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Research Article

Synthesis, Characterization And Anti-Bacterial Activity Of Novel Chalcone Derivatives

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ABSTRACT

Chalcones have been a class of important synthetic anti-microbial agents and effectively used in clinic for infectious diseases. In this study, chalcone derivatives of 5(1-Ethyl piperazine 4-yl) 2-Acetyl thiophene and p-Substituted Benzaldehyde have been synthesized and screened for antibacterial activities. All the synthesized compounds (TP1-TP4) were characterized by spectral studies and evaluated for in-vitro anti-bacterial activity. All the synthesized compounds (TP1-TP4) showed the antibacterial activity against strains of Bacillus substilis and TP1 and TP2 showed the antibacterial activity against strains of E.Coli when compared to that of the standard Amoxcillin

INTRODUCTION

Microbial resistance and the emergence of the multi-resistant bacterial strains known as super bugs pose a great threat to the currently available antimicrobial regime and thus increasing the demand for the development of newer antimicrobial agents with novel mechanism of action, better in efficacy and safety profile

Chalcones is a generic term given to compounds bearing the 1,3 diphenyl -2-propen-1-one frame work . Chalcones are the bichromophoric molecules separated by a keto -vinyl chain and belong to the flavonoid family chemically they consists of open chain flavonoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system, which is responsible for the wide spectrum of biological activities. A vast number of naturally occurring chalcones are poly hydroxylated in the aryl rings. Chalcones are one of the major classes of natural products which occur widely in nature particularly in coloured flowers and widely distributed in fruits, vegetables, spices and tea. Chalcones, considered as precursors of flavonoids and isoflavonoids are abundant in edible plants.

General structure of chalcone

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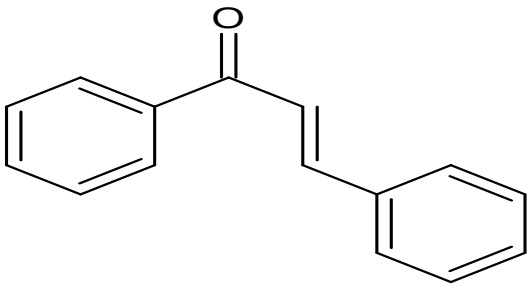


In recent years Chalcone derivatives have received significant attention owing to their diverse range of biological properties due to the large number of replaceable hydrogen's that allows a large number of derivatives and a variety of promising biological activities to be generated, e.g., anti-inflammatory [5], anti-gout [6], anti-histaminic [7], anti-oxidant [8], anti-obesity [9], anti-protozoal [10], hypnotic[11], anti-spasmodic[12]. Heterocycles bearing nitrogen, sulphur, and thiazole moieties constitute the core structure of a number of biologically interesting compounds. As chalcones are relatively easy to prepare, large numbers of derivatives can be synthesized by substituting with various aromatic and hetero aromatic nuclei. In fact, piperazine and thiophene have a vast biological activity and have been used as starting material in the synthesis of chalcone derivatives as part of an effort to discover novel antibacterial agents.

MATERIALS AND METHODS

All the chemicals and solvents were procured from the scientific syndicate pvt.Ltd. Melting points of all the synthesised compounds were recorded by using Scientech - 2211 digital auto melting/boiling point apparatus and are uncorrected. Progress of reaction was checked by TLC using Merck Silica gel 60 F-254 coated glass plates. Proton magnetic resonance (1HNMR) spectra were recorded on Bruker 400 MHz NMR spectrometer using CDCl3 as solvent. Chemical shifts were reported in parts per million relative to tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on Bruker- Alpha 201054 ATR eco Znse#DA810802D spectrophotometer

GENERAL PROCEDURE13-18

STEP 1: Preparation of 5-{(1- Ethyl piperazine 4-yl)}-2 acetyl thiophene

A mixture of N-ethyl piperazine (0.01 mole), 5 chloro 2 acetyl thiophine (0.01 mole), and anhydrous potassium carbonate (1.2 g) in methanol (25ml) was refluxed for three hour with stirring. After the completion of reaction the resultant mixture was cooled at room temperature. Then it was poured into ice cold water with constant stirring. The solid separated was purified by recrystallization.

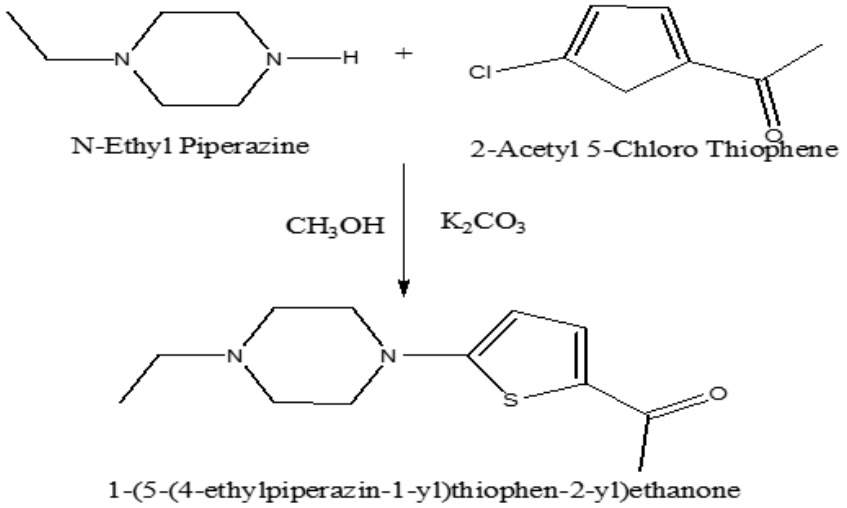
STEP 2: Preparation of TP1-TP4 Compounds

A mixture of 2-acetyl 5-chloro thiophene (0.01mol), para substituted benzaldehyde (0.01mol) and 40% aqueous potassium hydroxide was added to 30 mL of ethanol and was stirred at room temperature for about 2-6 h. The resulting product was kept overnight in refrigerator. The solid separated was purified by recrystallization.

SCHEME:

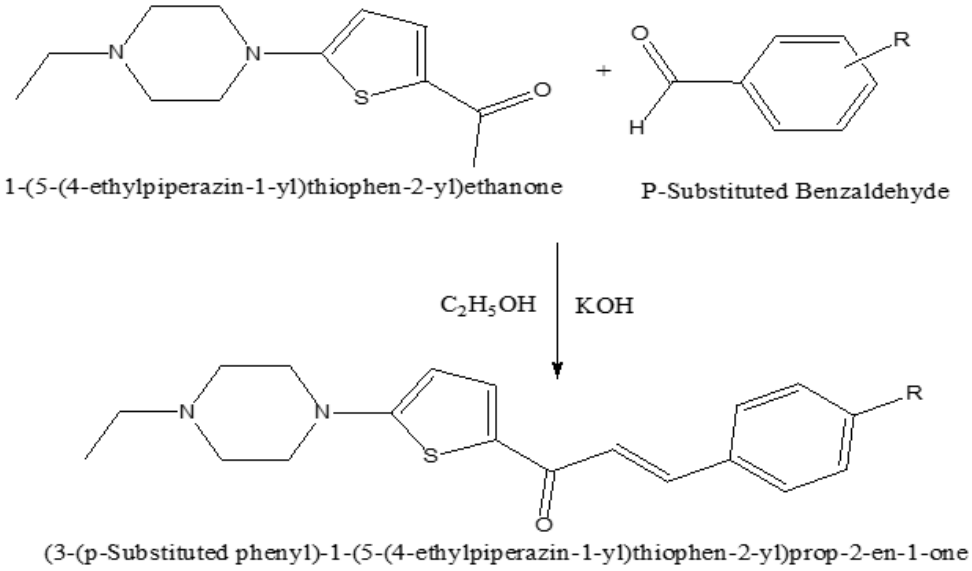
STEP 1

Synthesis of 1-(5-(4-ethylpiperazin-1-yl)thiophen-2-yl)ethanone.

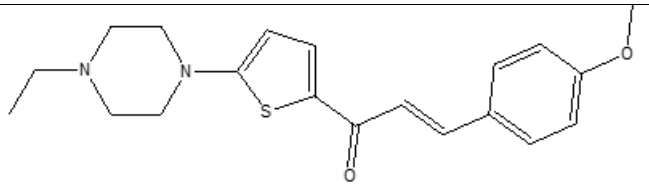


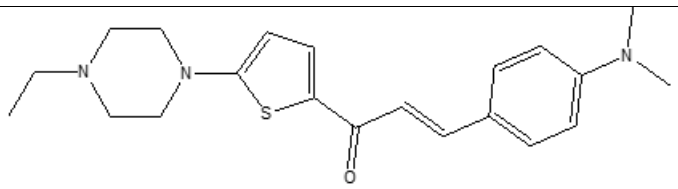
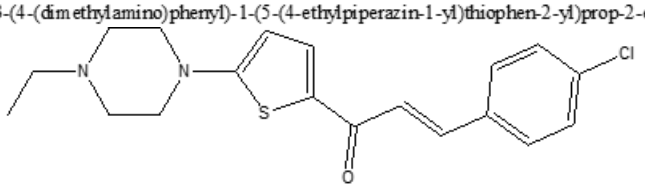
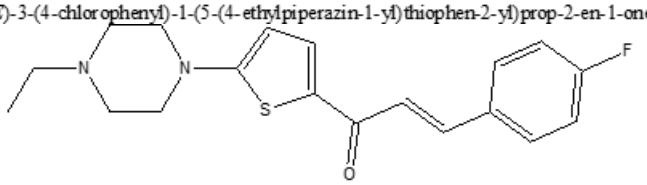
STEP 2

Synthesis of (3-(p-substituted phenyl)-1-(5-(4-ehylpiperazin-1-yl)thiophen-2-y)prop-2-en-1-one



LIST OF SYNTHESIZED COMPOUNDS.

Compound code	Structure & IUPAC NAME
TP 1	 (*E*)-1-(5-(4-ethylpiperazin-1-yl)thiophen-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one

TP 2	 (*E*)-3-(4-(dimethylamino)phenyl)-1-(5-(4-ethylpiperazin-1-yl)thiophen-2-yl)prop-2-en-1-one
TP 3	 (*E*)-3-(4-chlorophenyl)-1-(5-(4-ethylpiperazin-1-yl)thiophen-2-yl)prop-2-en-1-one
TP 4	 (*E*)-1-(5-(4-ethylpiperazin-1-yl)thiophen-2-yl)-3-(4-fluorophenyl)prop-2-en-1-one

BIOLOGICAL EVALUATION[19]:

All the synthesized compounds were screened for in vitro antibacterial activity against Bacillus subtilis (Gram positive), Escherichia coli (Gram negative) by Agar – well diffusion method. Amoxcillin was used as the reference antibacterial drug.

ANTI -BACTERIAL ASSAY

SUBCULTURING OF BACTERIA IN LIQUID BROTH

Inoculums of gram (+ve) bacillus subtilis strains and gram (-ve) Ecoli are collected from St Francis college, Begumpet.0.3gms of beef extract, 0.5gms of peptone and 0.5gms of Nacl are dissolved in 100ml of distilled water in a conical flask. Heat the medium prepared and filters it to remove particulates and un dissolved substances and sterilize it in autoclave for 15 minutes at 121oC with 15lb pressure and PH adjust to 7.Sterile liquid broth is divided into two equal portions and transferred into sterile boiling tubes.Loopful of bacteria from each bacteria inoculum is inoculated in each boiling tube and incubated in incubator for microbial growth (18 – 24 hrs at 370c)

PREPARATION OF NUTRIENT AGAR MEDIA:

Nutrient agar medium served as the basal medium and it was prepared by dissolving the Weighed quantities of peptone (20g) and beef extract (05g) in distilled water (400ml) by genius warming. Then specified amount of agar (20g) was dissolved by heating on boiling water bath. Then the volume was made up to 1000ml with distilled water and the PH of the solution was adjusted to 7.2 by adding sodium hydroxide solution [approximately 40%, 1.25ml for 100ml of the nutrient agar]. Then the media was sterilised by autoclaving at 1210c for 20 minutes, at 15lbs pressure.

SCREENING FOR ANTIBACTERIAL ACTIVITY

Agar well diffusion method was employed for the screening of antibacterial activity. Petri dish and media were heat sterilized in an autoclave at 121℃ for 20min. The plates were inoculated with microorganisms before it reaches the room temperature. After the solidification of plates, a hole with a diameter of 6 to 8mm is punched aseptically with a sterile cork borer .All the synthesized compounds and reference were dissolved in chloroform to get required concentration of 25 µg/ml, 75 µg/ml and 100 µg/ml. The solution of each compound, reference and a control (CHCl3) were added separately into

each well. Chloroform was used as a control, Amoxicillin employed as standard. Petri dish was incubated at 37℃ for 24 hrs. The diameter of zone of inhibition of bacterial growth around the well was measured in millimeter and values were recorded.

RESULTS AND DISCUSSION

PHYSICAL PROPERTIES OF SYNTHESIZED COMPOUNDS

Compound code	Molecular Formula	Molecular weight	Melting point	Percentage yield (%)	Solubility
TP1	$C_{20}H_{24}N_2O_2S$	356.484	80ºC-85ºC	92	Soluble in Chloroform and Acetone, insoluble in water
TP2	$C_{21}H_{27}N_3OS$	369.527	85ºC-88ºC	85	
TP3	$C_{19}H_{21}ClN_2OS$	360.9	90ºC-95ºC	88	
TP4	$C_{19}H_{21}FN_2OS$	344.44	100ºC-103ºC	93	

(E)-1-(5-(4-ehylpiperazin-1-yl)thiophen-2-yl)-3-(4methoxyphenyl)prop-2-en-1-one(TB1):

Compound TB1 was isolated as an off-green solid; IR SPECTRA 1255 ν (C-N str), 1641.71 ν (Aliphatic C=C str), 729.05 ν (C-S str in thiophene), 1715.35 ν (C=O str), 1056.93 ν (O-C str), 2980.98 ν (Aliphatic C-H str), 1H NMR (400 MHz, CDCl3):δ7.544-7.603ppm(4H,Ar-H), 7.758-7.796ppm (2H,Thiophene), 6.897-6.972ppm (2H,CH=CH), 3.828(3H,O-CH3); 13C NMR (100 MHz, CDCl3): d= 181.049 (C=O), 113.749 (2CH=C-O), 146.903 (=C-Ar), 144.375 (S-C=’), 147.900 (Ar C-N), 139.266 (3C,Thiophene’), 127.219 and 127.688 (C2 and C6-Ar), 130.389 (CH=CH), 130.873 (5C-Thiophene), 55.428 (O-CH3 ppm).

1(2E)-3-(4-dimethylaminophenyl)-1-[5-(4-ethylpiperazin-1-yl)thiophen-2-yl]prop-2-en-1-one (TB2):

Compound TB2 was isolated as an orange solid; IR SPECTRA 1224 ν (C-N str), 1626.17 ν (Aliphatic C=C str), 795.71 ν (C-S str in thiophene), 1715.35 ν (N-(CH3)2 str), 2915.35ν (Aliphatic C-H str), 1H NMR (400 MHz, CDCl3):δ7.445-7.306ppm(4H,Ar-H), 7.857-7.697 ppm (2H,Thiophene), 6.987-6.792ppm (2H,CH=CH), 2.828-2.856(6H,N-(CH3)2); 13C NMR (100 MHz, CDCl3): d= 180.149 (C=O), 119-479 (2CH=C-O), 144.309 (=C-Ar), 144.573 (S-C=’), 167.900 (Ar C-O), 138.626 (3C,Thiophene’), 127.339 and 127.868 (C2 and C6-Ar), 145.839 (CH=CH), 135.373 (5C-Thiophene), 39.428 (N-(CH3)2 ppm);

(2E)-3-(4-chlorophenyl)-1-[5-(4-ethylpiperazin-1-yl)thiophen-2-yl]prop-2-en-1-one (TB3) :

Compound TB3 was isolated as an off-white solid; IR SPECTRA 1225.38 ν (C-N str), 1589.51 ν (Aliphatic C=C str), 770.57 ν (C-S str in thiophene), 1646.67 ν (C=O str), 800.12 ν (C-Cl str), 1H NMR (400 MHz, CDCl3):δ7.254-7.533ppm(4H,Ar-H), 6.588-7.566ppm (2H,Thiophene), 6.987-7.072ppm (2H,CH=CH); 13C NMR (100 MHz, CDCl3): d= 179.949 (C=O), 114.479 (2CH=C-O), 146.129 (=C-Ar), 147.568 (S-C=’), 169.150 (Ar C-O), 141.266 (3C,Thiophene’), 126.912 and 127.068 (C2 and C6-Ar), 132.389 (CH=CH), 135.873 (5C-Thiophene) ppm);

(2E)-1-[5-(4-ethylpiperazin-1-yl)thiophen-2-yl]-3-(4-fluorophenyl)prop-2-en-1-one (TB4) :

Compound TB4 was isolated as an off-green solid; IR SPECTRA 1255 ν (C-N str),712.28 ν (C-S str in thiophene), 1705.35 ν (C=O str), 2973.84 ν (Aliphatic C-H str), 1032.82 ν (C-F str): 1H NMR (400 MHz, CDCl3):δ7.264-7.325 ppm(4H,Ar-H), 7.572-7.971ppm (2H,Thiophene), 6.567-6.256 ppm (2H,CH=CH), 13C NMR (100 MHz, CDCl3): d= 180.949 (C=O), 115.749 (2CH=C-O), 144.329 (=C-Ar), 144.741 (S-C=’), 170.150 (Ar C-O), 142.526 (3C,Thiophene’),

127.112 and 127.548 (C2 and C6-Ar), 133.382 (CH=CH), 136.543 (5C-Thiophene) ppm);

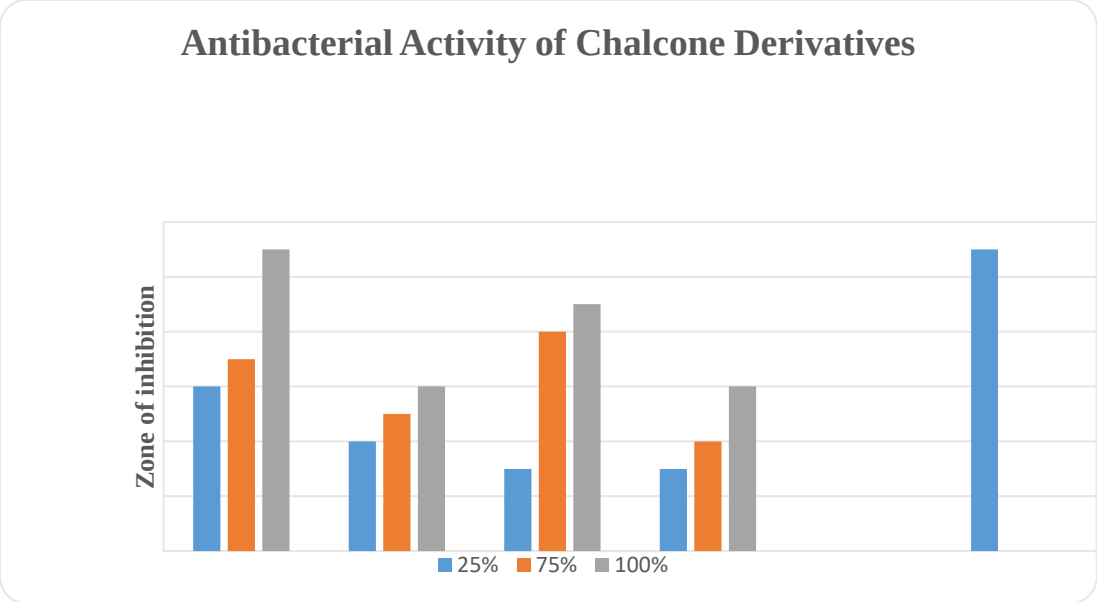
The synthesized compounds were characterized by IR , 1HNMR and 13C NMR. The spectral data of the synthesized compounds was found in accordance to the molecular structure.

ANTI-BACTERIAL ASSAY:

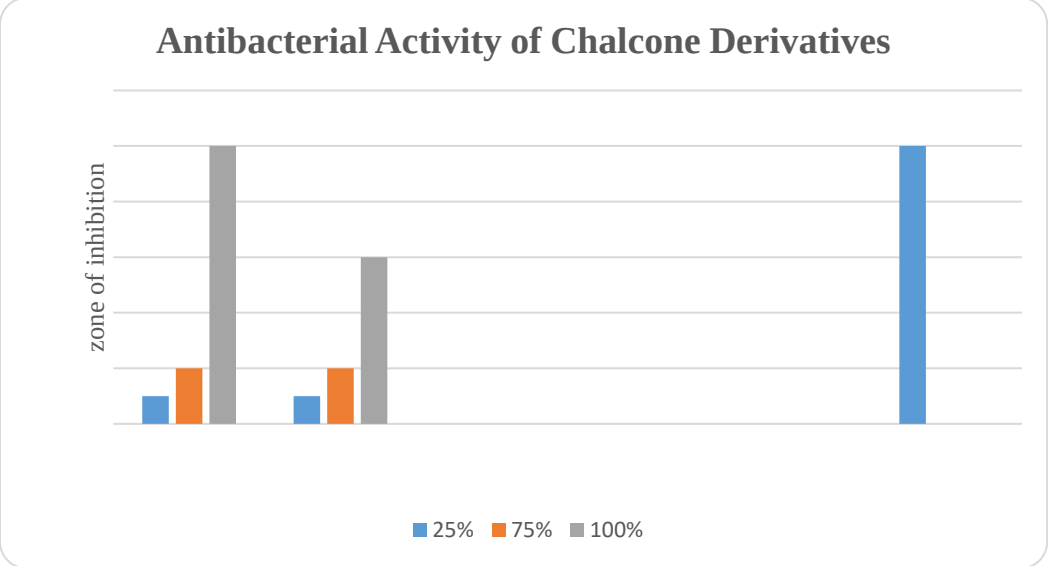
TABLE 4: DIAMETER OF ZONE OF INHIBITION (mm) OF COMPOUNDS AGAINST BACILLUS SUBTILIS GRAM +VE and ESCHERICHIA COLI (GRAM –VE

COMPOUND CODE	CONCENTRATION (%)	ZONE OF INHIBITION (mm)	
		BACILLUS SUBTILIS GRAM +VE	ESCHERICHIA COLI GRAM -VE
TP 1	25	8	4
	75	10	4
	100	11	8
TP 2	25	4	3
	75	5	5
	100	6	6
TP 3	25	3	-
	75	8	-
	100	9	-
TP4	25	3	-
	75	4	-
	100	6	-
CHLOROFORM (BLANK)	-	-	-
STANDARD (AMOXICILLIN)	25	11	10

BAR DIAGRAM SHOWING ANTI-BACTERIAL ACTIVITY
BACILLUS SUBTILIS (Gram +ve)



E.COLI (Gram –ve)



The synthesized compounds were subjected to anti-bacterial study by Agar well diffusion method for zone of inhibition.The anti-bacterial activity was tested against both gram positive and gram negative bacteria were compared with standard drug Amoxicillin. The concentrations of the synthesized drugs were taken as 25%, 75% & 100%; all the compounds were dissolved in chloroform.In the anti-bacterial study, Amoxicillin showed a zone of inhibition of 11mm and 10mm in concentration of 25% against the organism bacillus subtilis and E.coli.

All the synthesized compounds (TP1-TP4) show significant activity against bacillus substilis.Out of the synthesized compounds TP1 exhibits good activity, TP3 shows moderate activity and compounds TP2 & TP4 shows less activity against bacillus subtilis compared to standard drug. Synthesized compound TP1 exhibits good activity, TP2 shows moderate activity against E.Coli.

CONCLUSION:

In summary, 4 chalcone derivatives were synthesized and characterized by IR , 1HNMR and 13C NMR. The synthesized candidates were screened for their antibacterial activity. The antibacterial activity was evaluated against Gram positive and Gram negative strains using Agar well diffusion method. The synthesized compounds were found to be more active towards gram positive bacterial strains and TB1 and TB2 compounds were found to be active towards gram Negative bacterial strains which may be attributed due to the presence of Piperazine and thiophene fused chalcone nucleus. An broad study is warranted for the further establishment of these molecules in clinical trials.

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CONFLICT OF INTREST:

No conflicts of interest.

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