Preparation and characterization of some new heterocyclic compounds with evaluating of its biological activity. .

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Abstract :

New compounds of 2-amino 6-bromo benzothiazole [2], 2-(substituted benzylidene)-6 -bromobenzothiazole [3a-e], 2-(*p*-N,N-dimethylamino phenyl)- 2-yl)-tetrazolo)-6-bromobenzothiazole[4],- 2-(*p*-N,N-dimethylaminophenyl)-)– (4'-oxo-1̀,3̀-thiazolidin-2-yl)6-bromobenzothiazole[5], 2-(*p*-N,N-dimethylaminophenyl)-2-yl)– 2,3-dihydro-1,3-oxazpine-4,7-dione)-6-bromobenzothiazole[6], -2-(*p*-N,N-dimethylamino phenyl)- 2-yl) 2,3-dihydro-1,3-oxazpine-4,7-dione)-6-bromobenzothiazole[7], and 2-(*p*-N,N-dimethylamino phenyl) imidazolidine-4-one)- 6-bromo benzothiazole[8] have been synthesized. The structures of these compounds were identified by FT-IR,H-NMR,Uv spectra and checked by TLC. Some of these compounds were tested against bacteria (Escherchia coli and Staphococcus aureus).

تحضير وتشخيص بعض المركبات الغير متجانسة الحلقة مع تقييم فعاليتها البايولوجية.

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مفتاح الكلمات: بنزثايزول, تترازول, ثابازولدين

الملخص :

تم في هذا البحث تحضير مركبات جديدة من 2- أمينو-6-بروموبنزوثايزول(2), 2-(بنزالدين معوض)-6-بروموبنزوثايزول (3a -e), 2-(بارا-N,Ń- ثنائي مثيل امينوفنيل) -2-يل)-تترازولو)6 --بروموبنزوثايزول (4) , 2 -(بارا-N,Ń- ثنائي مثيل امينوفنيل) (4- اوكسو-1,3 ثايازوليدين-2-يل) -6-بروموبنزوثايزول (5) , 2-(بارا-N,Ń- ثنائي مثيل امينوفنيل) -2-يل) 2,3-ثنائي هيدرو-1,3-اوكسازبين -4,7-ثنائي اون)- -بروموبنزوثايزول (6) , 2 -(بارا-N,Ń- ثنائي مثيل امينوفنيل) -2-يل) 2,3-ثنائي هيدرو-1,3-اوكسازبين -4,7-ثنائي اون)- -بروموبنزوثايزول (7) , وكذلك , 2 -(بارا-N,Ń- ثنائي مثيل امينوفنيل) اميدازوليدين 4- اون)-6- بروموبنزوثايزول (8) . وتم تشخيص تراكيب المركبات المحضرة عن طريق اطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون والاشعة فوق البنفسجية و كذلك من خلال تقنية الطبقة الرقيقة. كذلك تمت دراسة التاثير البايولوجي للبعض من المركبات المحضرة ضد بكتريا اشرشيا كولي وستافوكوكس ايريس.

Introduction :

The synthesis of these heterocylces compounds has received considerable attention in recent years.Triazoles and thiadiazoles and their derivatives countries an important class of organic compounds with divers agricultural, industrial and biological activities including anti-microbial, sedative, anti-convulsant-inflammatory[1-4].

Benzthiazole and its derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications [5,6]. A large number of benzaimidazole derivatives have been found to exhibit various biological activities such as anti-inflammatory ,antifungal, antibacterial and anthelmintic activities[7-11]. The ring system in which a benzene ring is fused to the 4,5-positions of imidaizole is designated as benzimidazole[9].
Such as aminobenzothiazoles were recognized most effective structures as antimicrobial and antifungal [12].

Instruments:

Melting points were measured using hot stage ***Gallen Kamp*** melting point apparatus and were uncorrected. The F.T.IR spectra in the range (4000-400) cm^{-1} were recorded using KBr disk on a ***SHIMADZU*** F.T.IR 8300 spectrophotometer Japan. Uv/vis spectra were recorded on Uv-Cary-100 spectrophoto-meters in (ISSC). ^{1}H-NMR spectra were recorded a BRUKER-400 MHz operating with tetra methyl silane as internal standard in $CDCl_3$ and DMSO-d_6 as a solvent, measurements were made at Chemistry Department, AL-Albaite University-Jordan. Thin Layer Chromatography (TLC) was carried out using Fertigfollen precoated sheets type PolyGram silg, and the plates were developed with iodine vapor. The biological activity was performed by biology department/ college of Science,Tikrit University.

Methods:

1-Synthesis of 2-amino 6-bromo benzothiazole [2][13].

p-bromo aniline was dissolved in glacial acetic acid and added to ammonium thiocyanate solution. The reaction mixture was treated with bromine and stirred for four hours at lower temperature. The mixture was neutralized with NaOH. The product was filtered and washed with water and dried.

2-Synthesis of 2-(substituted benzylidene)- 6-bromo benzothiazole [3a-e] [14]**.**

A solution of 2-amino -6-bromo benzothiazole(0.01mol) and appropriate substituted benzaldehyde (0.01mol) in absolute ethanol with few drops of glacial acetic acid was refluxed for 3 hours. The reaction mixture cooled to room temperature, table (1). Yield 80%.

3-Synthesis of 2-(*p*-N,N-dimethylaminophenyl)- (6-bromo benzothiazole-2-yl)- tetrazolo-1-yl [4] [15]**.**

A mixture of (0.01mol) of Schiff bases [3] tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between (50-55)°C. The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.

4-Synthesis of 2-(*p*-N,N-dimethylaminophenyl)- (6-bromo benzothiazole-2-yl)- thiazolidin-4-one[5][(16)].

A (0.01) mole of 2- mercptoacetic acid was added dropwise to(0.01)mole of Schiff base in(20 ml)of dry benzene ,the mixture was refluxed for (24) hours then the solvent was evaporated and then the formed precipitate was re crystallized from ethylacetate and benzene,yield (75%).

5- Synthesis of 2-(*p*-N,N-dimethylamino phenyl)- (6-bromo benzothiazole 2-yl-2,3-dihydro-1,3-oxazpine-4,7-dione [6,7][(17)].

A mixture of Schiff base [3a] (0.01 mole) and (0.01) mole of maleic or phthaleic anhydride in (20 ml) of benzene was refluxed for (24) hours then the solvent evaporated and then the formed precipitate was re crystallized from appropriate solvents , yield (70%).

6- Synthesis of 2-(*p*-N,N-dimethylamino phenyl)- (6-bromo benzothiazole-2-yl)-imidazolidine-4-one –[8][(18)].

A mixture of Schiff base (0.01mole) and glycine (0.01mole) in (20 ml) of THF was refluxed for (24) hours then it cold to room temperature and the formed precipitate was filtered and re crystallized from ethanol , yield (75%).

Results and discussion:

The FT-IR spectrum of 2-aminobenzothiazole showed the appearance of bands at 3250 cm^{-1} due to amino group. Besides, the appearance of band of NH_2 group at 3430 cm^{-1}. The second step refers to the Schiff bases (3). The reaction occurs according to method described in the literature [(19)] , into absolute ethanol and in the catalytic amount of glacial acetic acid. The new band which appears at(1640 -1650)cm^{-1} in the IR spectrum of (3) which is attributed to the new azomethine (C=N) group.

The terazole [4] was characterized using FT-IR spectrum which showed the disappearance of band of azomethine (C=N) at the region (1640-1650) cm^{-1} and a band appeared in the region (3334)cm^{-1} due to ν(N-H)) stretching vibration. The analytical and spectral data are in accordance with the structures assigned.

The thiazolidene [5] was characterized using FT-IR spectrum which showed the disappearance of band of azomethine (C=N) at the region (1640-1650) cm^{-1} and a band appeared in the region (2534) cm^{-1} due to ν(C=S)) stretching vibration. The analytical and spectral data are in accordance with the structures assigned.

The FT-IR spectrum of compound [6] indicates the disappearance of azomethine band at (1640 cm^{-1}) and appearance of carbonyl bands of oxazepine ring. ^{1}H-NMR spectrum of compound [6], shows the following characteristic chemical shifts (DMSO-d_6) ppm. (δ 9.25) due to protons of (N-H) . Also, the (C-H) protons absorbed at (δ 4.4), (C-H) proton absorbed at(δ 3.4), four aromatic ring protons appear at the range (δ 7.3-7.8).

The titled compounds [7] and [8] were synthesized from the reaction between compound [3] and phthalic anhydride and glycine respectively.

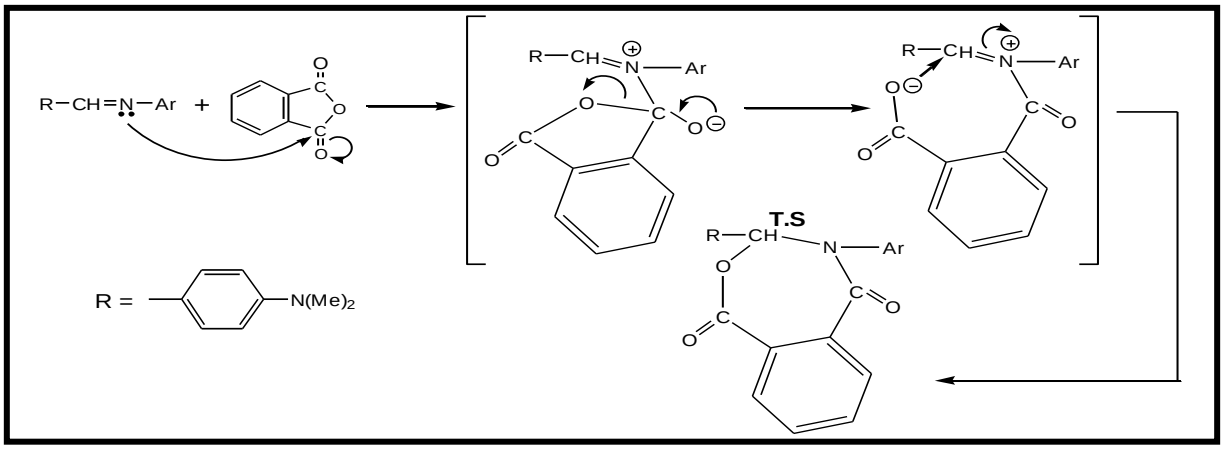
These compounds [7,8] were characterized by their melting points and FT-IR spectra .

Table (2): FT-IR spectral data of compounds [4,5].

Comp. No.	υ(N-H) cm^{-1}	υ(C-H) Aliphatic. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}exo	υ(C-H)ar cm^{-1}	Others
4	**3440**	**2970**	**1675**	**1612**	**3089**	**$N(CH_3)_2$** υ(N-Me) 1373
5	**-**	**2920**	**1662**	**1660**	**3082**	**-**

The compounds [1,3]oxazepine-4,7-dione [6,7] were synthesized from the reaction of compound [3] with maleic or phthalic anhydride in dry benzene.

The suggested mechanismof the reaction is shown in scheme(below):



Scheme , Mechanism steps for the prepared compounds [6,7].

The FT-IR spectrum of compound [7] as example was confirmed from the appearance of carbonyl group band at (1720 cm^{-1}) and (C-H) aliphatic band at (2924-2854 cm^{-1}), besides the (C=N) band of benzothiazole ring at (1610cm^{-1}) and bands at (1239 and 1118 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band,]. All the spectral data for other compounds are listed in table (3).

Table (3): FT-IR spectral data for (7,8) compounds.

Comp. No.	*υ(N-H) cm^{-1}*	*υ(C-H) Aliphatic. cm^{-1}*	*υ(C=O)cm^{-1}*	*υ(C=N) cm^{-1}*	*υ(C=C) cm^{-1}* **Ar**	*Others*
7	***3320***	***2950***	***1675***	***1650***	***1600***	

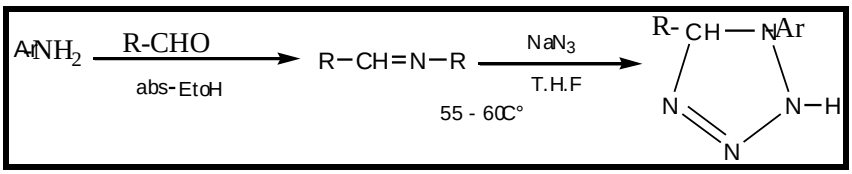
8	***3440***	***2989***	***1660***	***1620.09***	***1510***	***N(CH$_3$)*** $_2$1327 υ(C-N) 1168 υ(C-O) 1239-

Thiazolidinones play a vital role due to their wide range of biological activity and industrial importance as stabilizer for polymeric material.

Table (4): Physical properties of the synthesized compounds.

Comp. No.	*Molecular formula*	*Molecular Weight*	*Yield (%)*	*M.P (^{o}C)*	*Colour*
1	C_6H_6NBr	172	-	77-78	White
2	$C_7H_5N_2SBr$	229	75	229	Pale yellow
3	$C_{16}H_{14}N_3SBr$	360	73	222-224	Pale yellow
4	$C_{16}H_{15}N_6SBr$	403	70	160-163	Yellow
5	$C_{18}H_{16}N_3OS_2Br$	434	77	212-215	orange
6	$C_{20}H_{16}N_3O_3SBr$	458	72	203-205	Red
7	$C_{24}H_{18}N_3O_3Br$	476	60	164-166	orange
8	$C_{18}H_{17}N_4OSBr$	417	78	213-215	=

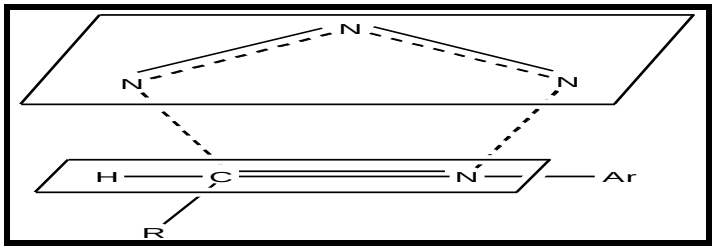
The synthesis and interesting pharmacological properties of tetrazole compounds were recently described. For synthesis of the target tetrazoles, the reaction sequence outlined in the scheme below. The compound [3] Schiff base was heated in water bath at (55 - 60°C) with sodium azide, to give the desired product. The titled compounds were characterized by their melting points, FT-IR spectra and checked by T.L.C.



Scheme : Regents and conditions of the preparation of tetrazole.[4]

The mechanism of the reaction systematically investigated as [3+2] cyclo additions which christened as a 1,3-dipolar cycloadditions[20]. It involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results in a five- member ring. Azides are a prominent class of 1,3-dipoles and azide 1,3-dipolar

cycloadditions. They are of great synthetic value and have been studied mechanistically in great detail. The common features of this type of reactions is best accommodated by a T.S. geometry in which the dipolarphile and its ligands lies in one plane, and the azide lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form bonds, scheme below.



Scheme: Approximate transition state geometry for azide addition.

The FT-IR absorption bonds, was utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at (1605-1635 cm^{-1}), attributed to (C=N) (imine group) stretching frequency is good evidence for the success of this step of reaction. It also, the IR spectra for these compounds were devoid of a strong band at (2120–2160)cm^{-1} attributed stretching frequency of a zide group. A band at (1531 cm^{-1}) was due to the cyclic (N=N) stretching of tetrazole ring and a band at (3390 cm^{-1}) was due to (N-H) grou

Imidazolidine derivatives prepared by the heating of Schiff bases derivatives with glycine (α-amino acetic acid) in THF the product were identified by the FT-IR spectrum which show the appearance of NH vibration in(3230-3390 cm^{-1}) and the disappearance of C=N band in 1612,or1662 cm^{-1} .

Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compound (8) was assayed for its antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*staphylococcus aurous*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (8).

The biological activity test showed that compounds with free (-SH) groups and free ($-NH_2$) groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also considered biologically active on *bacteria* .

Table (5) :Antimicrobial activity for some prepared compounds .

Comp. No.	*Staph. aureus*	*E. coli*
5	-	±
6	-	±
7	-	+
8	+	+

Key the symbols :(-) = No inhibition , (±) = 6-9 mm, (++) = 15-22 mm.

Conclusion:-

1. Compounds [5,6] showed slightly activity on Escherichia coli.
2. Compound [15] showed moderate activity on *Staphylococcus aureus* and ps.aerugenosa while compound [8] showed slight activity on this bacteria .

Compounds [5,6,7] showed no effect on *Staphylococcus aureus* .

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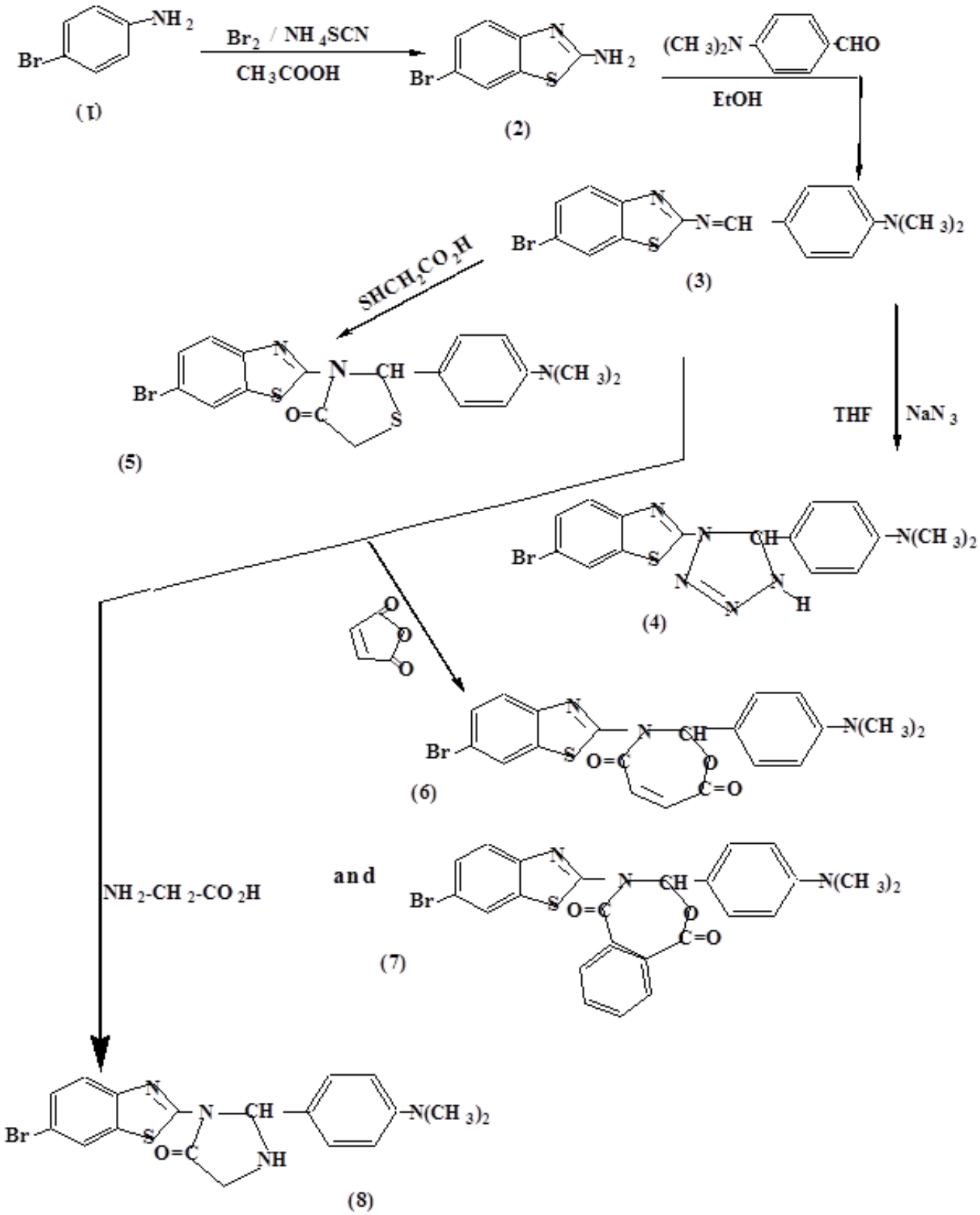
Br
NH 2
(1)
Br2 / NH 4SCN
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(2)
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CHO
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(3)
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