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Synthesis of potentially new Schiff bases of N-substituted-2-quinolonylacetohydrazides as anti-COVID-19 agents

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We report herein a new series of synthesized N-substituted-2-quinolonylacetohydrazides aiming to evaluate their activity towards SARS-CoV-2. The structures of the obtained products were fully confirmed by NMR, mass, IR spectra and elemental analysis as well. Molecular docking calculations showed that most of the tested compounds possessed good binding affinity to the SARS-CoV-2 main protease (M<sub>pro</sub>) comparable to Remdesivir.

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1. Introduction

Recently, human coronaviruses have attracted much interest. A new strain for Corona viruses (CoVs) identified in late December 2019 named SARS-CoV-2 resulted in a massive outbreak initially in Wuhan, China and propagated to different nations around the globe. The World Health Organization (WHO) declared the resulting disease named COVID-19 as a pandemic [1,2]. It is safe to say that a sufficient understanding of SARS-CoV-2, and the full clinical picture of the resulting COVID-19 disease will take some time [3-8].

Remdesivir (Fig. 1) an adenosine analogue, has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) [9,10] infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of the Ebola virus infection [11]. Remdesivir binds to ribonucleic acid (RNA)-dependent RNA polymerase and acts as an RNA-chain terminator. It displays potent in vitro activity against SARS-CoV-2 with an EC<sub>50</sub> at 48 h of 0.77 μM in Vero E6 cells. Remdesivir is highly selective for viral polymerases and is therefore expected to have a low propensity to cause human toxicity [12].

During last few decades, 4-hydroxy-2-quinolones as privileged structures in drug discovery are beyond doubt, one of the major areas in medicinal chemistry [13-15]. The 4-hydroxy-2-quinolines scaffold is widely found in alkaloids [16] and they are important as a characteristic building block for a series of significant biologically active compounds. Many efforts have been done on antiviral properties of quinolines and quinolones and their structural analogues against the human immunodeficiency virus (HIV), but their antiviral activity was also demonstrated against the human cytomegalovirus (HCMV), SARS corona virus, Zika virus, Chikungunya virus, hepatitis C virus (HCV), and Ebola virus [17-22]. The mechanism of action of antiviral quinolone remains unclear. Specific studies aimed at understanding the nature of drug's targets at the molecular level indicated that quinolones inhibit viral transcription [23].

Elvitegravir (Fig. 2) is the first quinolone-based anti-HIV drug, exhibiting potent inhibitory activity against integrase-catalyzed DNA strand transfer [24,25]. Another series of quinolone-3-carboxylic acids have been synthesized by introducing different hydrophobic groups at the N(1), C(2), C(7), and C(8) positions [26]. Most of the compounds of this group showed anti-HIV activity without cytotoxicity at a concentration of 100 μM.

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inhibitors [32], whereas synthesis of bis(6-substituted-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)naphtha-ene-1,4-dione VIII and (substituted N-(alkyl)bis-quinolinone)-triethylammonium salt VIV [33], were explored as candidates for extracellular signal-regulated kinases 1/2 (ERK1/2) having antineoplastic activity [33]. Recently, we have reported the synthesis of 5,12-dihydro-pyrazino[2,3-c:5,6-c']difuro[2,3-c:4,5-c']-diquinoline-6,14[(5H,12H)-dione X [34] and 2-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)–1,4-diphenyl-butan-1,4-dione XI [34]. Most indicative is our recent synthesis of 6-substituted-4-(2-(4-substituted-benzylidene)hydrazyl)quinolin-2(1H)-one derivative XII [35] which was evaluated for their in vitro cytotoxic activity against 60 cancer cell lines according to NCI protocol [35].

On the other hand, Schiff bases have large importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like analgesic [36–39], anti-inflammatory [36,38,40], anti-tubercular [41], anti-cancer [42,43], and so forth. So, from the highly biological and pharmaceutical activities of 4-hydroxy-2-quinolinones and Schiff bases, we focused in our paper to merging the activity of these compounds and compare them with Remdesivir (as one of the prospective drugs) against COVID-19.

2. Results and discussion

2.1. Chemistry section

Our research plan started by preparation of compounds 2a,b during reaction between quinolones 1a,b and ethyl bromoacetate. Compounds 2a,b reacted with hydrazine in EtOH and gave the corresponding 2-(2-oxo-1,2-dihydroquinolin-4-yl)oxy-acetohydrazide 3a,b in good yields (Scheme 1) [44,45]. By refluxing equimolar amounts of compounds 3a,b with an aldehyde in absolute ethanol with few drops of acetic acid gave our target new Schiff bases 4a-k in 75–90% yields (Scheme 1). The structure assignments of compounds 4a-k were established using different spectroscopic tools like IR, NMR (1H, 13C, 15N, 2D), elemental analyses and mass spectrometry. The elemental analysis showed that the corresponding molecular formula for all new compounds 4a-k are formed form one molecule of compound 3a,b and one molecule of the entered aldehyde with elimination
for a H$_2$O molecule. To illustrate the structure for the obtained compounds 4a-k, we choose compound 4b as an example which was assigned as N’-(4-bromobenzylidene)-2-((7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-acetohydrazide (4b) with a molecular formula C$_{28}$H$_{28}$BrN$_3$O$_3$ (m/z = 414). Its IR spectrum did not show any absorption band corresponding to hydrazine-NH$_2$, thus indicated that condensation has occurred (Fig. 4).

This was fully supported by its $^1$H NMR spectrum, which displayed a characteristic singlet at $\delta$$_H$ = 11.80, 11.34 ppm, integrating for two D$_2$O exchangeable protons which were assigned as NH-4e and NH-1, respectively. Also, a singlet at $\delta$$_H$ = 5.33 ppm (2H) corresponding to -OCH$_2$- (H-4c) was further confirmed from $^{13}$C NMR (Fig. 5) with a characteristic singlet at $\delta$$_C$ = 65.15 ppm (Table 1).

The protons of the phenyl group exhibit a 1:4-disubstituted system and was observed as a double-doublet at $\delta$$_H$ = 7.72 (d, $J$ = 8.5 Hz; 2H, H-o) and $\delta$$_H$ = 7.65 (d, $J$ = 8.5 Hz; 2H, H-m) and both of them give a 1H-$^1$H-COSY with each other (Table 1). The $^{13}$C NMR spectrum for compound 4b showed characteristic singlets at $\delta$$_C$ = 167.78, 163.25, 162.05, 147 and 21.28 which were assigned as C-4d, quinolone-C-2, C-4, C = N (C-4 g), and methyl group (C-7a), respectively (Table 2). In $^{15}$N-NMR, the signal at $\delta$$_N$ = 317.2 ppm, indicated as N-4f gave HMBC correlation with

**Scheme 1. Preparation of new Schiff bases 4a-k.**

**Table 1**

| $^1$H NMR | $^1$H-$^1$H COSY | Assignment |
|-----------|----------------|------------|
| 11.80 (s, 1H) | 11.34 (s, 1H) | NH-4e |
| 8.01 (s, 1H) | 7.76 (d, $J$ = 8.5 Hz, 1H) | H-4g |
| 7.72 (d, $J$ = 8.5 Hz, 2H) | 7.09 (s; 1H) | H-5 |
| 7.65 (d; $J$ = 8.5 Hz, 2H) | 7.03 (d; $J$ = 8.4 Hz; 1H) | H-6 |
| 5.74 (s, 1H) | 7.81, 7.76 | H-3 |
| 5.33 (s, 2H) | 7.09 | H-7a |

**Table 2**

|$^{13}$C NMR | HSQC | HMBC |
|-----------|-------|------|
| 167.78 | 11.80, 11.79, 5.33, 5.39 | C-4d |
| 163.25 | 11.78, 5.33, 4.81, 2.89 | C-2 |
| 162.05 | 11.78, 7.76, 5.74, 5.33, 4.85, 2.89 | C-4 |
| 162.93 | 8.02, 8.01, 7.96 | C-4 g |
| 141.07 | 7.81, 7.76, 7.72 | C-7 |
| 140.15 | 7.81, 7.76, 7.36 | C-8a |
| 133.20 | 8.29, 8.25, 8.02, 8.01, 7.65 | C-i |
| 131.74 | 7.67 | C-m |
| 129.02 | 7.72 | C-o |
| 123.20 | 7.03 | C-p |
| 122.76 | 7.81 | C-6 |
| 122.35 | 7.76 | C-5 |
| 114.88 | 7.09 | C-8 |
| 112.38 | 7.09, 7.57 | C-4a |
| 96.68 | 5.77, 5.74 | 11.34 |
| 65.15 | 5.33, 5.33, 4.85, 4.81 | 11.79 |
| 21.28 | 2.38 | 7.09, 7.03 |
| $^{13}$N NMR | HSQC | Assignment |
|-----------|-------|--------------|
| 317.2 | 8.02, 8.01 | N-4f |
| 177.9 | 11.80, 11.79 | N-4e |
| 144.4 | 11.39, 11.34 | N-1 |
proton at $\delta_H = 8.01$ ppm which was assigned as H-4 g and didn’t have any HSQC correlation, and this proton give HSQC correlation with carbon at $\delta_C = 142.93$ ppm, which was assigned as C-4 g that indicates the absence of hydrazine-NH$_2$ and condensation takes place on it, with other signals at $\delta_H = 177.9$ and 144.4 ppm, which were assigned as N-4e and N-1, respectively, and these nitrogen gave an HSQC correlation which indicates that these nitrogen atoms are carrying protons (Table 2). The former correlation indicates the E-form of the azomethine structure.

2.2. Molecular docking calculations

To reveal the binding modes and affinities of the synthesized compounds 4a-k with SARS-CoV-2 main protease ($M^{\text{pro}}$) and RNA-dependent RNA polymerase (RdRp), molecular docking calculations were performed using Autodock4.2.6 software. The predicted docking scores and binding features of compounds 4a-k with $M^{\text{pro}}$ and RdRp receptors are listed in Table 3.

According to the calculated docking scores (Table 3), compounds 4a-k showed good binding affinities towards $M^{\text{pro}}$ with values in range $-7.5$ to $-9.7$ kcal/mol. Compared to main protease ($M^{\text{pro}}$), the synthesized compounds showed lower binding affinities towards RdRP with docking scores in range $-6.5$ to $-7.7$ kcal/mol. However, molecular docking of Remdesivir gave binding affinities of $-8.5$ and $-5.6$ kcal/mol with $M^{\text{pro}}$ and RdRp, respectively (Table 3). Comparison of the binding affinities revealed that compound 4d exhibited the largest binding affinities towards both of $M^{\text{pro}}$ and RdRp with values of $-9.7$ and $-7.7$ kcal/mol, respectively. The high binding affinity of compound 4d towards $M^{\text{pro}}$ may be attributed to its potentiality to form four essential hydrogen bonds with lengths of 2.02, 2.22, 1.83 and 2.07 Å with LEU141, SER144, HIS163 and GLU166 amino acids, respectively (Fig. 6).

Analysis of the docked 4d-RdRp complex, compound 4d forms three essential hydrogen bonds with TYR619, ASP623 and GLU811 amino acids with average bond lengths of 2.19, 2.12 and 2.24 Å, respectively (Fig. 6). 2D LigPlus representations of interactions of

Fig. 5. $^{13}$C NMR spectrum of 4b.

Fig. 6. Cartoon backbone representation of predicted binding modes of compound 4d with SARS-CoV-2 (a) main protease ($M^{\text{pro}}$) and (b) RNA-dependent RNA Polymerase (RdRp). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
compounds 4a-k with important amino acid residues of SARS-CoV-2 Mpro are depicted in Fig. 7. Overall, the molecular docking results could support the postulation that the synthesized compounds may act as potent SARS-CoV-2 Mpro inhibitors.

3. Conclusion

In conclusion, a new series of N-substituted-2-quinolonylacetoxyhydrazides was here synthesized in order to evaluate their activity towards SARS-CoV-2 Mpro and RdRp. The NMR spectra (1H, 13C, 15N, 2D) were used to prove the structure of the isolated compounds. Molecular docking calculations showed that most of the tested compounds possessed good binding affinity to the main protease (Mpro) comparable to Remdesivir. Analysis of the docked (E)-N’-(3-methoxybenzylidene)-2-[(7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy]acetohydrazide-RdRp complex shows formation of three essential hydrogen bonds with TYR619 and GLU811 amino acids with average bond lengths of 2.19, 2.12 and 2.24 Å, respectively. Much work has been done to evaluate more quinolones compounds, especially in the direction to find out how drugs capable to treat infections caused by the SARS-CoV-2 virus.

4. Experimental

Melting points were determined on Stuart electrothermal melting point apparatus and were uncorrected. TLC analysis was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF254 indicator. Spectra were measured in DMSO-d6 on a Bruker AV-400 spectrometer (400 MHz for 1H, 100 MHz for 13C, and 40.54 MHz for 15N), purchased with assistance from the National Science Foundation (CHE 03-42251) at the Florida Institute of Technology, 150 W University Blvd, Melbourne, FL 32901, USA. Chemical shifts are reported vs TMS = 0 for 1H and 13C, and vs NH2 = 0 for 15N. 15N signals were detected indirectly, via HSQC and HMBC experiments. The samples were dissolved in DMSO-d6, s = singlet, d = doublet, dd = doublet of doublet and t = triplet. Mass spectrometry were recorded on a Varian MAT 312 instrument in EI mode (70 eV), at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany.

Synthesis of substituted (E)-N’-(substituted benzylidene)-2-[(7-substituted-2-oxo-1,2-dihydroquinolin-4-yl)oxy]acetohydrazide 4a-k.

A mixture of 3a,b (1 mmol), aldehydes (1 mmol) and a few drops of acetic acid in 20 mL of absolute ethanol which was stirred and refluxed for 6–8 h (the reaction was followed by TLC analysis). After the reaction’s completion, the solid was filtered off and washed with a hot ethanol to give pure compounds 4a-k.

(E)-N’-Benzyldiene-2-[(7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy]acetohydrazide (4a).

This compound was obtained as a colorless compound, yield 0.28 g (83%); Rf = 0.4 (Toluene: Ethyl acetate; 10:1). 1H NMR (DMSO-d6): δH = 11.75 (s; 1H, NH, H-4e), 11.34 (s; 1H, NH-1), 8.04 (s; 1H, H-4 g), 7.76 (m; 3H, H-5-a), 7.45 (m; 3H, H-m-p), 7.09 (s; 1H, H-8), 7.04 (d; J = 8.2, 1H, H-6), 5.73 (s; 1H, H-3), 5.34 (s; 2H, H-4c), 3.28 (s; 3H, H-7a); 13C NMR (DMSO-d6): δC = 167.87 (C-4d), 163.25 (C-2), 162.08 (C-4), 144.13 (C-4 g), 141.07 (C-7), 140.15 (C-8a), 133.89 (C-1), 129.98 (C-p), 127.75 (C-m), 126.99 (C-o), 122.76 (C-6), 122.35 (C-C), 114.87 (C-8), 112.38 (C-4a), 96.64 (C-3), 65.14 (C-4c), 21.28 (C-7a); 15N NMR (DMSO-d6): δN = 315.1 (N-4f), 177.4 (N-4e), 144.1 (N-1a). MS (70 eV): m/z = 335 (M+), 60. Anal. Calcd for C9H7N2O2: C 68.05; H 5.11; N 12.53. Found: C 68.11; H 4.99; N 12.66.

(E)-N’-(4-Bromobenzylidene)-2-[(7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy]acetohydrazide (4b).
Fig. 7. 2D LigPlus representation of interactions of compounds 4a-k with important amino acid residues of SARS-CoV-2 main protease (M<sub>pro</sub>).
This compound was obtained as a colorless compound, yield 0.300 g (72%); $R_f = 0.3$ (Toluene: Ethyl acetate; 10:1); $^{1}$H NMR (DMSO-d$_6$): $\delta$ (ppm) 11.45 (s; 1H, NH, H-4e); 5.79 (s; 1H, H-4); 7.76 (d, $J = 8.2$ Hz; 1H, H-5); 7.54 (d, $J = 8.86$ Hz; 2H, H-ə); 7.09 (s; 1H, H-8); 7.03 (d, $J = 8.3$ Hz; 1H, H-6); 6.75 (d, $J = 8.8$ Hz; 2H, H-m); 5.68 (s; 1H, H-3); 5.28 (s; 2H, H-4c); 2.98 (s; 6H, NMe$_2$); 2.38 (s; 3H, H-7a); $^{13}$C NMR (DMSO-d$_6$); $\delta_c$ = 167.62 (C-4d), 163.13 (C-2), 160.14 (C-4), 148.55 (C-4 g), 141.07 (C-7), 140.10 (C-8a), 125.71 (C-8), 122.75 (C-6), 122.63 (C-5), 114.87 (C-8), 112.40 (C-4a), 111.74 (C-m), 96.56 (C-3), 65.13 (C-4c), 59.50 (NMe$_2$), 21.28 (C-7a); $^{15}$N NMR (DMSO-d$_6$): $\delta_N = 303.6$ (N-4f); 176.4 (N-4e), 144.0 (N-1a), 52.8 (NMe$_2$). MS (70 eV); m/z (%) = 378 (M$^+$, 60). Anal. Calc. for C$_{22}$H$_{28}$N$_2$O$_3$ (378.42): C 66.65; H 5.86; N 14.81. Found: C 66.77; H 5.79; N 14.66.

(E)-N'-((3-Methoxybenzylidene)-2-((7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-acetohydrazide (4c).

This compound was obtained as a colourless compound, yield 0.280 g (77%); $R_f = 0.65$ (Toluene: Ethyl acetate; 10:1); $^{1}$H NMR (DMSO-d$_6$): $\delta$ (ppm) 11.76 (s; 1H, NH, H-4e); 11.34 (s; 1H, NH-1); 8.00 (s; 1H, H-4); 7.76 (d; $J = 8.2$ Hz; 1H, H-5); 7.37 (m; 1H, H-5']; 7.30, (m; 2H, H-2',6'); 7.09 (s; 1H, H-8); 7.02 (m; 2H, H-4',6'); 5.72 (s; 1H, H-3); 5.35 (s; 2H, H-4c); 3.80 (s; 3H, H-3a); 2.38 (s; 3H, H-7a); $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 167.83 (C-4d), 163.24 (C-2), 162.09 (C-4), 159.51 (C-3'), 143.94 (C-4 g), 141.21 (C-7), 140.15 (C-8a), 135.31 (C-1'), 129.86 (C-5'), 122.76 (C-6), 122.33 (C-5), 119.68 (C-6'), 115.94 (C-5'), 114.88 (C-8), 112.39 (C-4a), 111.64 (C-2'), 96.66 (C-3), 65.19 (C-4c), 55.15 (C-3'a), 21.27 (C-7a); $^{15}$N NMR (DMSO-d$_6$): $\delta_N = 316.1$ (N-4f), 177.5 (N-4e), 144.3 (N-1a). MS (70 eV); m/z (%) = 365 (M$, 27). Anal. Calc. for C$_{20}$H$_{18}$N$_2$O$_4$ (365.38): C 65.74; H 5.24; N 11.50. Found: C 65.66; H 5.09; N 11.44.

(E)-2-((7-Methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-((3,4,5-trimethoxybenzylidene)acetohydrazide (4e).

This compound was obtained as a colorless compound, yield 0.38 g (90%); $R_f = 0.45$ (Toluene: Ethyl acetate; 10:1); $^{1}$H NMR (DMSO-d$_6$): $\delta$ = 11.78 (s; 1H, NH, H-4e), 11.34 (s; 1H, NH-1), 7.95 (s; 1H, H-4 g), 7.76 (d; $J = 8.2$ Hz, 1H, H-5); 7.09 (s; 1H, H-8); 7.05 (m; 3H, H-2',6'), 5.70 (s; 1H, H-3); 5.37 (s; 2H, H-4c), 3.81 (s; 3H, H-3'a,5'a'), 2.89 (s; 3H, H-4'a'), 2.38 (s; 3H, H-7a); $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 167.81 (C-4d), 163.24 (C-2), 162.13 (C-4), 153.12 (C-3'), 143.92 (C-4 g), 141.06 (C-7), 140.15 (C-8a), 138.80 (C-4'), 129.40 (C-1'), 122.77 (C-6), 122.31 (C-5), 114.88 (C-8), 112.38 (C-4a), 104.34 (C-2'), 96.64 (C-3), 60.08 (C-4c), 55.92 (C-4'a), 35.73 (C-2'), 21.26 (C-7a); $^{15}$N NMR (DMSO-d$_6$): $\delta_N = 313.2$ (N-4f), 177.5 (N-4e), 143.9 (N-1a). MS (70 eV); m/z (%) = 425 (M$, 55). Anal. Calc. for C$_{22}$H$_{28}$N$_2$O$_3$: C 62.11; H 5.45; N 9.88. Found: C 62.28; H 5.59; N 10.01.

(E)-N'-((3-Methoxybenzylidene)-2-((7-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetohydrazide (4f).

This compound was obtained as a colorless compound, yield 0.275 g (82%); $R_f = 0.5$ (Toluene: Ethyl acetate; 10:1); $^{1}$H NMR (DMSO-d$_6$): $\delta$ = 11.75 (s; 1H, NH, H-4e), 8.04 (s; 1H, H-4 g), 8.01 (d; $J = 7.8$ Hz; 1H, H-8), 7.76 (dd; $J = 7.8, 2.2$ Hz; 2H, H-o), 7.69 (m; 1H, H-7), 7.54 (d; $J = 8.5$ Hz; 1H, H-5), 7.46 (m; 3H, H-m-p), 7.31 (m; 1H, H-6), 5.98 (s; 1H, H-3), 5.38 (s; 2H, H-4c), 3.58 (s; 3H, H-1a); $^{13}$C NMR (DMSO-d$_6$): $\delta_c$ = 167.71 (C-4d), 162.17 (C-2), 160.65 (C-4), 144.16 (C-4 g), 139.47 (C-8a), 133.89 (C-i), 131.48 (C-7), 129.98 (C-p), 128.75 (C-m), 127.01 (C-o), 122.88 (C-
The crystal structures of SARS-CoV-2 main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) were taken as templates for all molecular docking. Receptors were cleaned of water molecules, ions and the ligands. The protonation state of Mpro and RdRp was investigated using an H+ server, and all missing hydrogen atoms were added [48]. All molecular docking calculations were carried out using Autodock4.2.6 software [49]. All docking parameters were kept to default values, except the number of genetic algorithm (GA) runs and the maximum number of energy evaluations (eval) which were set to 250 and 25,000,000, respectively. The docking grid was set to 60Å x 60Å x 60Å with a grid spacing value of 0.375 Å, and the grid center was placed at the center of the active site. The geometrical structures of all synthesized compounds were minimized with a MMFF94s force field using SYBYL software [50] and the partial atomic charges were assigned using the Gasteiger method [51].

CRediT author statement and authorship

I would like to confirm and certify the authors' contributions as indicated in the following:

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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