SYNTHESIS of NEW 1,3-THIAZOLE DERIVATIVES; USING 2,4-DIFLUORO-1-NITROBENZENE and DIALKYLACETYLENE DICARBOXYLATE as MATERIALS

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ABSTRACT

The synthesis of heterocyclic compounds continues to be a central focus in medicinal and synthetic organic chemistry due to their diverse biological activities and structural versatility. In this study, we report the efficient preparation of a new series of 1,3-thiazole derivatives employing 2,4-difluoro-1-nitrobenzene and dialkylacetylene dicarboxylates as key starting materials. The reaction pathway involves the in situ generation of fluoroaniline derivatives of thiourea, which subsequently undergo cyclization with dialkylacetylenedicarboxylates in ethanol under mild conditions. This synthetic strategy provides a straightforward and practical route to thiazole scaffolds, affording products in good to excellent yields. The methodology demonstrates several advantages: operational simplicity, use of readily available reagents, and tolerance toward different substituents on the thiourea moiety. The incorporation of fluorine atoms into the aromatic ring is particularly noteworthy, as fluorinated heterocycles often exhibit enhanced pharmacological properties, including improved metabolic stability and binding affinity. Structural elucidation of the synthesized compounds was confirmed through spectroscopic techniques such as IR, ^1H NMR, ^13C NMR, and mass spectrometry, which validated the formation of the thiazole core. Given the importance of thiazole derivatives in drug discovery, agrochemicals, and material science, the present work contributes a valuable synthetic approach to expand the chemical space of these heterocycles. The developed protocol not only enriches the library of thiazole analogues but also opens avenues for further biological evaluation and functionalization. Overall, this study highlights a convenient and efficient method for constructing novel 1,3-thiazole derivatives, reinforcing their potential as promising candidates for future pharmaceutical applications.

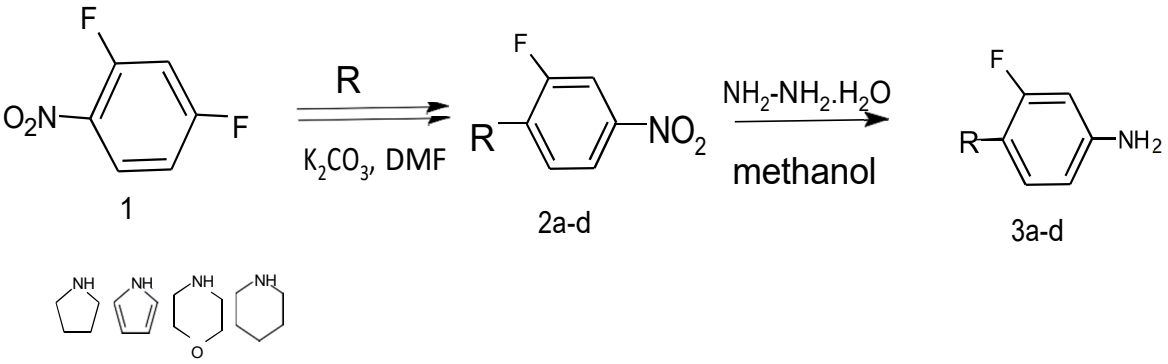
Keywords: Thiourea, dimethyl acetylene dicarboxylate, diethyl acetylene dicarboxylate

1. INTRODUCTION

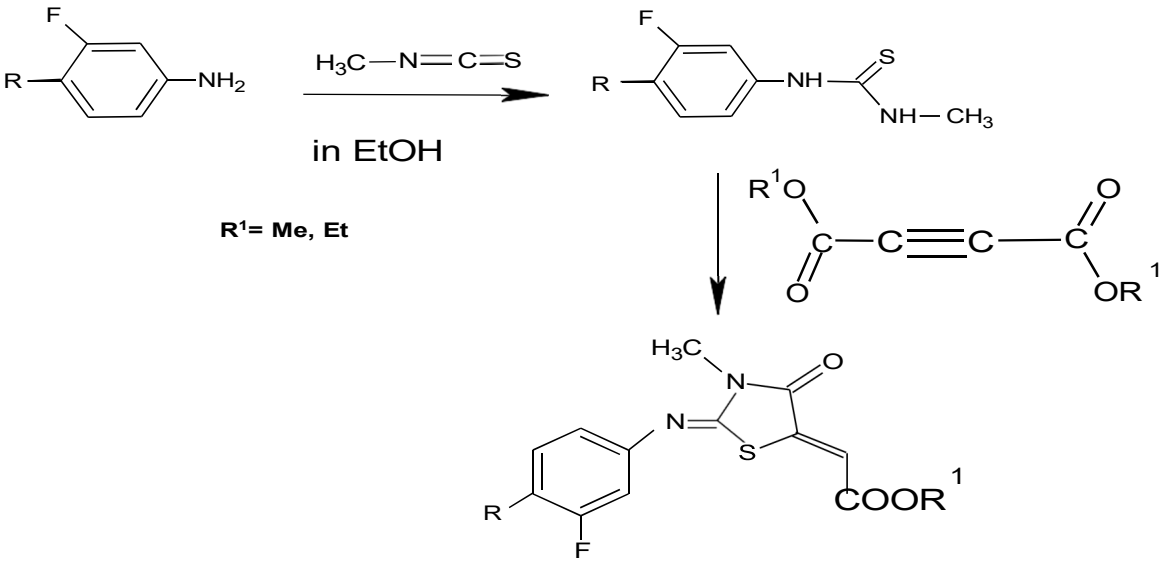
Since the past several decades, heterocyclic chemistry has been one of the most important disciplines in organic synthesis and pharmaceutical chemistry [1]. Noticeable numbers of these compounds have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [2,3], anti-tumor4, anti-hyperlipidemic [5], anti-hypertensive [6], anti-HIV infections [07], and several other biological properties [8,9].One of the most important groups of five-membered heterocycles including S and N atoms, are thiazolole compounds. Thiazole heterocycle is a component of many natural products and synthetic compounds exhibiting a wide range of biological activity [13,14]. The pharmacological activities and their coordination properties are important features to prepare metal complexes with potential therapeutical activity or as model of metal-enzyme[14]. In addition, the thiazole ring present in vitamin B1 serves as an electron ink and its coenzyme form is important for keto-acids decarboxylationp [15].

Reaction of dimethyl acetylene dicarboxylate (DMAD) with esters and amides of dithiocarboxylic acids are well known methods for preparation of five membered S, and S, N-heterocycles[16,17]. Thioureas possessing more than two N-H bonds react with (DMAD) to give 1:1 molar-methanol adducts [17]. Because of the importance of thiazole compounds,. studies on preparation of novel thiazole derivatives are of definite interest. Hence, we investigated the reaction between activated acetylenic compounds, and thiourea derivatives which afforded 1,3-thiazolone derivatives in good isolated yields.

SCHEME – I



SCHEME – II



2. Experimental

2.1. Materials and methods

All chemicals employed in the present study were either synthesized in our laboratory or procured from reputable suppliers such as Merck and Fluka, and were utilized without any additional purification to ensure consistency of results. The progress of all reactions was carefully monitored by thin-layer chromatography (TLC) using petroleum ether–ethyl acetate (3:1) as the mobile phase, which provided reliable separation and identification of intermediates and products. Melting points of the synthesized compounds were determined with precision using a hot-plate microscope apparatus, thereby confirming the purity and reproducibility of the samples.

Structural characterization was carried out through a comprehensive suite of spectroscopic techniques: infrared (IR) spectra were recorded in KBr pellets on a BRUKER FT-IR spectrophotometer to identify functional groups; ^1H and ^13C nuclear magnetic resonance (NMR) spectra were obtained on a Bruker 400-MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard, providing detailed insights into proton and carbon environments; and mass spectra were acquired on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV, which confirmed molecular weights and fragmentation patterns. Together, these analytical methods ensured accurate structural elucidation and validation of the synthesized thiazole derivatives, thereby supporting the reliability of the synthetic approach and the reproducibility of the experimental outcomes.

2.2. General procedure for synthesis of 3-fuoro-4-(1H-pyrol-1-yl)-aniline:

In a 100 mL three-necked flask equipped with a dropping funnel, soluton of 2,4-difluoro-1-nitrobenzene (2.5gm, 7.3mmol) in DMF(20ml), and solution of pyrrol/pyrrolidine/piperidine/ morpholin (2.75gm,37mmol in 25ml DMF) HMTA(1.25gm), CuI(0.5gm), K2CO3(0.75gm), are added and the mixture is refluxed for 20h.

The reaction mixture is then cooled The solid was filtered off and the filtrate was concentrated to give a crude product that was recrystallized from ethanol and petroleum ether solution (2:5) to form compounds 2a-d as yellow , yellowish white solids. In a 100 mL three-necked flask equipped with a dropping funnel, 1-(2-fluoro-4-nitrophenyl)-1H-pyrrol (3.0 g, 18.7 mmol) and ethanol (50 mL) were mixed and heated to reflux. Palladized charcoal (0.1 g, 5%) was added, then 80% hydrazine hydrate solution (10 mL) was added from a dropping funnel during 30 min.

The heating was continued for 8 h and then the mixture cooled. The solid was filtered off and the filtrate was concentrated to give a crude product that was recrystallized from ethyl acetate and petroleum ether solution (1:5) to afford compounds 3a as a yellow, yellowish white powders.Similar procedure is adopted to synthesize compounds 3b,3c,3d from 2b,2c,2d. (yield: 3.76 g, 85%); mp 130–131 °C,131-132°C, 135-136°C,137-138°C .

2.3.General Procedure for the Preparation of *N*-[3-fluoro-4-(1H-pyrrol-1-yl)phenyl]-*N*'methyulthiourea

A round-bottomed flask (100mL) was charged with 3-fluoro-4-(1*H*-pyrrol-1-yl)aniline (0.13 g, 0.5 mmol) and methyl isothiocyanate (0.73 g, 1 mmol) in ethanol (30 mL). The reaction mixture was refluxed for 24 hours, stood for 5 min, and 20 mL water was added. The residue was filtered and dried to give *N*-[3-fuoro-4-(1*H-pyrrol*-1-yl)phenyl] *N*'-methylthiourea as a white powder in 93% yield, m.p.: 189-190,

2.4.General Procedure for the Preparation of thiazol derivatives using :

N-[3-fuoro-4-(1*H-pyrrol*-1-yl)phenyl] *N'*-methylthiourea (0.3gm,1 mmol) was added to dialkyl acetylenedicarboxylate (1 mmol) in 5 mL ethanol. The mixture was refluxed for 30 minutes. The reactions were followed by thin layer chromatography (TLC) using hexane/ ethyl acetate (3:1) as an eluent. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered, dried, and recrystallized from ethanol. All the products obtained were characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and Mass.

Table no 01 -The spectral data for products

Name of Molecule	IR (KBr, νmax cm^{-1}):	H NMR (400 MHz, $CDCl_3$/DMSO-d_6, δ ppm):	MS (ESI/EI, m/z)
Ethoxycarbonyl-2Z-2-[(3-fluoro-4-(1-pyrrolyl) phenyl Z) imino]-3-methyl-1,3-thiazolidin-4-one	3110–3070 (Ar–H, pyrrolyl C–H), 2980–2870 (aliphatic C–H), 1735 (ester C=O), 1695 (C=O, thiazolidin-4-one), 1620 (C=N), 1585–1505 (Ar C=C), 1460 (C–N), 1375 (CH_3 bending), 1245 (C–O–C), 1155 (C–F), 745 (Ar–H out-of-plane).	1.28 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 2.28 (s, 3H, CH_3 at C-3), 4.22 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3),5.92–6.05 (m, 2H, pyrrole-H), 6.28–6.38 (m, 2H, pyrrole-H), 6.95 (dd, 1H, *J* = 8.5, 2.0 Hz, Ar-H), 7.26 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.52 (d, 1H, *J* = 2.0 Hz, Ar-H), 8.31 (s, 1H, CH=N).	397 $[M+H]^+$, 396 $[M]^+$, 351 (M – OC_2H_5), 323 (M – COOEt), 292 (thiazolidinone ring cleavage), 178 (fluoro-pyrrolylphenyl fragment), 67 (pyrrolyl cation).
Methoxycarbonyl-2Z-2-[(3-fluoro-4-(1-pyrrolyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	3120–3075 (Ar–H, pyrrolyl C–H), 2950–2850 (aliphatic C–H), 1740 (ester C=O), 1695 (C=O, thiazolidin-4-one), 1620 (C=N), 1580–1500 (Ar C=C), 1455 (C–N), 1375 (CH_3 bending), 1255 (C–O–C), 1150 (C–F), 745 (Ar–H oop).	2.30 (s, 3H, CH_3 at C-3), 3.78 (s, 3H, OCH_3), 5.90–6.05 (m, 2H, pyrrole-H), 6.28–6.40 (m, 2H, pyrrole-H), 6.95 (dd, 1H, *J* = 8.5, 2.0 Hz, Ar-H), 7.25 (d, 1H, *J* = 8.5 Hz, Ar-H),7.50 (d, 1H, *J* = 2.0 Hz, Ar-H),8.30 (s, 1H, CH=N).	383 $[M+H]^+$, 382 $[M]^+$, 351 (M – OCH_3), 292, 178, 67.
. Ethoxycarbonyl-2Z-2-[(3-fluoro-4-(1-pyrrolidinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2965–2850 (aliphatic C–H), 1735 (ester C=O), 1690 (C=O, thiazolidin-4-one), 1615 (C=N), 1575–1495 (Ar C=C), 1450 (C–N), 1245 (C–O–C), 1150 (C–F).	1.28 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 2.05–2.15 (m, 4H, pyrrolidine-CH_2), 2.30 (s, 3H, CH_3 at C-3), 3.25–3.35 (m, 4H, N-CH_2), 4.22 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 6.95–7.55 (m, 3H, Ar-H), 8.28 (s, 1H, CH=N).	411 $[M+H]^+$, 410 $[M]^+$, 365 (M – OC_2H_5), 292, 198.
. Methoxycarbonyl-2Z-2-[(3-fluoro-4-(1-pyrrolidinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2950–2850 (C–H), 1740 (ester C=O), 1695 (C=O), 1620 (C=N), 1580–1500 (Ar C=C), 1248 (C–O–C), 1150 (C–F).	2.05–2.15 (m, 4H, pyrrolidine-CH_2), 2.30 (s, 3H, CH_3), 3.25–3.35 (m, 4H, N-CH_2), 3.78 (s, 3H, OCH_3), 6.95–7.55 (m, 3H, Ar-H), 8.26 (s, 1H, CH=N).	397 $[M+H]^+$, 396 $[M]^+$, 365 (M – OCH_3), 292.
Ethoxycarbonyl-2Z-2-[(3-fluoro-4-(1-morpholinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2960–2850 (C–H), 1735 (ester C=O), 1690 (C=O), 1615 (C=N), 1570–1495 (Ar C=C), 1240 (C–O–C), 1115 (C–O, morpholine), 1150 (C–F).	1.28 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.20–3.30 (m, 4H, N-CH_2), 3.65–3.75 (m, 4H, O-CH_2), 4.22 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 6.95–7.55 (m, 3H, Ar-H), 8.30 (s,	427 $[M+H]^+$, 426 $[M]^+$, 381 (M – OC_2H_5), 292.

		1H, CH=N).	
Methoxycarbonyl-2Z-2-[(3-fluoro-4-(1-morpholinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2950–2850 (C–H), 1740 (ester C=O), 1695 (C=O), 1620 (C=N), 1580–1500 (Ar C=C), 1250 (C–O–C), 1115 (C–O), 1150 (C–F).	2.30 (s, 3H, CH_3), 3.20–3.30 (m, 4H, N-CH_2), 3.65–3.75 (m, 4H, O-CH_2),3.78 (s, 3H, OCH_3), 6.95–7.55 (m, 3H, Ar-H),8.28 (s, 1H, CH=N).	413 $[M+H]^+$, 412 $[M]^+$, 381 (M – OCH_3), 292.
Ethoxycarbonyl-2Z-2-[(3-fluoro-4-(1-piperidinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2945–2850 (C–H), 1735 (ester C=O), 1690 (C=O), 1615 (C=N), 1570–1490 (Ar C=C), 1245 (C–O–C), 1150 (C–F).	1.28 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.45–1.65 (m, 6H, piperidine-CH_2), 2.30 (s, 3H, CH_3),3.25–3.35 (m, 4H, N-CH_2), 4.22 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 6.95–7.55 (m, 3H, Ar H), 8.32 (s, 1H, CH=N).	425 $[M+H]^+$, 424 $[M]^+$, 379 (M – OC_2H_5), 292.
Methoxycarbonyl-2Z-2-[(3-fluoro-4-(1-piperidinyl)phenyl)imino]-3-methyl-1,3-thiazolidin-4-one	2945–2850 (C–H), 1740 (ester C=O), 1695 (C=O), 1620 (C=N), 1580–1500 (Ar C=C), 1250 (C–O–C), 1150 (C–F).	1.45–1.65 (m, 6H, piperidine-CH_2), 2.30 (s, 3H, CH_3), 3.25–3.35 (m, 4H, N-CH_2), 3.78 (s, 3H, OCH_3), 6.95–7.55 (m, 3H, Ar-H), 8.30 (s, 1H, CH=N).	411 $[M+H]^+$, 410 $[M]^+$, 379 (M – OCH_3), 292.

3. Results And Discussion

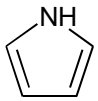
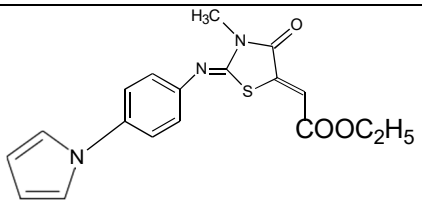
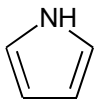
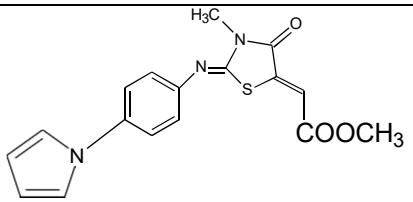
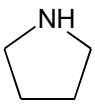
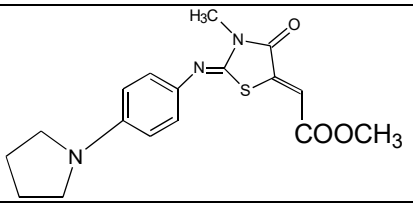
In this paper, we describe an investigation of the cyclo-addition of thiourea derivatives 3 with DMAD and DEAD to prepare new thiazole derivatives in a one-step procedure resulting in good to excellent yields.

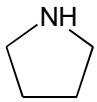
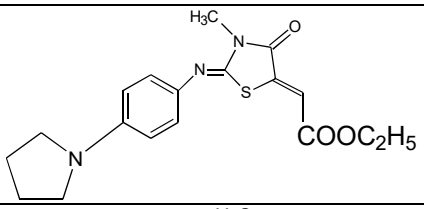
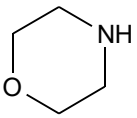
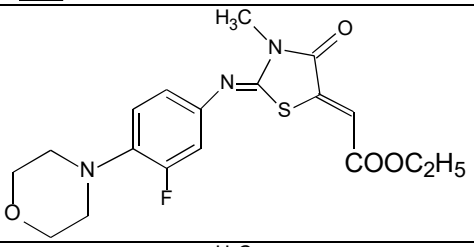
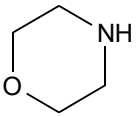
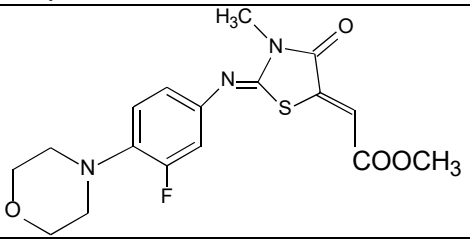
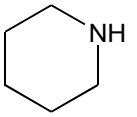
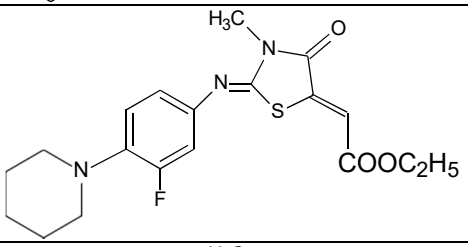
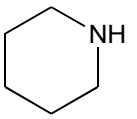
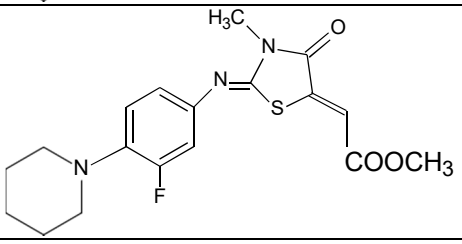
The cycloaddition of these isolable and stable thiourea derivatives, with dialkyl acetylene dicarboxylates proceeds, by a simple one step procedure. Compounds 5a-h were prepared in 82, 84, 95,87,89,92,83 and 97% yields, respectively. Thus the cycloaddition represented in scheme2 was accomplished by mixing the equimolar quantities of dialkyl acetylene dicarboxylates and thiourea derivatives in ethanol at reflux conditions. Thiourea derivatives have two active sites, nitrogen and sulfur, that are capable to react with the dialkyl acetylene dicarboxylates. Therefore, either the S or NH group of thiourea derivatives will attack the dialkyl acetylene dicarboxylates, followed by ring closure to produce the final products.

The structures of compounds 5a-h were assigned by consideration of their IR, ^{1}H NMR, ^{13}C NMR spectroscopic and mass spectrometric data. For example, the ^{1}H NMR spectrum of 5a shows a singlet for methyl protons at 2.28 ppm. In the ^{13}C NMR spectrum of 5a, signal corresponding to carbonyl group was observed at 165.7 ppm. The mass spectrum of 5a contained the molecular ion peak at m/z = 396.

To study the generalizability of this process, several examples were studied and are summarized in table 02. In all cases studied, the reaction proceeded very well to give the corresponding thiazoles in good yields.

Table 02: 1,3 thiazole derivatives

Sr No	Ar	R	Product	Melting Pt.[°C]	%yield
5a.		$COOC_2H_5$		185-186	82
5b.		$COOCH_3$		183-184	84
5c.		$COOCH_3$		181-182	95

5d.		$COOC_2H_5$		179-180	87
5e.		$COOC_2H_5$		181-182	89
5f.		$COOCH_3$		188-189	92
5g.		$COOC_2H_5$		193-194	83
5h.		$COOCH_3$		191-192	97

4. Conclusions

The present work describes the successful synthesis of a novel series of thiazole derivatives through the condensation of thiourea derivatives with dialkyl acetylene dicarboxylates in ethanol, which serves as an environmentally benign green solvent. This protocol offers several noteworthy advantages, including operational simplicity, cleaner reaction profiles, and consistently satisfactory product yields. The ease of isolation and purification of the resulting compounds further enhances the practicality of the method, making it accessible for routine laboratory applications. Importantly, the procedure aligns well with the principles of green chemistry by minimizing hazardous reagents and employing ethanol as a sustainable solvent, thereby reducing environmental impact. Collectively, these features establish the described approach as a valuable and efficient synthetic route for generating thiazole-based heterocycles, which hold significant potential for further exploration in pharmaceutical and material science research.

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