



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Synthesis and Molecular docking of Novel 2-Phenyl-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one Derivatives as Anti-HIV-1 NNRT Inhibitors

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Received 8 May 2015; Accepted 20 June 2015

Abstract: A series of 2-phenyl-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one derivatives have been synthesized by reaction of 4-amino-1,2,4-triazole with an appropriate substituted aldehydes to obtain various phenyl-N-(4H-1,2,4-triazol-4-yl)methanimine as Schiff bases which on treatment with thioglycolic acid afforded the title compounds. The purity of compounds has been confirmed by TLC. Structures of these compounds were established on the bases IR, ¹H NMR, ¹³C NMR and Mass spectral data. Excellent yields, mild reaction condition and simple experimental work-up procedure are some of the advantages of this method. The obtained derivatives were studied for their molecular docking as anti-HIV-1 NNRTI activity. All synthesized compounds from thiazolidinone series were be docked into the non-nucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT. Compound **4i**, **4n** and **4h** was found to be good around -8.708, -8.567 and -6.429 respectively, with respective to native ligand TMC278, was found to be -13.413 which confirms that these compounds might have potent RT inhibition activity.

Keywords: Thiazolidinone, Schiff bases, Anti-HIV-1 NNRTI activity.

Introduction

There are several biologically active molecules which contain diverse heteroatom such as nitrogen, sulphur and oxygen, that always drawn the attention of researcher over the years mainly because of their biological importance. Out of such all biologically active heterocycles 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at

position 1 and 3, respectively and a carbonyl group at position 4 have been subjected to widely study in the recent years. The 4-thiazolidinone nucleus is very versatile and has featured in a number of clinically used drugs. They have found number of pharmacological uses as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agents. It has been comprehensively reported that presence of arylazo [1], sulfamoylphenylazo

[2] or phenylhydrazono [3] moieties at different positions of the thiazolidone ring enhanced antimicrobial activity and it has been reported that 4-thiazolidinone shows antibacterial activity due to its inhibitory activity of enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan [4]. Numerous reports have appeared in the literature which emphasize their chemistry and pharmacological uses [5-7].

Human immunodeficiency virus type 1 (HIV-1) was identified in the development of acquired immune deficiency syndrome (AIDS). Reverse transcriptase is a key enzyme in the HIV replication of virus and has been a key target for developing anti-HIV drugs. Reverse transcriptase nucleoside inhibitors, reverse transcriptase non-nucleoside inhibitors and protease inhibitors have been clinically used for the treatment of HIV infections. The result of observations enhances the discovery of 4-thiazolidinone as a new class of highly potent non-nucleoside inhibitors [8-11].

1,2,3-Triazole and 1,2,4-triazole moieties possess enormous importance in the medicinal chemistry due to their use as precursors in the synthesis of various biologically active heterocyclic compounds [12]. They are used as antifungal, antibacterial, antiviral, anti-HIV and antitumor activities, selective β 3-adrenergic receptor agonist [13-15], herbicidal, anti-tuberculosis, tyrosinase inhibitors, anti-allergic and glycosidase inhibitors [16-18].

Therefore, it is imperative to look for new chemical entities having broad-spectrum activity against a variety of clinically relevant mutant RT enzymes with minimal cytotoxicity. Recently, several methods have been reported for synthesis of 4-thiazolidinone derivatives because of its huge biological and medicinal importance. They have been synthesized by one-pot three-component condensation and also by two step reactions of substituted aromatic amines, aldehydes, and thioglycolic

acid in the presence of DCC [19], [BMIM]BF₄, [MOEMIM]TFA [20], *Saccharomyces cerevisiae* [21], silica gel [22] and organocatalysis in aqueous micellar medium [23]. Most of the methods have their own merits. However, these procedures described the synthesis of only a narrow range of thiazolidinone derivatives and also suffered from using of expensive catalyst, long reaction times, low yield, and poor selectivity or commercial unavailability.

As part of our research program, herein we report the synthetic utility of iodine for the synthesis of phenyl-N-(4n-1,2,4-triazol-4-yl) methanimine derivatives as Schiff base from substituted aldehydes and 4-amino-1,2,4-triazole in ethanol. These Schiff bases on refluxing with thioglycolic acid at 60 °C give 4-thiazolidinone derivatives.

Experimental

General details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F₂₅₄, Merck grade was used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. IR, ¹H and ¹³C NMR spectra were recorded on a Bruker AV-300 MHz spectrometer in CDCl₃ solvent. Mass spectra were taken on Polaris-Q ThermoScientific MS.

General procedure for the preparation of phenyl-N-(4n-1,2,4-triazol-4-yl)methanimine derivatives (3a-o): To a mixture of 4-amino-1,2,4-triazole (1 mmol) and substituted benzaldehyde (1 mmol) in solvent ethanol (5 mL), iodine (0.1 mmol) was added. The reaction mixture was vigorously stirred at 45 °C for 1-2hrs (monitored by TLC). Then yellowish crystals were appeared. It was filtered, washed with aqueous sodiumthiosulphate solution and recrystallised with ethanol to afford analytically

pure product.

General procedure for synthesis of 2-phenyl-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one derivatives(4a-o): A mixture of 3(a-o) (1 mmol) and excess of mercaptoacetic acid 3 (1 ml) was heated at 60°C until reaction was complete, as shown by TLC (about 3 h). Ethyl acetate (5 ml) was added; the organic layer was washed with saturated NaHCO₃ (3 × 20 ml) and water (1 × 10 ml), dried with MgSO₄, and ethyl acetate was evaporated on vacuum to give an yellow crystals and recrystallised with EtOH.

Characterization of some representative compounds

Phenyl-N-(4n-1,2,4-triazol-4-yl)methanimine (3a): Light Yellow solid; **M.P.(178°C):** 183-185; **IR (cm⁻¹):** 3100, 1610, 1550,1440,1420,730,690; **¹H NMR (300 MHz, CDCl₃):** δ 6.5-7.2 (m, 3H), 7.5 (m, 2H), 8.2 (s, 2H), 9.2 (s, 1H); **¹³C-NMR (300 MHz, CDCl₃):** δ 162, 152, 135, 133, 131, 128; **MS:** *m/z* 172 (M⁺).

2-Chlorophenyl)-N-(4n-1,2,4-triazol-4-yl)methanimine(3b): Light Yellow solid; **M.P.(186°C):** IR(cm⁻¹): 3050, 1600, 1500, 1420, 1400, 730; **¹H NMR (300 MHz, CDCl₃):** δ 6.8(d,1H), 7.0 (dd, 1H), 7.6 (dd, 2H), 8.5 (s,2H), 9.3 (s, 1H); **¹³C-NMR (300 MHz, CDCl₃):** δ 160, 150.40, 138.54, 136.45, 134.25, 131.29, 130.65, 128.05, 125.35; **MS:** *m/z* 206 (M⁺).

4-Chlorophenyl)-N-(4n-1,2,4-triazol-4-yl)methanimine(3d): Light Yellow solid; **M.P.(198°C):** IR(cm⁻¹): 3100, 1590, 1520, 1500, 1420, 1400, 830; **¹H NMR (300 MHz, CDCl₃):** δ 6.5-6.8 (dd,2H), 7.2-7.5 (dd, 2H), 7.9 (s, 2H), 9.1 (s, 1H); **¹³C-NMR (300 MHz, CDCl₃):** δ 163, 152.45, 137.54, 135.46, 134.26, 131.28, 130.35, 125; **MS:** *m/z* 206 (M⁺).

2-Phenyl-3-(4n-1,2,4-triazol-4-yl)thiazolidin-

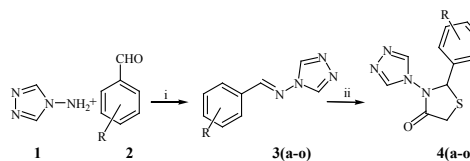
4-one(4a): Yellowish solid; **M.P.(156°C):** IR(cm⁻¹): 3000,1720,1600,1580,1510,1420,1377,651; **¹H NMR (300 MHz, CDCl₃):** δ 3.4,3.3 (dd, 2H), 6.2(s,1H), 7.7-7.4(m,5H), 8.3(s,2H); **¹³C-NMR (300 MHz, CDCl₃):** δ 170.42, 145.80, 138.94, 128.47, 127.00, 54.30, 34; **MS:** *m/z* 246 (M⁺).

2-(2-Chlorophenyl)-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one(4b): Yellowish solid; **M.P.(168°C):** IR(cm⁻¹): 3090,1710,1610,1595,1507,1420,1380,670; **¹H NMR (300 MHz, CDCl₃):** δ 3.4 (dd, 2H), 4.9(s,1H), 7-7.15(m,4n), 8.5(s,2H); **¹³C-NMR (300 MHz, CDCl₃):** δ 171.00, 145.30, 135.00,131.45, 129.50.52,129.00,127.40,110.12 ,46.40, 35.00; **MS:** *m/z* 280 (M⁺).

2-(4-Chlorophenyl)-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one(4d): Yellowish solid; **M.P.(143°C):** IR(cm⁻¹): 3100,1713,1600,1590,1505,1430,1373,651; **¹H NMR (300 MHz, CDCl₃):** δ 3.5 (dd, 2H), 5.8(s,1H), 6.7(d,2H), 7.2(d,H), 8.5(s,2H); **¹³C-NMR (300 MHz, CDCl₃):** δ 169.90, 146.20, 138.00,134.45, 133.52,130.23, 52.40, 35.90; **MS:** *m/z* 280(M⁺).

2-(4-Nitrophenyl)-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one(4n): Yellowish solid; **M.P.(121°C):** IR(cm⁻¹): 3050,1710,1600,1550,1410,1377,1370,645; **¹H NMR (300 MHz, CDCl₃):** δ 3.3 (s, 2H), 5.9(s,1H), 7.2(s,2H),8.2(s,2H), 8.05(s,2H); **¹³C-NMR (300 MHz, CDCl₃):** δ 172.00, 149.30, 146.00,145.40, 130.50, 55.30, 35.00; **MS:** *m/z* 291 (M⁺).

Result and discussion:



Scheme 1: Reagent and conditions: i) I₂, Ethanol, Stir at 45 °C, 1-2hrs. ii) Thioglycolic acid, reflux at 60 °C, 2-3 hrs.

Table 1. Exploration of the substrate scope for the synthesis of phenyl-N-(4n-1,2,4-triazol-4-yl) methanimine (3) and 2-phenyl-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one derivatives(4)

Entry	R	Time (min)	3(a-o) ^a	M.P. (°C)	Yield %	4(a-o) ^b	Time (min)	M.P. (°C)	Yield ^b %
1	H	80	3a	178	89	4a	150	156	85
2	2-Cl	83	3b	186	78	4b	160	168	70
3	3-Cl	90	3c	167	67	4c	130	152	76
4	4-Cl	102	3d	198	85	4d	135	143	83
5	3-Br	95	3e	210	86	4e	155	124	78
6	4-Br	92	3f	193	75	4f	175	129	74
7	3-NO ₂	78	3g	205	70	4h	178	138	84
8	4-NO ₂	70	3h	189	90	4h	140	118	87
9	2-Cl,4-F	85	3i	195	87	4i	145	132	77
10	2-I	75	3j	220	82	4j	166	161	84
11	3-F	87	3k	168	72	4k	163	148	75
12	4-I	98	3l	176	68	4l	153	135	78
13	2-CH ₃	115	3m	183	65	4m	158	170	68
14	4-CH ₃	120	3n	215	60	4n	170	121	70
15	4-OCH ₃	110	3o	170	63	4o	180	145	65

^aSubstituted benzaldehyde (1 mmol), 4-amino-1,2,4-triazole (1.0 mmol), I₂ (0.1mmol), EtOH (5 mL), at room 45°C. ^bSchiff base (a-n) (1mmol),thioglycolic acid(1mmol),60 °C.

Chemistry

The various substituted Schiff base of phenyl-N-(4n-1,2,4-triazol-4-yl)methanimine (3a–o) was prepared by reacting 4-amino-1,2,4-triazole with substituted aromatic aldehydes. Thus obtained Schiff base was further converted into thiazolidinone derivatives (4a–o) on treatment with thioglycolic acid as shown in scheme-1. The purity of compounds was confirmed by TLC using precoated silica gel as stationary phase, using appropriate solvent system as mobile phase and iodine vapors as visualizing agent. Structure of the title compounds were confirmed by IR, NMR and Mass spectral studies.

Fifteen derivatives of both Schiff bases and its thiazolidinone derivatives were reported. Structure of the synthesized compounds was

established on the basis of IR, ¹H NMR, ¹³C NMR and Mass spectral data. The general spectral characters of 3a–o showed absorption bands ranging from 1555–1610 cm⁻¹ for imines (>C=N–) formation. Similarly compounds 4a–o have showed absence of absorption band at 1555–1610 cm⁻¹ and sharp bands at 1690–1730 cm⁻¹. Further characteristic absorption band at 1370-1380 cm⁻¹ and 651-645 cm⁻¹ gave conformation of thiazolidinone ring in their respective spectra.

In particular, it must be pointed out that ¹H NMR of compounds 3a–o showed presence of a singlet between δ 9.1–9.3 ppm indicated the formation of imines (-CH=N–) by simple condensation process using iodine as a catalyst. Further characteristic peak at δ 7.8-8.5 ppm indicated the presence aromatic protons of triazole ring in their structure. The compounds

(3a–o) show multiplet at δ 6.9–8.3 ppm for aromatic protons. Title compound 4a–o has shown singlet or doublet of doublet at δ 3.3–3.5 ppm ($-\text{CH}_2$ of thiazolidinone) and the absence of peak at δ 9.1–9.3 ppm confirmed the formation of thiazolidinone. ^{13}C NMR spectral data for the title compounds most characteristic peak around δ 172–169 ppm ($\text{C}=\text{O}$) and δ 55.0–49.0 ppm ($-\text{CH}$) indicated the formation thiazolidinone ring. Electron impact mass spectra showed an accurate molecular ion peak at m/z 246, 280, 280, 280, 323.97, 323.97, 291.04, 291.04, 298.01, 371.95, 264.05, 371.95, 260.07, 260.07 and 276.07 for title compounds 4a–o respectively.

Anti-HIV activity:

Material and Methods

To guide the lead optimization strategy and rationalize the SARs, modeling study was performed to examine the possible binding conformations of our newly synthesized compounds and their interaction mode with RT, using Glide (Glide 5.8, Schrodinger, 2012) [24]. Structure-based docking studies were carried out to investigate the intermolecular interaction between the ligand and the targeted enzyme. The coordinates of the non-nucleoside binding site were taken from the crystal structure of HIV-1 reverse transcriptase (RT) in complex with TMC278 (Rilpivirine) (PDB code: 2ZD1) [25]. Docking study of all the molecules from 2-phenyl-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one series was carried out with enzyme reverse transcriptase PDB ID: 2ZD1. The ligands were prepared by using LigPrep (LigPrep 2.5, Schrodinger, 2012) [26]. The protein was refined using the protein preparation wizard present in Maestro 9.3 (Maestro 9.3, Schrodinger, 2012) [27]. All the water molecules were deleted. H atoms were added to the protein, including the protons necessary to define the correct ionization and tautomeric states of the amino acid residues. Prime interface module incorporated

in Maestro was used to add the missing residues of the side chain. Each structure minimization was carried out with the impact refinement module, using the OPLS-2005 force field to alleviate steric clashes potentially existing in the structures. Minimization was terminated when the energy converged or the root mean square deviation reached a maximum cutoff of 0.30 Å. To find out active site grid was prepared using grid generation panel of glide with the default settings. Grid is prepared for defining the binding site of native ligand on the receptor. The ligand was selected to define the position and size of the active site (Friesner et al., 2004; Halgren et al., 2004) [28–29]. Glide XP docking was used for docking purposes.

Docking Studies

Docking score of compound **4i**, **4n** and **4h** was found to be -8.708, -8.567 and -6.429 respectively. All molecules from 4-thiazolidenone series were docked into the non-nucleoside inhibitor binding pocket (NNIBP) of HIV-1 RT. As illustrated in Figs. 1(**1a**, **1b** and **1c**), the substituted aromatic and thiazolidenone moiety of compound **4h**, **4i**, and **4n** of the 2-phenyl-3-(4n-1,2,4-triazol-4-yl)thiazolidin-4-one ring interacts through CH- π /hydrophobic interactions into the hydrophobic binding pocket, surrounded by the aromatic portion of Leu234, Val106, Phe227, Val179, Tyr138, Leu100, Tyr 181, Trp229 and Tyr188. From the two dimensional Fig. 1 (**1a**, **1b** and **1c**) and three dimensional view Fig. 2(**2a**, **2b** and **2c**), it is observed that Val179, Tyr 188, Leu234, Trp 229, Tyr181 and Pro95 is juxtaposed for better interaction with the aromatic ring of thiazolidinone moiety.

The aromatic moiety at C-2 and nitro/chloro-fluoro substitutions on aromatic ring of the thiazolidinone ring (compound **4h** and **4i**) makes π - π interaction into the hydrophobic binding pocket, surrounded by the aromatic side chains of portion of Trp229 residue. Carbonyl group of thiazolidinone moiety of **4i**

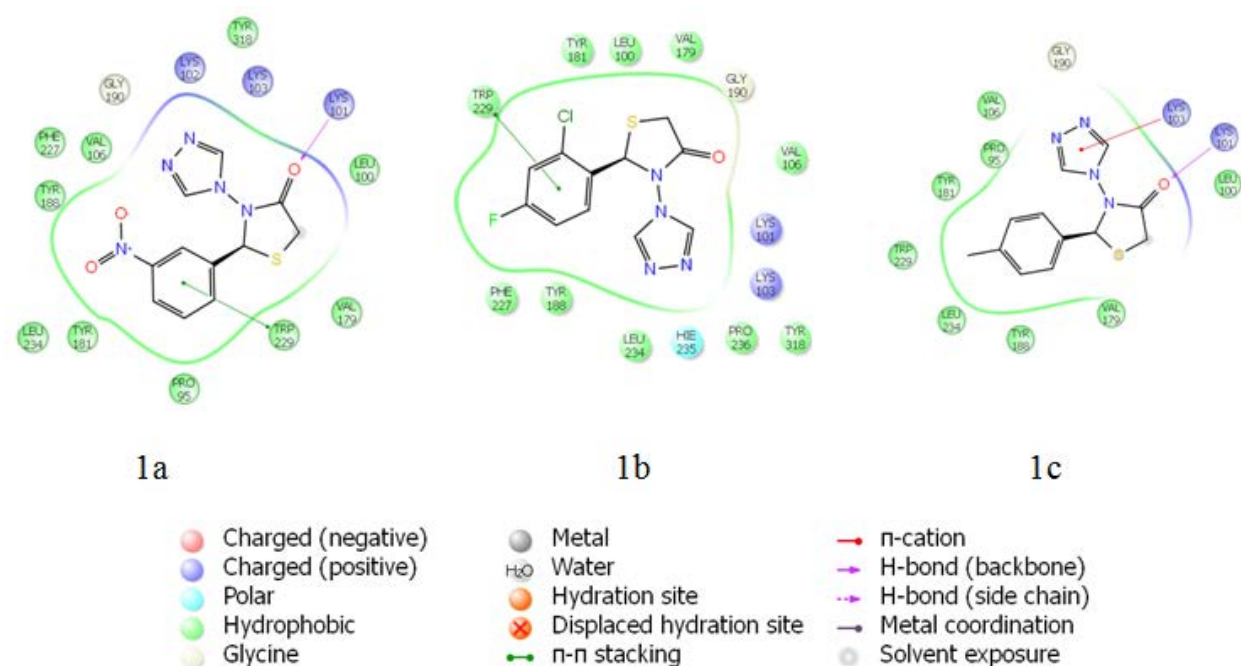


Figure 1: Two dimensional view of the binding interaction of the most active compounds, 4h (1a), 4i (1b) and 4n (1c) with active site of HIV-1 reverse transcriptase (RT) in complex with TMC278.

Abbreviations: VAL, valine; LEU, leucine; GLY, glycine; ASP, aspartate; SER, serine; ALA, alanine; LYS, lysine; ILE, isoleucine; HIE, histidine epsilon H; MET, methionine; THR, threonine.

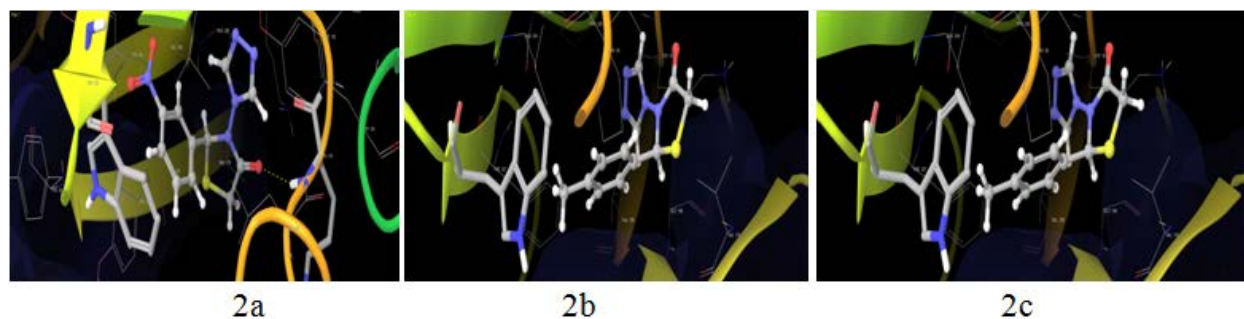


Figure 2: Three dimensional view of the binding interaction of the most active compounds, 4h (2a), 4i (2b) and 4n (2c) with active site of HIV-1 reverse transcriptase (RT) in complex with TMC278.

and **4n** makes H-bond interaction at the back bone of Lys101 (fig.1b and 1c). It has been also observed that triazolyl moiety of compound **4n** forms π -cation with Lys 103.

The decrease in activity of remaining compounds of thiazolidinone derivatives was due to lack of π - π interaction with Trp229 and H-bond interaction at the back bone of Lys101.

Docking score of compound **4i**, **4n** and **4h** was found to be -8.708, -8.567 and -6.429 respectively while docking score of native ligand was found to be -13.413 which confirm that these compounds might have potent RT inhibition activity. Further, *in silico* binding studies suggested that inhibitors possessing π - π interaction with the aromatic side chains of Phe227 and Trp229 improves the inhibitor selectivity for RT and thus helps in further drug design attempts to obtain potent 4-thiazolidinone derivatives.

Conclusion:

In this paper we report the synthesis and molecular docking studies of novel series of 2-phenyl-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one derivatives (**4a-o**). The derivatives were prepared by condensation between 4-amino-1,2,4-triazole with various substituted aromatic aldehydes to obtain Schiff bases, further it was condensed with thioglycolic acid to obtain title compounds (**4a-o**). Docking score of compound **4i**, **4n** and **4h** was found to be -8.708, -8.567 and -6.429 respectively, while of native ligand was found to be -13.413 which confirms that these compounds might have potent RT inhibition activity. The decrease in activity of rest of the compounds was due to lack of π - π interaction with Trp229 and H-bond interaction at the back bone of Lys101. This study suggested that inhibitors possessing π - π interaction with the aromatic side chains of Trp229 and H-bond interaction at the back bone of Lys101 improves the inhibitor selectivity for RT.

Acknowledgment:

We acknowledge Dr. P. L. More, Dnyanopasak College, Parbhani for providing necessary facilities, Vishnu Chemical Laboratory Hyderabad for providing spectral data is highly appreciated.

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