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Synthesis, Characterization, and Antioxidant Screening of Some New Azo Compounds Containing Pyrazole Moiety from Metoclopramide Drug

Youssef Mohsen Ibrahim*, Mona Ismail Khalaf
Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq

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Abstract

In this work, some new pyrazole derivatives were prepared through the reaction of the diazonium salt of metoclopramide with acetylacetone to give 5-chloro-*N*-(2-(diethylamino)ethyl)-4-((2,4-dioxopentan-3-yl) diazenyl)-2-methoxybenzamide (**1**) in 80% yield. Compound **1** was then reacted with some hydrazine derivatives to afford the corresponding pyrazole derivatives in 75-93% yields. Some new azo compounds (**6-10**) were also prepared in 77-95% yields by treatment of the diazonium salt of metoclopramide with some phenol and aniline derivatives. The prepared compounds were characterized using FT-IR and ^{1}H NMR spectroscopy. Some of these compounds were then tested to see how well they worked as antioxidants.

Keywords: Acetylacetone, Pyrazole, Antioxidant.

تخليق وتشخيص و فحص المضاد للأكسدة لبعض مركبات الآزو الجديدة التي تحتوي على جزيئات البيروزول من عقار الميتوكلوبراميد

يوسف محسن ابراهيم* ، منى اسماعيل خلف
قسم الكيمياء, كلية العلوم ,جامعة بغداد , بغداد , العراق

الخلاصة

في هذا العمل، تم تحضير بعض مشتقات البايروزول الجديدة من خلال تفاعل ملح الدايزونيوم للميتوكلوبراميد مع الأسيتايل أسيتون مركب **1** بمنتوج 80%. تم بعد ذلك تفاعل المركب **1** مع بعض مشتقات الهيدرازين لتوفير مشتقات البايروزول المقابلة بنسبة 75-93%. كما تم تحضير بعض مركبات الآزو **6-10** الجديدة بنسبة 77-95٪ بمعالجة ملح الدايازونيوم لميتوكلوبراميد مع بعض مشتقات الفينول و الأنيلين. تم تمييز المركبات المحضرة باستخدام التحليل الطيفي FT-IR و ^{1}H NMR. ثم تم اختبار بعض هذه المركبات لمعرفة مدى نجاحها كمضادات للأكسدة.

1- Introduction

Pyrazoles are five-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds in the azole family. Over the years, several synthesis methods and synthetic analogues have been

*Email: yusifyusif07805295500@gmail.com

reported. The presence of the pyrazole nuclei in different structures leads to diversified applications in different areas such as technology, medicine, and agriculture. They are specifically described as protein glycation inhibitors, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidants, and antiviral agents [1].

The diminished types of pyrazoles are called pyrazoline (II or III), while the completely diminished structure is pyrazolidine (IV) [2]. A pharmacologically significant active scaffold with almost all known pharmacological activities is pyrazole and its derivatives. The presence of this nucleus in medications from various therapeutic classes is notable; among them are the effective anti-inflammatory celecoxib and the antipsychotic CDPPB [1]. The weight-loss medication rimonabant and the antidepressant dorzolamide have demonstrated pyrazole moiety's pharmacological potential [1,3,4]

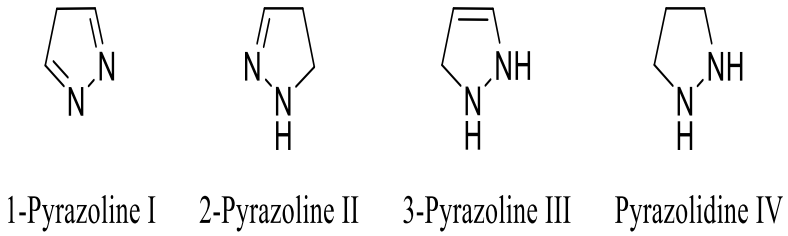


Figure 1: Pyrazole ring structures

Azo mixtures are used in many useful applications, including fiber shaders [5,6], and have acquired unique importance in the pharmaceutical industry since they have played an instrumental role in the organic system [7], indirect photonic and photonic technologies [8], suitable storage [9], nitrogen-fixing, and carcinogens [10]. At the same time, some azo compounds are moderately harmful and produce unfriendly results that can be perceived in the long run, but act as an important part of bimolecular mixtures, for example, hemoglobin and vitamin B12 [11]. Buildings can grow and become stronger because the -N=N- bunch and diketones are combined into a single compound [12,13].

2. Experimental

Instrumentation

All compounds were purchased from the Aldrich, Merck, and BDH organizations. The prepared compounds' FT-IR spectra were recorded on a KBr disc using a Shimadzu FT-IR-8400 Fourier transform infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrophotometer using DMSO-d_6 as a solvent. The melting points of the prepared compounds are not entirely settled by Gallen Kamp hairlike dissolving point device.

*Synthesis of 5-chloro-N-(2-(diethylamino)ethyl)-4-((2,4-dioxopentan-3-yl)diazenyl)-2-methoxybenzamide (**1**)*

In a 100-mL round-bottom flask, a mixture of metoclopramide hydrochloride (2 g, 6 mmol) in concentrated hydrochloric acid (18 mL) and distilled water (18 mL) was placed in an ice bath (at a temperature between 0 and 5 °C). A solution of sodium nitrite (500 mg, 6 mmol) in distilled water (5 mL) was then added drop by drop with stirring to a solution of acetylacetone (600 □L, 6 mmol) and sodium methyl oxide (500 mg, 6 mmol) in ethanol (10 mL). This solution was then added to the reaction mixture and stirred for 2 hours. The solid

crude material was filtered, washed with three times with water, dried and recrystallized from benzene. The physical properties of compound **1** are shown in Table 1.

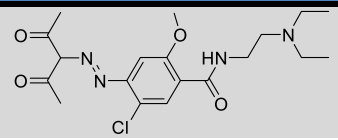
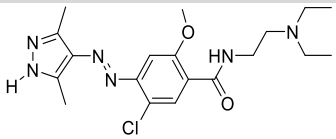
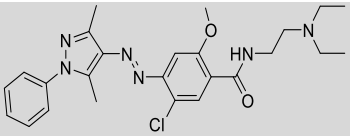
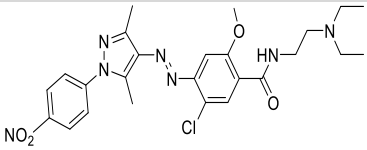
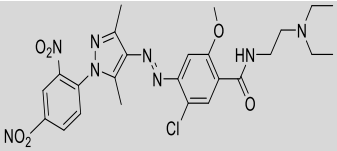
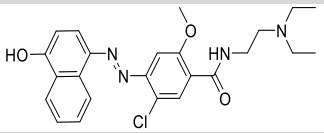
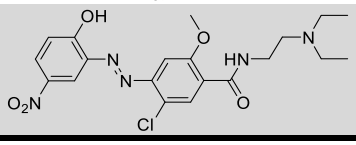
*Synthesis of pyrazole derivatives **2-5** [1,14]*

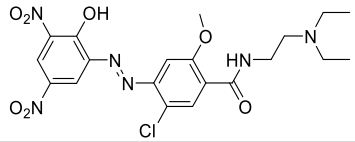
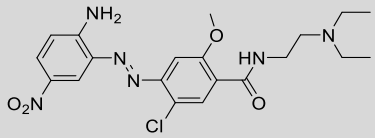
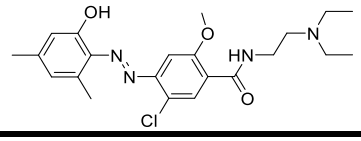
In a 100-mL round-bottom flask, compound **1** (2 g, 5 mmol) was dissolved in absolute ethanol (20 mL) before adding hydrazine hydrate (4 mL, 99%), phenyl hydrazine (500 □L, 5 mmol), 4-nitrophenyl hydrazine (700 mg, 5 mmol), or 2,4-dinitrophenyl hydrazine (980 mg, 5 mmol). The reaction mixture was then refluxed for 6 hours. The solid crude material was filtered, washed with cooled water, and dried. Table 1 lists the physical properties of these compounds (**2-5**).

*Synthesis of azo compounds **6-10***

A solution of metoclopramide hydrochloride (2 g, 6 mmol) in distilled water (10 mL). The solution was then cooled to 0-5 °C using an ice bath. $NaNO_2$ (50 mg, 6 mmol) was dissolved in distilled water (5 mL). Then, the first solution was added slowly and stirred for 10 minutes. This mixture was slowly added to a solution of several substituted phenols (6 mmol) in methanol (15 mL) and NaOH (2 mL, 10%) at 0-5 °C and stirred for 30 minutes. Before it can be cleaned in distilled water that has been cooled and dried with hot steam, the colored object needs to be filtered. Table 1 shows the physical properties of the prepared compounds (**6-10**).

Table 1: Some of the physical properties of the prepared compounds **1-10**

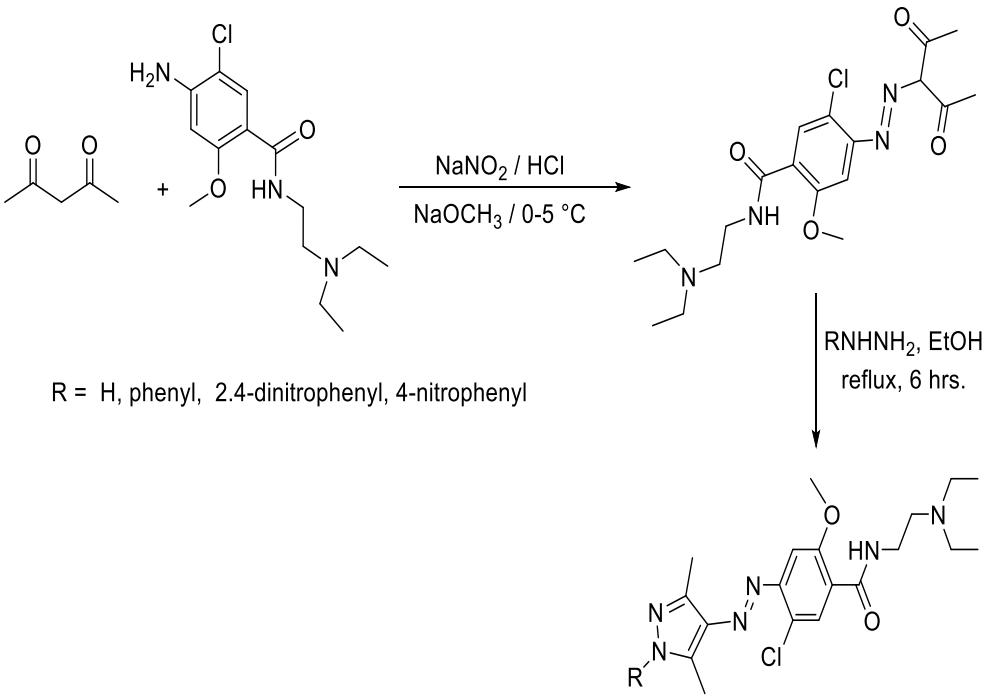
No.	Compound structure	Molecular formula and Molecular weight (g\mol)	m.p. (°C)	Colour	Yield (%)	Solvent of recrystallization
1		$C_{19}H_{27}O4ClN_4$ 410	170-175	Yellow	80	**Ethanol: H_2O**
2		$C_{19}H_{27}O_2ClN_6$ 406.91	188-190	Orange	75	**Ethanol**
3		$C_{25}H_{31}O_2ClN_6$ 483.22	180-184	Red	82	**Ethanol**
4		$C_{25}H_{30}O_4ClN_7$ 528	228-231	Orange	87	**Ethanol**
5		$C_{25}H_{29}O_6ClN_8$ 573	198-200	Yellow	93	**Ethanol**
6		$C_{24}H_{27}O_3ClN_4$ 454.95	107-110	Red	95	**NaOH:H_2O**
7		$C_{20}H_{25}O_5ClN_5$ 449.89	93-95	Yellow	84	**NaOH:H_2O**

8		$C_{20}H_{24}O_7ClN_6$ 494.89	118-120	Yellow	86	**NaOH:H_2O**
9		$C_{20}H_{25}O_4ClN_6$ 448.91	180-183	Grey	77	**HCl:H_2O**
10		$C_{22}H_{29}O_3ClN_4$ 432.95	135-137	Red	76	**NaOH:H_2O**

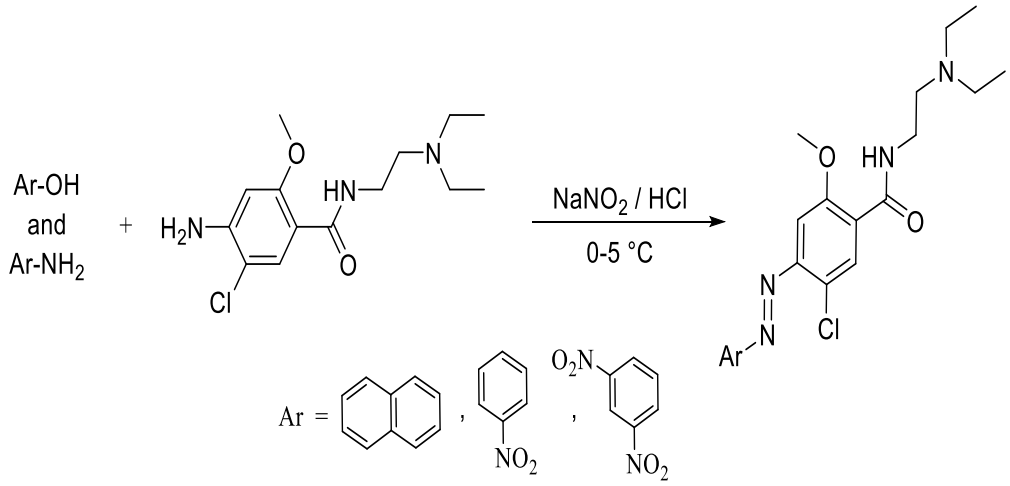
3. Results and discussion

3.1. Chemistry

The first part of our work includes the synthesis of azo compounds bearing pyrazole rings **2-5**, as shown in Scheme 1. These compounds were prepared in two steps; the first step included a reaction between 4-amino-5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxybenzamide and $NaNO_2$ in an acidic medium to yield the corresponding diazonium salt, which was treated later with acetylacetone in the presence of sodium methoxide as a base. The desired product **1** was obtained with an 80% yield. The second step in this part included preparing pyrazole derivatives *via* the reactions of compound **1** with hydrazine hydrate, phenylhydrazine, 4-nitrophenyl hydrazine, and 2,4-dinitrophenylhydrazine, which provided the desired products **2-5** in good to excellent yields (75-93%).



Scheme 1 - Synthesis of compounds **2-5**



Scheme 2: Synthesis of compounds **6-10**

Table 2: FT-IR spectral data (ν, cm^{-1}) of the compounds **1-5**

Comp. No.	C-H Aromatic	C-H Aliphatic	C-O	C=N Imine	C-N	N=N Azo	C=C Aromatic	N-H Amide	C=O Amide	Other bands
1	3055	2970 2935	1170	-	1303	1556	1602 1471	3382	1650	**1683 C=O ketone**
2	3001	2970 2937	1045	1645	1344	1510	1577 1473	3193	1634	**1408 N-N**
3	3056	2968 2933	1251	1631	1305	1552	1595 1463	3251	1650	**1409 N-N**
4	3002	2970 2937	1251	1641	1251	1579	1595 1463	3286	1650	**1519 Asymmetric NO_2 1338 Symmetric NO_2 1409 N-N**
5	3020	2972 2875	1172	1641	1309	1556	1618 1546	3313	1683	**1512 Asymmetric NO_2 1332 Symmetric NO_2 1415 N-N**

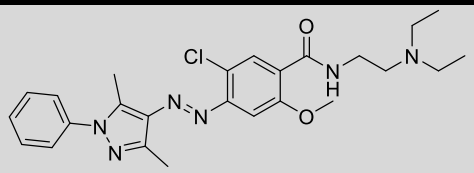
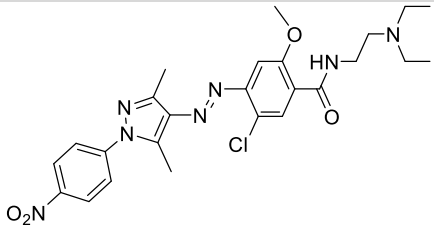
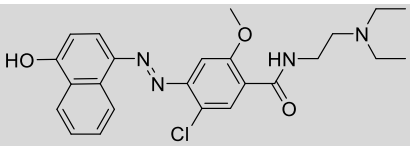
The second part of our work includes the synthesis of azo compounds **6-10**, as shown in Scheme 2. These compounds were prepared *via* the reaction of 4-amino-5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxy benzamide with $NaNO_2$ in an acidic medium to give the corresponding diazonium salt, which was treated with various phenols and amines to afford the desired azo compounds **6-10**. The FT-IR spectra of these compounds showed absorption bands in the range of 3457 cm^{-1} attributed to the N-H stretching vibrations. The absorptions in the 1467 cm^{-1} range are caused by aromatic C=C stretching vibrations. The absorption in the range between 1178 and 1258 cm^{-1} is due to C-N stretching vibrations, and the range between 1521 and 1499 cm^{-1} is for N=N vibrations (Tables 2 and 3). The absorptions from 1510 to 1579 cm^{-1} refer to C=N vibrations. The ^1H NMR spectrum of compound **1** shows signals at 1.12 and 1.90 ppm for the four CH_3 groups. Signals at 2.6, 2.7, and 3.5 ppm are attributed to

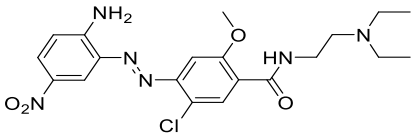
the CH_2 groups. The chemical shift of the methoxy group was at 4.0 ppm. Mutilate signals between 7.0 and 8.0 belong to the aromatic protons. The singlet signal at 9.0 ppm is for the N-H proton. The ^{1}H NMR spectrum of compound **2** shows signals at 1.1 and 2.52 ppm for the four CH_3 groups. Signals at 2.6, 2.8, and 3.5 ppm are attributed to the CH_2 groups. The chemical shift of the methoxy group was at 4.0 ppm. Mutilate signals from 7.0 to 8.0 ppm belong to the aromatic protons. The singlet signal at 8.5 ppm is for the N-H proton. The ^{1}H NMR spectrum of compound **3** shows signals at 1.2 ppm for the two CH_3 groups. Signals at 2.7, 2.8, and 3.7 ppm are attributed to the CH_2 groups. The chemical shift in the methoxy group was at 3.90 ppm. Mutilate signals from 7.0 to 8.0 ppm belong to the aromatic protons. The singlet signal at 8.4 ppm is for the OH proton. The singlet signal at 8.6 ppm is for the N-H (Table 4).

Table 3: FT-IR spectral data (ν□□cm^{-1}) for the compounds **6-10**

Compound number	C-H Aromatic	C-H Aliphatic	C-O	C-N	N=N Azo	C=C Aromatic	N-H Amide	C=O Amide	Other bands
6	3051	2970 2939	1215	1276	1543	1600 1462	3278	1627	**3429 ν(OH)**
7	3079	2972 2875	1111	1311	1492	1581 1458	3228	1681	**3475 ν(OH)**
8	3028	2970 2939	1151	1303	1550	1598 1467	3357	1649	**ν(OH) 3380**
9	3015	2970 2935	1107	1249	1597	1635 1381	2981	1655	**1512 Asymmetric NO_2 1332 Symmetric NO_2**
10	3028	2970 2939	1151	1232	1467	1649 1521	3357	1660	-

Table 4: ^{1}H NMR spectral data (δ, ppm)

Compound number	Structure	^{1}H NMR spectral data (δ ppm)
1		**9.0 (s,1H, NH), 7.0-8.0 (m, 7H, Ar-H), 4.0 (s, 3H, OCH_3), 3.3-3.5 (m, 2H, CH_2), 2.7-2.9 (m, 2H, CH_2), 2.3-2.5 (m, 4H, $2CH_2$), 1.9 (s, 6H, $2CH_3$), 1.10-1.12 (m, 6H, $2CH_3$)**
2		**8.5 (s, 1H, NH), 7.0-8.0 (m, 6H, Ar-H), 4.0 (s, 3H, OCH_3), 3.5-3.7 (m, 2H, CH_2), 2.8 (s, 3H, CH_3), 2.4-2.6 (m, 2H, CH_2), 2.52 (s, 3H, CH_3), 2.2-2.3 (m, 4H, $2CH_2$), 1.1-1.3 (m, 6H, $2CH_3$)**
3		**8.6 (s, 1H, NH), 8.4 (s, 1H, OH), 7.0-8.0 (m, 8H, Ar-H), 3.90 (s, 3H, OCH_3), 3.5-3.7 (m, 2H, CH_2), 2.8-2.9 (m, 2H, CH_2), 2.4-2.7 (m, 4H, $2CH_2$), 1.2-1.3 (m, 6H, CH_3)**

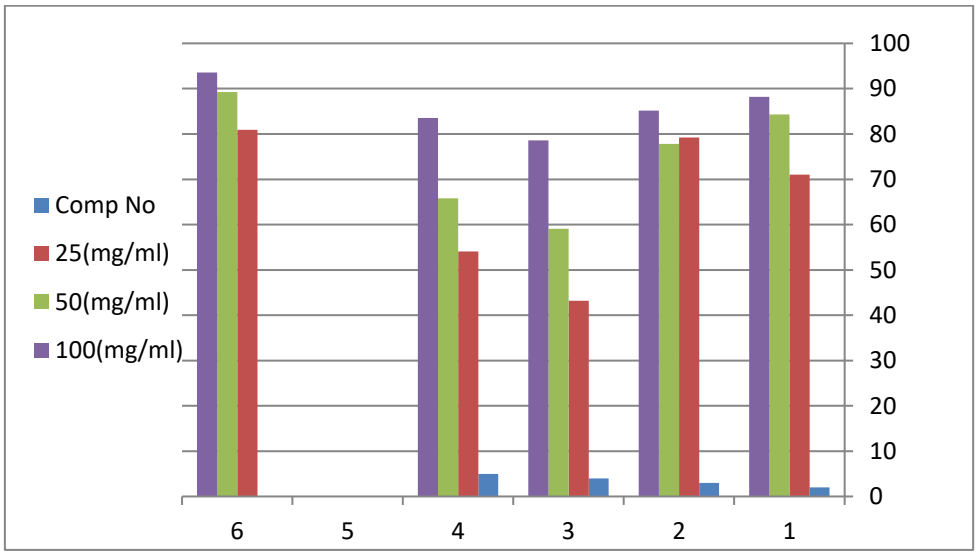
4		**9.0 (s, 1H, NH), 7.0-8.0 (m, 5H, Ar-H), 3.9 (s, 3H, OCH_3), 3.7 (s, 2H, NH_2), 3.2-3.7 (m, 2H, CH_2), 3.1-3.3 (m, 4H, $2CH_2$), 2.6-2.8 (m, 2H, CH_2), 1.3-1.5 (m , 6H, CH_3)**

3.2. Antioxidant activity - DPPH radical detoxification activity [15-17]

1،1-Diphenyl-2-picrylhydrazyl (DPPH): Re-treated in ethanol (100 mL), keeping the solution protected from light. Various concentrations (25, 50, and 100 ppm) of some of the produced chemicals were prepared. It was prepared by mixing the compound (1 mg) with ethanol (10 mL) to make 100 ppm, which was then diluted to 50 and 25 ppm, etc. Ascorbic acid (vitamin C): Similar concentrations were prepared.

Table 5: Antioxidant activities of compounds **2-5**

Compound number	25 (mg/mL)	50 (mg/mL)	100 (mg/mL)
2	71.03	84.29	88.2
3	79.21	77.81	85.17
4	43.18	59.12	78.57
5	54.07	65.82	83.53
Ascorbic acid	80.95	89.25	93.54



4. Conclusion

In this work, varieties of pyrazole derivatives were synthesized from azo-acetylacetone derivatives and azo compounds bearing metoclopramide. The derivatives of these compounds were studied and tested as antioxidants, and they showed good efficacy compared to vitamin C.

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