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DESIGN AND FACILE METHOD FOR SYNTHESIS OF NOVEL 1, 3, 4-OXA DIAZOLE DERIVATIVES BY USING BIGINELLI REACTION

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Abstract: An efficient synthesis of 3,4-dihydropyrimidinones from the aldehyde, β-keto ester and urea in ethanol, using Zirconium tetrachloride as the catalyst. A new series of 6-methyl-4-(thieno[2,3-*d*]pyrimidin-6-yl)-5-(5-p-Substituted-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1H)-one derivatives (7a-j) were synthesized after refluxing 6-methyl-2-oxo-4-(thieno[2,3-d]pyrimidin-6-yl)-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (5) with different aromatic/Heterocyclic carboxylic acids (6a-j) in the presence of $POCl_3$.The chemical structures of these compounds were confirmed by various physico-chemical methods viz. IR, ^{1}H-NMR, EI-Mass, ^{13}C-NMR analysis.

Key words: Biginelli reaction, dihydropyrimidine-2(1H)-ones, zirconium tetrachloride; β-ketoesters; dihydropyrimidinones, 1, 3, 4-oxadiazole.,

Introduction:

Many dihydropyrimidinones (DHPMs) and their derivatives are pharmaceutically important as calcium channel blockers, antihypertensive agents and α_1-1-aantagonists**.[I]** The biological activity of some alkaloids isolated recently has been attributed to the dihydropyrimidinone moiety**.[II]** The simple and direct method for the synthesis of dihydropyrimidinones reported by Biginelli in1893, involves the one-pot condensation of an aldehyde, a β-keto ester and urea under strongly acidic conditions**.[III**] However, this method suffers from low yields especially in the case of aliphatic and substituted aromatic aldehydes. This has led to the development of multistep synthetic strategies that produce somewhat better yields but lack the simplicity of the one-pot, one-step synthesis**.[IV-V]**

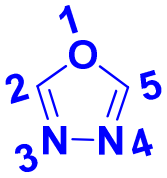
Thus, Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest and several improved procedures have recently been reported**.[IIIb,VI]** The use of zirconium(IV) chloride as an efficient Lewis acid for various transformations such as electrophilic amination of activated arenes**,[VII]** trans thioacetylization of acetals,**VIII** deoxygenation of heterocyclic-N-oxides,[**IX]** reduction of nitro compounds,[**X]** conversion of carbonyl compounds to 1,3-oxathiolanes**[XI]** and Friedel–Crafts reactions has been well documented in the literature. Herein we wish to report a simple and efficient method for the

synthesis of 3,4-dihydropyrimidin-2(1H)-ones using zirconium tetrachloride as the catalyst. The reaction of thieno[2,3-*d*]pyrimidine-6-carbaldehyde, ethyl acetoacetate and urea in the presence of 10 mol% zirconium(IV) chloride in refluxing ethanol gave the corresponding dihydropyrimidinone in 90% yield.

In recent decades there has been constant interest in the chemistry of azoles Because more than hundred azole derivatives are used today as drugs .Azoles are Heterocyclic compounds characterized by a five-membered ring which contains an atom of nitrogen and at least one other non carbon atom, nitrogen, sulphur or oxygen. These compounds are aromatic and have two double bonds. Azoles include pyrazole; imidazole; triazole; tetrazole; thiazole; thiadiazole; isothiazole; oxazole and oxadiazole nucleus.

The synthesis of novel 1,3,4-oxadiazole derivatives, and investigation of their chemical properties and biological behavior has accelerated in the last two decades. In recent years the number of scientific studies with these compounds has increased considerably.

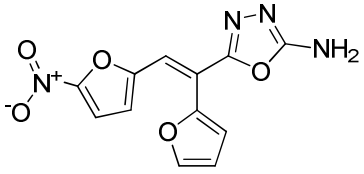
Oxadiazole [1] is five member cyclic compound with one oxygen and two nitrogen atoms in the ring**[XII].**

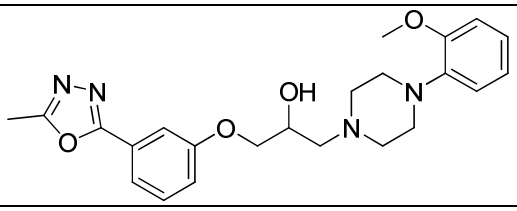
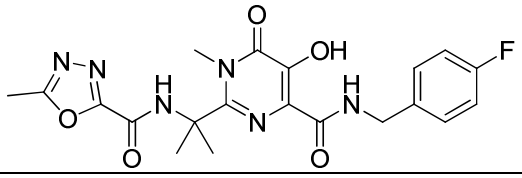
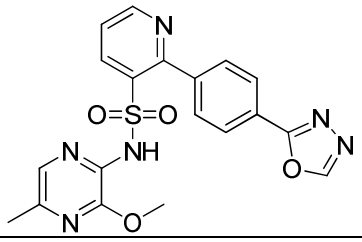


1,3,4-oxadiazoles have occupied unique place in the field of medicinal chemistry due to their wide range of activities**[XIII].** The review of literature shows that 1,3,4-oxadiazole nucleus possess antimicrobial **[XIII],** antifungal [**XIV]**, anti-inflammatory[**XV]**, anticonvulsant **[XVI],**antioxidant, Antihypertensive Activity[**XVII]**, analgesic [**XVIII]** and mutagenicacctivity[**XIX]**.

Number of drugs available in the market such as tiodazosin, nosapidil, furamizole are 1,3,4-oxadiazole derivatives**[XX]**. Apart from these biological activities, 1,3,4-oxadiazole derivatives were found to have some material applications in the field of liquid crystals and photosensitizer[**XXI]**. Literature survey reveals that 1,3,4-oxadiazole derivatives posses a broad spectrum of biological activities[**XXII-XXV]**, Antihypertensive Activity Consequently, they have attracted increasing attention in the field of drug discovery.

Examples of 1, 3, 4-oxadiazole nucleus containing drugs:

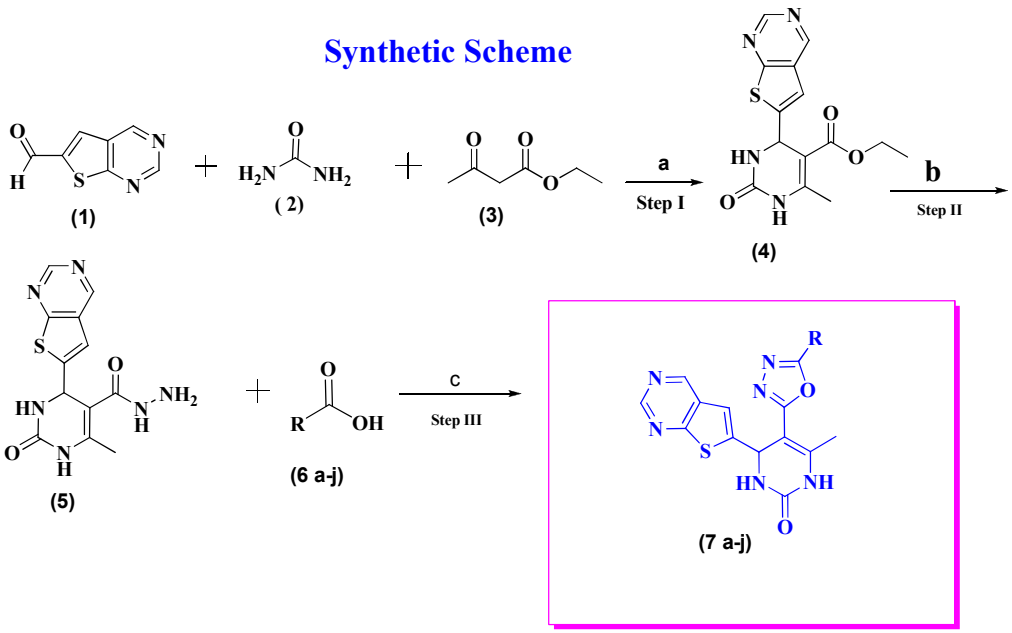
Name	**Structure**	**Medicinal use**
Furamizole		Anti-bacterial agent
Nesapidil		Anti-arrhythmic

		agent
Raltegravir		Antiretroviral drug (Treatment of HIV infection)
Zibotentan;		Anti cancer agent

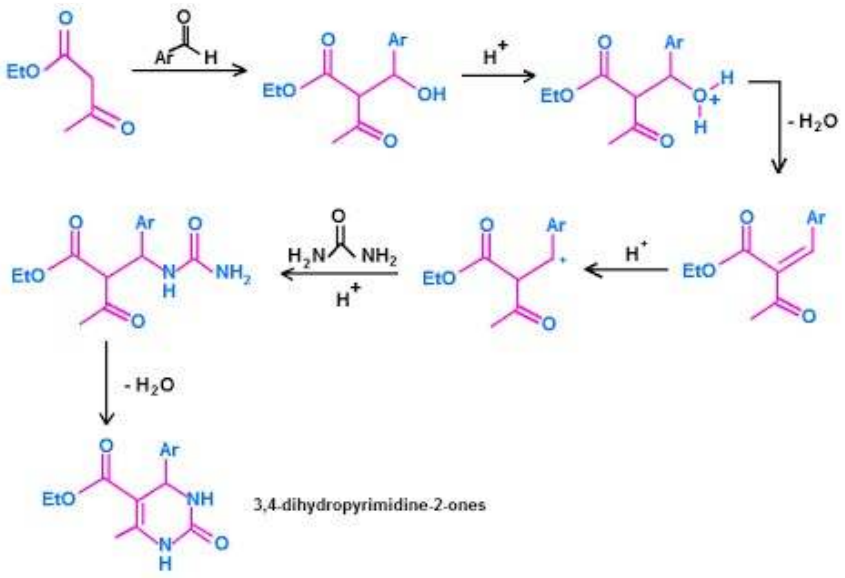
Materials and Methods

Materials and Methods Melting points of the synthesized compounds were determined in Open-glass capillaries using GUNA melting point apparatus and are uncorrected. IR Absorption spectra were recorded in the 4000-400 cm-1 range on a Shimadzu FTIR-8400s Using KBr pellets, ^{1}H-NMR and C^{13}NMR were recorded on Bruker-NMR, 400 MHz Spectro photometer. EI-Mass spectra were recorded by Agilent-NMR, 400 MHz Spectro photometer. TLC was done on F254 grade silica-60 from SD Fine.

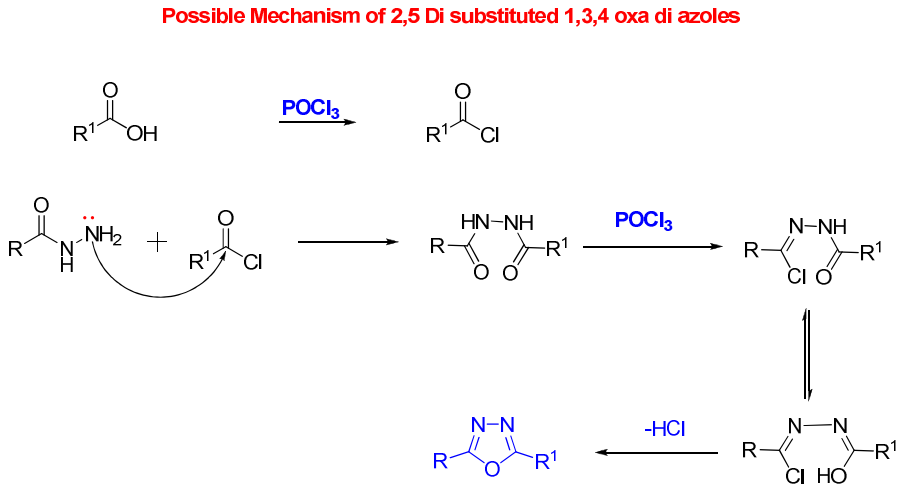
Synthetic Scheme



Reagents and Reaction conditions: **(a)** $ZrCl_4$, Ethanol, reflux, Conc.HCl, 4-5hrs (b) Hydrazine hydrate, Ethanol, Reflux, 16 hrs (c) $POCl_3$, Reflux, 6 hrs.



Mechanism of Biginelli reaction



Synthesis of Ethyl 6-methyl-2-oxo-4-(thieno [2, 3-*d*] pyrimidin-6-yl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (4) [XXVI]:

A mixture containing an appropriate β-ketoester (10 mmol), thieno[2,3-*d*]pyrimidine-6-carbaldehyde (1) (10 mmol), urea (15mmol) and $ZrCl_4$ (10 mol%) in ethanol (15 ml) was refluxed for 4 h. After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product. The obtained yield is 85%.

IR (KBr): 3414, 3230, 3109, 2936, 1702, 1649, 1599 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.17 (s, 1 H), 8.72 (s, 1 H), 6.62 (s, 1 H), 5.14 (s, 1 H), 4.25 (q, J = 7.2 Hz, 2 H), 1.18 (t, J = 7.2 Hz, 3 H), 2.28 (s, 3 H).

EI-Mass: 319.27M^+, +Ve mode).

Synthesis of 6-methyl-2-oxo-4-(thieno[2,3-*d*]pyrimidin-6-yl)-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (5) :

To a solution of compound (4) (0.05 mol,15.2g),in ethyl alcohol (50 mL) was added with excess of 99% hydrazine hydrate and refluxed for 24 hr. Reaction mixture was concentrated and allowed to cool, separated crystals was filtered, dried and re-crystallized from minimum amount of ethyl alcohol. The obtained yield is 75%.

IR (KBr, cm^{-1}): 3320 (-N-H str.), 3230, 3109, 2936, 1702, 1649, 1599 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 9.27 (s, 1 H), 8.78 (s, 1 H), 6.65 (s, 1 H), 5.14 (s, 1 H), 2.28 (s, 3 H).

EI-Mass: 305.17(M^+, +Ve mode).

Synthesis of

6-methyl-5-(5-phenyl-1, 3, 4-oxadiazol-2-yl)-4-(thieno [2, 3-*d*] pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one (7a),

6-methyl-4-(thieno [2, 3-*d*] pyrimidin-6-yl)-5-(5-p-tolyl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1H)-one (7b),

5-(5-(4-methoxyphenyl)-1, 3, 4-oxadiazol-2-yl)-6-methyl-4-(thieno[2,3-*d*]pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one (7c),

6-methyl-4-(thieno [2,3-*d*]pyrimidin-6-yl)-5-(5-(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1H)-one (7d),

6-methyl-4-(thieno[2, 3-*d*]pyrimidin-6-yl)-5-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1H)-one (7e),

6-methyl-5-(5-(pyridin-4-yl)-1, 3, 4-oxadiazol-2-yl)-4-(thieno [2,3-*d*]pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one (7f),
6-methyl-4-(thieno [2, 3-*d*]pyrimidin-6-yl)-5-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1H)-one (7g),
5-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methyl-4-(thieno[2,3-*d*]pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one (7h),
6-methyl-5-(5-(thiazol-2-yl)-1,3,4-oxadiazol-2-yl)-4-(thieno[2,3-*d*]pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one (7i),
6-methyl-5-(5-(oxazol-2-yl)-1,3,4-oxadiazol-2-yl)-4-(thieno[2,3-*d*]pyrimidin-6-yl)-3,4-dihydropyrimidin-2(1H)-one(7j) :

To the equi molar mixture of compounds 5 and 6(a-i), catalytic amount of $POCl_3$ was added and it was refluxed for 4-6 hrs. The reaction mixture was poured over crushed ice and neutralized by sodium carbonate solution. The precipitate formed was filtered and dried. The crude product was purified by the Column chromatography.

Spectroscopic data. 7a:

^{1}H NMR (DMSO-d_6): δ 9.27 (s, 1 H), 8.72 (s, 1 H), 7.21–7.32 (m, 5 H), 6.14 (s, 1 H), 5.14 (s, 1 H), 2.24 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 14.1.

IR (KBr): 3520, 3230, 3150, 1705, 1690 cm^{-1}.

EI-Mass: 391.17(M^+, +Ve mode).

7b:

^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1 H), 8.78 (s, 1 H), 7.28 (d, 2 H), 7.88 (d, 2 H), 6.34 (s, 1 H), 5.54 (s, 1 H), 2.24 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 21.33,15.1.

IR (KBr): 3540, 3240, 3150, 1705, 1695 cm^{-1}.

EI-Mass: 405.15(M^+, +Ve mode).

7c:

^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.08 (d, 2 H), 8.05 (d, 2 H), 6.64 (s, 1 H), 5.58 (s, 1 H), 3.91 (s, 3 H), 2.26 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 55.33,15.1.

IR (KBr): 3540, 3240, 3150, 1710, 1690, 1150 cm^{-1}.

EI-Mass: 421.15(M^+, +Ve mode).

7d:

^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.16 (d, 2 H), 8.05 (d, 2 H), 6.64 (s, 1 H), 5.58 (s, 1 H) ,2.26 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.13.

IR (KBr): 3540, 3240, 3150, 1710, 1690, 1340 cm^{-1}.

EI-Mass: 473.15(M^+, -Ve mode).

7e:

^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.66 (d, 2 H), 8.25 (d, 2 H), 6.64 (s, 1 H), 5.58 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.13.

IR (KBr): 3540, 3240, 3150, 1710, 1690, 1360 cm^{-1}.

EI-Mass: 457.15(M^+, -Ve mode).

7f:
^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.96 (d, 2 H), 8.75 (d, 2 H), 6.64 (s, 1 H), 5.58 (s, 1 H), 2.26 (s, 3H).
^{13}C NMR (DMSO-d_6): δ = 165.4, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.13.
IR (KBr): 3540, 3240, 3150, 1710, 1690, 1340 cm^{-1}.
EI-Mass: 392.45(M^+, +Ve mode).
7g:
^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.26 (d, 1 H), 7.75 (d, 1 H), 7.74(d, 1H), 6.64 (s, 1 H), 5.58 (s, 1 H), 2.26 (s, 3H).
^{13}C NMR (DMSO-d_6): δ = 165.23, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.15.
IR (KBr): 3540, 3240, 3150, 1710, 1690, 940 cm^{-1}.
EI-Mass: 397.45(M^+, +Ve mode).
7h:
^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.86 (d, 1 H), 7.85 (d, 1 H), 7.14(d, 1H), 6.64 (s, 1 H), 5.58 (s, 1 H), 2.26 (s, 3H).
^{13}C NMR (DMSO-d_6): δ = 165.63, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.15.
IR (KBr): 3540, 3240, 3150, 1710, 1690, 960 cm^{-1}.
EI-Mass: 381.35(M^+, +Ve mode).
7i:
^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.86 (s, 1 H), 7.76 (d, 1 H), 7.65 (d, 1 H), 6.64 (s, 1 H), 5.58 (s, 1 H), 2.3 (s, 3H).
^{13}C NMR (DMSO-d_6): δ = 165.53, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.15.
IR (KBr): 3540, 3240, 3150, 1710, 1690, 940 cm^{-1}.
EI-Mass: 395.35(M^+, -Ve mode).
7j:
^{1}H NMR (DMSO-d_6): δ 9.34 (s, 1 H), 8.76 (s, 1 H), 7.16 (d, 1 H), 7.69 (d, 1 H), 6.64 (s, 1 H), 5.58 (s, 1 H), 2.3 (s, 3H).
^{13}C NMR (DMSO-d_6): δ = 165.43, 157.2, 150.25, 148.4, 144.9, 128.4, 127.3, 126.3, 59.2, 15.15.
IR (KBr): 3540, 3240, 3150, 1710, 1690, 940 cm^{-1}.
EI-Mass: 380.35(M^+, -Ve mode).

Results and Discussion

The three component condensation reactions proceeded smoothly in refluxing ethanol and were completed within 4–6 h. Many pharmacologically important moieties may be substituted on the aromatic ring with high efficiency under the zirconium tetrachloride catalyzed conditions. Aromatic aldehydes carrying either electron-donating or withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Besides its simplicity and mild reaction conditions, this method is effective for the preparation of DHPMs. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxy, halides, etc., under the reaction conditions. The advantage of the $ZrCl_4$ for this reaction lies in its simplicity. This method utilizes readily available reagents at low cost and also affords high yields of DHPMs in short reaction times.Thus, this procedure offers easy access to substituted dihydropyrimidinones with a variety of substitution patterns. Among the various solvents such as acetonitrile, methanol, THF and ethanol used for the

transformation, ethanol and methanol were found to be the best. generality of the reaction with respect to aldehyde, ketoesters and urea. It is presumed that the reaction may proceed through the imine intermediate formed from the aldehyde and urea, stabilized by the zirconium ion followed by the addition of the β-ketoester enolate and cyclodehydration to afford the dihydropyrimidine.

Conclusion

An efficient synthesis of 3, 4-dihydropyrimidinones from the aldehyde, β-keto ester and urea in ethanol, using Zirconium tetrachloride as the catalyst.

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