *Amomum aculeatum. J. Nat. Prod.* **2008**, *71*, 390–395.
- (13) Greenbaum, D. C. Is chemical genetics the new frontier for malaria biology? *Trends Pharmacol. Sci.* 2007, 29, 51–56.
- (14) (a) Wong, Y.-S. Synthesis of (±)-aculeatins A and B. *Chem. Commun.* 2002, 686–687. (b) Peuchmaur, M.; Wong, Y.-S. Diastereodivergent strategies for the synthesis of homochiral aculeatins. *J. Org. Chem.* 2007, 72, 5374–5379. (c) Peuchmaur, M.; Wong, Y.-S. Studies towards the synthesis of aculeatin C. *Synlett* 2007, 2902–2906.
- (15) Other synthetic approaches to aculeatins: (a) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Márquez, R.; Bulger, P. G. Biomimetic synthesis of (±)-aculeatin D. *Tetrahedron* 2005, *61*, 2353–2363. (b) Falomir, E.; Álvarez-Bercedo, P.; Carda, M.; Marco, J. A. Enantioselective synthesis and absolute configurations of aculeatins A and B. *Tetrahedron Lett.* 2005, *46*, 8407–8410. (c) Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. Enantioselective synthesis and absolute configurations of aculeatins A, B, D, and 6-epi-aculeatin D. *Tetrahedron* 2006, *62*, 9641–9649. (d) Chandrasekhar, S.; Rambabu, Ch.; Shyamsunder, T. Total synthesis of aculeatins A and B via a tethered oxa-Michael approach. *Tetrahedron Lett.* 2007, *48*, 4683–4685. (e) Ramana, C. V.; Srinivas, B. A carbohydrate-based approach for the total synthesis of aculeatin D and 6-epi-aculeatin A. *J. Org. Chem.* 2008, *73*, 3915–3918.
- (16) Clemens, R. J.; Hyatt, J. A. Acetoacetylation with 2,2,6-trimethyl-4H-1,3-dioxin-4-one: a convenient alternative to diketene. J. Org. Chem. 1985, 50, 2431–2435.
- (17) Recent examples with unprotected secondary alcohols: (a) De Rosa, M.; Acocella, M. R.; Villano, R.; Soriente, A.; Scretti, A. A convenient catalytic procedure for the highly enantioselectrive aldol condensation of O-silyldienolates. *Tetrahedron: Asymmetry* 2003, 14, 2499–2502. (b) Fettes, A.; Carreira, E. M. Leucascandrolide A: synthesis and related studies. J. Org. Chem. 2003, 68, 9274–9283. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. Total synthesis of (+)-dactylolide through an efficient Peterson olefination and Prins cyclization reaction. *Angew. Chem., Int. Ed.* 2005, 44, 3485–3488.
- (18) Narasaka, K.; Pai, F. C. Stereoselective reduction of β -hydroxyketones to 1,3 diols. Highly selective 1,3-asymmetric induction via boron chelates. *Tetrahedron* **1984**, *40* (12), 2233–2238.
- (19) Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride. J. Am. Chem. Soc. 1988, 110, 3560–3578.

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