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In vitro anti-leishmanial activities of germatranyl and Silicon incorporated diorganotin derivatives: Synthesis and spectroscopic properties

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Abstract

A series of germanium and silicon incorporated diorganotin derivatives of general formula

$$[N(OCH_2CH_2)_3GeCH(R^1)CH_2CO_2]_2\,SnR^2_2$$

where R^1 = H_3C, C_6H_5, *p*-$CH_3C_6H_4$, *p*-FC_6H_4; R^2 = $H_2CSi(CH_3)_2C_6H_5$, $H_2CC_6H_5$, *p*-$CH_3C_7H_7$ were synthesized by the reaction of appropriate diorganotin dichlorides and germatranyl (substituted) propionic acid in 1:2 mole ratio, respectively. The evidence regarding their structure is mainly based on spectroscopic data obtained by multinuclear (^{1}H, ^{13}C, ^{29}Si, ^{119}Sn) NMR and ^{119m}Sn Mössbauer, IR and mass spectral studies in combination with melting points and elemental analyses. The compounds have been screened for *in vitro* anti-leishmanial activity against promastigotes of *Leishmania major* and the results offer potent activities which are better than the standard drug, pentamidine, for one compound.

Keywords: *Germatrane, Silicon, Diorganotin, Spectroscopy, Antileishmanial activity*

Introduction

There is a continuing interest in the syntheses and biological studies of organotin compounds because of inherent potential chemotherapeutic applications and structural diversity present in their molecules [1,2]. Organotin carboxylates are the most ubiquitous owing to their important biocidal activity [3,4]. Toxicological and pharmaco-kinetic studies of germanium revealed its low mammalian toxicity, after these informations, developments were oriented towards its biological applications as chemotherapeutic agents [5–7]. Germatranes have been examined for their neurotropic, antitumour, and radioprotective properties [8]. The existence of co-relation between the bioactive properties of organogermanium and organotin compounds and the close analogy between the organic chemistry of germanium and silicon paved the way for the syntheses of useful mixed metal complexes [9–14].

The toxicity of organotin deivatives containing silicon in the alkyl group bonded to tin has been comprehensively lowered by the introduction of germatranyl moiety as a part of carboxylate ligand in these compounds [12–14]. The toxicity of the germatranyl propionic acids were determined as their LD_{50} vales and found in range 60–80 ug/mL. The LD_{50} values of the synthesized compounds are over 200 ug/mL and their activities show the potential to be used as drugs. Unfortunately, epidemic diseases such as leishmaniasis, caused by the parasite protozoa in the genus *Leishmania*, are spreading in different parts of the world as a result of non-availability of the high priced drugs or more seriously due to the

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development of parasitic resistance against the available drugs. In continuation of our previous works [14–15], now we report herein the syntheses, spectroscopic characterization, and antileishmanicial activities of some germanium and silicon substituted diorganotin dicarboxylates (Scheme 1).

Experimental

Materials and instruments

Phenyldimethyl chlorosilane and methyl substituted cinnamic acid were purchased from Aldrich, UK and used as received. Germanium dioxide, all diorganotin dichlorides and triethylamine were purchased from Aldrich, USA and used without further purification. All the chemicals used were of reagent grade and all organic solvents were dried prior to use according to the reported methods [16]. For the details of apparatus and instruments used see elsewhere [14,15,17].

General synthetic procedures

Synthesis of precursors. Germatranyl-3-propionic acids and bis[phenyl(dimethysilylmethylene)]tin dichloride were synthesized and characterized in accordance to our earlier report [15].

Synthesis of compounds. The target compounds (**1**–**8**) were synthesized by following the general procedure. The appropriate amount of the respective germatranyl substituted propionic acid (2 mmol) was suspended in a flask containing ethanol and fitted with a reflux condenser. The stoichiometric amount of triethylamine was added followed by dropwise addition of the respective diorganotindichloride (1 mmol) at 0°C and the mixture was refluxed for 6–8 h. After cooling, solid triethylamine hydrochloride was filtered off and the solvent was removed under vacuum to yield crude solid product. The solid was dissolved in dichloromethane and recrystallized using *n*-hexane:chloroform mixture (1:3) as white solid but unfortunately could not obtain fine crystals for single crystal X-ray analysis.

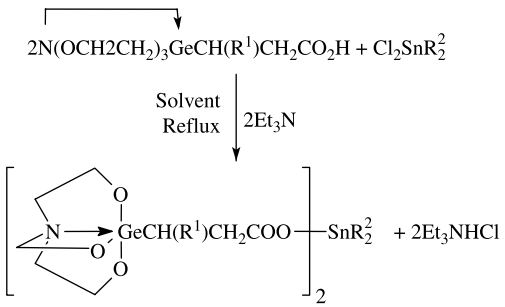
In Vitro *Antileishmanial assay*

Leishmania major (MHOM/PK/88/DESTO) promastigotes, cultivated in bulk were aseptically be sedimented down at 300 rpm, counted with the help of improved Neubaver chamber under the microscope and diluted with the fresh medium to a final concentration of 2×10^6 parasites/mL. The compounds to be checked were dissolved to a final concentration of 1.0 mg in 0.1 mL of PBS (Phosphate Buffered Saline, pH 7.4 containing 0.5% MeOH, 0.5% DMSO).

In a 96 well microtiter plate, 90 μL of the parasite culture (2.0×10^6 parasites/mL) was added in different wells. 10 μL of the experimental compound was added in culture and serially diluted so that minimum concentration of the compound is 0.1 μg/mL. 10 μL of PBS (Phosphate buffered saline, pH 7.4 (containing 0.5% MeOH, 0.5% DMSO) was added as negative control while pentamidine to a final concentration of 1.0 mg/mL was added separately as positive control. The plate was incubated between 21–22°C in dark for 5 days during which control organisms multiply 6 times. The culture was examined microscopically on an improved Neubaver chamber and IC_{50} values of compounds possessing antileishmanial activity were calculated [18]. All assays were performed in triplicate.

Results and discussion

Some germanium and silicon substituted organotin-carboxylates of general formula $[\overline{N(OCH_2CH_2)_3GeCH(R^1)}CH_2CO_2]_2SnR^2_2$ were synthesized by the reaction of diorganotin dichlorids and germatranyl substituted propionic acid (1:2 mole ratio) in the presence



Where $R^2 = H_2CSi(CH_3)_2C_6H_5$ (**1-4**); $R^1 = H_3C$ (**4**), C_6H_5 (**1**), p-$H_3CC_6H_4$ (**2**), p-FC_6H_4 (**3**): $R^2 = H_2CC_6H_5$ (**5,6**); R1 = H_3C (**5**), C_6H_5 (**6**): R_2 = p-$CH_3C_7H_6$ (**7,8**), R^1 = p–$CH_3C_6H_4$ (**7**), C_6H_5 (**8**).

Scheme 1. Synthesis of Diorganotin derivatives.

Table I. Physico-analytical data for compounds*of general formula.

$$[N(OCH_2CH_2)_3GeCH(R^1)CH_2CO_2]_2SnR^2_2$$

S. No.	R^1	R^2	Molecular formula (Mol. Wt.)	Elemental Analysis Calculated (Found) %			M.P. (°C)	Yield (%)
				C	H	N		
1	C_6H_5	$H_2CSi(CH_3)_2C_6H_5$	$C_{48}H_{66}O_{10}N_2Si_2Ge_2Sn$ (1150)	50.07 (50.03)	5.70 (5.56)	2.43 (2.48)	192–194	79
2	*p*-$CH_3C_6H_4$	$H_2CSi(CH_3)_2C_6H_5$	$C_{50}H_{70}O_{10}N_2Si_2Ge_2Sn$ (1180)	58.52 (58.40)	5.02 (5.10)	2.00 (2.40)	175–177	60
3	*p*-FC_6H_4	$H_2CSi(CH_3)_2C_6H_5$	$C_{48}H_{64}O_{10}F_2N_2Si_2Ge_2Sn$ (1186)	48.53 (48.50)	5.39 (5.35)	2.36 (2.40)	190–192	80
4	CH_3	$H_2CSi(CH_3)_2C_6H_5$	$C_{38}H_{62}O_{10}N_2Si_2Ge_2Sn$ (1026)	44.43 (44.35)	6.04 (5.80)	2.72 (2.65)	188–189	70
5	CH_3	$H_2CC_6H_5$	$C_{34}H_{32}O_{10}N_2Ge_2Sn$ (892)	44.82 (45.90)	5.49 (5.88)	3.07 (2.68)	130–132	65
6	C_6H_5	$H_2CC_6H_5$	$C_{44}H_{64}O_{10}N_2Ge_2Sn$ (1034)	51.05 (50.07)	5.22 (5.20)	2.70 (2.65)	140–142	72
7	*p*-$CH_3C_6H_4$	p-$CH_3C_7H_6$	$C_{48}H_{62}O_{10}N_2Ge_2Sn$ (1090)	52.73 (52.75)	5.85 (6.0)	2.56 (2.66)	135–137	65
8	C_6H_5	p-$CH_3C_7H_6$	$C_{46}H_{56}O_{10}N_2Ge_2Sn$ (1060)	51.87 (50.95)	5.63 (5.50)	2.63 (2.54)	133–135	65

* White solid compound; soluble in $CHCl_3$ and DMSO

of triethylamine as a base. The compounds (**1–8**) are quite stable in moist-air and their physico-analytical data are presented in Table I. The molecular structures of the synthesized compounds were established on the basis of the data obtained by elemental analyses and spectroscopic studies like multinuclear (^{1}H,^{13}C, ^{29}Sn,^{119}Sn) NMR, ^{119m}Sn Mössbauer, IR and mass spectrometry.

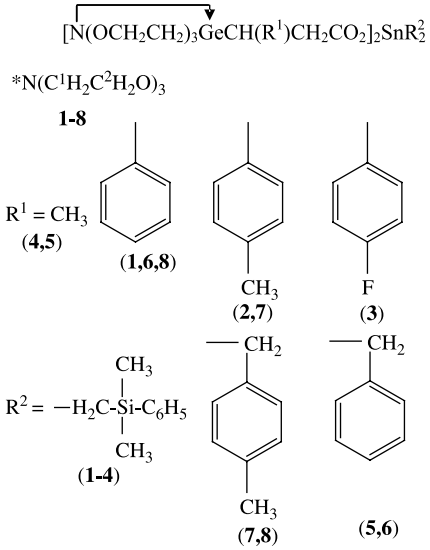
Spectroscopic investigations

NMR spectrscopy. The ^{1}H NMR data of compounds **1–8** are given in Table II. The CH_2 group attached to silicon and tin resonated up-field in the region of 0.06–0.8 ppm which is due to the electropositive nature of both the two atoms. The cyclic skeleton of germatranes, comprises an AABB spin system, give two triplets around 3.6–3.9 ppm for OCH_2 and 2.7–2.9 ppm for NCH_2 moiety with vicinal coupling constant, $^3\mathcal{J}$ (AB) value of 5–6 Hz in solution ($CDCl_3$) [15]. Methyl group attached to silicon absorbs at 0.1–0.3 ppm. The unit CH_2CHGe, having three non-equivalent protons in germatranyl propionate framework, comprises an ABX system by presenting CHGe a chiral centre and CH_2 as a prochiral centre. The methylene protons (A,B) resonate at 2.9–3.2 ppm showing two pseudoquartets along with geminal coupling constant ($\mathcal{J}_{gem}$ 14.8 ± 1 Hz) and two different vicinal coupling constants ($\mathcal{J}_{vic}$ 4.5, 12.5 ± 1 Hz). The H_X of the chiral centre resonate further downfield at about 3.8–4.1 ppm. For figure and more details see elsewhere [19]. The CH_2 group of benzyl moiety resonated at 2.5 ppm as a singlet for compounds (**5–8**). Phenyl group of the benzyl moiety and phenyl attached to germanium overlap in aromatic region and pose some difficulty to be differentiated. Thus, all the protons in the compounds have been identified and the total numbers of protons estimated from the peak height of the integration curves agree well with their expected molecular formulae.

The ^{13}C NMR spectral data are presented in Table III. The methylenic carbon directly attached to tin and/or silicon atoms resolved at up-field due to the electropositive nature of these two atoms. The carbon atoms linked to germanium atom through oxygen and nitrogen in germatranyl moiety resonate at 56 and 51 ppm, respectively. The aromatic carbon resonances were assigned by comparison of experimental chemical shift values with those calculated from incremental method [20] and then compared with the literature values [21]. The chemical shifts values of carboxylate carbon for these compounds appear in range 172–182 ppm. The ^{119}Sn chemical shift data for some selected compounds are given in Table IV. Now it is well established that compounds with different geometries about tin atom produce chemical shift in moderately well defined ranges, and for these compounds δ (^{119}Sn) values lie in between 99

Table II. ^{1}H NMR data[*ab] of organotin (IV) derivatives of general formula.

Comp.	$N(CH_2CH_2O)_3$	R^1	CH_2	CH	R^2		
					H_3C-Si	H_2C-Sn	Phenyl
1	2.8(t) [5.7] 3.6(t) [6.0]	Phenyl	2.9	3.8	0.18(s)	0.24(s)	7.0–7.4 (m)
2	2.9(t) [5.7] 3.7(t) [5.5]	Phenyl 0.17(s)	3.4	3.8	0.15(s)	0.26(s)	7.0–7.6 (m)
3	2.7(t) [6] 3.7(t) [5.7]	Phenyl	3.2	3.9	0.14(s)	0.3(s)	6.8–7.2 (m)
4	2.8(t) [5.7] 3.6(t) [5.5]	1.17(d) [7.2]	3.1	3.8	0.13(s)	0.28(s)	7.3–7.5 (m)
5	2.8(t) [5] 3.8(t) [5.5]	1.12(d) [7.1]	3.0	4.1	–	Phenyl 2.5(s)	6.8–7.2 (m)
6	2.9(t) [6] 3.9(t) [6.5]	Phenyl	3.2	4.0	–	Phenyl 2.5(s)	7.3–7.4 (m)
7	2.9(t) [5.4] 3.6(t) [5.6]	Phenyl 2.3(s)	3.1	3.9	–	Phenyl 2.2(s)	6.8–7.2 (m)
8	2.7(t) [5.4] 3.5(t) [5.8]	Phenyl	3.3	3.8	–	Phenyl 2.3(s)	7.0–7.3 (m)



a = In $CDCl_3$ at 298K, b = Chemical shift in ppm, multiplicity is given as: s = singlet, d = doublet, t = triplet, m = multiplet, nJ(1H1H) in Hz.

Table III. ^{13}C, ^{29}Si NMR data[ab] of organotin (IV) derivatives of general formula.

S.No.		1	2	3	4	5	6	7	8
$N(CH_2CH_2O)_3$	1	51.4	51.3	51.2	50.9	51.0	50.9	51.4	51.2
	2	56.0	56.8	56.7	56.1	56.1	56.4	56.2	55.9
^{1}R	i	141.9	140.9	139.8	16.3	16.5	136.9	141.1	133.5
	o	126.7	128.6	128.3	–	–	130.0	127.9	130.0
	m	127.5	129.0	114.8	–	–	125.5	129.0	125.0
	p	132.0	133.9 (21.3)⋆	162.6	–	–	128.0	135.0 (21.5)⋆	128.1
^{2}R	α	142.0	141.2	141.9	142.0	137.1	136.9	137.8	136.0
	β	133.5	133.4	132.9	133.5	129.9	130.0	129.1	131.0
	γ	128.0	130.1	127.4	129.1	127.5	128.0	128.5	127.3
	δ	128.2	128.5	128.4	129.2	125.5	125.5	125.4 (18.1)⋆	125.0 (19.2)⋆
H_3C-Si		0.55	0.52	0.04	0.18	–	–	–	–
H_2C-Sn		9.28	9.3	9.4	8.99	9.5	9.3	9.8	9.0
R^2-HC		34.9	37.2	36.6	23.7	33.5	36.0	36.6	33.5
H_2C		45.8	46.2	39.2	23.9	37.0	39.0	36.8	41.5
COO		179	180.6	179	174.1	172.0	178.5	182	179
^{29}Si		–	−3.02	–	−2.94	–	–	–	–

⋆Substituents at phenyl is indicated in () at respective carbon; [a]In $CDCl_3$ at 298K; [b]Numbering of carbon atoms is in accordance to the footnote of Table-II.

Table IV. ^{119m}Sn Mössbauer and ^{119}Sn NMR data (in $CDCl_3$) of the selected compounds.

Comp.	QS (mms^{-1})	IS (mms^{-1})	ρ (QS/IS)	δ ^{119}Sn NMR (ppm)
1	3.20	1.22	2.62	−123.45
2	3.24	1.29	2.51	−109.66
3	3.22	1.26	2.55	–
4	3.24	1.23	2.63	−119.78
5	3.27	1.22	2.68	–
7	3.21	1.30	2.46	−115.40
8	–	–	–	−105.37

to 123 ppm [15,22]. In conclusion NMR parameters suggested that there are dynamic processes connected with the coordination of the carboxylate oxygens to the tin atom in these compounds. It appears that a weakly hexacoordinated tin generates a deformed octahedron or skew trapezoidal bipyramid geometry with four strong and two somewhat weaker bonds. The data, thus, reflect consistency with the literature values [22–24].

Infrared spectroscopy. Important IR data for the compounds are presented in Table V. A characteristic strong band at about 700 cm^{-1} demonstrates N → Ge coordination mode for germatrane derivatives. Two absorption bands at about 900 and 820 cm^{-1} are of typical for the Ge-O skeleton. Absorptions around 610 and 520 cm^{-1} are assigned to Sn-C asymmetric and symmetric modes respectively whereas a weak band around 440 cm^{-1} indicates Sn-O stretching vibration [13,21]. Another important parameter, $\Delta\nu$ $(= \nu(COO)_{asym} - \nu(COO)_{sym}]$ described effectively the nature of bonding of the carboxylate group to tin(IV) [19]. The $\Delta\nu$ values lie in range 202–222 cm^{-1} which suggests bidentate nature of the carboxylate ligand in these diorganotin derivatives.

^{119m}Sn Mössbauer spectroscopy. The Mössbauer parameters, quadrupoles splitting (QS) and isomer shift (IS), provided useful indirect evidence for proposing the solid-state structure of organotin compounds and the ^{119m}Sn Mössbauer data are given in Table IV. The observed QS values range 3.21–3.29 mms^{-1} which correspond to monomeric hexacoordinated *trans*-R_2SnO_4 geometry around tin in these compounds. The IS values for these lie in range 1.22–1.26 $mms.^{-1}$

The ρ-values (QS/IS) for the compounds fall in range 2.46–2.68 which demonstrated higher than four coordination at tin [19,25]. There is a distortion from perfect octahedral geometry in these diorganotin derivatives due to high electronegativity of carboxylate oxygens which give QS values similar to those for trigonal bipyramidal geometry.

Mass spectrometry. Main fragment ions observed in the mass spectra of a selected compound are listed in Table VI. Here primary decomposition occurs due to the elimination of one ligand, followed by loss of R-group attached to tin or CO_2 molecules. The base peak is at m/z 220 which corresponds to the germatranyl ion in the compound [25]. This species might result from the cleavage of Ge-C bond in parent ion. It has been reported [21] that the fragmentation of germatrane takes place via two routes; the first of which is the loss of three formaldehyde molecules ($m/z = 30$) in succession from the molecular ion while the second route is associated with the elimination of OCH_2CH_2 moiety ($m/z = 44$) successively to give metal ion. Thus mass spectral data are supportive to the proposed molecular structures of the compounds and the absence of molecular ion peaks demonstrated that there is no intermolecular coordination.

Biological studies

Antileishmanicidal data is presented in Table VII. The compounds (**1–8**) were screened for their antileishmanial activity against promastigotes of *Leishmania major in vitro* and demonstrated good activity. Leishmaniasis is group of human parasitic diseases caused by a group of parasitic protozoa in the genus *Leishmania*. Leishmania are digenetic in their life cycle

Table V. Characteristic IR data ($cm^{(-1)}$) of organotin(IV) derivatives (**1-8**).

Comp.	$\nu(COO)_{asym}$	$\nu(COO)_{sym}$	$\Delta\nu$	Δ(Ge(O)	ν(Ge(N)	ν(Sn(C)	ν(SnO)
1	1598	1396	202	901, 832	674	612, 535	430
2	1622	1419	203	903, 840	690	610, 534	431
3	1602	1392	210	900, 830	680	620, 535	440
4	1601	1394	207	911, 828	690	614, 533	426
5	1598	1392	206	900, 852	664	617, 523	451
6	1595	1388	207	899, 821	690	619, 535	450
7	1604	1402	202	895, 825	692	620, 541	417
8	1590	1384	206	898, 817	695	620, 545	460

Table VI. Mass fragment of a selected compound **2**.

Fragments	*m/z* (Intensity)
$[(H_2CCH_2O)_3NGeCH(CH_3C_6H_4)CH_2COO]_2Sn[CH_2Si(CH_3)_2(C_6H_5)]_2^+$	1180 (n.o)
$[(H_2CCH_2O)_3NGeCH(CH_3C_6H_4)CH_2COO]Sn[CH_2Si(CH_3)_2C_6H_5]_2^+$	798 (3)
$[(H_2CCH_2O)_3NGeCH(CH_3C_6H_4)CH_2COO]Sn[CH_2Si(CH_3)_2C_6H_5]^+$	649 (2)
$[(H_2CCH_2O)_3NGeCH(CH_3C_6H_4)CH_2COOSn]^+$	502 (4)
$[(H_2CCH_2O)_3NGeCH(CH_3C_6H_4)CH_2]^+$	458 (5)
$[(CH_2CH_2O)_3NGeCH(C_6H_4CH_3)CH_2COOH]^+$	383 (15)
$[Sn(CH_2Si(CH_3)_2C_6H_5)_2]^+$	418 (14)
$[(CH_2CH_2O)_3NGe]^+$	220 (100)
$[Sn(CH_2Si(CH_3)_2C_6H_5)]^+$	269 (4)
$[SnCH_2SiCH_3]^+$	177 (15)
$[CH(C_6H_4CH_3)CH_2COO]^+$	162 (60)
$[(CH_2CH_2O)NGeH(CH_2)_2]^+$	160 (18)
$[(CH_2CH_2O)_3N]^+$	146 (50)
$[N(CH_2CH_2)_2O]^+$	86 (50)
$[SnH]^+$	121 (10)
$[Sn]^+$	120 (15)

i.e., they exist in two different morphological forms; the promastigotes and the amastigotes present in the insect and the mammalian host, respectively. The female sandfly injects these promastigotes into the skin of the mammalian host during blood meal whereas humans are accidental hosts.

Compounds **1**–**8** were randomly screened for their antileishmanial activity and almost all of these germatranyl substituted organotin carboxylates exhibited potential leishmanicidal activity and their IC_{50} values fall in the range of 1.3–12.25 μg/mL. The antileishmanial activities of newly synthesized complexes **1**–**8** was compared with the standard drug pentamidine ($IC_{50} = 2.56$ μg/mL). The activity of each compound was determined in triplicate. Compound **2** was found to be the most active compound of the series having IC_{50} value 1.30 μg/mL, which is even better than standard pentamidine. A limited structure activity relationship (SAR) study suggests that the activity of compounds largely depends upon the R^1 and R^2 groups. In compound **1**, where R^1 and R^2 are phenyl and ($CH_2Si(CH_3)_2C_6H_5$) showed less activity ($IC_{50} = 12.15$ μg/mL) as compared to compound **2**, where R^1 is *p*-$CH_3C_6H_4$ and R^2 is ($CH_2Si(CH_3)_2$-C_6H_5), which clearly indicates that suitable R^1 substitution is responsible for antileishmanial activity.

Table VII. *In vitro* antileishmanial activity data for compounds (1–8).

Compound	IC_{50} (μg/ml)
1	12.15
2	1.30
3	Inactive
4	6.00
5	12.25
7	12.25
8	12.25
Petamidine (Standard Drug)	2.56

However, comparison of activities of compounds **4** and **5** suggests that activity is also depends upon R^2 groups as reflected by less activity of compound **5** ($R_2 = CH_2C_6H_5$) than compound **4** ($R^2 = CH_2$-$Si(CH_3)_2C_6H_5$). The study demonstrated that the nature and position of the substituent on the phenyl ring is crucial for displaying the antileishmanial activity as in case of compound **3** (R^1 *p*-FC_6H_4) which is found to be inactive. However, there is notable variation in the activity with changes in the nature of R^1 and R^2 groups present in the complex. In conclusion, compound **2** was found to be a potential lead compound for further study in the search for a better antileishmanial chemotherapeutic agent.

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