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Green Regioselective Synthesis of (Purin-6-yl)hydrazones

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Abstract—Some unique purine hydrazinylidene derivatives were synthesized by the regioselective reaction of 2,6-dichloropurine with hydrazine hydrate, followed by condensation with commercially available 1,3-dicarbonyl compounds according to a green chemistry approach. The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, IR, and mass spectra and elemental analyses. The regioselectivity of chlorine substitution in 2,6-dichloropurine was established by HMBC (Heteronuclear Multiple Bond Correlation) NMR technique.

Keywords: 2,6-dichloropurine, regioselective synthesis, green chemistry.

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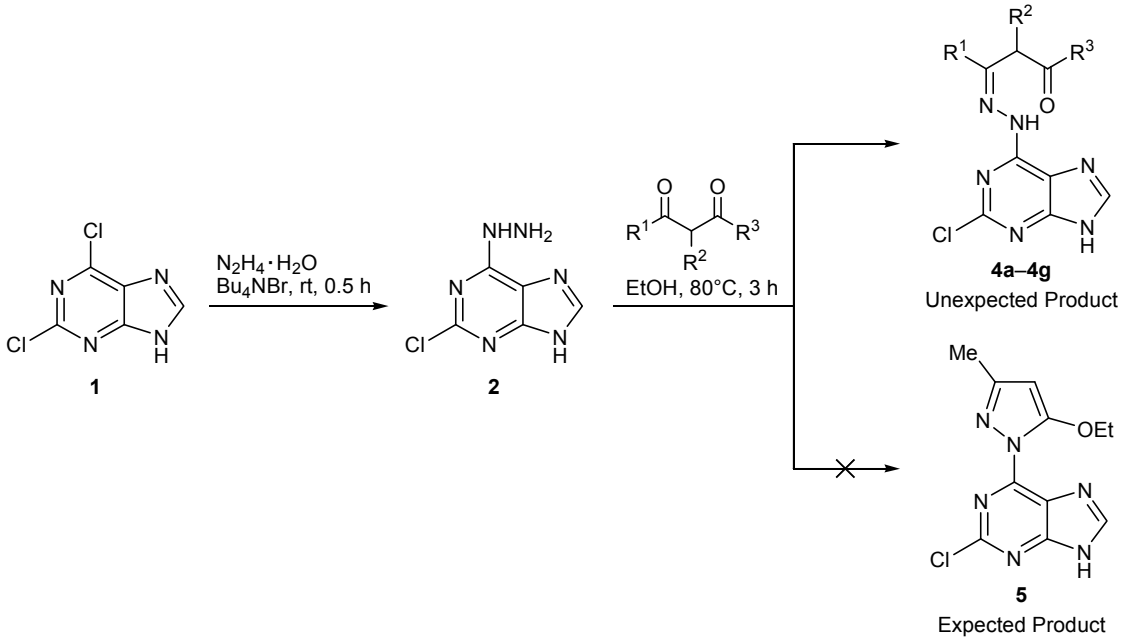
Nucleotides are among the most crucial cellular components for plant growth, development, and metabolism [1]. Purines, pyrimidines, nucleosides, and nucleotides belong to a biologically important class of compounds [2, 3]. Analysis of the U. S. FDA-approved drugs database reveals that 59% of small molecule drugs contain a nitrogen heterocycle [4]. In recent years, purine-fused aliphatic and aromatic derivatives have attracted considerable attention because of their valuable biological activities, medicinal properties, and specific conjugated structures [5, 6]. Although great endeavors have been devoted to the synthesis of purine-fused non-cyclic derivatives, it still remains an important and challenging goal for chemists since only a few data are available on such syntheses involving several steps [7].

Traditional transition metal-catalyzed cross-coupling reactions [8] (Pd, Pt, Sn, B, Mg, Si, etc.) have contributed significantly to the formation of new carbon–carbon bonds and to the synthesis of various C^6-substituted purine derivatives [9]. In addition, the N^9-position of synthetic purines has been substituted by different (non)functionalized aromatic, aliphatic, alicyclic, or heterocyclic moieties, and various biological properties of the resulting compounds have been reported [10, 11].

Our goal was to develop a simple procedure applicable for the quick preparation of diverse target compounds with highly variable substituents. Taking into account a large number of available building blocks such as amines, hydroxy compounds, terminal and internal alkynes, cyclic and acyclic moieties, etc. [12], we intended to use simple precursors. Herein, we focused our efforts on the introduction of chemical diversity into the purine scaffold in order to obtain biologically active compounds..

1-(2-Chloro-9*H*-purin-6-yl)hydrazine (**2**) was synthesized in 98% yield by treatment of 2,6-dichloropurine (**1**) with hydrazine hydrate in the presence of tetrabutylammonium bromide (TBAB) as phase-transfer catalyst. The subsequent reaction of **2** with various 1,3-dicarbonyl compounds **3a**–**3g** in ethanol under reflux afforded the corresponding hydrazones **4a**–**4g** instead of expected pyrazole derivatives like **5** (Scheme 1). The reaction conditions were optimized using the condensation of **2** and **3a** as model reaction (Table 1). The best result was achieved by heating the reactants in boiling ethanol (80°C) for 3 h without any catalyst (yield 92%, entry no. 1). When the reaction was carried out in the presence of acid (concd. HCl, TsOH, AcOH) or base catalyst [ethyl(diisopropyl)-amine, DIPEA] in such solvents as ethanol, methanol, THF, or DMF, the yield of **4a** was poor (entry nos. 2, 3) or no compound **4a** was formed (entry nos. 4, 5) despite prolonged reaction time (24 h). In no case pyrazole **5** was detected in the reaction mixture.

Scheme 1.



R^1 = Me (**a**, **c**, **d**, **f**, **g**), CN (**b**), CF_3 (**e**); R^2 = H (**a**–**e**), Me (**f**), F (**g**); R^3 = OEt (**a**, **b**, **d**–**g**), pyrazin-2-yl (**c**), OMe (**d**).

The structure of hydrazones **4a**–**4g** was confirmed by FT-IR, ^{1}H and ^{13}C NMR, and mass spectra. The mass spectra of **4a**–**4g** showed peaks of chlorine-containing ions with an intensity ratio of 3 : 1 typical of the presence of one chlorine atom. The IR spectra of **4a**–**4g** contained absorption bands at about 3380 and 1730 cm^{-1} assigned to stretching vibrations of the secondary amino groups and carbonyl group, respectively. The 8-H proton of the purine fragment resonated in the ^{1}H NMR spectrum of **4a** at δ 8.4 ppm, and no any other signal was observed in the aromatic region, indicating the formation of hydrazone rather than pyrazole structure. The signals at δ 12.2 and 11.1 ppm were assigned to the NH protons of the purine (9-H) and hydrazone moieties, respectively. Furthermore, two CH_3 and two CH_2 signals were present in the aliphatic region. The ^{13}C NMR spectra were also in agreement with the proposed hydrazone structure.

Heteronuclear multiple-bond correlation (HMBC) technique was utilized to determine the site of substitution of chlorine in the initial 2,6-dichloropurine molecule. The HMBC spectrum of **4a** is shown in Fig. 1, and the observed correlations are listed in Table 2. Only six types of protons showed correlations with carbon nuclei. No correlations were observed for the NH protons, whereas the 8-H proton (δ 8.41 ppm) displayed couplings with C^7, C^6, and C^{10}. The latter correlation provides evidence for the substitution at C^6. The other ^{1}H–^{13}C correlations were also consistent with the hydrazone structure of **4a**.

In summary, a green chemistry procedure has been developed for the synthesis of (2-chloro-9*H*-purin-6-

Table 1. Optimization of the reaction of (2-chloro-9H-purin-6-yl)hydrazine (**2**) with ethyl 3-oxobutanoate (**3a**)

Entry no.	Solvent/temperature, °C	Catalyst (mmol)	Reaction time, h	Yield of **4a**, %
1	Ethanol/80	–	3.0	92
2	Ethanol/80	Concd. aq. HCl (0.01–0.2)	24	25
3	Methanol/70	*p*-Toluenesulfonic acid (0.01–0.5)	24	15
4	THF/60	Acetic acid (0.01–0.5)	24	–
5	DMF/110	Ethyl(diisopropyl)amine (DIPEA) (0.01–0.09)	24	–

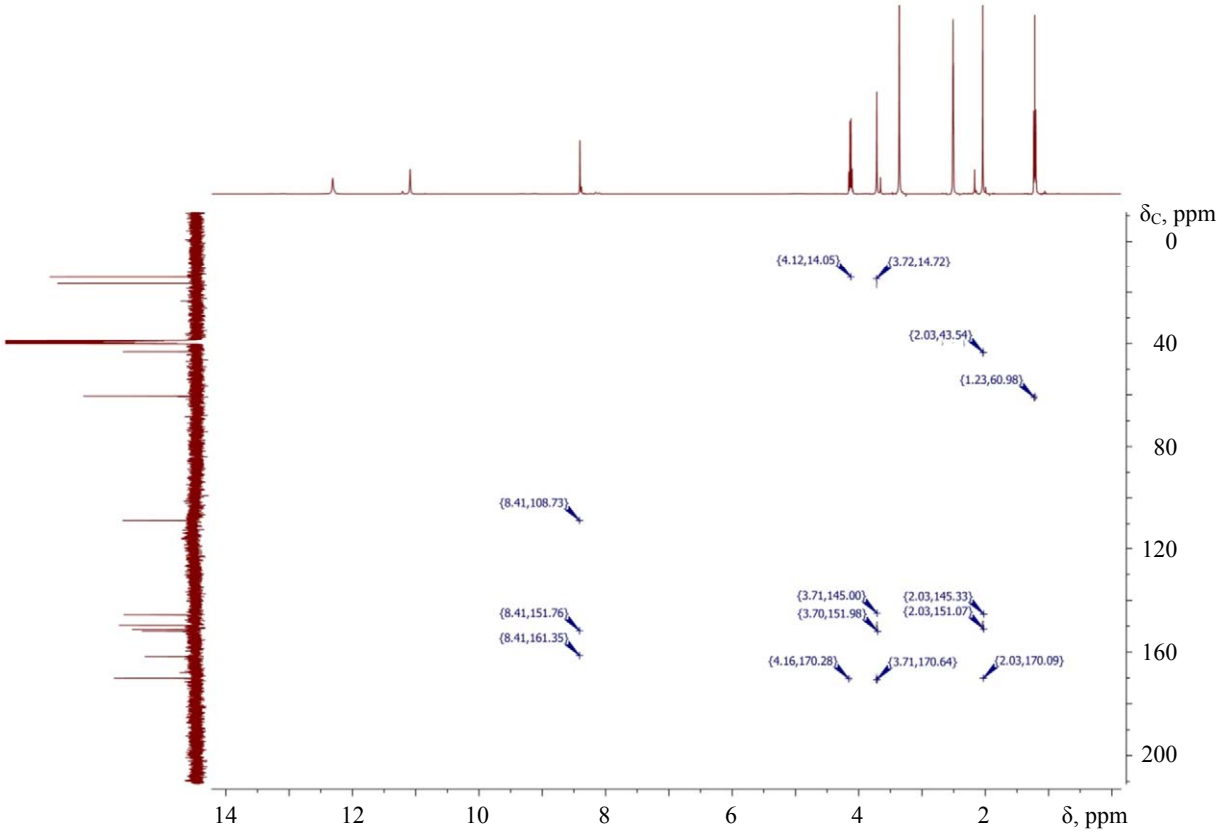
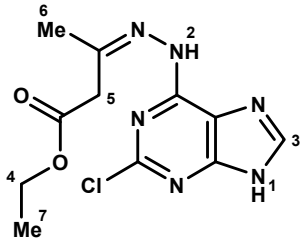
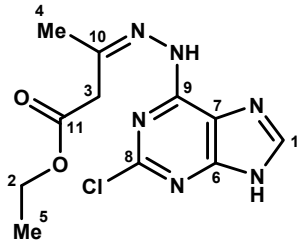


Fig. 1. 2D ^{1}H–^{13}C HMBC spectrum of **4a**.

Table 2. Correlations in the ^{1}H–^{13}C HMBC spectrum of **4a**



^{1}H



^{13}C

Carbon no.	δ_C, ppm	Proton no.	δ, ppm	HMBC Correlations
1	145.65	1	12.232	–
2	60.44	2	11.108	–
3	43.17	3	8.411	8.41↔108.81, 8.41↔151.87, 8.41↔161.7
4	16.58	4	4.103–4.156	4.12↔14.03, 4.16↔170.15
5	14.03	5	3.719	3.72↔14.03, 3.71↔151.98, 3.71↔145.65, 3.71↔170.15
6	151.87	6	2.035	2.03↔43.17, 2.03↔145.65, 2.03↔151.24, 2.03↔170.15
7	108.81	7	1.20–1.23	1.23↔60.44
8	151.24			
9	149.61			
10	161.7			
11	170.15			

yl)hydrazones of various 1,3-dicarbonyl compounds in 89–95% yield. Spectroscopic data have confirmed the formation of hydrazones rather than expected pyrazole derivatives, and the regioselectivity of chlorine substitution in 2,6-dichloro-9*H*-purine by hydrazine has been determined by using HMBC technique.

EXPERIMENTAL

All chemicals and solvents were purchased from Sigma–Aldrich, Merck, Finar, and Spectrochem Ltd. and were used without further purification. Thin-layer chromatography was accomplished on 0.2-mm precoated Silica gel G60 F254 plates (Merck); visualization was made under UV light (λ 254 and 365 nm). The IR spectra were recorded on a Shimadzu IR Affinity-1S spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II spectrometer at 400 and 101.1 MHz, respectively, using DMSO-d_6 as solvent; the chemical shifts are referenced to tetramethylsilane. The mass spectra were obtained on an Agilent 7820A/5977B GC/MS-QP instrument. Solvents were evaporated with a Roteva rotary evaporator. Melting points were measured in open capillaries and are uncorrected. Supplementary data containing FID files and spectra of the representative compounds are available from the authors.

1-(2-Chloro-9*H*-purin-6-yl)hydrazine (2). A mixture of 2,6-dichloro-9*H*-purine (0.5 mmol), hydrazine hydrate (0.98 mL), and tetrabutylammonium bromide (TBAB) (0.003 mmol) was stirred at room temperature for 30 min. The originally light yellow colour changed to dark yellow after reaction completion (TLC, ethyl acetate–hexane, 3:7). The mixture was poured into ice water and stirred at room temperature for 20 min, and the precipitate was filtered off and dried. ^{1}H NMR spectrum, δ, ppm: 12.50 br.s (1H, 9-H), 9.16 s (1H, 6-NH), 8.12 s (8-H), 5.00–4.59 br.s (2H, NH_2). Mass spectrum: *m*/*z* 184.59 $[M]^+$.

Compounds 4a–4g (*general procedure*). A mixture of **2** (0.54 mmol) and 1,3-dicarbonyl compound **3a**–**3g** (0.54 mmol) in ethanol was stirred at 80°C for 3 h. After completion of the reaction (TLC), the mixture was poured into ice water, and the solid was filtered off, dried, and purified by silica gel column chromatography (60–120 mesh) using ethyl acetate–hexane (2:8) as eluent.

Ethyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]butanoate (4a). Yield 95%, light yellow powder, mp 146–148°C. IR spectrum, ν, cm^{-1}: 3486 (N–H), 3124 (C–H_{arom}), 2978 (C–H_{aliph}), 1778 (C=O), 1638 (C=C_{arom}), 1367 (C–N), 1245 (C–O), 930 (δC–H_{arom}), 788 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.32 s (1H, 9-H), 11.08 s (1H, 6-NH), 8.41 s (1H, 8-H), 4.12 q (2H, OCH_2), 3.71 s (2H, CH_2), 2.03 s (3H, CH_3), 1.23–1.20 t (3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR spectrum, δ_C, ppm: 166.97, 154.27, 149.37, 147.37, 144.36, 128.87, 127.09, 61.18, 36.37. Mass spectrum: *m*/*z*: 296.71 $[M]^+$. Found: C 44.54; H 4.46; Cl 11.90; N 28.32; O 10.78. $C_{11}H_{13}ClN_6O_2$. Calculated, %: C 44.53; H 4.42; Cl 11.95; N 28.32; O 10.78.

Ethyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]-3-cyanopropanoate (4b). Yield 93%, light yellow powder, mp 151–154°C. IR spectrum, ν, cm^{-1}: 3376 (N–H), 3120 (C–H_{arom}), 2984 (C–H_{aliph}), 2359 (C≡N), 1738 (C=O), 1628 (C=C_{arom}), 1373 (C–N), 1233 (C–O), 943 (δC–H_{arom}), 781 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.35 s (1H, 9-H), 11.10 s (1H, 6-NH), 8.45 s (1H, 8-H), 4.09 q (2H, OCH_2), 3.70 s (2H, CH_2), 1.27–1.23 t (3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR spectrum, δ_C, ppm: 168.28, 159.27, 146.37, 143.37, 141.36, 123.09, 63.18, 35.37. Mass spectrum: *m*/*z* 307.70 $[M]^+$. Found: C 42.97; H 3.21; Cl 11.51; N 31.89; O 10.42. $C_{11}H_{10}ClN_7O_2$. Calculated, %: C 42.94; H 3.28; Cl 11.52; N 31.86; O 10.40.

3-[2-(2-Chloro-9*H*-purin-6-yl)hydrazinylidene]-1-(pyrazin-2-yl)butan-1-one (4c). Yield 95%, dark yellow powder, mp 156–159°C. IR spectrum, ν, cm^{-1}: 3372 (N–H), 3121 (C–H_{arom}), 2998 (C–H_{aliph}), 1724 (C=O), 1687 (C=N), 1623 (C=C_{arom}), 1361 (C–N), 913 (δC–H_{arom}), 785 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.29 s (1H, 9H), 11.11 s (1H, 6-NH); 8.97 s, 8.69 d, and 8.61 d (1H each, pyrazine); 8.43 s (1H, 8-H), 3.78 s (2H, CH_2), 2.13 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 182.82, 166.97, 153.27, 148.37, 147.20, 144.86, 128.97, 126.99, 55.18, 26.37. Mass spectrum: *m*/*z*: 330.73 $[M]^+$. Found, %: C 47.20; H 3.30; Cl 10.74; N 33.86; O 4.90. $C_{13}H_{11}ClN_8O$. Calculated, %: C 47.21; H 3.35; Cl 10.72; N 33.88; O 4.84.

Methyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]butanoate (4d). Yield 89%, dark yellow powder, mp 148–149°C. IR spectrum, ν, cm^{-1}: 3396 (N–H), 3114 (C–H_{arom}), 2978 (C–H_{aliph}), 1727 (C=O), 1620 (C=C_{arom}), 1373 (C–N), 1236 (C–O), 1141 (C–O), 925 (δC–H_{arom}), 785 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.38 s (1H, 9-H), 11.07 s (1H, 6-NH), 8.43 s (1H, 8-H), 3.73 s (2H, CH_2), 2.13 s (3H, CH_3), 1.18–1.10 s (3H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 167.97, 156.17, 150.27, 145.21, 144.96, 129.83, 123.29, 62.88, 35.48. Mass spectrum: *m*/*z* 282.69 $[M]^+$. Found, %: C 42.47; H 3.95; Cl 12.56; N 29.70;

O 11.32. $C_{10}H_{11}ClN_6O_2$. Calculated, %: C 42.49; H 3.92; Cl 12.54; N 29.73; O 11.32.

Ethyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]-4,4,4-trifluorobutanoate (4e). Yield 94%, light yellow powder, mp 157–160°C. IR spectrum, ν, cm^{-1}: 3376 (N–H), 3111 (C–H_{arom}), 2982 (C–H_{aliph}), 1725 (C=O), 1628 (C=C_{arom}), 1375 (C–F), 1361 (C–N), 1236 (C–O), 930 (δC–H_{arom}), 785 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.31 s (1H, 9-H), 11.18 s (1H, 6-NH), 8.43 s (1H, 8-H), 4.16 q (2H, OCH_2), 3.69 s (2H, CH_2), 1.25–1.21 t (3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR spectrum, δ_C, ppm: 170.25, 153.27, 151.47, 145.97, 142.76, 129.07, 126.19, 61.18, 46.37. Mass spectrum: *m*/*z* 350.68 $[M]^+$. Found, %: C 37.68; H 2.82; Cl 10.19; F 16.22; N 23.94; O 9.15. $C_{11}H_{10}ClF_3N_6O_2$. Calculated, %: C 37.67; H 2.87; Cl 10.11; F 16.25; N 23.96; O 9.12.

Ethyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]-2-methylbutanoate (4f). Yield 92%, dark yellow powder, mp 145–148°C. IR spectrum, ν, cm^{-1}: 3387 (N–H), 3109 (C–H_{arom}), 2972 (C–H_{aliph}), 1718 (C=O), 1613 (C=C_{arom}), 1376 (C–N), 1232 (C–O), 925 (δC–H_{arom}), 785 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 12.29 s (1H, 9-H), 11.07 s (1H, 6-NH), 8.45 s (1H, 8-H), 4.16 q (2H, OCH_2), 3.76 q (1H, CH), 2.09 s (3H, CH_3), 1.55 d (3H, CH_3), 1.24 t (3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR spectrum, δ_C, ppm: 177.63, 166.27, 154.21, 149.57, 149.87, 143.66, 129.87, 128.09, 61.18, 41.34, 36.37. Mass spectrum: *m*/*z* 310.74 $[M]^+$. Found, %: C 46.40; H 4.86; Cl 11.42; N 27.01; O 10.31. $C_{12}H_{15}ClN_6O_2$. Calculated, %: C 46.38; H 4.87; Cl 11.41; N 27.05; O 10.30.

Ethyl 3-[2-(2-chloro-9*H*-purin-6-yl)hydrazinylidene]-2-fluorobutanoate (4g). Yield 89%, light yellow powder, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3386 (N–H), 3119 (C–H_{arom}), 2982 (C–H_{aliph}), 1718 (C=O), 1620 (C=C_{arom}), 1373 (C–N), 1352 (C–F), 1232 (C–O), 933 (δC–H_{arom}), 786 (C–Cl). ^{1}H NMR spectrum, δ_C, ppm: 12.37 s (1H, 9-H), 11.09 s (1H, 6-NH), 8.39 s (1H, 8-H), 4.15 q (2H, OCH_2), 3.77 s (1H, CH), 2.03 s (3H, CH_3), 1.23 t (3H, $CH_2C\mathbf{H}_3$). ^{13}C NMR spectrum, δ_C, ppm: 170.45, 165.97, 154.77, 149.57, 147.27, 145.96, 129.27, 121.92, 61.28, 36.47. Mass spectrum: *m*/*z* 314.70 $[M]^+$. Found: C 41.97; H 3.84; Cl 11.29; F 6.02; N 26.72; O 10.16. $C_{11}H_{12}ClFN_6O_2$. Calculated, %: C 41.98; H 3.84; Cl 11.27; F 6.04; N 26.70; O 10.17.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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