# New N-difluoromethylindoles: features of N-difluoromethylation of indoles with electron-donor or electron-withdrawing substituents

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The study of the difluoromethylation of various indole derivatives containing both electron-donating and electron-withdrawing groups was carried out. N-Difluoromethyl derivatives of indole with methoxy, methyl, nitro, cyano, amino groups and bromine atom were isolated and fully characterized.

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## Introduction

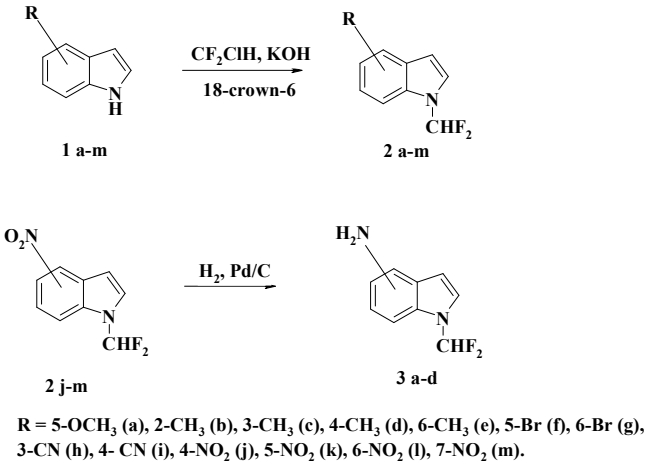
Indole ring is widely spread in nature and is the core structural subunit of numerous biologically active compounds. Natural products such as Tryptophan, Serotonin and Melatonin contain the indole ring. Indole derivatives are implicated in a wide range of pathophysiological conditions such as cancer, microbial and viral infections, inflammation, depression, hypertension *etc* [1].

Many drugs, widely used in medicine, for example Indomethacin, Arbidol, Tenidap are derivatives of indole. The overview of the chemistry, biology, toxicology of indoles focusing on their applications as drugs was presented in several review articles [2-4]. The presence of a fluorine atom or fluorine-containing groups in a drug molecule often results in the improvement of important pharmacological characteristics and in the reducing toxicity [3, 4]. Recently, difluoromethyl group has become one of the most popular substituents in medicinal and agricultural chemistry. Introduction of $CF_2H$ group can affect membrane permeability, binding affinity and lipophilicity [5]**.** However, N-difluoromethylation of indoles has been studied insufficiently till now. Despite the fact that the first N-difluoromethylation of indole derivative was performed long ago in 1961, to obtain N-difluoromethylindole-2-carboxylic acid ethyl ester [6], difluoromethylation of unsubstituted indole was carried out only in 2005 with chlorodifluoromethane (Freon-22) under phase-transfer catalysis [7,8]. The further information about such compounds is meager and has random character. This is partially due to the fact that some indole derivatives with difluoromethyl group at nitrogen atom are very sensitive to the traces of acid, and their autocatalytic decomposition occurs during storage [7]. So far, the N-difluoromethyl

derivatives of indole with donor substituents only have not been described. Presence of electron-withdrawing substituents increases the stability of the N-difluoromethyl indole derivatives. N-Difluoromethyl-5-cyanoindole and N-difluoromethyl-2-methyl-5-cyanoindole were described [9] as a starting materials for the synthesis of new biologically active compounds, a series of N-difluoromethylindoles with a cyano-group in positions 2 and 3 were also described [10]. N-Difluormethyl-6-bromoindole was mentioned in the patent [11] but no experimental details and no physical constants were given. In this work, we studied difluoromethylation of indole derivatives with substituents of various electronic nature. Freon-22 was used as a difluoromethylating agent. This is a very cheap and readily available reagent, which was widely used for difluoromethylation of phenols, thiols and azoles on a multikilogram scale. The ozone depletion potential of Freon-22 is low (0.05), and its usage is not banned in many countries.

**Results and discussion**

The indoles **1a-m**, containing a donor substituent – methoxy group in position 5 (**1a**), methyl group in positions 2 (**1b**), 3 (**1c**), 5 (**1d**) and 6 (**1e**); a weakly withdrawing substituent (bromine atom) in positions 5 (**1f**), 6 (**1g**), and strongly-withdrawing substituents - the cyano group in positions 3 (**1h**), 4 (**1i**) and the nitro group in positions 4 (**1j**), 5 (**1k**), 5 (**1l**) and 7 (**1m**) were chosen as the starting compounds. The difluoromethylation by Freon-22 was performed in two-phase system THF-aq. alkali under phase-transfer catalysis (Scheme 1). The reaction conditions and the stability of the final products are strongly depending on the nature of the substituent on the indole ring.




**Scheme 1.** Difluoromethylation of indoles and reduction of nitrocompounds to amines

Difluoromethylation of indole derivatives with donor groups or bromine atom **1a-g** was carried out using 50% aq. potassium hydroxide in the presence of 18-crown-6 to obtain N-difluoromethyl derivatives **2a-g** by analogy with previous work [8]. The reaction was exothermic and the reaction mixture was self-heated up to 50 °C. It should be noted that in case of indoles **1a-e**, the difluoromethylation did not go to the completion, even when a large excess of Freon-22 and alkali, or alkali concentration above 50% were used. An equilibrium mixture of both initial and final products was formed. Heating the reaction mixture above 50 °C leads to decomposition. Simultaneous usage of two

catalysts - crown ether and tetrabutylammonium bromide has only modest impact of the reaction outcome. The products **2a-e** cannot be separated from the initial indoles **1a-e** by fractional distillation, or crystallization with heating, because in these cases their decomposition occurs. Earlier, other researches failed to isolate compound **2c** [7]. The desired product was detected in the reaction mixture, but it was stated that this compound is insufficiently stable for isolation either by column chromatography or distillation. However we found that the products **2a-e** can be isolated by flash chromatography on silica gel if 1% of triethylamine was added to the eluent to prevent their decomposition. Thus, we obtained compounds **2a-e** with a purity of 97% in low to moderate yields (20-45%). It is also necessary to add triethylamine to the isolated product to prevent decomposition during storage.

In the case of indole derivatives containing a bromine atom in the ring (**1f** and **1g**), the difluoromethylation reaction was carried out in similar conditions, but it proceeds to completion and the desired products can be isolated by distillation in high yield (80-85%). Although, products **2f** and **2g** still require storage in a refrigerator in the presence of triethylamine as a stabilizer.

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Indole derivatives containing cyano group (**1h** and **1i**) or nitro group (**1j-m**) were difluoromethylated under milder conditions than the previously mentioned indoles **1a-f**. This is explained by higher acidity of compounds **1h-m**, with the formation of the intermediate salt that is more stable and less reactive. Difluoromethylation of the indole derivatives with cyano group can be performed at 25-30°C. Thus, the hydrolysis of the cyano group under alkaline conditions was almost excluded. Compounds **2h** and **2i** were isolated in about 82-85% yield, compared with that described in the patent [9], where the yield of N-difluoromethyl-5-cyanoindole was 67%. The yields of nitro-containing products **2j-m** reach 90%. All products **2 h-m** are stable and can be stored for a long time at room temperature without a stabilizer.

The nitro group in the compounds **2j-m** can be reduced to an amino group by the action of hydrogen on Pd/C to obtain amino-compounds **3a-d** in high yields. They are also quite stable substances due to the presence of the basic amino group in the molecule that reduces the acidophobic nature of the indole derivative (Scheme 1). Compounds **3a-d** can also be stored at room temperature without a stabilizer.

**Conclusions**

We studied the difluoromethylation of various indole derivatives containing both electron-donating and electron-withdrawing groups. The conditions for the isolation of unstable difluoromethyl derivatives of indole, which contain methyl or methoxy groups have

been found. N-Difluoromethyl derivatives of indoles with nitro, cyano and amino groups have been obtained in high yields. These compounds can be important intermediates in the synthesis of new practically useful substances.

## Experimental

Melting points were measured in open capillary and are given uncorrected. $^{1}$H NMR spectra (400 MHz) and $^{19}$F NMR-spectra (376.5 MHz) were recorded on a Varian-Mercury-400 spectrometer using TMS and $CCl_3F$ as internal standards. Monitoring of the reaction progress was performed on Silufol UV-254 TLC plates. Column chromatography was conducted with Kieselgel MN-60.

*N-difluoromethylindoles **2a-m** (general procedure).*

Indole **1a-m** (0.1 mol) and 0.5 g of 18-crown-6 were dissolved in THF (150 mL), and the solution was saturated with $CF_2ClH$. To the vigorously stirred reaction mixture 50% aq. KOH (60g, 1 mol of KOH and 60 mL of water) was added dropwise for 20 min under the stream of $CF_2ClH$. An exothermic reaction occurred; the temperature rose to 45-50 °C. The intensive stream of $CF_2ClH$ was bubbled through the reaction mixture with vigorous stirring for 2-3h until gas absorption stopped.

In the case of compounds **2a-e** 0.5 g of $Bu_4NBr$ was added as a co-catalyst. The reaction mixture turned dark during difluoromethylation. After gas absorbtion finished $CH_2Cl_2$ (100 mL) and water (200 mL) were added, the organic layer was separated and the solvent was evacuated. The desired products **2a-e** were isolated from the residue by flash chromatograpy. Eluent: hexane-$CH_2Cl_2$ 2:1 with 1% of triethylamine as a stabilizer. Compounds **2a-e** after isolation have to be immediately placed in the cold with adding of 1-2 drops of triethylamine, as without stabilizer their complete decomposition occurs in 10-12 h at room temperature.

In the case of N-difluoromethylbromoindoles **2f,g** the reaction was monitored by TLC until initial bromoindole disappeared. MTBE (200 mL) and water (200 mL) were added, the organic layer was separated, washed with water (3x200 mL) and the solvent was evacuated. The residues were distilled in vacuo to obtain pure products **2f,g**. It should be noted, that compounds **2f,g** are still very sensitive to traces of acids and have to be stored in the cold with triethylamine as a stabilizer.

In the case of N-difluoromethylcyanoindoles **2h,i** the reaction mixture was cooled, keeping temperature not above 30 °C to prevent hydrolysis of the cyano group. The reaction was monitored by TLC until initial cyanoindole disappeared. Water (1L) was added; the precipitate formed was

filtered, dried in vacuo and crystallized from $CCl_4$-hexane 1:1 with $SiO_2$ as an additive.

In the case of N-difluoromethylnitroindoles **2j-m** cooling is not necessary. The reaction was performed at 35-40 °C (self-heating). The end of reaction can be easily determined by the colour changing from bright cherry-red to yellow. After reaction completion, water (1L) was added; the precipitate formed was filtered and crystallized from methanol.

*N-Difluoromethyl-5-methoxyindole* ***(2a)***. Yield 6.30 g, 32%, as a white solid; mp 71-72 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 3.88 (3H, s, $OCH_3$), 6.58 (1H, d, *J* 3 Hz), 6.96-6.99 (1H, m), 7.11 (1H, d, *J* 3 Hz), 7.21 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.23-7.26 (1H, m), 7.47-7.51 (1H, m). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 92.6 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_9F_2NO$: C, 60.91; H, 4.60; N, 7.10. Found: C, 60.79; H, 4.47; N, 7.15.

*N-Difluoromethyl-2-methylindole* ***(2b)***. Yield 5.25 g, 29%, as a white solid; mp 69-70 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.54 (3H, s, $CH_3$), 6.32 (1H, s), 7.10-7.29 (3H, m), 7.29 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.50-7.56 (1H, m). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 93.1 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_9F_2N$: C, 66.29; H, 5.01; N, 7.73. Found: C, 65.79; H, 4.98; N, 7.65.

*N-Difluoromethyl-3-methylindole* ***(2c)***. Yield 8.15 g, 45%, as a white solid; mp 52-54 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.34 (3H, s, $CH_3$), 7.08 (1H, s), 7.23 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.25-7.40 (2H, m), 7.52-7.62 (2H, m). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 90.9 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_9F_2N$: C, 66.29; H, 5.01; N, 7.73. Found: C, 65.98; H, 4.93; N, 7.85.

*N-Difluoromethyl-4-methylindole* ***(2d)***. Yield 4.95 g, 28%, as a white solid; mp 47-49 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.61 (3H, s, $CH_3$), 6.72 (1H, d, *J* 3 Hz), 7.10 (1H, d, *J* 6 Hz), 7.28 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.24-7.32 (2H, m), 7.43 (1H, d, *J* 6 Hz). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 90.5 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_9F_2N$: C, 66.29; H, 5.01; N, 7.73. Found: C, 66.09; H, 5.21; N, 7.80.

*N-Difluoromethyl-6-methylindole* ***(2e)***. Yield 4.70 g, 27%, as a colorless oil solidified in refrigerator; mp 10-12 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.53 (3H, s, $CH_3$), 6.62 (1H, d, *J* 3 Hz), 7.10 (1H, d, *J* 6 Hz), 7.22 (1H, d, *J* 3 Hz), 7.25 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.28-7.39 (1H, m), 7.55 (1H, d, *J* 6 Hz). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 90.5 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_9F_2N$: C, 66.29; H, 5.01; N, 7.73. Found: C, 66.12; H, 5.17; N, 7.77.

*N-Difluoromthyl-5-bromolindole* ***(2f)***. Yield 19.8 g, 79%, as a colorless oil; bp 89-90 °C (1 Torr). $^1$H NMR (400 MHz, $CDCl_3$), δ: 6.61 (1H, d, *J* 3 Hz), 7.19 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.23 (1H, d, *J* 3 Hz), 7.32-7.36 (1H, m), 7.40-7.50 (1H, m), 7.51-7.54 (1H, m). $^{19}$F NMR

(376.5 MHz, $CDCl_3$), δ: - 90.5 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6BrF_2N$: C, 43.93; H, 2.46; N, 5.69. Found: C, 44.09; H, 2.51; N, 5.80.

*N-Difluoromthyl-6-bromolindole* ***(2g)***. Yield 20.7 g, 82%, as a colorless oil; bp 92-94 °C (1 Torr). $^1$H NMR (400 MHz, $CDCl_3$), δ: 6.59 (1H, d, *J* 3 Hz), 7.18 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.22 (1H, d, *J* 3 Hz), 7.32-7.36 (1H, m), 7.40-7.50 (1H, m), 7.71 (1H, s). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 90.9 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6BrF_2N$: C, 43.93; H, 2.46; N, 5.69. Found: C, 44.11; H, 2.41; N, 5.77.

*N-Difluoromethyl-3-cyanoindole* ***(2h)***. Yield 16.45 g, 86%, as a white solid; mp 81-82 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 7.32 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.55-7.45 (2H, m), 7.62 (1H, d, *J* 6 Hz), 7.78 (1H, d, *J* 6 Hz), 7.83 (1H, m). $^{19}$F NMR (376.5 MHz, DMSO-$d_6$), δ: - 94.5 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_6F_2N_2$: C, 62.50; H, 3.15; N, 14.58. Found: C, 62.68; H, 3.23; N, 14.85.

*N-Difluoromethyl-4-cyanoindole* ***(2i)***. Yield 16.05 g, 84%, as a white solid; mp 88-89 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 6.82 (1H, d, *J* 3 Hz), 7.26 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.33 (1H, m), 7.42 (1H, d, *J* 3 Hz), 7.60 (1H, d, *J* 6 Hz), 7.81 (1H, d, *J* 6 Hz). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 91.9 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_{10}H_6F_2N_2$: C, 62.50; H, 3.15; N, 14.58. Found: C, 62.58; H, 3.18; N, 14.69.

*N-Difluoromethyl-4-nitroindole* ***(2j)***. Yield 17.16 g, 83%, as a yellow solid; mp 95-96 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 7.35 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.40-7.43 (2H, m), 7.50-7.55 (1H, m), 7.93 (1H, d, *J* 6 Hz), 8.23 (1H, d, *J* 6 Hz). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 95.9 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; N, 13.20. Found: C, 50.78; H, 3.18; N, 13.29.

*N-Difluoromethyl-5-nitroindole* ***(2k)***. Yield 19.29 g, 91%, as a yellow solid; mp 88-89 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 6.82 (1H, d, *J* 3 Hz), 7.35 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.47 (1H, d, *J* 3 Hz), 7.63 (1H, d, *J* 6 Hz), 8.19 (1H, d, *J* 6 Hz), 8.58 (1H, s). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 96.5 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; N, 13.20. Found: C, 50.77; H, 2.80; N, 13.19.

*N-Difluoromethyl-6-nitroindole* ***(2l)***. Yield 18.90g, 90%, as a yellow solid; mp 101-103 °C. $^1$H NMR (400 MHz, DMSO –$d_6$), δ: 6.31 (1H, d, *J* 3 Hz), 7.82 (1H, d, *J* 6 Hz), 8.02-8.20 (2H, m), 8.20 (1H, t, *J* 60 Hz, N-$CHF_2$), 8.67 (1H, s). $^{19}$F NMR (376.5 MHz, DMSO –$d_6$), δ: - 96.0 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; N, 13.20. Found: C, 50.82; H, 3.08; N, 13.41.

*N-Difluoromethyl-7-nitroindole* ***(2m)***. Yield 18.67g, 89%, as a yellow solid; mp 61-63 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 6.82 (1H, d, *J* 3 Hz), 7.32 (1H, d, *J* 3 Hz), 7.63 (1H, m), 7.84 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.93 (1H, d, *J* 6Hz),

8.01 (1H, d, *J* 6Hz). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 96.0 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; N, 13.20. Found: C, 50.91; H, 2.88; N, 13.39.

*N-Difluoromethylaminoimdoles* ***3a-d*** *(general procedure).*

N-Difluoromethylnitroindoles **2j-m** (0.05 mol) were dissolved in methanol (100 mL) and 0.5 g of 10% Pd/C was added to the solution. The reaction mixture was stirred under $H_2$ atmosphere and was monitored by TLC until initial product disappeared. After filtration the solvent was evaporated and the residue was crystallized from benzene.

*N-Difluoromethyl-4-aminoindole* ***(3a)****.* Yield 6.90g, 76%, as a white solid; mp 82-84 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 3.80 (2H, s, $NH_2$), 6.53-6.59 (2H, m), 7.02-7.15 (2H, m), 7.23 (1H, m) 7.25 (1H, t, *J* 60 Hz, N-$CHF_2$). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 91.9 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38. Found: C, 59.58; H, 4.18; N, 15.39.

*N-Difluoromethyl-5-aminoindole* ***(3b)****.* Yield 7.45g, 82%, as a white solid; mp 42-44 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 3.61 (2H, s, $NH_2$), 6.48 (1H, d, *J* 3 Hz), 6.72-6.76 (1H, m), 6.92 (1H, d, *J* 3 Hz), 7.15 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.19-7.40 (2H, m). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 91.3 (d, *J* 60 Hz, N-$CHF_2$). $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38. Found: C, 59.50; H, 4.15; N, 15.58.

*N-Difluoromethyl-6-aminoindole* ***(3c)****.* Yield 7.28g, 80%, as a white solid; mp 80-81 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 3.70 (2H, s, $NH_2$), 6.44 (1H, d, *J* 3 Hz), 6.62-6.65 (1H, m), 6.92 (1H, s), 7.07 (1H, d, *J* 3 Hz), 7.11 (1H, t, *J* 60 Hz, N-$CHF_2$), 7.39-7.40 (1H, m). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 91.3 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38. Found: C, 59.38; H, 4.44; N, 15.47.

*N-Difluoromethyl-7-aminoindole* ***(3d)****.* Yield 7.33g, 81%, as a white solid; mp 76-78 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 3.46 (2H, s, $NH_2$), 6.60 (1H, d, *J* 3 Hz), 6.62-6.65 (1H, m), 7.07-7.24 (3H, m), 7.67 (1H, t, *J* 60 Hz, N-$CHF_2$). $^{19}$F NMR (376.5 MHz, $CDCl_3$), δ: - 91.7 (d, *J* 60 Hz, N-$CHF_2$). Anal. calcd for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38. Found: C, 59.28; H, 4.51; N, 15.27.

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