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Design and Synthesis of 3-Sulfenyl Indole based Antiviral Compounds

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Abstract

Sulfenyl indole moieties, in particular, 2 or 3-substituted Sulfenyl indoles are prevalent in diverse natural products, biologically active compounds, and pharmaceuticals, which are required for curing many diseases, such as virology, cancers, HIV, allergies, respiratory disorders, etc. Owing to their prevalence in natural and synthesized functional organic molecules, indoles keep receiving tremendous attention in the research and application of many disciplines such as chemistry, biology, pharmaceuticals. In this context, our main objective is to synthesize derivatives of 3-Substituted Sulfenyl Indole as Anti-Viral compounds (primarily against DENV).

Keywords: Viral compounds, Indole, Synthesis

Introduction

Indole is a versatile privileged small heterocyclic molecule in medicinal chemistry. It is prevalent in different bioactive natural products including small serotonin to complex alkaloids and many synthetic drugs. Sulfenyl group incorporation is a common and commonly used transformation for the synthesis of important commercial materials, medicinal compounds, and privileged scaffolds of natural chemicals. Recently, medicinal and organic chemists have been particularly interested in 3-sulfenylindoles because of their intriguing and potent applications in a variety of therapeutic areas, including virology[1], cancer,[2] heart disease,[3] anti-inflammatory,[4] and many are currently in the drug discovery pipeline.

Dengue Virus:

A member of the Flaviviridae family of viruses, the Dengue virus (DENV) is a single-stranded RNA virus. The dengue virus is spread through the bite of female mosquitoes, especially Aedes aegypti mosquitoes. The four serotypes of dengue, known asDENV [5-8], can result in a variety of clinical symptoms, ranging from a low fever to serious and often lethal illnesses including dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF).[5] Dengue is estimated to cause 400 million cases[6] and 22,000 fatalities worldwide each year.[7]Up to 80% of DENV-infected individuals do not show any symptoms, and those who do typically have a severe febrile illness marked by a high temperature, joint and muscular discomfort, and occasionally rash.[8] As of right now, there isn't a specific antiviral medication that is authorized to treat DENV infection; instead, the disease is mostly managed symptomatically.[9] The World Health Organization (WHO) reports that about half of the world's populationis at danger due to the dengue virus, which has become more commonplace globally over the past ten years[10].

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There are the following points about dengue:

- The dengue virus (DENV), which causes dengue, is a virus that infects people when an infected mosquito bites them.
- Dengue is currently a threat to around half of the world's population, with 100–400 million cases reported per year.
- Dengue is primarily found in urban and semi-urban areas in tropical and subtropical climates globally.
- Although the majority of DENV infections are asymptomatic or result in moderate sickness, or on rare occasions, it can cause more serious instances, including fatalities.
- Vector control is essential to dengue prevention and management. Dengue and severe dengue have no particular cure, yet the mortality rates from severe dengue are significantly reduced by early discovery and access to quality medical care.
- A common viral infection in warm, tropical settings is dengue, which is spread by mosquitoes. Any one of the four closely related dengue virus serotypes can cause an infection, and these viruses can cause a wide range of symptoms, from extremely mild (unnoticeable) ones to serious ones that would need hospitalization and medical attention. Severe situations may result in fatalities. The patient can control the symptoms they suffer, but there is no cure for the illness itself.

Fig. Dengue Virus

- The WHO identified dengue as one of the ten diseases that could pose a threat in 2019 earlier this year, and outbreaks that are occurring in several nations now support this assessment. Seasonal patterns are common in dengue epidemics, with transmission frequently peaking during and following wet seasons.

Antiviral drugs:

A family of medications called antiviral medicines is used to treat viral infections.[11] A broad-spectrum antiviral is effective against a variety of viruses, whereas most antivirals only target certain viruses.[12] Antiviral medications belong to the class of antimicrobials, a wider group that also includes medications based on monoclonal antibodies, antibiotics (also known as antibacterial), antifungals, and anti-parasitic medications.[13] Antivirals can be used to treat infections because the majority of them are thought to be generally safe for the host. They must be differentiated from virucides, which are not medications but rather substances that destroy or deactivate virus particles both inside and outside the body. Certain plants, like eucalyptus and Australian tea trees, naturally produce virucides.[14]

Sulfenylindole as antiviral agent:

A virus is a tiny infectious agent with 4-200 protein-encoded genetic material, either DNA or RNA.[15]It produces several deadly viral infections when it replicates in host cells. Worldwide, viral infections are thought to be the cause of about 60% of illnesses. These infections include hepatitis, pneumonia, chickenpox, influenza, chikungunya, HIV/AIDS, SARS, ZIKA, MARS, EBOLA, and the newly widespread COVID-19 disease, which resulted in a pandemic.[16-18]In addition to the broad range of medicinal qualities of indole-based drug candidates, indole scaffolds have been thoroughly investigated in antiviral research; some of them, such as "Indomethacin" and "Arbidol," have been identified as prospective drugs and are being pursued against SARS-Cov and Covid-19.[19-20]Delavirdine and arbidol are two examples of commercially available antiviral medications that include indole.Sulfur is also a necessary element that is crucial for the upkeep of biological processes including those involving enzymes, the mediating of electron transfer reactions, the transfer of ribonucleic acids (tRNAs), and the possibility for new chemical,

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medicinal, and agricultural agents.[21–26] Due to the fact that nitrogen and sulfur are components of almost every class of medication, these elements are used in a variety of metabolic processes. The C-S bond-bearing indoles, or sulfenylated or sulfonylated indoles, are a common structural motif with significant biological activities.especially antiviral, anticancer, and antibacterial properties, among the many varieties of indole-containing architectures .[27]

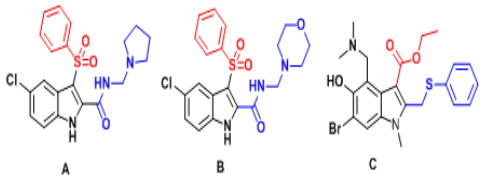

Figure 7. Sulfenyl indoles as anti-viral agents

Thus, the development of new drug candidates to treat dengue is an unmet need.

Basis of work:

Consequently, the development of small molecules as an anti-dengue agent to tackle this threat would be of significant importance. Several small molecules of diverse heterocyclic nucleus have been developed and shown potent activity. In addition, indole is a highly valuable privileged heterocyclic compound, and its significance is attributed to its widespread presence in numerous drugs, natural products, and drug-like molecules, showcasing a broad spectrum of biologicalactivities.[28]Among them, sulfenyl indole-based compounds have demonstrated therapeutic potential for different activities such as antibacterial activity,[29]inhibition of tubulin polymerization **I**, antiviral agent **II**, antiviral (arbidol) **III**, and antitumor **IV**.[30]

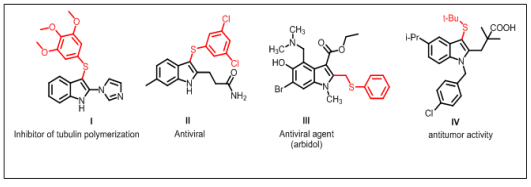

Fig. Some biologically active sufenylated indoles

Umifenovir(Arbidol) is an example of antiviral medicine for treating anti-influenza and recently used for the treatment of COVID-19 viral infections.[31] Our group has been extensively involved in the synthesis of small molecules for different therapeutic diseases and recently we have reported novel synthetic methods for 3-sulfenyle indoles and explored them for antibacterial activity.[28] In continuation of the longstanding interest and to tackle dengue threat, a series of amide groups containing functionalized 3-sulfenyl indoles were synthesized for the development of novel antiviral candidates.

Result and Discussion

Our work bases of above report:

Optimization table:

Entry No.	Base (eq.)	2a (eq.)	Solvent	Time (h)	Temperature	Yields (%)[a]
1	Cs_2CO_3(2)	1	ACN	48	RT	60
2	KOH (2)	1	ACN	48	RT	51
3	NaH (2)	1	ACN	48	RT	53
4	NaOH (2)	1	ACN	48	RT	50
5	K_2CO_3(2)	1	ACN	48	RT	45
6	$NaHCO_3$(2)	1	ACN	48	RT	ND
7	Na_2CO_3(2)	1	ACN	48	RT	ND
8	Cs_2CO_3(2)	1	THF	48	RT	5
9	Cs_2CO_3(2)	1	1,4-dioxane	48	RT	ND
10	Cs_2CO_3(2)	1	Toluene	48	RT	10
11	Cs_2CO_3(2)	1	DME	48	RT	5
12	Cs_2CO_3(2)	1	Ethanol	48	RT	5
13	Cs_2CO_3(2)	1	ACN	8	50 °C	94

Reaction condition: 1a (0.2 mmol, 1 equiv), **2a** (0.2 mmol, 1 equiv), Cs_2CO_3 (2 equiv), ACN solvent, 50 °C.

We started the investigation with the compound **3a** {synthesized from corresponding 5-bromoindole(**1a**) and thiolphenol (**2a**)}and **4a**as model substrates in the presence of Cs_2CO_3at room temperature in MeCN, which delivered the 5-bromo-3-(phenylthio)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-indole (**5a)** in 60% yield. The synthesized *N*-alkylated product**5a** was confirmed by spectral data such as ^1H, ^{13}C NMR, and HRMS. However, for the best optimization condition for alkylation, different reaction parameters like bases, solvents, and temperature were investigated. First, we screened different bases like KOH, NaH, NaOH,K_2CO_3, $NaHCO_3$, andNa_2CO_3 inacetonitrile at room temperature which afforded the productan inferior yield of 45-53% Other solvents like THF, 1,4-dioxane,

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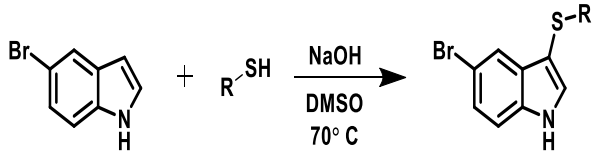
toluene, DME, and ethanol could not improve the yield of theproduct **5a** (5-10%), and starting material remained intact. Furthermore, the desired product **5a** could be obtained in 94% yield using Cs_2CO_3 in MeCN solvent at higher temperature (50 °C).

Derivatives of *N*-alkyl of 3-aryl Sulfenyl Indole and its antiviral activity:

With the above optimum condition, we began our study with the synthesis of the first series of compounds of *N*-pyrrolidine ethyl 3-sulfenyl indoles, starting from 5-bromoindole (**1a**)and thiophenols (**2a**). The basis of selecting 5-bromoindole in the first series was our previous study, showed bromine in 5th position played key role in activity.[27] With this fact, 5-bromoindole nucleus was fixed and the substitution on the thiophenol group was varied in the first series. Subsequently, a series of *N*-alkyl-3-sulfenylindoles (**5a-5d**) were synthesizedin good to excellent yields (83-94%) from synthesized 3-sulfenyl indoles (**3a**) and 1-(2-chloroethyl) Pyrrolidine hydrogen chloride (**4a**) as shown in (**Table 3.2a**). All the synthesized compounds were investigated for activity against dengue virus. First, we tested the cytotoxicity of the synthesized compounds(**5a-5d**) using Vero cell line. However, compounds **5a-5d** were treated in Vero cellsat different concentrations and found toxic with CC_{50} values lower than 100 µM. After that, the cytotoxicity of compounds with halogen-substitution such as 4-Br phenyl (4-Br) at thiol was check, and they were found toxic.

Experimental section:

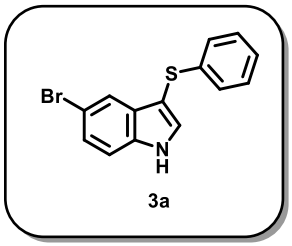
Experimental procedure for the synthesis of 3-sulphenyl indoles (3):



1 2 3

A mixture of indoles 1 (1.0 mmol), thiols 2 (2 mmol), and NaOH (2 mmol) in 8 mL DMSO was stirred in a 25 mL round bottom flask at 70 °C temperature for 7 h. The reaction progress was monitored by TLC (25% ethyl acetate in hexane). After completion of the reaction mixture was diluted with 10 mL water and extracted with (3 x 25 mL) EtOAc. Now, combined the organic layer, dry over anhydrous Na_2SO_4, and concentrate by rotavapor. The crude product was purified by column chromatography using 10-30% ethyl acetate in hexane as eluent resulting in pure products in high yields whose spectral well matched with reported literature values.

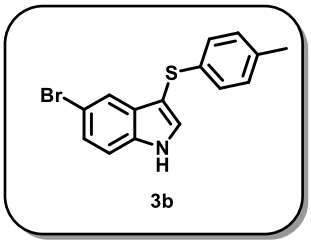
5-bromo-3-(phenylthio)-1H-indole (3a):



3a

General procedure was followed for the synthesis of **3a** by the reaction of 5-bromoindole (196 mg, 1.0 mmol) and benzenethiol (204 µL, 2.0 mmol) in the presence of NaOH (80 mg, 2.0 mmol) in DMSO at 70 °C for 7h.Pure compound **3a** (102 mg, yield: 82%) was obtained as an off-white solid after column chromatography using 9% EtOAc in hexane as eluent.**^{1}H NMR (400 MHz, $CDCl_3$):**δ 8.51 (s, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 1.9, 8.7 Hz, 1H), 7.33 (dd, J = 0.6, 8.6 Hz, 1H), 7.23-7.18 (m, 2H), 7.12-7.08 (m, 3H). **^{13}C{1H} NMR (125 MHz, $CDCl_3$):**δ 138.7, 135.2, 131.9, 131.0, 128.8, 126.1, 125.9, 125.1, 122.3, 114.5, 113.1, 102.9. **HRMS (ESI^+):** m/z: $[M+H]^+$ calculated for $C_{14}H_{11}BrNS$: 303.9795, found: 303.9793.

5-bromo-3-(p-tolylthio)-1H-indole (3b):



3b

General procedure was followed for the synthesis of **3b** by the reaction of 5-bromoindole (196 mg, 1.0 mmol) with *p*-toluene thiol (248 mg, 2.0 mmol) in the presence of NaOH (80 mg, 2.0 mmol) in DMSO at 70 °C for 7h. Pure compound **3b**(yield: 87%) was obtained as a white solid after column chromatography using 9% EtOAc in hexane as eluent.**^{1}H NMR (400 MHz, $CDCl_3$):**δ 8.41 (s, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 1.8, 8.6 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.02-6.97 (m, 4H), 2.25 (s, 3H). **^{13}C{1H} NMR (100 MHz, $CDCl_3$):**δ 135.1, 135.0, 135.0, 131.6, 131.0, 129.6, 126.4, 126.1, 122.3, 114.4, 113.0, 103.5, 20.9. **HRMS (ESI^+):**

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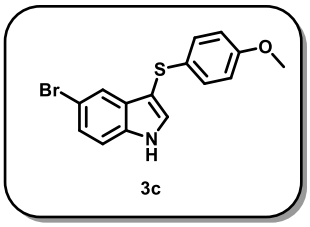
m/z: $[M+H]^+$ calculated for $C_{15}H_{13}BrNS$: 317.9952, found: 317.9940.

5-bromo-3-((4-methoxyphenyl)thio)-1H-indole (3c):

General procedure was followed for the synthesis of **3c** by the reaction of 5-bromoindole (196, 1.0 mmol) with *p*-methoxybenzene thiol (130µL, 2.0 mmol) in the presence of NaOH (80 mg, 2.0 mmol) in DMSO at 70 °C for 7h. The pure compound **3c**(yield: 86%) was obtained as a white solid after column chromatography using 10% EtOAc in hexane as eluent.**^{1}H NMR (400 MHz, $CDCl_3$):**δ 8.37 (s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 1.8, 8.6 Hz, 1H), 7.27 (dd, J = 0.5, 8.6 Hz, 1H), 7.14-7.10 (m, 2H), 6.77-6.73 (m, 2H), 3.74 (s, 3H).**^{13}C{1H} NMR (100 MHz, $CDCl_3$):**δ 158.1, 135.2, 131.3, 131.0, 129.1, 128.9, 126.1, 122.4, 114.8, 114.5, 113.1, 104.8, 55.5. **HRMS (ESI$^+$):** m/z: [M+2] calculated for $C_{15}H_{12}BrNOS$: 334.9824, found: 334.9849.

5-bromo-3-((4-bromophenyl)thio)-1H-indole (3d):

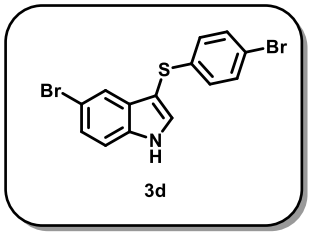
General procedure was followed for the synthesis of **3d** by the reaction of 5-bromoindole (196 mg, 1.0 mmol) and*p*-bromobenzene thiol (378 mg, 2.0 mmol) in the presence of NaOH (80 mg, 2.0 mmol) in DMSO at 70 °C for 7h. The pure compound **3d**(yield: 85%) was obtained as a white solid after column chromatography using 10% EtOAc in hexane as eluent.**^{1}H NMR (400 MHz, DMSO-d_6):** δ 11.95 (s, 1H), 7.85 (d, J = 2.7 Hz, 1H), 7.48 (dd, J = 2.3, 8.3 Hz, 2H), 7.41-7.38 (d, J = 8.6 Hz, 2H), 7.31 (dd, J = 1.9, 8.7 Hz, 1H), 6.95 (d, J = 8.6 Hz, 2H).**^{13}C{1H} NMR (100 MHz, DMSO-d_6):** δ 138.4, 135.5, 134.3, 131.7, 130.4, 127.3, 124.9, 120.2, 117.8, 114.6, 113.1, 98.5. **HRMS (ESI$^+$):** m/z: [M+2] calculated for $C_{15}H_{12}BrNOS$: 334.9824, found: 334.9849.



3c

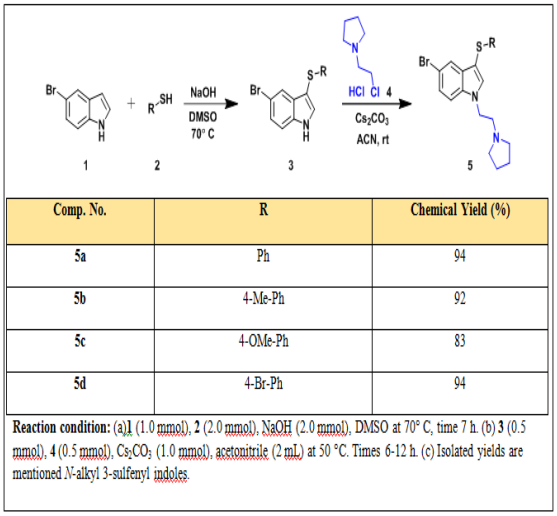
3.4b. General procedure for the synthesis of N-alkyl-3-sulfenyl indole derivatives (5):

Synthesis of **5** by the reaction of **3** (0.5 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (4, 0.5 mmol), in the presence of Cs_2CO_3 (1 mmol) at 50 °C was stirred in acetonitrile (5 mL) for 6-8 h. The reaction progress was monitored by TLC. After completion of the reaction mixture was diluted with 10 mL water and extracted with (3 x 25 mL) EtOAc. Now, combined the organic layer, dried over anhydrous Na_2SO_4, and concentrated by rotavapor. The crude product was purified by column chromatography using 2-5% methanol in ethyl acetate as eluent resulting from pure products (**5a-5d**) obtained in 83-94% yields.



3d

Table: Chemical yields of compounds (5a-5d)

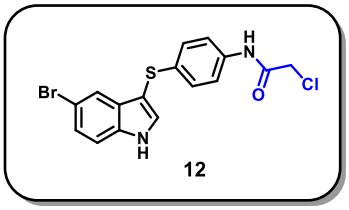


Comp. No.	R	Chemical Yield (%)
5a	Ph	94
5b	4-Me-Ph	92
5c	4-OMe-Ph	83
5d	4-Br-Ph	94

Reaction condition: (a)**1** (1.0 mmol), **2** (2.0 mmol), NaOH (2.0 mmol), DMSO at 70° C, time 7 h. (b) **3** (0.5 mmol), **4** (0.5 mmol), Cs_2CO_3 (1.0 mmol), acetonitrile (2 mL) at 50 °C. Times 6-12 h. (c) Isolated yields are mentioned *N*-alkyl 3-sulfenyl indoles.

3.5a. Experimental procedure and characterization of the compounds (12):

The compound N-(4-((5-bromo-1H-indol-3-yl)thio)phenyl)-2-chloroacetamide (**12**) was synthesized by the reaction of **3** (319 mg, 1 mmol) and chloro acetyl chloride (**11**, 240 µL, 3.0 mmol) in the presence of Et_3N (418 µL, 3.0 mmol) in toluene (10 mL) at reflux for 2 h. The reaction progress was monitored by thin-layer chromatography. After completion of the reaction, diluted with (20 mL) water and extracted with EtOAc (3 x 25 mL). Combined the organic layer and dried over sodium sulfate. Now, the organic



12

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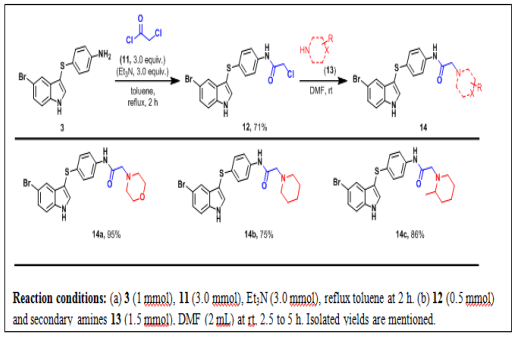
layer was evaporated by rotavapor, and the crude product was purified by column chromatography using 80% DCM in hexane as eluent. Pure product **12** was obtained (281 mg, 71%) as a white solid; M.P. 161-163 °C; HPLC purity: 98%; **^{1}H NMR (400 MHz, DMSO-d_6):**δ 11.87 (s, 1H), 10.26 (s, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.49 – 7.45 (m, 4H), 7.30 (dd, J = 8.6, 1.9 Hz, 1H), 7.06 – 7.03 (m, 2H), 4.21 (s, 2H).**^{13}C NMR (100 MHz, DMSO-d_6):**δ 164.4, 136.0, 135.4, 133.8, 133.0, 130.5, 126.6, 124.7, 120.3, 120.1, 114.5, 112.8, 99.9, 43.4.**HRMS (ESI$^+$)** m/z calculated for $C_{16}H_{13}BrClN_2OS$ $[M+H]^+$: 394.9615; found: 394.9611.

Table. Substrate scope concerning amide group containing secondary amines



Reaction conditions: (a) **3** (1 mmol), **11** (3.0 mmol), Et_3N (3.0 mmol), reflux toluene at 2 h. (b) **12** (0.5 mmol) and secondary amines **13** (1.5 mmol), DMF (2 mL) at rt. 2.5 to 5 h. Isolated yields are mentioned.

Conclusion

We designed and synthesized *N*-alkyl and amide groups containing 3-sulfenyl indoles, offering functional simplicity and wide tolerance for various 3-sulfenyl groups and substituted secondary amines. In quest of potential candidates for DENV, two series comprising a total of 8 compounds were systematically designed and synthesized. In vitro antiviral activity was conducted against DENV-2 and a preclinical study was done. Through careful examinations, **14a** was identified as a hit compound during in vitro studies. Consequently, **14a** emerged as a potential lead molecule for the development of a new class of DENV-2 infection inhibitors, showcasing the efficacy of our synthesized compounds in combating viral infections.

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