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Water-soluble combinations of dexanabinol: prodrugs and analogs

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Design, synthesis and study of water-soluble esters of dexanabinol are described. The solubility, stability and *in vitro* activity of various polar or permanently charged derivatives resulting by acylation of the allylic hydroxyl or phenol functionalities was investigated. Several combination can be used as water-soluble prodrugs, and others as active congeners of dexanabinol.

1. Introduction

Dexanabinol [1] the (+)3*S*,4*S*-5′-(1′,1′-dimethylheptyl)-7-hydroxy-Δ^6-tetrahydrocannabinol or (6aS-trans)-6,6-dimethyl-3-(1,1-dimethylheptyl)-1-hydroxy-6a,7,10,10a-tetrahydro-6*H*-dibenzo [*b*,*d*] pyran-9-methanol (IUPAC), a synthetic nonpsychotropic cannabinoid is a noncompetitive-*N*-methyl-D-aspartate (NMDA) receptor antagonist [2], an effective radical scavenger [3] and a tumor necrosis factor (TNFα) inhibitor [4]. Various *in vivo* studies indicated that dexanabinol is safe and well-tolerated upon acute as well as chronic exposure in rat, rabbit and primates. Results obtained in trauma (closed head injurity in the rat [5], optic nerve crush [6] in the rat) and stroke/cardiac arrest models demonstrated that dexanabinol has significant neuroprotective action at relatively low doses and confers significant protection against both the neurobehavioral and histopathological effects of transient global forebrain ischemia [7]. Based on these results, dexanabinol is currently developed as a neuroprotectant agent for the treatment of brain damage associated with stroke, head trauma and cardiac arrest. Successful phase I and II clinical studies were performed in severe head trauma patients [8].

An obstacle in the development of dexanabinol as a single dose neuroprotective agent, having the intravenous route as the best way of administration, is its very poor solubility in water, which makes formulation in aqueous compositions extremely difficult. While the bulky lipophilic 1′,1′-dimethylheptyl side-chain should reduce water solubility, the two hydroxyl groups present in the molecule of dexanabinol would be expected to induce a moderating influence. The compound was however found to be practically insoluble in water.

A possible explanation for this behavior is that the OH groups of dexanabinol cannot form hydrogen bonds with the solvent since they are already involved in more favorable intramolecular or intermolecular (dexanabinol-dexanabinol) interactions. There are data indicating that dexanabinol forms molecular aggregates, such as dimers through powerful hydrogen bonding.

2. Water-soluble esters as potential prodrugs of dexanabinol

Cosolvent systems containing Cremophor EL have been used in *in vivo* models including phase I and II clinical [8]. However, cremophor is associated with allergic-type side effects and accordingly cremophor-based formulations are not unanimously accepted. Other technologies for solubilization of dexanabinol in aqueous compositions including alternative cosolvent-based formulations and water-soluble prodrug approaches have been investigated.

Water-soluble derivatives of dexanabinol (**1**) designed to readily release the drug by hydrolysis following i.v. administration were synthesized and examined. They can be used as prodrugs, or active analogs depending on their hydrolytic and enzymatic stability and on their intrinsic activity.

Various polar combinations or combinations bearing a permanent charge were synthesized for dexanabinol as esters at the allylic (C-7) or phenolic (C-3′) OH, the two sites of the molecule suitable for reversible modification. This series included glycinate and N-substituted glycinates [9–12], esters of amino acids containing tertiary or quaternary heterocyclic nitrogen [13], phosphates [14], hemiesters of dicarboxylic acids [15]. In total, more than 40 esters were synthesized and subjected to a preliminary screening process. Since the most important requirements for a prodrug targeted for i.v. formulation are: solubility in water, stability in water and rapid hydrolysis in human plasma, these properties were primarily investigated, for most of these derivatives.

3. Synthesis of water-soluble esters of dexanabinol

The allylic hydroxyl group at the C-7 position of **1** is more reactive than the sterically hindered and rigid phenolic C-3′ group. Due to this difference in reactivity, the acylation of **1** occurred preferentially at the allylic hydroxyl group, although small amounts of phenolic esters were sometimes present in the products.

Reaction of **1** with N-protected (*t*-BOC) glycine in a mixture of acetonitrile-dimethylformamide in the presence of dicyclohexylcarbodiimide (DCC) as dehydrating agent and 4-(dimethylamino) pyridine (DMAP) (catalyst) gave the 7-(N-*t*-BOC) glycyl ester of dexanabinol. The *t*-BOC protecting group was then removed by hydrochloric acid in ethyl acetate solution affording the HCl salt of the glycyl ester of dexanabinol (**2**) in pure form. Several N-substituted derivatives of the glycinate ester of **1** were prepared by acylation of dexanabinol with bromo or chloroacetic anhydride in toluene followed by reaction of the 7-bromoacetyl or chloroacetyl dexanabinol (**7**) with either dialkylamines to give *N*,*N*-dialkylglycyl dexanabinol (**3** dimethyl; **4** diethyl), and its HCl salts or with trialkylamines to give the permanent charge-bearing chloroacetic trialkylammonium acetyl bromides or chlorides **5**–**10**.

Amino acid esters bearing nitrogen heretocycles (morpholine, N-methyl piperazine) and their quaternary derivatives were synthesized by acylation of the allylic alcohol or the phenol of **1** with heterocyclic moiety containing acids. The synthesis of the phenolic (C-3′) esters was accomplished by acylation of the 7-O protected dexanabinol. The hydrobromide salts **11**–**14** were then prepared by treatment of the free base esters with HBr in methylene chloride. The quaternary *N*-methylmorpholinium and piperazinium iodides **15**–**18** were obtained by quaternization of free bases with methyl iodide in acetone.

A convenient protection procedure of the allylic C-7 hydroxylic group of **1** proved to be via the trifluroacetate, easily obtained by reacting **1** in chloroform with trifluoroacetic acid [24]. The acylation of the phenolic group was then accomplished in the conditions used for the allylic alcohol. The allylic alcohol was easily deprotected by simply washing the methylene chloride solution of the product with 5% aqueous sodium bicarbonate. The hydrobromide salt **19** and the quaternary derivative **20** were obtained as described before.

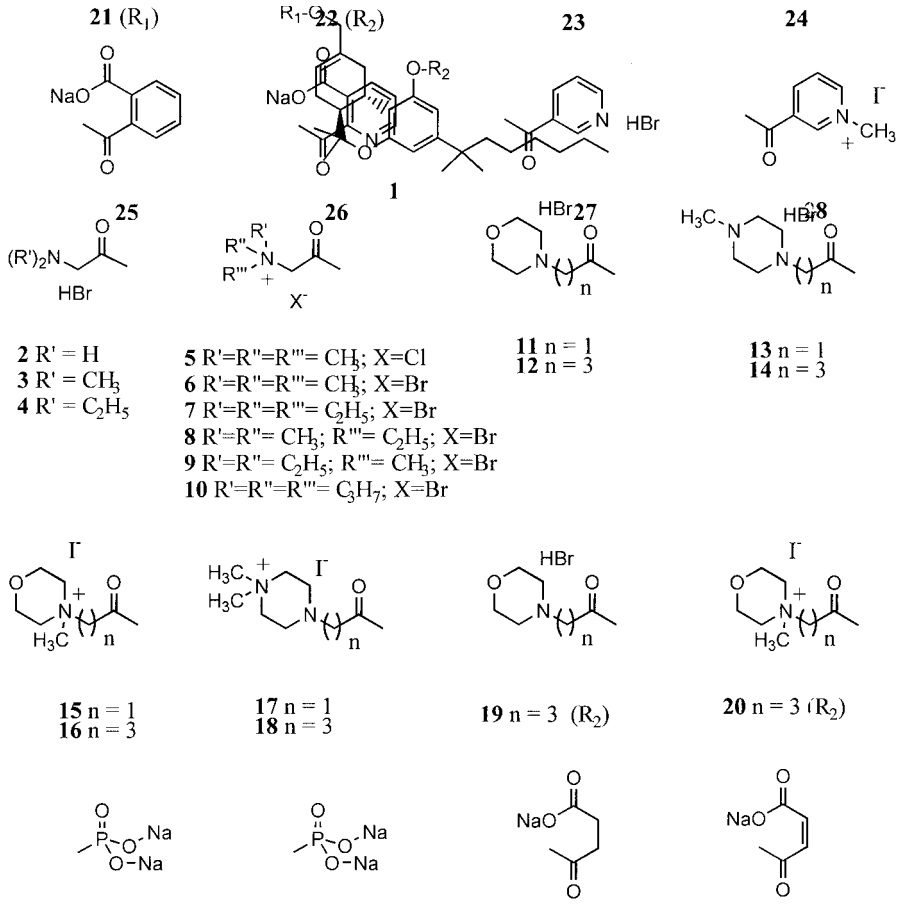
Allylic (**25**) and phenolic (**26**) phosphates of **1** were synthesized. The reaction of **1** with di-*t*-butylphosphorochloridate in pyridine in the presence of triethylamine at −20 °C resulted in the 7-(di-*t*-butyl) phosphate, which reacted with trifluoroacetic acid in chloroform at room temperature for 30 min to give the 7-dihydrogen phosphate. The sodium salt **25** was prepared using ethanolic NaOH.

The phenolic phosphate was synthesized from the protected **1** with phosphorus oxychloride in pyridine; by the treatment of the resulting protected phenolic phosphate with aqueous $NaHCO_3$ the dihydrogen phosphate resulted. The sodium salt **26** was obtained by reaction with ethanolic NaOH. Hemiesters at C-7 have been synthesized. The acylation of **1** with slight excess of acylating agent (acid anhydride) mainly afforded allylic esters accompanied in some cases by small amounts of 3′,7-diesters. Acid anhydrides (succinic, maleic, phthalic, quinolinic) were used as acylating agents, the reaction medium being toluene. Basic catalysts (triethylamine, pyridine) were employed to increase the reaction rate. No diesters were formed when succinate, maleate and phthalate esters were prepared. Hemiesters **21**–**24** are generally more stable in the form of ammonium and tris (hydroxymethyl)aminomethane salts than as free acids.

By reacting **1** with nicotinoyl chloride, in pyridine, **27** resulted. Small amounts of the phenolic and 3′,7-diester were removed by column chromatographic purification. By N-methylation of the nicotinate with methyl iodide in nitromethane, the pyridinium quaternary salt **28** resulted.

4. Solubility in water of dexanabinol esters

Prodrugs of practical use should have adequate solubility and sufficient stability in water to allow for formulation and storage; they should rapidly (ideally spontaneously) convert to the active parent drug within the body [17]. Most of dexanabinol esters having polar or permanent charge bearing groups have increased, sometimes dramati-



Water soluble combinations of dexanibol (I)
All allylic esters (R_1) except for **19**, **20** and **22** (R_2, phenolates)

cally, solubility in water or 10% aqueous ethanol as compared to **1**. The solubility is in the range of 2 to 8 mg/ml. In the glycinate series, however, the determined solubilities were: 53.42, 52.24, 47.47, 46.95 and 5.01 mg/ml for **6**, **5**, **9**, **7** and **8**, respectively (no data are available for **10**) [11]. This spectacular increase in the solubility of the esters as compared to dexanabinol, which is practically insoluble in water, is a result of both the polar moiety introduced by the permanently charged ammonium ion, and of the fact that formation of dimers by hydrogen bonding is less probable if not impossible in these combinations. It is difficult to explain some anomalies in solubilities in the examined series. While derivatives **5** and **6**, were expected to have the best solubility, due to smaller, less lipophilic, alkyl groups linked to the quaternary nitrogen, the much lower solubility of **8** as compared to **7** and **9** is somewhat unexpected. The contra ion, Cl^- or Br^- in **5** and **6**, respectively, does not have much influence, the two esters having almost similar solubility in water.

5. Hydrolytic stability of dexanabinol esters

In a screening process, the stability in water of various dexanabinol esters was determined experimentally at time zero and after 1 h and 24 h of incubation at 37 °C [9–14]. Dexanabinol which resulted by hydrolysis was quantitated by HPLC (Table 1). All the amino acid type esters proved to be relatively stable in water; no spontaneous hydrolysis was noticed for these compounds. Less than 0.5% of the glycinate hydrolyzed after 24 h; the *N*,*N*-dialkyl amino acetates were also stable in water; the diethyl derivative was not hydrolyzed after 24 h; the quaternary salts were somewhat less stable in water, but still only 6.2–7.5% of dexanabinol was recovered after 24 h incubation. In each case the stability was higher at the pH of distilled water (5.5), as compared to physiological pH (7.4). Stability of selected quaternary ammonium moiety containing glycinates was determined at other pHs as well: at stronger basic pH (9.0) the tested prodrugs were rapidly hydrolyzed as expected (half lives could not be calculated due to the fast rate of hydrolysis) while at more acidic pH (such as at 1.2, the pH of the stomach fluid) their stability increased considerably. Obviously the base-catalyzed hydrolysis is much more faster than the acid-catalyzed.

Stability in water of selected esters containing heterocyclic nitrogen was also investigated. The results indicate that the investigated esters were stable in water for as long as 24 h. The most stable was **14** which released less than 3% of **1** in 24 h. Derivative **12** and the corresponding phenolic ester **19** were somewhat less stable but still more than 90% of the compounds were found unchanged after 24 h of incubation.

Both phosphate esters were very stable in water. In the hemiester series, while the succinate was quite stable, the maleate released 26% and 33% dexanabinol after 1 h and 24 h, respectively; the hemiphthalate also hydrolyzed but only 7% of parent compound was detected after 24 h.

Table 1: Stability of selected dexanabinol esters

Compd.	Time (h)	Dexanabinol recovered (%)			
		Water	Plasma		
			Rat	Dog	Human
2	1	0.40	NA	0.88	0.95
	24	4.64	NA	16.49	22.32
3	0	4.10	NA	0.00	0.00
	1	4.28	10.82	0.00	5.15
	24	5.59	100.00	1.52	9.30
4	0	0.00	0.00	0.00	0.00
	1	0.00	15.68	0.74	0.00
	24	0.65	65.85	7.28	4.15
6	0	1.82	0.00	0.00	0.00
	1	1.88	86.00	95.54	91.92
	24	7.52	100.00	100.00	105.15
7	0	1.76	NA	NA	NA
	1	3.64	50.20	57.90	67.70
	24	6.21	63.70	69.50	67.80
12	1	7.97	23.02	6.09	5.81
	24	7.87	32.06	9.37	8.06
14	1	2.74	43.60	2.86	2.11
	24	2.98	101.74	12.68	8.70
19	0	0.00	0.00	0.00	0.00
	1	5.58	87.00	8.79	8.32
	24	11.43	100.00	59.06	54.99

6. Stability in plasma of dexanabinol esters

Prodrugs of practical use should rapidly (ideally spontaneously) convert to the active drug within the body. It is known that esterase activity and specificity and hence the stability of carboxylic esters in blood are species-specific. Their activity generally decreases in the order: rodents > rabbit > dog > humans. The hydrolytic stability of dexanabinol esters was determined in rat, dog and human blood, with data obtained from human blood experiments most relevant. The glycinate salt is relatively stable in all examined media. The *N*,*N*-dimethylglycinates are even more stable, being only poorly hydrolyzed in dog and human plasma. The quaternary ammonium salt-type glycinates on the other hand readily hydrolyzed in plasma of various sources, including human (the trimethylammoniumacetyl bromide and chloride hydrolyzed practically completely after 1 h). Stability of **5** and **7** in human whole blood and plasma was determined at body temperature (37 °C). At a concentration of 200 μg/ml, half lives were 102 and 114 min (whole blood) and 47 min and 90 min (plasma) for **5** and **7**, respectively. At lower concentration, which better reflects the real situation (doses used in clinical trials are in the range of ∼100–300 mg dexanabinol/person), **5** hydrolyzed even faster, $t_{1/2}$ in plasma being 26.3 min at 50 μg/ml and very short at 20 μg/ml (70% of prodrug hydrolyzed at time point zero). Clearly, the catalytic effect of the blood esterases resulted in a rapid release of the parent dexanabinol from the prodrug conjugate in human plasma.

In the case of heterocyclic esters, the fastest hydrolysis occurred again in rat plasma. Compound **12** hydrolyzed only 23% and 32% after 1 and 24 h respectively, while **14** and especially **19** appeared to be better substrates for rat blood esterases, hydrolyzing completely after 24 h. No significant difference was observed however in the stability of these compounds in dog and human plasma. The stability increased in both dog and human as compared to the rat plasma. Both allylic esters (**14** and particularly **12**) released only small amounts of **1** after 24 h of incubation. More importantly, in human plasma, hydrolysis was less than 10%. The phenolic ester **16** was again the least stable, hydrolyzing ∼60% in dog and 55% in human plasma.

The phosphate esters proved to be extremely stable in blood. The hemisuccinate **23** only hydrolyzed in rat plasma, the phthalate **25** was stable in all the biological material used, while the hemimaleate **24** was unstable in rat

plasma but only partially hydrolyzed in dog and human plasma (50% in 24 h).

Based on these studies, the quaternary ammonium moiety containing glycinates and in particularly the trimethylammonium acetate ester, was selected as the most appropriate candidate for further development as a prodrug for dexanabinol.

7. *In vitro* activity of dexanabinol esters

Three different assays were employed to determine the activity and toxicity of these combinations: (a) NMDA receptor binding as measured by the ability to displace a known antagonist ([^{3}H] TCP or [^{3}H] MK-801) [2, 18] (b) *in vitro* protection of neurons against NMDA-induced toxicity and (c) neuronal cell toxicity potential [20, 21].

For assay (a), brains were removed from Sprague-Dawley rats and membranes suspended in pH 7.4 buffer and incubated at 25 °C for 2 h with the radio ligand [^{3}H] MK-801 alone or in the presence of examined compounds. Non-specific binding was determined in the presence of TCP. Suspensions were filtered (GF/B filters presoaked in polyethylene imine) and the ligand-receptor complex was determined using scintillation counter. Data were analyzed using the iterative non-linear least squares curve fitting program LIGAND [19].

For assays (b) and (c), cortical cells derived from Sprague-Dawley rats were cultured for 10 days, then exposed to dexanabinol esters in the presence (for protection determinations) or in the absence (for toxicity evaluation) of NMDA for 20 h. Cell mortality was quantitatively assessed by measurement of the lactate dehydrogenase (LDH) levels of the extracellular medium.

The receptor binding properties, summarized in Table 2, are proper to dexanabinol esters since no enzymatic hydrolysis occurred during determinations. Since essays b and c required longer incubation time, some of the esters hydrolyzed partially or completely during activity determinations. In this situations activity and toxicity was attributed to the release dexanabinol.

Interestingly, some of the esters, stable in biological media, manifested intrinsic neuroprotective activity in specific *in vitro* tests (Table 3). For example, the 7-glycinate ester **2** inhibits the binding of [^{3}H]MK-801, at an IC_{50} of 13.8 μM, having a 90.5% inhibition at 100 μM concentration, as compared to dexanabinol (IC_{50}, 7.5 and 92.5% inhibition at 100 μM). The protection against NMDA toxicity of the glycinate at 5 μM concentration is 89% as compared to 92% for dexanabinol. The 7-*O*-[2-(*N*-methyl-4-morpholinium)-butyryl dexanabinol (**16**) has even better receptor binding properties (IC_{50} 2 μM and inhibition 94% at 100 μM) and activity (95% protection against NMDA induced toxicity at 5 μM concentration) than dexanabinol. This compounds could be developed as water soluble congeners of dexanabinol.

Table 2: Receptor binding properties of selected dexanabinol esters

Compd.	Inhibition of [^{3}H] MK-801 binding	
	Average IC_{50} (μM)	Inhibition at 100 μM (%)
1	7.5	92.5
2	13.8	90.5
3	17.5	85.0
4	58.0	63.0
6	8.2	83.5
7	17.8	88.0
12	6.8	92
13	2.0	97
14	19.0	94
15	8.0	91
16	2.0	94
17	3.8	95
19	6.0	90
20	3.0	95
21	10.0	77.5
22	12.0	72.1
23	5.0	NA
24	2.8	NA
25	102	NA
26	56.0	10.0

Table 3: Neuroprotective activity of dexanabinol esters

Compd.	Hydrolysis (% of release of dexanabinol) after 20 h incubation (mean recovery ±10 % SD)	Mean protection against NMDA toxicity (% protection at 5 μM)
1	–	92.0
2	40.0	89.0
3	59.0	21
4	24.0	41
6	85.0	99.0
7	55.0	100.0
13	11.5	86.0
14	14.4	69.0
15	80.0	77.0
16	4.5	95.0
17	20.4	83.0
19	79.0	77.0
21	0.0	Not active
22	0.0	Not active
23	15	98
24	20	99
25	8	Not active
26	30	85

8. *In vivo* distribution of a dexanabinol prodrug

In vivo tissue distribution of dexanabinol as mediated by a selected water-soluble prodrug was performed in a rodent model [12, 13]. 7-Acetyl-trimethylammonium chloride ester (**5**) was used for these studies at a dose of 6.75 mg/body weight. The prodrug in an aqueous solution, was injected via tail vein in three groups of Sprague-Dawley rats (250–300 g body weight), animals were sacrificed by decapitation at various time points (5, 15, 30, 60, 120, 240, 480 and 1440 min) and blood and brain tissues were collected and concentrations of dexanabinol determined by LC/MS methods. The results are given in Tables 4 and 5. In agreement with the *in vitro* experiments, a rapid hydro-

Table 4: Plasma concentrations of dexanabinol after i.v. administration of compound 5 to rats

Time (min)	Concentration (μg/ml)				
	Animal			Average	SEM
	#1	#2	#3		
5	39.83	19.55	28.70	29.36	5.86
15	9.22	9.91	13.07	10.73	1.19
30	1.35	2.26	9.40	4.34	2.54
60	1.85	0.33	1.60	1.26	0.47
120	0.50	0.17	0.53	0.40	0.12
240	0.36	0.12	0.28	0.25	0.07
480	0.36	0.07	0.13	0.19	0.09
1440	0.17	0.08	0.13	0.12	0.03

Table 5: Brain concentrations of dexanabinol after i.v. administration of Compound 5 to rats

Time (min)	Concentration (μg/ml)				
	Animal			Average	SEM
	#1	#2	#3		
5	2.61	1.55	2.02	2.06	0.31
15	0.54	0.78	0.93	0.75	0.11
30	0.36	0.47	0.88	0.57	0.16
60	0.36	0.44	0.53	0.44	0.05
120	0.21	0.37	0.20	0.26	0.05
240	0.22	0.38	0.51	0.37	0.08
480	0.59	0.35	0.60	0.51	0.08
1440	0.35	0.28	0.78	0.47	0.16

Note: Administered dose: 6.75 mg prodrug **5**/kg.

lysis of the prodrug was noticed. At 5 min following the administration, plasma levels of ~30 μg/ml were obtained. At the same time point, brain concentrations of dexanabinol reached a peak concentration of 2 μg/g as well. As the blood concentration of dexanabinol decreased following a typical two-compartment pharmacokinetic model, brain concentrations became also lower. However the brain/blood concentration ratio increased from 0.07% at 5 and 15 min to 0.13, 0.35, 0.65, 2.48, 2.68 and 3.90 at 30, 60, 120, 240, 480 and 1440 min, respectively. Obviously, the lipophilic compound was retained by the brain tissues, while eliminated from blood. Even after 24 h, detectable levels of dexanabinol were identified in brain. It is important that peak concentrations of drug can be obtained rapidly (5 min) after administration, since the faster the neuroprotectant agent reaches the target, the more effective it is. It has to be mentioned that distribution results generated in a rodent model cannot be generally extrapolated to humans, knowing the fact that esterases in mice and rats are much more active than in more evolved mammals. However, in the case of the examined combinations it was proven that human blood esterases act quite rapidly as well, this being actually the main criteria of their selection from a large number of various water soluble combinations; it is safe then to affirm that the presented distribution study should well mimic the behavior of the prodrug in humans.

9. Conclusions

The study which involved design, synthesis and study of numerous water-soluble esters of dexanabinol resulted in identification of a group of compounds which might be used as prodrugs. These esters which are salts of the allylic *N*-trimethyl- and -triethyl amino acetates (**9a**, **b**) are fairly soluble and stable in water while rapidly hydrolyze in human plasma. *In vivo* distribution studies indicated that prodrugs of these type can be used for i.v. administration of dexanabinol, as appropriate brain concentrations of the active drug were registered following their use. Due to the limited stability in aqueous solutions the prodrug should be stored as a liophilized powder and reconstituted in water prior the use.

Several esters which are too stable in plasma to be used as prodrugs (**13**, **16**) have intrinsic neuroprotective properties and could be developed as water-soluble congeners of dexanabinol.

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