MULTI COMPONENT ONEPOTSYNTHESIS OF HEXAHYDRO QUINOLINE DERIVATIVES PROMOTED BY TRANSITION METAL CATALYST

Dr. Ramarao Abburi[1], B, V, Durgarao[2], Dr.K.Apparao[3], Dr.DVL.Sirisha[4], Dr.N.Krishnarao[4*]

1. Department of chemistry, P.B.Siddhartha College of arts &Science, Vijayawada, AP, 520010

2. Department of DFS (chemistry), ONGC, RJY, AP, India, 533106

3. Department of chemistry,Dr.BR Ambedkar University, Srikakulm, AP,India

4*. Department of chemistry, PRISM PG.DG.College, Visakhapatnam, AP, India

ABSTRACT:

The purpose of this work is to create new hexahydroquinoline using different Lew's acid catalysts, like $ZrOCl_2 8H_2O$ and strong base (triethylamine), and examine their effects on bacteria that infect cutaneous wounds. Small amounts of zirconium oxychloride octahydrate hydrate and triethylamine catalysts were used in a one-pot multicomponent reaction involving malonitrile, dimedone, and aromatic aldehydes in ethanol solvent under reflux for this purpose. The impact of the resulting products on Gram-positive (*B. subtilis and S. aureus*) and gram-negative (*E. coli and P. aeruginosa)* microorganisms were examine. The structure of the products was determined using sophisticated spectroscopic tools such as ^{1}H NMR, ^{13}C NMR, and LCMS elemental analysis. The protocol has been used because of its excellent yield, short reaction time, mild reaction conditions, and straightforward workup process. 80–91% yields of the synthetic derivatives were obtained.

KEYWORDS:

Multicomponent reaction, Lew's acid catalyst, conventional, hexahydroquinoline, Antimicrobial activity

1. INTRODUCTION

The convergent synthetic reactions known as multicomponent reactions (MCRs) occur when three or more starting materials react to produce a product in which all or most of the atoms contribute to the final product[1,2]. A one-pot synthesis is a method used in chemistry to increase a chemical reaction's efficiency by subjecting a reactant to multiple chemical reactions in a single reactor. Several heterocyclic moieties are very useful and essential for human life, so, many recent reports have confirmed that heterocyclic compound could exhibit numerous biological activities [3], By keeping dangerous and exogenous microorganisms out of the body, the skin boundary protects it. On the other hand, an infection can result from germs entering through a skin break. Infection-causing pathogens like Pseudomonas aeruginosa and Staphylococcus aureus exhibit specific destructiveness factors that promote their adherence and attack. Multidrug-resistant bacterial diseases in skin wounds have become a major threat to global health due to the misuse of antibiotics over the past few decades. In order to treat infected wounds, new agents must be created. Effective antibiotic administration aids in preventing bacterial biofilm infection and the development of bacterial resistance

The researchers have been interested in the synthesis of nitrogen-containing heterocycles because of their pharmacological characteristics, which include antibacterial qualities [5, 6]. One of the most important tools in organic chemistry, one-pot multicomponent reactions are crucial for creating a wide range of complexly structured compounds, particularly the previously mentioned heterocycles. A significant class of nitrogen-containing heterocyclic compounds, quinolones has a variety of biological activities, The hexahydroquinoline is a well-known structural scaffold of many natural products and synthetic medications, and it possesses a wide range of biological properties. These are utilized as Antibacterial activity [4-6], Antifungal [7], Anti-inflammatory [8, 9], Anticancer [10-13], Insecticidal activities [14], antitubercular activities [15], Anti –diabetic [16], analgesic activity]17], antihistaminic activity[18], .Thus, using multicomponent one-pot reactions to synthesize compounds with the quinolone structural skeleton is crucial for the pharmaceutical industry.

In this work, we have created a sophisticated, effective, simple, and straightforward method for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile and its nine derivatives using aryl aldehydes, dimedone, malononitrile, ammonium acetate, and a catalytic amount of $ZrOCl_28H_2O$ and triethyl amine as base (Scheme-1). In terms of Lew's acid catalyst promoted by the conventional one pot processes, the catalyst's effect combined with the technique results in an excellent product yield. When compared to the other microwave methods, this methodology has several important benefits including atom economy, the use of solvent, mild catalyst conditions, short reaction times, and a more comfortable workup procedure.

2. MATERIAL AND METHODS

2.1. EXPERIMENTAL

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals. They were used without further purification before use. The melting points were recorded in open capillaries using a Agrawal melting-point B-540 apparatus. 1H NMR and 13CNMR spectra were obtained on a Bruker instrument (400 MHz and 100MHz) and chemical shifts are reported in δppm. Mass spectra were measured using high-resolution ESI–MS Thermo spectrometers (70 eV).

2.2.Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile and its derivatives (5a-e)

A mixture of substituted aromatic aldehydes **1** (mol), dimedone **2** (1 mol), malononitrile **3** (1 mol), ammonium chloride **4** (1 mol) was dissolved in 50mL clean and dry RBF and catalytic amount of lews acid catalyst $ZrOCl_28H_2O$ until completion of the reaction. The identification of the reaction was monitored by TLC (ethyl acetate-hexane, 2:8). The reaction mixture was poured in crushed ice and filtered. The crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic techniques and compared with the standard method

Spectral data of titled derivatives (5a-5h):

2.2.1.1-Amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (5a)

Pale pink color solid ; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm; 1.098(s, 3H, CH_3), 1.547 (s, 3H, CH_3), 1.781 (s, 2H, CH_2), 2.548 (d, 2H, CH_2), 4.658 (s, 1H, CH), 6.125 (s, 2H,NH_2), 6.894-7.254 (m, 5H, Ar-H), 8.574 (s, 1H, NH);^{13}C NMR (100 MHz, CDCl3) δ ppm: 27.54, 28.23, 31.54, 43.02, 53.88, 59.20, 112.75, 114.63, 122.29, 125.02, 127.72, 128.44, 132.74, 144.55, 150.50, 164.52, 197.02; LCMS (*m/z*): 294.24 $[M+H]^+$

2.2.2.2-Amino-4-(4-hydroxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5b)

Pale yellow solid; Yeild-89%, M.p-220-222^{0}C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 1.091(s, 3H, CH_3),1.210 (s, 3H, CH_3), 1.990 (dd, 2H, J=7.5 Hz, 1.2Hz, CH_2), 2.770 (d d, 2H, J=12.0, CH_2), 4.357 (s, 1H, CH), 5.884 (s, 2H,NH_2), 6.895-7.045 (m , 2H , Ar-H), 7.114-7.234, (m , 2H, Ar-H), 9.014 (s, 1H, NH), 9.450(s,1H,-OH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm : 26.95, 28.37, 31.53, 37.51, 43.42,51.63, 57.60, 110.59, 116.44, 118.57, 128.9, 132.52, 151.05, 162.70, 196.54; LCMS(*m/z*): 309.34[M+H$]^{]+}$

2.2.3.2-Amino-4-(4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5c)

Pale brown solid ; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 1.123 (s, 3H, CH_3), 1.421(s, 3H, CH_3), 2.210 (s,2H,-CH_2), 2.30-2.40 (dd, 2H, Ar) ,), 3.670 (s, 3H, -OCH_3), 4.571 (s, 1H, CH), 5.847 (s, 2H, NH_2), 6.945 (dd, J=2.1, 7.8Hz , 2H, Ar), 7.145 (dd,J-5.7Hz,1.2Hz,2H, Ar-H), 8.774(s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm : 27.92, 31.59, 38.55, 45.01, 54.54, 60.70, 110.20, 122.59, 126.99, 128.22, 129.84, 130.34, 152.55, 154.50,164.29, 196.70; LCMS(*m/z*): ; 324.35$[M+H]^+$

2.2.4.2-Amino-4-(4-methylphenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5d)

Pale Yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 0.974(s, 3H, CH_3), 1.246 (s, 3H, CH_3), 1.944 (s, 2H, CH_2), 2.741 (s, 2H, CH_2), 4.658 (s, 1H, CH), 5.976 (s, 2H,NH_2), 7.092-7.248 (m ,2H Ar-H), 7.294-7.456 (m, 2H, Ar-H), 8.746 (s, 1H, NH); ^{13}C NMR(100 MHz, $CDCl_3$)δ ppm ; 28.69, 28.95, 31.45, 40.71, 53.74, 59.70, 110.72, 122.49, 125.09,128.62, 129.04, 132.44, 144.55, 151.60, 163.74 ,195.15; LCMS(*m/z*): 307.65[M+H]+

2.2.5.2-Amino-4-(2-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5e)

White compound; 1HNMR (400 MHz, $CDCl_3$) δ ppm : 0.955(s, 3H,CH_3), 1.158 (s, 3H, CH_3), 1.972 (dd, 2H, J=10.4 Hz, CH_2),2.756 (dd, 2H, J=12.6, CH_2), 4.632 (s, 1H, CH), 5.827 (s,2H, NH_2), 6.847-7.214, (m , 4H, Ar-H), 8.775, (s 1H,NH); ^{13}C NMR (100 MHz, CDCl3) δ ppm : 27.85, 32.03, 37.21,44.32,50.43, 57.65, 113.59,117.54,119.57, 131.49, 135.62, 150.45,164.50, 196.74; LCMS(*m/z*): 311.36[M+H]+

2.2.6.2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinolone (5f)

Pale yellow solid, ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 1.092 (s, 3H,CH_3), 1.325 (s, 3H CH_3), 2.095 (dd, 2H, J=9.4 Hz, CH_2), 2.728 (dd, 2H, J=12.4, CH_2), 4.814 (s, 1H, CH), 5.997 (s,2H, NH_2), 7.014-7.450 (m, 4H, Ar-H), 8.425, (s, 1H,NH); ^{13}C NMR (100 MHz, $CDCl_3$)δppm : 28.32, 31.53, 39.41, 43.73,51.05, 58.20, 112.55, 116.84, 118.57, 131.59, 135.52, 152.55, 161.50,195.54; LCMS(*m/z*): 327.85$[M+H]^+$

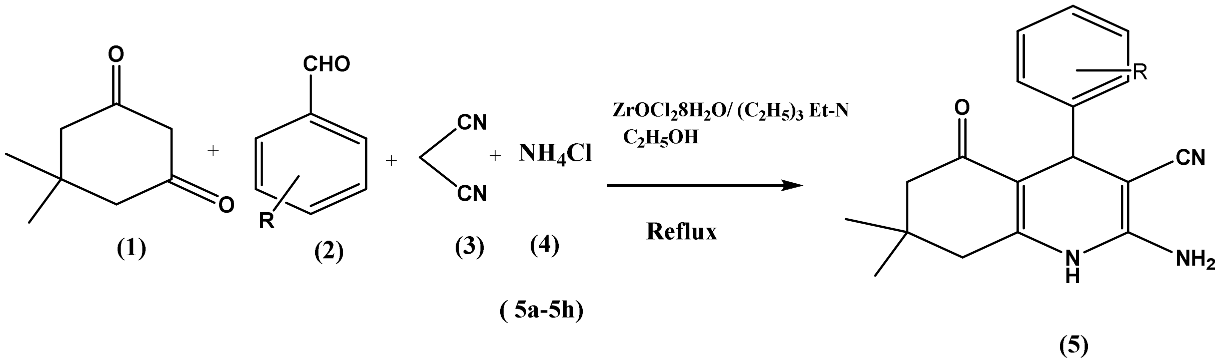
2.2.7.2-Amino-4-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5g)

Pale red solid, ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: δ 1.021 (s, 3H,CH_3), 1.254 (s, 3H, CH_3), 1.911(dd, 2H, J=12.4 Hz, CH_2), 2..920 (dd, 2H, J=14.0, CH_2), 4.775 (s, 1H, CH), 6.125 (s,2H, NH_2), 7.054-7.328 (m ,4H Ar-H), 8.658 (s 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm : 27.02, 31.24, 38.53, 44.54, 52.18, 58.52, 110.52, 115.63, 115.77, 131.53, 138.92, 155.55, 161.70,198.59; LCMS(*m/z*): ; 372.67 [M+H]+

2.2.8.2-Amino-4-(4-Nitrophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline (5h)

Yellow solid, ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: δ 1.105 (s, 3H,CH_3), 1.412 (s, 3H, CH_3), 2.085 (dd, 2H, J=10.6 Hz, CH_2), 2..745 (d d, 2H, J=8.8 , CH_2), 4.810 (s, 1H, CH), 6.324 (s,2H, NH_2), 7.127-7.475 (m ,4H Ar-H), 8.748 (s 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm : 28.15, 32.75, 39.51, 43.65, 53.18, 59.52, 114.52, 116.63, 117.77, 130.53, 137.92, 156.55, 162.70,197.59; LCMS(*m/z*): ; 354.24 [M+H]+

3. RESULTS AND DISCUSSION



R = H, 4-OH,4-OCH_3, 4-CH_3
4-F,4-Cl,4-Br,4-NO_2

(Scheme-1)

3.1. Chemistry:

Initially, here dimedone, aryl aldehydes, malononitrile, and ammonium chloride in a catalytic amount of ZrOCl28H2O, an initial attempt has been made to develop a new synthetic protocol and one-pot synthesis for selectively substituted hexahydroquinoline derivatives. to investigate this conventional method of procedure t (Scheme 1).According to a review of the literature, every compound in scheme-1 had a lengthy completion time (almost 180 minutes and more) and a comparatively low yield (82–91%).Conventional methods could achieve the same transformation with a moderate to excellent yield (91%) and a shorter reaction time (Table 1).These named derivatives' reaction conditions were optimized using a variety of catalysts, catalyst concentrations, and solvents. Zirconium oxychloride ($ZrOCl_2$) catalyst produced a higher yield of derivatives than oxidative related catalysts like titanium dioxide (TiO_2), zinc oxide (ZnO), and iodine, despite the fact that different amounts of catalyst were used during the reaction (Table I).

Table-I: The optimization of the various for titled synthesis (5c):

Entry	Catalyst	Time (min)	Yield (%)
1	I_2	90	53
2	$ZrOCl_2$	90	91
3	TiO_2	90	64
4	ZnO	90	59

In order to maximize the quantity of catalysts, aromatic aldehyde was first chosen as a probe. Even after the reaction mixture was refluxed in water for ninety minutes, the formation of the 5c did not proceed without catalyst. Catalyst concentration was optimized throughout the reactions, and it was found that 2 mol% catalysts were adequate to advance the reactions (Table -2). Higher catalyst concentrations did not significantly improve the outcomes.
The results are summarized in Table-2.

Entry	Catalyst mole %	Time (min.)	Yield(%)b
1	No catalyst	90	10
2	0.5	90	34
3	1.0	90	57
4	1.5	90	71
5	2.0	90	91
6	2.5	90	91

[a] All reactions were carried out using 2.0 mol% $ZrOCl_28H_2O$ at reflux.

[b] Isolated yields.

For the probe reaction with 2.0 mol% of $ZrOCl_28H_2O$ as catalyst at reflux conditions, a variety of solvents, including acetonitrile, MDC, THF, water, and ethanol, were investigated in order to determine the optimal solvent. It has been observed that the poor yield was obtained with other organic solvents while the best yield was obtained in ethanol. Table-3 displays the study's findings

Table- 3: Synthesis of 5c in the presence of different solvents [a]

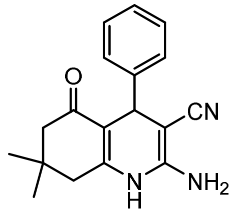
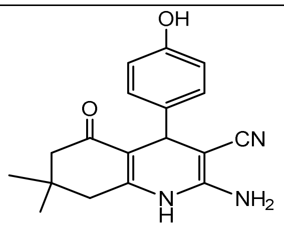
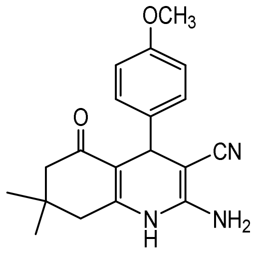
Entry	Solvents	Time (min.)	Yield(%)[b]
1	Acetonitrile	150	52
2	MDC	210	48
3	THF	120	62
4	Ethanol	90	91
5	Water	240	41

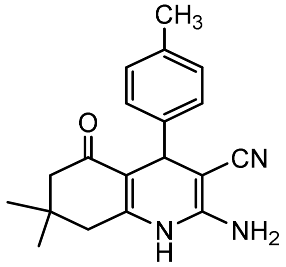
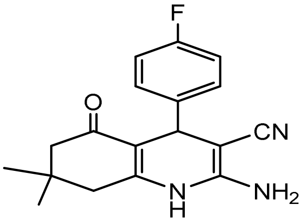
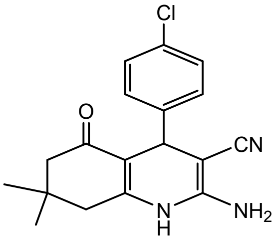
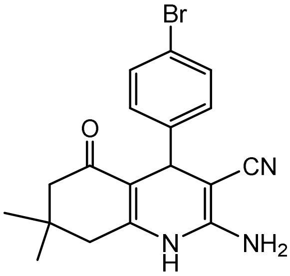
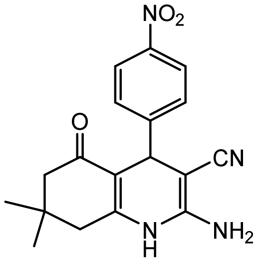
[a] All reactions were carried out in ethanol medium

.

[b] Isolated yields

Table-4: Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile in the presence of 2 mol% $ZrOCl_2 8H_2O$ under reflux conditions

Entry	Ar	Product	Time (min.)	Yield (%)b	M.P. (_C) Found
1	C_6H_5		90	78	210-212
2	4-OHC_6H_4		90	88	220-222
3	4-$OCH_3C_6H_4$		90	91	230-232

4	$4\text{-}CH_3C_6H_4$		90	85	225-227
5	$4\text{-}FC_6H_4$		90	83	212-214
6	$4\text{-}ClC_6H_4$		90	85	235-237
7	$4\text{-}BrC_6H_4$		90	87	254-256
8	$4\text{-}NO_2C_6H_4$		90	80	241-243

3.2. Characterization of the titled derivatives:

The spectral data from the synthesized derivatives were used to determine their structures. The suggested structures were completely consistent with the spectral information of the synthetic route of a novel compound. Based on their chemical shifts, multiplicities, and coupling constants, the signals of the corresponding protons of the prepared titled compounds were confirmed in the nuclear magnetic resonance spectra (^{1}H NMR). The structure of the intended analog was determined by spectral analysis evidence, such as ^{1}HNMR, ^{13}CNMR, LCMS, and elemental analysis. The keto group of desired compounds appeared at 198.24. ^{1}HNMR values of various aromatic protons at 7.485-6.894δppm, the containg exhibited 9.014-8.425 δ ppm of NH protons. The quaternary protons is at 4.814- 4.357 δppm, the hydroxyl proton appear at 9.450 δppm, the methoxy protons at 3.670 δppm and methyl protons shown at 2.776-1.774 δ ppm

Hence l, it was found that the catalyst was stimulated to increase the yield of the reaction. Compared to derivatives with halogen or electron-releasing groups, which also produced remarkable yields, derivatives with electron-attracting groups generated more products. The catalyst's benefits included commercial availability, ease of handling, a fast reaction time when applied, high product yields, ease of work-up, and named products that were purified using a non-chromatographic method.

3.3. ANTIMICROBIAL ACTIVITY OF COMPOUNDS

The micro broth dilution method was used to assess the desired derivatives' *in vitro* antibacterial and antifungal properties. Gram-positive (*B. subtilis and S. aureus*) and gram-negative (*E. coli and P. aeruginosa)* microorganisms were used to test the invitro antibacterial activity. A. Niger and C. albicans microorganisms were used to test the invitro antifungal activity. Ketonozole and streptomycin were the standard medications used in this investigation for both antifungal and antibacterial screening. The Culture Collection and Geneank (MTCC), located in Chandigarh, India, was the commercial source of the standard strains used to screen for antibacterial and antifungal activities. Sabouraud dextrose broth was utilized for the growth of fungi and Mueller Hinton broth as a nutrient medium for bacteria. By comparing the turbidity, the inoculum size for the test strain was changed to 108 CFU/mL. Primary and secondary evaluations were used to document the outcomes. The compounds under investigation and standard medications were diluted twice to create the stock solution (2000 µg/mL).

Table-5: Antimicrobial activity screening activity synthesized scaffold:

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
5a	06	09	07	05	05	06
5b	19	18	17	16	16	14
5c	21	20	20	18	15	16
5d	16	19	17	15	14	15
5e	18	16	17	14	12	14
5f	**23**	**24**	**21**	**21**	**19**	**20**
5g	**25**	**24**	**20**	**22**	**21**	**20**
5h	12	14	11	15	18	17
Streptomycin	30	30	27	27	NA	NA
Fluconazole	NA	NA	NA	NA	25	25
DMSO	---	----	---	---	---	---

The results of the aforementioned Table-5 showed that the antibacterial activity of compounds 5b, 5c, 5d, and 5e was primarily exhibited by the electron-donating group of the compound, i.e., these derivatives showed good active potent, whereas the electron-withdrawing group of compounds "5f and 5e" showed excellent potent active due to halogen bearing groups. Due to the presence of electron-releasing group groups, compounds 5b, 5c, and 5d showed good active potential. Additionally, we found that the antifungal activity of compounds (5a–5h) varied; compound 5h demonstrated moderate activity, and the compound's rate demonstrated low to moderate activity.

4. CONCLUSION

In the present work, we have improved an effective one-step four-component conventional method strategy of HHQ derivatives **(5a-5 h)** subjected to $ZrOCl_28H_2O$ as a Lew's acid catalyst and the following protocol of the four reagents including substituted aromatic aldehydes, ammonium chloride , activated methylene and 5,5-dimethyl-1,3-cyclohexanedione. The purpose of this catalyst has reveals that the development in reaction rate, in addition to the productivity and selectivity observed and $ZrOCl_28H_2O$ was evaluated as a powerful catalyst for the synthesis of the designed derivatives. The advantages of the current protocol include its efficiency, high product yield, short reaction time and operational simplicity. The desired derivatives were evaluated antimicrobial activity against bacterial as well as fungal strains with references standard drugs such as Ketonozole and streptomycin

5. ACKNOWLEDGEMENTS:

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