Synthesis, cytotoxic evaluation of substituted cinnamic-based 1,2,4-triazolo thiadiazoles

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In an attempt to find a new class of cytotoxic agents, a series of 3,6-disubstituted-[1,2,4] triazolo[3,4-b] [1,3,4]thiadiazoles have been synthesized using undecenoic acid and various cinnamic acids. The structures of the synthesized compounds have been confirmed using \textsuperscript{1}H and \textsuperscript{13}C NMR, IR and mass spectroscopy. The prepared compounds have been evaluated for their \textit{in vitro} cytotoxic activities against four human cancer cell lines namely, HeLa, B16-F10, SKOV3, MCF7 and CHO-K1 Normal Cell line using MTT assay. Compounds 6a and 6h show promising activity against HeLa (IC\textsubscript{50} value 8.92\,µM) and SKOV3 cell lines (IC\textsubscript{50} value 9.43 \,µM). Majority of the compounds show significant activities against HeLa cell line with the IC\textsubscript{50} values ranging from 8.92 to 13.44 \,µM. All the compounds show good activity against SKOV3 cell line with the IC\textsubscript{50} values ranging from 9.43 to 19.34 \,µM. Majority of the compounds are non toxic towards the Chinese hamster ovary (CHO-K1) normal cell line.

Keywords: Undecenoic acid, cinnamic acids, triazolothiadiazole, cytotoxicity, cancer cell line

Cancer is one of the most alarming diseases in worldwide, it is considered to be the second leading cause of death globally after heart diseases. This severe public health problem brings a huge burden on society all over the world. Therefore, continuous efforts are needed to develop novel compounds with selective, efficient, and safe drugs by chemical modifications remains a great challenge to medicinal research. Cinnamic acid is a naturally occurring aromatic fatty acid present in cinnamon oil and many other balsams. Studies reported that cinnamic acid derivatives are potent antimicrobial, antiviral, antioxidant and antiinflammatory agents\textsuperscript{1–3}. Several cinnamamide derivatives were reported for a wide range of biological activities such as anticancer, antimitotic, antioxidant and seed germination inhibitory effects\textsuperscript{4–6}. In recent years, cinnamic acid derivatives have attracted much attention due to their antioxidant\textsuperscript{7}, antitumor\textsuperscript{7}, antimicrobial\textsuperscript{8} and antitubercular activities\textsuperscript{9,12}.

1,2,4-triazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry research. Studies revealed that these molecules exhibit diverse pharmacological properties such as antibacterial, antifungal\textsuperscript{13}, antitubercular\textsuperscript{14}, anticancer\textsuperscript{15}, anticonvulsant\textsuperscript{16}, antiinflammatory\textsuperscript{17}, analgesic\textsuperscript{18} and molluscicidal properties\textsuperscript{19–22}. The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention in recent years due to their synthetic and biological importance. Triazolothiadiazoles and triazolothiadiazines are a class of fused heterocyclic compounds that attracted great interest in medicinal chemistry due to their varied biological activities such as antifungal\textsuperscript{23,24}, antibacterial\textsuperscript{25,26}, antiviral\textsuperscript{27}, anthelmintic\textsuperscript{28,29}, antitumour\textsuperscript{30}, analgesic\textsuperscript{31} and antiinflammatory activities\textsuperscript{32,33}.

Fatty acids and their derivatives are known for their biological activities such as antimicrobial\textsuperscript{34,35}, antifungal\textsuperscript{36}, and pesticidal\textsuperscript{37} activities. These fatty acid analogs have been found to be associated with diverse biological activities such as antiinflammatory\textsuperscript{8}, antioxidant\textsuperscript{39}, antifeedant\textsuperscript{40}, antiparasite\textsuperscript{41}, antimicrobial\textsuperscript{42} and neuroprotective\textsuperscript{43}. Studies reported that a variety of modified fatty acids are significant molecules in the treatment of cancers\textsuperscript{32,44,45}. Undecenoic acid derivatives were also
found to exhibit promising biological activities such as antifungal, antibacterial, antiviral and anticancer activities.\textsuperscript{42,45}

In view of the above facts, in the present study a series of 3,6-disubstituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles were synthesized using undecenoic acid and various cinnamic acids and these compounds were evaluated for their biological activities.

**Results and Discussion**

The target compounds were synthesized as outlined in Scheme I. Undec-10-enoi acid was converted to the methyl ester by using methanol and few drops of concentrated sulphuric acid. Methyl ester was treated with hydrazine hydrate to get Undec-10-eneydrazide, which was further reacted with carbon disulfide in ethanolic potassium hydroxide to yield corresponding dithiocarbazinate in good yield. Dithiocarbazinate was directly reacted with hydrazine hydrate under refluxing conditions to yield triazole. Condensation of triazole with various substituted cinnamic acids in presence of POCl\textsubscript{3} yielded triazolothiadiazoles (6a-t). The synthesized compounds were characterized by \textsuperscript{1}H, \textsuperscript{13}C NMR, ESI-MS, HRMS and IR spectral analysis.

**Biological activity**

The cytotoxicity of all the synthesized compounds were screened against four human cancer cell lines namely, HeLa Homo sapiens cervix adenocarcinoma (ATCC® CCL-2.1\textsuperscript{TM}), B16-F10 Mouse skin melanoma (ATCC® CRL-6475\textsuperscript{TM}), SKOV3 Human Ovarian cancer (ATCC® HTB-77\textsuperscript{TM}), MCF7 Human Breast Adenocarcinoma ((ATCC® HTB-22\textsuperscript{TM}) and CHO-K1-Chinese hamster ovary cells, Normal Cell line (ATCC® CCL-61\textsuperscript{TM}) using MTT assay. Doxorubicin was used as a positive control. IC\textsubscript{50} values of the test compounds for 24 h on each cell line was calculated and presented in Table I.

Compounds 6a and 6h showed promising activity against HeLa (IC\textsubscript{50} value 8.92µM) and SKOV3 cell lines (IC\textsubscript{50} value 9.43 µM), respectively. Majority of the compounds showed significant activities against HeLa cell line with the IC\textsubscript{50} values ranged from 8.92 to 13.44µM (except 6h, 6i and 6j which showed the moderate values). In case of SKOV3 cell line, all the compounds showed good activity with the IC\textsubscript{50} values ranged from 9.43 to 19.34 µM (except 6a which showed the moderate value). Compounds 6h, 6i and 6j showed good activities against MCF-7 cell line (IC\textsubscript{50} values ranging between 15.21 to 16.04 µM). Majority of the compounds were non toxic towards the Chinese hamster ovary (CHO-K1) normal cell line.

**Experimental Section**

All the chemicals used in these schemes were of analytical grade and they were obtained from different...
commercial sources and used without any further purification. Reactions were monitored on micro TLC plates (coated with TLC grade silica gel, obtained from Merck). Column chromatography was performed by using silica gel (100-200 mesh) procured from Qualigens (India) using freshly distilled solvents. All the ¹H and ¹³C NMR spectra were recorded with a Bruker Avance (for ¹H NMR at 300 MHz, 400 MHz, 500 MHz and for ¹³C NMR at 75 MHz, 100MHz, 125 MHz) spectrometer, using TMS δ = 0 ppm and δ 77.00 ppm as internal standard (δ) in CDCl₃ at 25°C. The chemical shift values are presented in ppm (parts per million) units. Mass spectra were recorded with HRMS. IR spectra were recorded in chloroform on a Perkin-Elmer FT-IR spectrum BX.

Synthesis of methyl undec-10-enoate, 2
To a stirred solution of undec-10-enoic acid (73.45 mmol) in methanol (100 mL), a few drops of concentrated H₂SO₄ was added. The reaction mixture was refluxed for 10 h. Progress of the reaction was monitored by micro TLC. After completion of the reaction, methanol was removed under reduced pressure and water was added and the title compound was extracted with ethyl acetate, dried over anhydrous sodium sulphate and concentrated under vacuum to afford the title compound. ¹H NMR (300 MHz, CDCl₃): δ 5.75-5.85 (m, -CH=CH₂-, 1H), 4.91-5.01 (m, -CH=CH₂-, 2H), 3.66 (s, -OCH₃, 2H), 2.28-2.31 (t, -CH₂-, J = 7.4 Hz, 2H), 2.01-2.06 (m, -CH₂-, 2H), 1.59-1.65 (m, -(CH₂)₅-, 10H); ESI-MS: [M+H]⁺ m/z 199.

Synthesis of undec-10-enehydrazide, 3
To a stirred solution of methyl undec-10-enoate (2) (59.93 mmol) in ethanol (90 mL), hydrazine hydrate (269.68 mmol) was added. The reaction mixture was refluxed for about 10 h. Progress of the reaction was monitored by micro TLC. After completion of the reaction, the solvent was evaporated under reduced pressure, ice water (50 mL) was added and the mixture was stirred for 15 min. The solid obtained was filtered and dried under vacuum to yield undec-10-enehydrazide as a white solid. ¹H NMR (300 MHz, CDCl₃): δ 5.75-5.85 (m, -CH=CH₂-, 1H), 4.91-5.01 (m, -CH=CH₂-, 2H), 2.67-3.01 (broad-s, -NH₂, 2H), 2.12-2.16 (t, -CH₂-, J = 7.3 Hz, 2H), 2.00-2.06 (m, -CH₂-, 2H), 1.59-1.66 (m, -(CH₂)₅-, 10H); ESI-MS: [M+H]⁺ m/z 199.

Synthesis of potassium 2-(undec-10-enoyl) hydrazine-1-carbodithioate, 4
Potassium hydroxide pellets (106.54 mmol) were dissolved in ethanol (40 mL). To this solution, undec-10-enehydrazide (53.27 mmol), carbon disulfide (117.19 mmol) were added successively and the contents were stirred at RT for 8 h. Progress of the reaction was monitored by micro TLC. After completion of the reaction, diethyl ether (100 mL) was added to the reaction mixture and stirred for 10 min. The solid obtained was filtered and dried under vacuum to yield potassium 2-(undec-10-enoyl) hydrazine-1-carbodithioate as an off-white solid.

Table I — Cytotoxicity of the synthesized compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>IC₅₀ values (µM)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HeLa</td>
</tr>
<tr>
<td>6a</td>
<td>8.92 ± 0.92</td>
</tr>
<tr>
<td>6b</td>
<td>9.50 ± 0.93</td>
</tr>
<tr>
<td>6c</td>
<td>10.85 ± 0.73</td>
</tr>
<tr>
<td>6d</td>
<td>10.03 ± 0.91</td>
</tr>
<tr>
<td>6e</td>
<td>10.83 ± 0.74</td>
</tr>
<tr>
<td>6f</td>
<td>10.78 ± 1.03</td>
</tr>
<tr>
<td>6g</td>
<td>13.44 ± 1.0</td>
</tr>
<tr>
<td>6h</td>
<td>19.37 ± 0.51</td>
</tr>
<tr>
<td>6i</td>
<td>40.48 ± 0.53</td>
</tr>
<tr>
<td>6j</td>
<td>33.82 ± 0.74</td>
</tr>
<tr>
<td>Standard Drug</td>
<td>-</td>
</tr>
</tbody>
</table>

Doxorubicin
Mitomycin C

NA = No activity, HeLa: Homo sapiens cervix adenocarcinoma (ATCC® CCL-2.1™), B16-F10: Mouse skin melanoma (ATCC® CRL-6475™), SKOV3: human ovarian cancer cell line (ATCC No. HTB-77™), MCF-7: human breast adenocarcinoma cells (ATCC No. HTB-22™), CHO-K1: Chinese hamster ovary cells, Normal Cell line (ATCC® CCL-61™).
Synthesis of 4-amino-5-(dec-9-en-1-yl)-4H-1,2,4-triazole-3-thiol, 5

Hydrazine hydrate (45.38 mmol) was added to potassium 2-(undec-10-enoyl) hydrazine-1-carboxbithioate (45.38 mmol) and the contents were refluxed for 5 h. Progress of the reaction was monitored by micro TLC. After completion of the reaction, the reaction mixture was acidified with concentrated hydrochloric acid. The obtained precipitate was filtered and dried under vacuum to get the crude compound which was subjected to silica gel column chromatography to give the required product with 69% yield. ESI-MS: [M+H]+ m/z 255.

General procedure for the synthesis of bridged compounds, 6a-j

A mixture of 4-amino-5-(dec-9-en-1-yl)-4H-1,2,4-triazole-3-thiol (0.1 mol), various substituted cinnamic acids (0.1 mol) and phosphorus oxychloride (10 L) were refluxed for 6 h. Progress of the reaction was monitored by micro TLC. After completion of the reaction, the reaction mixture was cooled to RT and poured onto crushed ice and the title compound was extracted with ethyl acetate, dried over anhydrous sodium sulphate. The crude compound was subjected to silica gel column chromatography to give the required product.

3-(Dec-9-en-1-yl)-6-(3,4-difluorostyryl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6c: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 75: 25, v/v) as an off white solid. ESI-MS: [M+H]+ m/z: 403.17625. Found: 403.17632

3-(Dec-9-en-1-yl)-6-(3,4-dimethoxystyryl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6c: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 80: 20, v/v) as an off white solid with 68% yield. 1H NMR (500 MHz, CDCl3): 6 7.23-7.23 (m, 1H, Ar-H), 7.13-7.15 (m, 2H, Ar-H), 7.06-7.09 (m, 1H, Ar-H), 6.90-6.92 (m, 1H, Ar-H), 5.76-5.84 (m, 1H, CH2-CH=CH2), 4.91-5.00 (m, 2H, CH2-CH=CH2), 3.95 (s, 3H, CH3), 3.94 (s, 3H, CH3), 3.05-3.08 (m, 2H, CH2), 2.01-2.05 (m, 2H, CH2), 1.85-1.90 (m, 2H, CH2), 1.25-1.45 (m, 10H, (CH2)5), 119.8, 115.6, 114.0, 111.1, 109.1, 55.9, 55.8, 33.6, 29.1, 29.0, 28.9, 26.6, 24.9; IR (CHCl3): 3631, 3423, 2925, 2853, 2812, 1647, 1476, 1036 cm−1; HR-MS (ESI): m/z [M+H]+ Calcd for C21H18O4NS: 427.12162; Found: 427.12150 (C21H18O4NS).

6-(2-(1,1'-Biphenyl)-4-yl)vinyl)-3-(dec-9-en-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6d: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 80: 20, v/v) as an off white solid with 69% yield. 1H NMR (400 MHz, CDCl3): 6 7.37-7.42 (m, 1H, Ar-H), 7.21-7.31 (m, 3H, Ar-H), 7.10-7.14 (d, 1H, -CH=CH-), 5.75-5.85 (m, 1H, CH2-CH=CH2), 4.91-5.01 (m, 2H, CH2-CH=CH2), 3.05-3.09 (t, 2H, CH2), 2.01-2.06 (m, 2H, CH2), 1.85-1.92 (m, 2H, CH2), 1.25-1.45 (m, 10H, (-CH2)5); 13C NMR (100 MHz, CDCl3): 6 164.5, 151.8, 148.5, 138.9, 137.8, 131.2, 124.3, 119.0, 118.1, 117.0, 115.9, 115.7, 114.3, 30.6, 31.7, 29.3, 29.1, 28.9, 28.7, 26.5, 24.8, 22.5; IR (CHCl3): 3418, 3058, 2922, 2853, 1958, 1613, 1590, 1470, 1096, 947 cm−1; HR-MS (ESI): m/z [M+H]+ Calcd for C21H18F2N4S: 403.17625. Found: 403.17441 (C21H18F2N4S).

6-(2-(1,1'-Biphenyl)-4-yl)vinyl)-3-(9-hexadecyloxyvinyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6d: This compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 80: 20, v/v) as an off white solid with 68% yield. 1H NMR (500 MHz, CDCl3): 6 7.23-7.23 (m, 1H, Ar-H), 7.13-7.15 (m, 2H, Ar-H), 7.06-7.09 (m, 1H, Ar-H), 6.90-6.92 (m, 1H, Ar-H), 5.76-5.84 (m, 1H, CH2-CH=CH2), 4.91-5.00 (m, 2H, CH2-CH=CH2), 3.95 (s, 3H, CH3), 3.94 (s, 3H, CH3), 3.05-3.08 (m, 2H, CH2), 2.01-2.05 (m, 2H, CH2), 1.85-1.90 (m, 2H, CH2), 1.25-1.45 (m, 10H, (-CH2)5); 13C NMR (125 MHz, CDCl3): 6 165.4, 152.0, 148.5, 143.3, 140.0, 139.8, 139.1, 129.8, 128.1, 127.7, 127.0, 128.0, 117.8, 114.1, 33.7, 31.8, 29.6, 29.2, 29.1, 28.8, 26.7, 25.0, 22.6; IR (CHCl3): 3423, 2925, 2853, 1602, 1512, 1466, 1247 cm−1; HR-MS (ESI): m/z [M+H]+ Calcd for C27H25N3O3S: 443.22639. Found: 443.22322 (C27H25N3O3S).
3-(Dec-9-en-1-yl)-6-(2,4-difluorostyryl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6f: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 75: 25, v/v) as an off white solid with 83% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.66 (d, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 5.75-5.85 (m, 1H, \( CH_2-CH=CH_2 \)), 4.91-5.00 (m, 2H, \( CH_2-CH=CH_2 \)), 3.05-3.07 (t, 2H, \( CH_2-CH=CH_2 \)), 2.00-2.07 (m, 2H, \( CH_2-CH=CH_2 \)), 1.84-1.92 (m, 2H, \( CH_2-CH=CH_2 \)), 1.25-1.45 (m, 10H, \( (-CH_2)_2 \)); \(^1^C\) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 166.4, 151.9, 148.6, 139.0, 137.5, 134.4, 130.0, 133.5, 131.1, 129.1, 126.5, 119.8, 114.1, 33.7, 32.4, 31.8, 29.6, 29.4, 29.0, 28.8, 26.6, 24.9; IR (CHCl\(_3\)): 3631, 3423, 2925, 2854, 2344, 1958, 1639, 1485, 1070, 772 cm\(^{-1}\); HR-MS (ESI): m/z \([M+H]^+\) 435.1187.

3-(Dec-9-en-1-yl)-6-(3,4-dichlorostyryl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6i: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 75: 25, v/v) as an off white solid with 81% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.66 (d, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 5.75-5.85 (m, 1H, \( CH_2-CH=CH_2 \)), 4.91-5.00 (m, 2H, \( CH_2-CH=CH_2 \)), 3.05-3.07 (t, 2H, \( CH_2-CH=CH_2 \)), 2.00-2.07 (m, 2H, \( CH_2-CH=CH_2 \)), 1.84-1.92 (m, 2H, \( CH_2-CH=CH_2 \)), 1.25-1.45 (m, 10H, \( (-CH_2)_2 \)); \(^1^C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 164.6, 151.9, 148.6, 138.5, 137.3, 131.4, 127.7, 126.0, 120.5, 114.1, 33.0, 13.8, 29.6, 24.9, 29.0, 28.8, 26.6, 24.9; IR (CHCl\(_3\)): 3423, 2925, 2854, 1602, 1466, 1248, 1175, 1034, 755 cm\(^{-1}\); HR-MS (ESI): m/z \([M+H]^+\) 435.1838.

6-(4-Chlorostyryl)-3-(dec-9-en-1-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole, 6j: The crude compound was subjected to silica gel column chromatography and the required product was eluted in a solvent mixture (Hexane: EtOAc, 75: 25, v/v) as an off white solid with 83% yield. \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.49-7.51 (s, 2H, Ar-H), 7.40-7.42 (s,2H, Ar-H), 7.25-7.29 (d, 1H, \( CH_2-CH=CH_2 \)), 5.75-5.84 (m, 1H, \( CH_2-CH=CH_2 \)), 4.91-5.00 (m, 2H, \( CH_2-CH=CH_2 \)), 3.05-3.08 (t, 2H, \( CH_2-CH=CH_2 \)), 2.01-2.05 (m, 2H, \( CH_2-CH=CH_2 \)), 1.85-1.92 (m, 2H, \( CH_2-CH=CH_2 \)), 1.25-1.45 (m, 10H, \( (-CH_2)_2 \)); \(^1^C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 164.9, 151.9, 148.5, 139.0, 138.9, 131.4, 127.7, 126.0, 120.5, 114.1, 33.0, 29.6, 24.9, 29.0, 28.8, 26.7, 24.9; IR (CHCl\(_3\)): 3424, 2923, 2853, 1637, 1488, 1427, 1095, 772 cm\(^{-1}\); HR-MS (ESI): m/z \([M+H]^+\) 385.1866.
the earlier study (Vishnu Sravan et al., 2016). Four different cancer cell lines and one normal cell line namely, HeLa Homo sapiens cervix adenocarcinoma (ATCC® CCL-2.1™), B16-F10 Mouse skin melanoma (ATCC® CRL-6475™), SKOV3 Human Ovarian cancer (ATCC® HTB-77™), MCF7 Human Breast Adenocarcinoma (ATCC® HTB-22™) and CHO-K1-Chinese hamster ovary cells, Normal Cell line (ATCC® CCL-61™) were obtained from the ATCC (Bethesda, MD, USA) and maintained in DMEM supplemented with 10 % FBS, 2 mM l-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 °C in a 5 % CO₂ incubator. After seeding of cells in 96 well culture plate, allowed to attach properly. Test compounds of different concentrations ranging from 1 to 50 µM were added in triplicates and incubated for 24 h. The cells were then incubated with MTT (0.5 mg/mL) for 3 h and to dissolve the insoluble formazan crystals 100 µL DMSO was added to each well. Finally, the absorbance of the plates was measured using a Synergy H1 multi-mode plate reader, USA. Doxorubicin was used as a positive control for the comparison.

Conclusions

In conclusion, a series of substituted cinnamic-based 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazoles were synthesized. All the synthesized compounds were evaluated for their cytotoxic activities. 2,3-dimethoxy and 4-trifluoro methyl derivatives exhibited promising activities against HeLa and SKOV3 cell lines. Most of the compounds were nontoxic against the normal cell line (Chinese hamster ovary cell, CHO-K1).

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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