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Artigo

SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-{5-(4-METHYLPHENYL) DIAZENYL-4-PHENYL-1, 3-THIAZOL-2-YL}BENZAMIDE DERIVATIVES

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In the present study, various amides of 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole was synthesized and their biological activities were evaluated. All the synthesized compounds were characterized by the combination of elemental analysis and standard spectroscopic methods. They are screened for anti-bacterial activity against *Escherichia coli* and *Staphylococcus aureus* as well as screened for antifungal activity against *Aspergillus niger* and *Apergillus oryzae* by cup plate method at 1 µg/ mL concentration in DMF.

Keywords: aminothiazole derivatives; amide linkage; microbial activity.

INTRODUCTION

It is well known in literature that nitrogen and sulfur containing compounds are essentially used in medical purpose for the treatment of different kinds of fungal and bacterial infections along with treatment of gastric ulcer, cancer etc.[1] The organic moiety having nitrogen and sulfur atom results towards higher efficiency against various diseases.[2] Sulfur is capable of forming both σ and π bonds therefore the studies of their binding interaction with receptor moiety was also an interesting field of research during last few years.[3] Thiazoles are useful structural units in the field of medicinal chemistry and have reported to exhibit a variety of biological activity.[4,5] The thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, like thiamine (vitamin-B), also in some antibiotics drugs like penicillin, micrococcin,[6] and many metabolic products of fungi and primitive marine animal etc. Thiazole derivatives are of considerable interest from therapeutic point of view because of their utility as antibacterial and antifungal,[7] anti-inflammatory,[8] analgesic,[9] antitubercular,[10] central nervous system (CNS) stimulate,[11] anti-HIV,[12] algicidol[13] etc. Thiazole containing N=C=S moiety have been used as antiphychotics[7] and antimalarial.[14] Thiazole derivatives are well explored as useful clinical agents and some of the derivatives of thiazoles have shown inhibition towards herpes simplex virus.[15] Some derivatives of 2-aminothiazoles bearing arylazo moiety at position-5 have shown good cytotoxic activities and cytopathic activity.[16,17] Garg and Sharma[18] synthesized and studied the properties of a series of compounds having the mixed structure. They prepared some new potential antineoplastic viz. N-phenyl-N'-2-(4-phenyl-5-arylazothiazolyl) thiocabamide having arylazo group and a modified azomethine linkage. Mehra *et al.*[17] reported synthesis of various N-benzoyl-N'-2-(4-aryl-5-arylazothiazolyl)thiocarbamides by condensation of 2-amino-4-aryl-5-arylazothiazoles with benzoyl isothiocyanate and tested for their antineoplastics. Husain and Srivastava[19] reported synthesis of series of N^5-(4-aryl-5-arylazothiazol-2-yl- or 5-aryl-1, 3, 4- oxadiazole-2-yl-aminocarbonyl)-4-methyl-1-piperazino/piperidino biguanides from N^5-ethoxycarbonyl-4methyl-1-piperazino/piperidino-biguanides. A few compounds of the series, when administered orally in rats, cause reduction in the blood sugar to a significant extent but most of these have been found to be toxic. Jain *et al.*[20] were synthesized Schiff's base of 2-amino-4-phenyl-5-arylazothiazoles with different nitro derivatives of benzaldehyde to study their biological activities. Amides are known as microbial agents.[21] Furthermore, in nature, the selective binding for substrate such as anion is achieved via the positional alignment of the amide hydrogen bonds.[21] While plant extracts[22] and isolated pure nature products,[23] have been used for antimicrobial activities, there are few reports of amides as antimicrobial agents.[24] In continuation of our pervious work[25,26] in this article, we report the synthesis of some novel amide of 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole with a view to evaluate their biological activity.

RESULTS AND DISCUSSION

Fusion of acetophenone with thiourea in presence of iodine gave 2-amino-4-phenylthiazole (**I**).[27] Any halide can be used for cyclisation purpose. However in the present study, iodine was used because it is easy to handle. In second step, 4-methylbenzenediazonium chloride (**II**),[28] obtained by the usual diazotization of 4-methylaniline, was coupled with 2-amino-4-phenylthiazole (**I**) using sodium acetate in ethanol. Sodium acetate acts as buffer, which can control the pH of solution. Coupling gave 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole (**III**). Different substituted aromatic acid chlorides (**IV**) were prepared by the reaction of the corresponding aromatic acid with excess of thionyl chloride by heating on a water-bath till the evolution of hydrogen chloride gas ceased. Finally, the target amino thiazole derivatives with amide linkage[29] (**V**) were obtained by condensation of 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole (**III**) with appropriate substituted acid chlorides (**IV**) by employing Schotten-Bauman synthesis protocol.

The synthetic route for the preparation of the compounds N-[5-(4-Methylphenyl)diazenyl-4-phenyl-1,3-thiazol-2-yl]benzamide derivatives (**V**) is outlined in Scheme 1. The elemental analyses, FTIR and ^{1}H NMR spectra are fully consistent with the structure.

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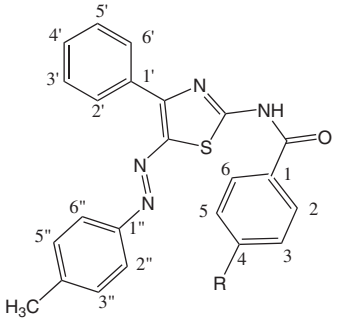
Structure

The absorption bands of the representative compounds appeared in the region 3350-3400 for -NH- stretching, 1590-1600 for -NH- bending, 1650-1675 for -C=O-, 1625-1650 for -N=N-, 1375 for -C=S- stretching, 1200 for C-O bending and 1000 as well as 790 due to stretching of thiazole nucleus. In the IR spectrum of the N-[5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazol-2-yl]-benzamide derivatives (**V**) peaks of -C=O- stretching, -NH- bending and stretching indicated the presence of amide linkage. The ^{1}H NMR spectrum of the representative compounds of N-[5-(4-Methylphenyl)diazenyl-4-phenyl-1,3-thiazol-2-yl]-benzamide derivatives (**V**) exhibited singlet in the region of δ 13.23-13.45 for amide proton, while all aromatic protons appeared in the region of δ 7.47-8.39. The disappearance of the -NH_2 signal from the ^{1}H NMR spectrum and the presence of singlet in the region of δ 13.23–13.45 indicates that the -NH_2 group has been converted to amide linkage.



Antibacterial activity[30,31]

The compounds were tested *in-vitro* for their antibacterial activity against two micro-organisms viz. *Escherichia coli* and *Staphylococcus aureus,* which are pathogenic in human beings.

Antifungal activity[30,31]

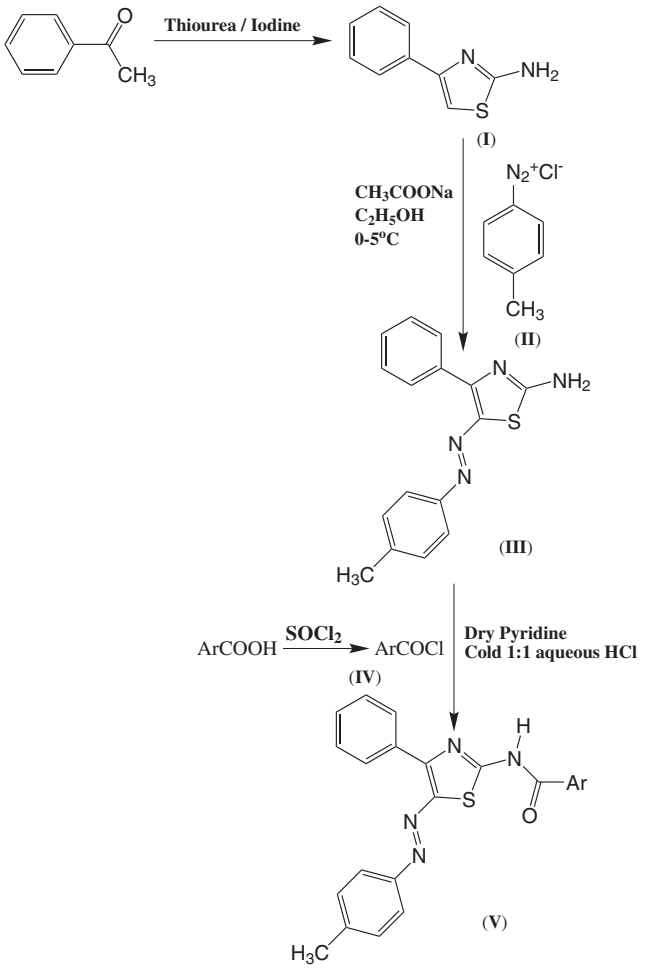
The compounds were tested *in-vitro* for their antifungal activity against *Aspergillus niger* and *Aspergillus oryzae.*

EXPERIMENTAL

Material and methods

The requisite starting materials such as acetophenone, iodine, thiourea, 4-methylaniline, sodium acetate, sodium nitrite, pyridine, substituted aromatic acids, thionyl chloride, sulphuric acid etc. were procured from Aldrich Company and used without any further purification. All the solvents were purified and dried by standard method. All melting points were determined in open capillary tube and uncorrected. At the initial stage, purity of compounds was checked by thin layer chromatography (Merck kieselgel 60F_{254} pre-coated plates). Microanalysis of the compounds was performed on a Carlo Erba EA 1108 carbon-hydrogen analyzer and the values obtained are in close agreement with those calculated. FTIR spectra were recorded via KBr pellets, using Shimadzu FTIR-408 spectrophotometer. ^{1}H NMR spectra were obtained with Perkin–Elmer R-32 spectrometer at 300MHz using tetramethylsilane (TMS) as an internal reference standard. The chemical shift are quoted as δ (parts per million) downfield from the reference. DMSO-d_6 was used as solvent for all the compounds.

The synthetic route to N-{5-(4-Methylphenyl)-sdiazenyl-4-phenyl-1, 3-thiazol-2-yl} benzamide derivatives is illustrated in Scheme 1.



Where Ar=Phenyl; 2-Chlorophenyl; 4-Chlorophenyl; 2,4-Dichlorophenyl; 2-Methylphenyl; 3-Methylphenyl; 4-Methylphenyl; 3-Nitrophenyl; 4-Nitrophenyl; 3,5-Dinitrophenyl; 4-Bromophenyl; Phenylmethylene; 2-Naphthoxymethylene; 4-Phenylphenyl; Cinnamic acid; Nicotin; Isonicotin; 4-Methoxyphenyl; 2-Iodophenyl; 2-Chlorophenylmethylene; 2,4-Dichlorophenoxymethylene; 4-Chloro-3-nitrophenyl.

Scheme I*. The synthetic route to N-[5-(4-Methylphenyl)-diazenyl-4-phenyl-1, 3-thiazol-2-yl]benzamide derivatives*

2-Amino-4-phenylthiazole (**I**) was synthesized by reported method[27] given in literature. M. P.: 148°C (Reported[27] M. P.: 147°C) Yield: 80%.

4-Methylbenzenediazonium chloride (**II**) was synthesized by reported[28] method given in literature. 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole (**III**) was synthesized by slow addition of 0.02 mole of an ice-cold solution of 4-methylbenzenediazonium chloride (**II**) in cooled solution of 0.02 mole of 2-amino-4-phenylthiazole and 15 gms of sodium acetate in ethanol. The reaction mixture was diluted with cold water. The separated solid was collected by filtration. The solid obtained was washed successively with water (2 x 150 mL) and was crystallized by aqueous ethanol (1:1). M. P.: 180 °C. Yield: 70%. Elemental analysis: calculated for $C_{16}H_{14}N_4S$: C, 65.30; H, 4.76; N, 19.04%. Found: C, 65.12; H, 4.68; N, 18.97%. FTIR *spectrum (KBr)* ν_{max}/cm^{-1}: 3150 (-NH_2), 1600, 1625 (-N=N-), 1510, 1475, 1300, 1250, 1190, 1075, 1025 and 790 (st. of thiazole nucleus). ^{1}H NMR *spectrum* (DMSO-d_6): δ 2.20 (s, 3H, -CH_3), 7.45-7.65 (m, 5H, Ar-H at C-3', C-4', C-5', C-3" and C-5"), 7.95 (d, *J* = 8.2, 2H, Ar-H at C-2' and C-6'), 8.10 (d, *J* = 8.1, 2H, Ar-H at C-2" and C-6"), 8.80 (br, 2H, -NH_2).

Aromatic acid chlorides (**IV**) were synthesized by refluxing substituted aromatic acid (0.01 Mole) in excess of thionyl chloride. Excess of thionyl chloride was distilled off under reduced pressure and the acid chloride left behind as a residue was used in next reaction without further purification.

N-[5-(4-Methylphenyl)diazenyl-4-phenyl-1,3-thiazol-2-yl] benzamide derivative (**V**) was synthesized by condensing equimolar quantity of 2-amino-5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazole (**III**) and an appropriate substituted aromatic acid chloride (**IV**) respectively, in dry pyridine. The reaction mixture was poured in cold aqueous (1:1) HCl. The solid material obtained was filtered off and was chromatographed on silica gel (100-200 mesh) using mixture of ethyl acetate and hexane (20:80) as eluent. Removal of solvent from the eluted afforded a solid material, which was crystallized repeatedly from alcohol. The reaction products were obtained as reddish to orange solids in the range of 50-80% yield. The purity of all these compounds was checked by thin layer chromatography (Merck kieselgel 60F254 pre-coated plates). The data of elemental analysis, FTIR and ^{1}H NMR of few representative members with general structural formula are given below.

Analysis data for R = -H, elemental analysis: calculated for $C_{23}H_{18}N_4OS$: C, 69.34; H, 4.52; N, 14.07%. Found: C, 69.20; H, 4.34; N, 13.91 %. FTIR *spectrum* (KBr) ν_{max}/cm^{-1}: 3375 (-NH-), 1675 (-C=O-), 1650 (-N=N-) 1590 (-NH-), 1525, 1450, 1375 (-C=S-), 1200, 1100, 950, 875, and 770 (st of thiazole nucleus). ^{1}H NMR *spectrum*: δ 2.25 (s, 3H, -CH_3), 7.48-7.68 (m, 8H, Ar-H at C- 3, C-4, C-5, C-3', C-4',C-5', C-3" and C-5"), 7.79 (d, *J* = 8.0 Hz, 2H, Ar-H at C-2" and C-6"), 8.13 (d, *J* = 8.1 Hz, 2H, Ar-H at C-2' and C-6'), 8.26 (d, *J* = 7.7 Hz, 2H, Ar-H at C-2 and C-6), 13.23 (s, 1H of -NH-).

Analysis data for R = -Cl, elemental analysis: calculated for $C_{23}H_{17}N_4OClS$: C, 63.81; H, 3.93; N, 12.94%. Found: C, 63.81; H, 3.71; N, 12.89 %. FTIR *spectrum* (KBr) ν_{max}/$_{cm}^{-1}$: 3350 (-NH-) 1650 (-C=O-), 1625 (-N=N-) 1600 (-NH-), 1500, 1475, 1375 (-C=S-), 1200, 1100, 950, 875, and 770 (st of thiazole nucleus). ^{1}H NMR *spectrum*: δ 2.25 (s, 3H, -CH_3), 7.47-7.66 (m, 7H, Ar-H at C- 3, C-5, C-3', C-4',C-5', C-3" and C-5"), 7.79 (d, *J* = 7.8 Hz, 2H, Ar-H at C-2" and C-6"), 8.14 (d, *J* = 8.2 Hz, 2H, Ar-H at C-2' and C-6'), 8.23 (d, *J* = 8.0 Hz, 2H, Ar-H at C-2 and C-6), 13.31 (s, 1H of -NH-).

Analysis data for R = -NO_2, elemental analysis: calculated for $C_{23}H_{17}N_5O_3S$: C, 62.30; H, 3.83; N, 15.80%. Found: C, 62.12; H, 3.69; N, 15.71%. FTIR *spectrum* (KBr) ν_{max}/cm^{-1}: 3400 (-NH-) 1650 (-C=O-), 1625 (-N=N-) 1600 (-NH-), 1525, 1450, 1375 (-C=S-), 1200, 1100, 950, 875, and 770 (st of thiazole nucleus). ^{1}H NMR *spectrum:* δ 2.15 (s, 3H, -CH_3), 7.52-7.61 (m, 7H, Ar-H at C- 3, C-5, C-3', C-4',C-5'), 7.81 (d, *J* = 8.1 Hz, 2H, Ar-H at C-3" and C-5"), 8.26 (d, *J* = 8.2 Hz, 2H, Ar-H at C-2" and C-6"), 8.32-8.39 (m, 4H, Ar-H at C-2', C-6', C-2 and C-6), 13.45 (s, 1H of -NH-).

Analysis data for R = -CH_3, elemental analysis: calculated for $C_{24}H_{20}N_4OS$: C, 69.90; H, 4.85; N, 13.59%. Found: C, 69.75; H, 4.79; N, 13.43%. FTIR *spectrum* (KBr) ν_{max}/cm^{-1}: 3390 (-NH-) 1645 (-C=O-), 1630 (-N=N-) 1605 (-NH-), 1525, 1440, 1370 (-C=S-), 1200, 1100, 950, 875, and 770 (st. of thiazole nucleus). ^{1}H NMR *spectrum* (DMSO-d_6) (400 MHz): δ 2.28 (s, 6H, 2 X Ar-CH_3), 7.46-7.75 (m, 7H, Ar-H at C-3, C-5, C-3', C-4', C-5', C-3" and C-5"), 7.76 (d, *J* = 8.0 Hz, 2H, Ar-H at C-2" and C-6"), 8.15 (d, *J* =8.1 Hz, 2H, Ar-H at C-2' and C-6'), 8.30 (d, *J* =7.7 Hz, 2H, Ar-H at C-2 and C-6), 13.21 (s, 1H of -NH-).

Analysis data for R = -Br, elemental analysis: calculated for $C_{23}H_{17}N_4OBrS$: C, 57.86; H, 3.56; N, 11.74%. Found: C, 57.79; H, 3.49; N, 11.63%. FTIR *spectrum* (KBr) ν_{max}/cm^{-1}: 3375 (-NH-) 1655 (-C=O-), 1635 (-N=N-) 1610 (-NH-), 1520, 1435, 1370 (-C=S-), 1200, 1100, 950, 875, and 770 (st. of thiazole nucleus). ^{1}H NMR *spectrum* (DMSO-d_6) (400 MHz): δ 2.21 (s, 3H, 2 X Ar-CH_3), 7.41-7.78 (m, 7H, Ar-H at C-3, C-5, C-3', C-4', C-5', C-3" and C-5"), 7.76 (d, *J* =

Table 1. M.P and antimicrobial activity data of N-{5-(4-Methylphenyl)-diazenyl-4- phenyl-1, 3-thiazol-2-yl} benzamide derivatives (V)

Sr. No.	Ar	M.P (°C)	Anti Bacterial		Anti Fungal	
			E. coli Blank 12 mm	*S. aureus* Blank 12 mm	*A. niger* Blank 10 mm	*A. oryzae* Blank 10 mm
1	Phenyl	230	++	++	++	++
2	2-Chlorophenyl	158	+++	++	++	++
3	4-Chlorophenyl	225	+++	++	++	++
4	2,4-Dichlorophenyl	180	+++	++	++	+++
5	2-Methylphenyl	120	++	++	++	++
6	3-Methylphenyl	165	++	++	++	++
7	4-Methylphenyl	115	++	++	++	++
8	3-Nitrophenyl	245	+++	++	++	++
9	4-Nitrophenyl	268	+++	++	++	++
10	3,5-Dinitrophenyl	>300	+++	++	++	+++
11	4-Bromophenyl	200	++	++	++	++
12	Phenylmethylene	169	++	++	++	++
13	2-Naphthoxymethylene	250	++	++	++	++
14	4-Phenylphenyl	>300	++	++	++	++
15	Cinnamic acid	110	++	++	++	++
16	Nicotin	187	++	++	++	++
17	Isonicotin	225	++	++	++	++
18	4-Methoxyphenyl	119	++	++	++	++
19	2-Iodophenyl	287	++	++	++	++
20	2-Chlorophenyl methylene	180	+++	++	++	++
21	2,4-Dichlorophenoxy methylene	276	+++	++	++	+++
22	4-Chloro-3-nitro phenyl	278	++	++	++	+++
23	Furacin (As a Standard)		+++	+++	-	-
24	Grieseofulvin (As a Standard)		-	-	-	+++

++: (12-13 mm Diameter); +++: (>13 mm Diameter); -: Not active. Note: All the compounds are crystallized by alcohol.

8.0 Hz, 2H, Ar-H at C-2" and C-6"), 8.11 (d, *J* = 8.1 Hz, 2H, Ar-H at C-2' and C-6'), 8.25 (d, J=7.7 Hz, 2H, Ar-H at C-2 and C-6), 13.26 (s, 1H of -NH-).

Analysis data for R = -OCH_3, elemental analysis: calculated for $C_{24}H_{20}N_4O_2S$: C, 67.28; H, 4.67; N, 13.08%. Found: C, 67.15; H, 4.57; N, 13.03%. FTIR *spectrum* (KBr) ν_{max}/cm^{-1}: 3350 (-NH-) 1650 (-C=O-), 1625 (-N=N-) 1600 (-NH-), 1525, 1440, 1370 (-C=S-), 1200, 1100, 950, 875, and 770 (st. of thiazole nucleus). ^{1}H NMR *spectrum* (DMSO-d_6) (400 MHz): δ 2.25 (s, 3H, Ar-CH_3), 3.98 (s, 3H, Ar-OCH_3), 7.42-7.70 (m, 7H, Ar-H at C-3, C-5, C-3', C-4', C-5', C-3" and C-5"), 7.73 (d, *J* = 8.0 Hz, 2H, Ar-H at C-2" and C-6"), 8.12 (d, *J* = 8.1 Hz, 2H, Ar-H at C-2' and C-6'), 8.26 (d, J=7.7 Hz, 2H, Ar-H at C-2 and C-6), 13.17 (s, 1H of -NH-).

All compounds were screened for antibacterial activity against *E. coli* and *S. aureus* by cup plate method.[30,31] For anti bacterial activity, we had taken 20 gms of Luria-Bertani broth (Hi media M-575) and 25 gms of agar-agar in 1000 mL distilled water and heated till dissolved. Then, the mixture was sterilized by autoclaving at 15 lbs pressure and 121 °C for 15 min. Here, agar-agar was used to solidify the solution. After that, 6 Petri dishes having flat bottom were taken and filled with about 18 mL of above solution. The plates were overlaid with 4 mL soft agar-agar containing 0.1 mL test culture. Four wells were bored on each plate with 8 mm diameter cork bore aseptically. Now we had dissolved the compound in DMF having 1000 ppm concentration and added 0.1 mL of testing solution into each well. This solution was allowed to diffuse at 4 °C. After 20 min diffusion, the plate was incubated at 37 °C for overnight. After incubation, we observed the zone of inhibition and measured the diameter of the zone. For anti fungal activity, we had taken 20 gms Sabouraud dextrose instead of Luria-Bertani broth and followed the same procedure as described above.

CONCLUSION

Table 1 summarizes the melting point and antimicrobial activity data of N-[5-(4-methylphenyl)-diazenyl-4-phenyl-1, 3-thiazol-2-yl] benzamide derivatives (**V**). All the synthesized compounds showed good antimicrobial activity. Table 1 indicates that chloro and nitro derivatives exhibits good activity against *E. coli.* While other derivatives exhibited moderate activity against *E. coli.* All the derivatives show moderate activity against *S. aureus* and *A. niger*. Dichloro and dinitro derivatives have good activity against *A. oryzae.* Whereas, other derivatives has moderate activity.

As all the newly synthesized amino thiazole derivatives with amide linkage has good to moderate anti-bacterial and anti-fungal activity, they can be used for the development of new drugs for treatment of bacterial and fungal diseases.

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