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SYNTHESIS AND CHARACTERIZATION OF SOME NITROGEN CONTAINING HETEROCYCLIC DERIVATIVES *VIA* NOVEL CHALCONES

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ABSTRACT

Chalcones have great importance in natural as well as synthetic chemistry. It is one of the wonderful precursors used for the synthesis of different 5, 6, 7 – membered heterocyclic compounds. Whereas Nitrogen atoms containing heterocyclic compounds are medicinal important due to their biological activities. After reviewing the literature survey, I found out, that nitrogen-containing five-membered heterocyclic pyrazoles have different synthetic methods & pharmacological activities. This prompted me to prepare highly stable five-membered ring structures like 1, 3, 5-triphenyl 1H Pyrazolone and its derivatives via novel Chalcones synthesized by aromatic ketones and aldehydes in alkaline medium having heterocyclic moiety. These compounds were characterized using IR, ^{1}H-NMR, and Mass spectra and Elemental analysis. As per literature, they possess some potent biological activities. Therefore, antibacterial and antifungal activities were screened for these derivatives. most of the compounds were found to be the most active against bacterial & fungal human pathogens.

KEYWORDS: Chalcones, Heterocyclic, Nitrogen, Pathogens, Pyrazolone, Screening.

1. INTRODUCTION

Heterocycles are an inevitable part of the designing of drug moieties, in that N – heterocycles, constitute an important class of natural and synthetic products many of which exhibit useful biological activities.[1] An interest in pyrazoles are five-membered heterocyclic systems having two adjacent nitrogen atoms within rings.[2,3] It has only one endo-cyclic double bond and is basic. Substituted Pyrazoline and its derivatives are highly privileged structures and well-known heterocycle. It is embedded with different functional groups &

exhibits important biological activities. Thus, a significant amount of research has been directed towards this class. A significant portion of research in heterocyclic chemistry has been devoted to 2-pyrazolines containing different aryl groups as substituents, as evident in the literature.

Lnsuasty *et al* synthesized novel pyrazolic analogs of Chalcones and their 3-aryl-4-(3-aryl-4, 5-dihydro-1Hpyrazo-5-yl)-1-pyrazole derivatives as potential antitumor agents.[4] In this synthesis, Chalcones were treated with hydrazine afforded the new racemic 3-aryl-4-(3-aryl-4, 5-dihydro-1Hpyrazo-5-yl)-1-pyrazole or their N-acetyl derivatives and its reactions were carried out in DMF or acetic acid respectively. Tala has synthesized biologically active Chalcone and Pyrazole derivatives by reacting 3- isopropyl-4- methoxy benzaldehyde with various aromatic ketones by using alkali as catalyst.[5,6] Sattar has synthesized some Pyrimidine, Pyrazoles, Pyridine derivatives and their reactivity Descriptors.[7] Pandya synthesized halogenated chalcones in a synthetically affordable route.[8] The 2-Pyrazoline derivatives were synthesized by involving of series of chalcones with hydrazine hydrate, catalysed by acetic acid. Vanillin and other aldehyde containing Chalcones and its 2-Pyrazolines are important in Pharmaceutical Chemistry.

2-Pyrazolines have been reported to show a broad spectrum of biological activities including antibacterial,[9] antifungal,[10] Anti-inflammatory,[11] and antidepressant activities.[12] The 2-pyrazoline function is quite stable and has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize new compounds possessing biological activities. Several methods are employed in the synthesis of 2-pyrazolines, including the condensation of Chalcones with hydrazine & phenyl hydrazine.[13-17] as well as condensation with thiosemicarbazone in ethanol under strong basic or acidic conditions.[18] Asha Chate et al synthesized a series of new chalcones and dihydroxy chalcones by a novel approach under ultra-sonication.[19] This method offers significant advantages such as efficiency and mild reaction conditions under short reaction time.

The desired Chalcones were synthesized by reacting 6-(3-acetyl-phenylamino) pyridazin-3(2H)-one with substituted aromatic aldehydes in presence of alkali. In a typical case, equimolar quantities of chalcones and phenyl hydrazine hydrochloride in presence of acetic acid and pinch off of sodium acetate, led to the formation of 2-pyrazolines.

2. MATERIALS AND METHODS

All chemicals were purchased from reputed compony of AR grade. Melting points were determined by the open tube capillary method and are uncorrected the purity of the compound was checked on thin-layer chromatography (TLC) plates (silica gel) in the solvent system n- hexane-ethyl acetate 4:6 the spots were detected in iodine chamber.

EXPERIMENTAL METHODS

1. 6-(4-acetylphenyl amino) -3- chloro pyridazine (A)

Equimolar quantities (0.01mol) of 3, 6 - dichloro Pyridazine (1.48 g) and 4-amino acetophenone (1.35 g) on condensation in ethanol solvent for four hours. The progress of reaction was monitored by thin layer chromatography (TLC) using system Hexane: pet ether (3:7) system. After completion of reaction as indicated by TLC, the reaction mixture is then poured in ice-cold water the solid compound was obtained is filtered and dried by IR lamp then recrystallized by using isopropanol solvent to gives compound (A) in 78% yield. Pale-Yellow powder, Mp 165^{0}C R_f 0.4 (Silica gel, ethanol). IR (cm-1): 3244, 3300, 1665, 1670, ^{1}H NMR (DMSO-d_6): δ 2.75 (s, 3H. CH_3), δ 7. 28 (d, 1H, Jα,β *=16Hz*, H β), 6.92-7.15 (m, 5H, Ar-H), 6.94-7.15 (m, 5H, Ar-H), 6.80-6.88 (d, 1H J=*9.8 Hz*, CH pyridazine), 7.18-7.23 (d, 1H, J= *9.9 Hz*, CH Pyridazine), 6.99 (d, 1H, -CO-CH=) 7.35-7.45 (d, 1H, J= *7.8Hz*, Ar-CH=), 8.48-9.52 (t, 1H, NH pyridazine D_2O exchangeable); HRMS(M^+H) calculated for $C_{12}H_{10}ClN_3O$, m/z 247, Anal. Calcd for $C_{12}H_{10}ClN_3O$: C, 52.00; H, 4.15; N, 14.39, O, 6.9. found: C, 60.10; H, 4.40; N, 15.40. O, 7.02.

2. 6-(4-acetylphenyl) amino) pyridazin-3(2H)-one (B)

Compound A (2.47g. 0.01mol) heated under reflux in glacial acetic acid solvent (20 ml) for 5 h. The progress of reaction was monitored by thin layer chromatography (TLC) using system Hexane: pet ether (2:8) system. the reaction mixture was evaporated to half its volume then the oxidized product cooled. The formed precipitate was filtered, washed with water, and recrystallized from ethanol to gives (B) in 62% yield. Faint yellow fine powder, Mp 182^{0}C R_f 0.35 (Silica gel, ethanol). IR (cm-1): 3260 (Ar, C=C Stre.), 3250 (N-H Stre.), 1685, 1670 (>C=O), 1H NMR (DMSO-d_6): δ 2.60 (s, 3H. CH_3), 6.80-6.90 (d, 2H J= 9.8 Hz, CH pyridazine), 7.20-7.30 (d, 1H, J= 9.8Hz, CH pyridazine), 7.40 – 7.50 (t. 1H. J=8.0 Hz, Ar-H), 7.20-7.30 (d. 1H. J= 7.8Hz, Ar-H), 8.02 (s. 1H, Ar-H), 8.70 (s, 1H, NH pyridazine D_2O exchangeable) 11.90 (s, 1H, NH pyridazine D_2O exchangeable).

HRMS (M^+H) calculated for $C_{12}H_{11}N_3O$, m/z 229, Anal. Calcd. for $C_{12}H_{11}N_3O$.: C, 62.84; H, 4.85; N, 19.56, O, 13.5. found: C, 65.00; H, 4.90; N, 20.10. O, 14.00.

3. 6-({4-[(2E)-3-phenylprop-2-enoyl] phenyl} amino) pyridazin-3(2H)-one (C_1)

Compound B (4.58 g. 0.02 mol) and benzaldehyde (2.12 g. 0.02 mol) were well mixed with one pallet of solid KOH over an ice bath. Then the reaction flask was loosely corked and kept 180 W in a domestic oven,[20] for 4.5 minutes with an interval of 30 seconds. The progress of reaction was monitored by thin layer chromatography (TLC) using system Hexane: pet ether (3:7) system. After 4.5 minutes the reaction mixture was diluted with H_2O and acidified with HCl (50%). The separated solid was filtered and crystallized from glacial acetic acid to give (C) in 76%. Yellow powder. Mp 195^{0}C Rf 0.48 (Silica gel, ethanol). IR (cm^{-1}): 3244 (Ar. C=C Str.), 3400 (N-H Str.), 1680 (C=O),1530 (-CH=CH-, Str.); ^{1}H NMR (DMSO-d_6):): δ 7. 28 (d, 1H, Jα, β =*16Hz*, H β), 6.92-7.15 (m, 5H, Ar-H), 6.94-7.15 (m, 5H, Ar-H), 6.80-6.88 (d, 1H J=*9.8 Hz*, CH pyridazine), 7.18-7.23 (d, 1H, *J= 9.9 Hz*, CH Pyridazine), 6.99 (d, 1H, -CO-CH=) 7.35-7.45 (d, 1H, J= 7.8Hz, Ar-CH=), 7.48-7.52 (t, 1H, NH pyridazine D_2O exchangeable).

HRMS (M+H) calculated for $C_{19}H_{15}N_3O_2$, m/z 317, Anal. Calcd for $C_{19}H_{15}N_3O_2$,: C, 73.04; H, 4.85; N, 14.02 O, 10.6. found: C, 73.10; H, 4.72; N, 13.65 O, 11.00.

4. 6-{[4-(1, 5-diphenyl-1H-pyrazol-3-yl) phenyl] amino} pyridazin-3(2H)-one(E_1)

Compound C (1.6 g 0.005 mol.), phenyl hydrazine hydrochloride (0.72 g 0.005 mol in the solvent of 10 ml glacial acetic acid and pinch off sodium acetate is added and the reaction mixture was reflux for 3.5 hrs at 110^{0}C temp. The progress of reaction was monitored by thin layer chromatography (TLC) using system Ethyl acetate: pet ether (2:7) system. The solid obtained was collected and recrystallized from the ethanol to give (D) in 66% Yellow powder. Mp 170^{0}C R_f 0.25 (Silica gel, ethanol). IR (cm^{-1}): 3240 (Ar-C=C Str.), 3250 (N-H Str.), 1675 (C=O); ^{1}H NMR (DMSO-d_6):):): δ 1.9 (dd, 2H), 3.7 (d, 1H), 4.1 (Brs, 1H, -NH), 5.9 (dd, 1H), 7.10-7.15 (d, 1H J=*9.8 Hz*, CH pyridazine), 6.4 (dd, 1H, Ar-H), 6.7 (dd, 1H), 6.8 (dd, 1H, Ar-H), 6.9 (s, 1H, Ar-H), 7.1 (Brs, 1H, -NH), 6.40 - 7.05 (s, 5H, Ar-H), 7.1 (t, 1H, Ar-H), 7.05 - 7.25 (s, 5H, Ar-H); HRMS(M^+H) calculated for $C_{25}H_{21}N_5O$, m/z 407, Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19; O, 03.95; found. C, 74.20; H, 5.24; N, 17.44; O, 4.02**.**

3. RESULT AND DISCUSSION

Schematic work

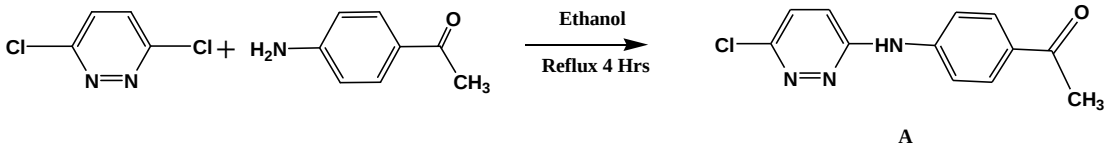


Fig. 1: Synthesis of novel Ketones having hetero moiety.

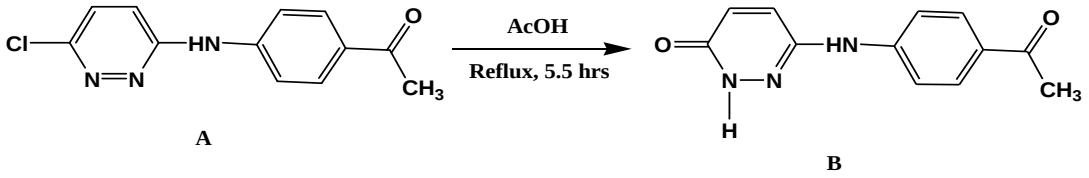


Fig. 2: Oxidation of novel ketones.

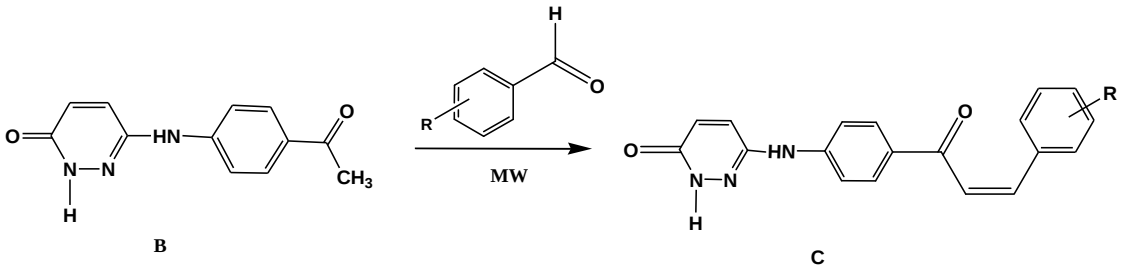
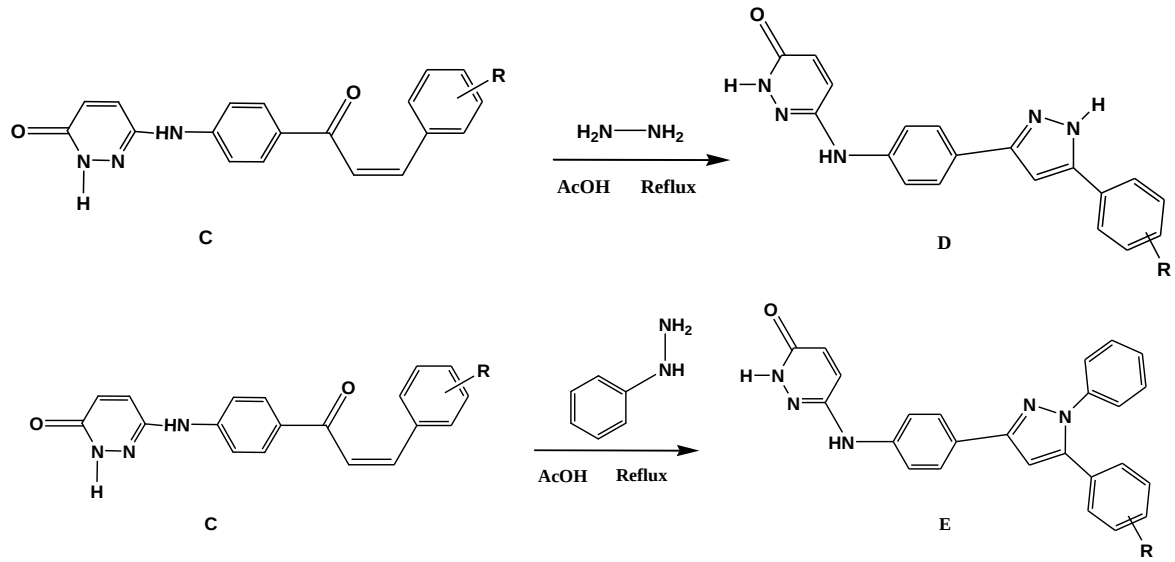


Fig. 3: Synthesis of novel Chalcones from novel Ketones.

Synthesis of Pyrazolone



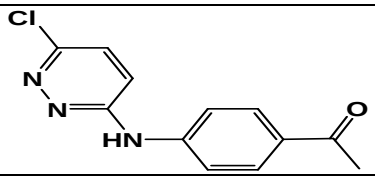
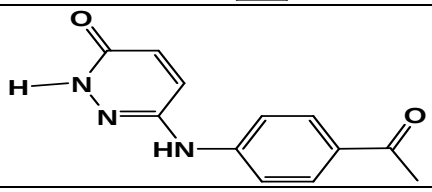
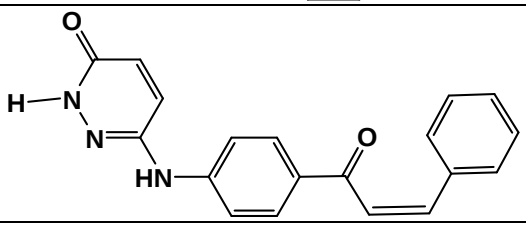
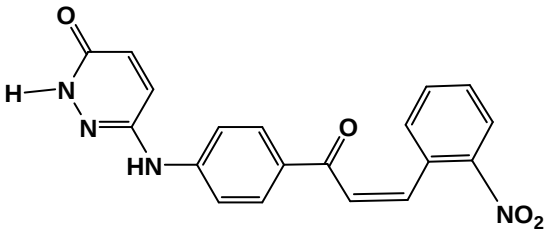
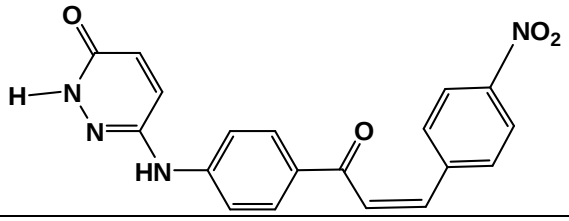
R= -H R=o-NO_2 R= o - NO_2

Fig. 4: Synthesis of novel Pyrazoline derivatives from novel Chalcones.

Antibacterial and Antifungal activity

All synthesized compounds were screened for their antibacterial & antifungal activity against human pathogens. The Gram-negative and gram-positive bacteria like E. Coli, S. Aureus, A. Niger, and C. Albicans using the agar diffusion method,[20] at a concentration of 20 mg/ml. DMSO is used as a solvent. Entry B_2 Pyrazolone derivatives were found to be more potent for antibacterial and antifungal activities. Entry of B_{2a} is found moderately active as compared to B_2. Novel chalcones comparatively are active against pathogens. They are found more active than the references Penicillin and Griseofulvin respectively. The results of anti-fungal activities were recorded as the average diameter of inhibition zone in mm, which are mentioned in table 2. Its antibacterial and antifungal activities were found moderate to excellent than their references used.

Table 1: Synthesis of newer Chalcones & Pyridazin-3(2H) derivatives.

Entry	Product	M. P.	Yield
A		165 ^{0}C	78%
B		182 ^{0}C	62%
C_1		180 ^{0}C	76%
C_2		358 ^{0}C	55%
C_3		260 ^{0}C	75%

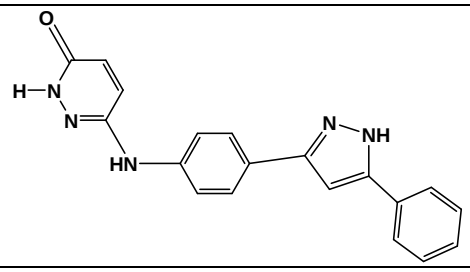
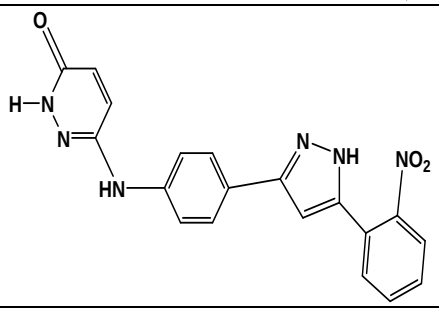
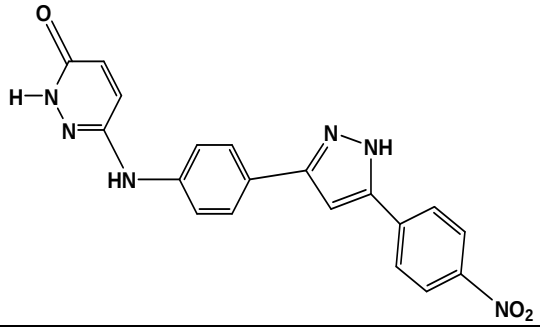
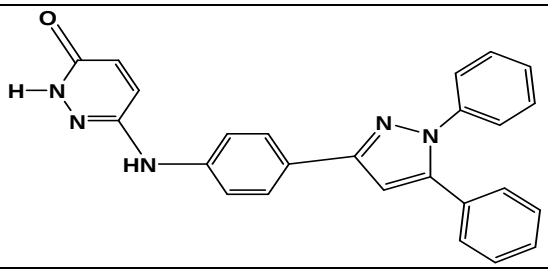
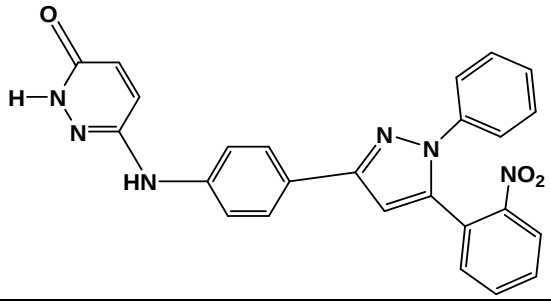
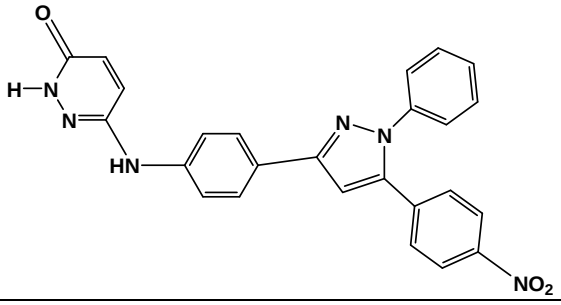
D_1		175 ^{0}C	68%
D_2		215	55%
D_3		205 ^{0}C	74 %
E_1		170 ^{0}C	66%
E_2		220 ^{0}C	52%
E_3		202 ^{0}C	75%

Table 2: Antimicrobial activity of synthesized compounds.

Entry	Bacteria		Fungi	
	E. Coli (ATCC8739)	S. aureus (ATCC6538)	Niger (ATCC16404)	C. albicans (ATCC10231)
D_1	12.5mm	11mm	-	9.5mm
D_2	11mm	10mm	-	14
D_3	10	9 mm	13	10
E_1	11.5	8 mm	-	13
E_2	12	7	-	15
E_3	14	16	14	21
Penicillin	12	9		
Griseofulvin			10	11

Zone of inhibition in mm

4 CONCLUSIONS

I have synthesized 1*H*-pyrazolone containing 6-aminopyridazin-3(2*H*)-one derivative from newly prepared acetophenone. The yield obtained in all the steps in this transformation is satisfactory and it has been found to have significant medicinal importance. Different methods were reported for the preparation of the 2-Pyrazoline class of compounds. After the pioneering work of Fischer and Knoevenagel in the 19th century, the reaction of α, β-unsaturated aldehydes and ketones with phenyl hydrazine in acetic acid under reflux condition became the most popular method for the preparation of 2-pyrazolines.[20] Tupare *et al* reported when the molar ratio of chalcones 3 and phenyl hydrazine hydrochloride was 1:1, the yield of 1, 3, 5-triphenyl 2-pyrazoline obtained was insufficient. But by increasing the molar ratio to 1:2 and 1:3 the yield of products was also increased. It may be possible, that sodium acetate is in favour of the release of phenyl hydrazine from phenyl hydrazine hydrochloride.[21] So, the reaction condition we chose was the molar ratio of Chalcone: Phenyl hydrazine: Sodium acetate was 1:2:0.15. We have performed the reaction of Chalcones with phenyl hydrazine hydrochloride or hydrazine hydrate by refluxing at 210^0C, the yield of 2-pyrazoline was 52% - 75% (Table 1). From the results, the optimum reaction condition was chosen: Chalcone (3mmol), phenyl hydrazine hydrochloride- ride (6mmol), Sodium acetate (0.3 mmol). Under this reaction system, a series of experiments for the synthesis of pyridazin-3(2H)-one derivative was performed. Novel chalcones and pyrazolines were found active against human pathogens. Some of them found more active than the references Penicillin and Griseofulvin respectively.

5. ACKNOWLEDGMENT

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