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Synthesis, Identification and Evaluation Antioxidant of Some New Pyrazole and Pyrimidine Derivatives From Metoclopramide Drug

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Abstract:
Oxidative stress is recognized as a major contributor to the development of serious diseases. Therefore, there is a significant demand in medicinal chemistry for the discovery of new potent antioxidants with high efficiency and low toxicity. In this context, we describe the design, synthesis, molecular modeling, and antioxidant evaluation of novel hybrids containing pyrazole or pyrimidine. The compounds were designed, synthesized, and characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and physical properties. The synthetic process begins by reacting Metoclopramide with sodium nitrite, followed by a coupling reaction with methyl acetoacetate and acetylacetone, respectively, to form stable and colored compounds [S1, S2] in an alkaline medium of sodium hydroxide. Subsequently, the Metoclopramide derivative [S1] is treated with hydrazine hydrate and its derivatives to produce pyrazole compounds [S3-S8]. Finally, compound [S2] reacted with urea or thiourea to give pyrimidine compounds [S9, S10].

Keywords: Metoclopramide, coupling reaction, pyrazole, pyrimidine, antioxidant

تحضير وتشخيص وتقييم مضادات الأكسدة لبعض مشتقات البايرازول والبيريميدين الجديدة من عقار الميتوكلوبراميد

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الخلاصة
يُعتبر الإجهاد التأكسدي عاملًا رئيسيًا في تطور الأمراض الخطيرة ، لذلك، هناك طلب كبير في الكيمياء الطبية لاكتشاف مضادات أكسدة قوية جديدة ذات كفاءة عالية وسمية منخفضة .في هذا السياق، نصف تصميم وتحضير وتقييم مضادات الأكسدة لمشتقات جديدة تحتوي على البايرازول والبيريميدين .تم تصميم المركبات وتحضيرها وتشخيصها باستخدام تقنياتFT-IR، ^{1}H-NMR ، و^{13}C-NMR، بالإضافة إلى دراسة بعض الخواص الفيزيائية .يبدأ المسار التحضيري بتفاعل عقار الميتوكلوبراميد مع نتريت الصوديوم، متبوعًا

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بتفاعل ازدواج مع ميثيل أسيتو أسيتات وأسيتيل أسيتون، مما يؤدي إلى تكوين مركبات ثابتة وملونة [S1,S2] في وسط قلوي باستخدام هيدروكسيد الصوديوم .بعد ذلك، تفاعل مشتق الميتوكلوبراميد [S1] مع الهيدرازين ومشتقاته ليعطي مركبات البايرازول [S3–S8].أخيرًا، تفاعل المركب [S2] مع اليوريا أو الثايويوريا للحصول على مركبات البيريميدين [S9, S10].

1. Introduction:

Metoclopramide, also known as 4-amino-5-chloro-[N]-[2-(diethylamino) ethyl]-2-methoxybenzamide) (Figure 1), is commonly used in both adult and pediatric medicine as an antiemetic or gastrointestinal prokinetic drug. It is frequently prescribed to treat gastroparesis in patients with diabetes. Symptoms include nausea, vomiting, a satiety feeling, and a loss of zest [1,2].

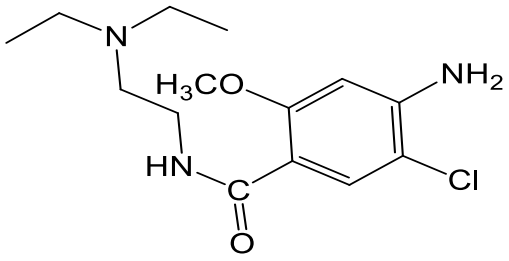


Figure 1: Structure of the Metoclopramide drug.

Oxidative stress is induced by the free radical damage to cell membranes and nucleic acids, which results in ageing, cancer, atherosclerosis, and Alzheimer's disease [3]. The studies on small-molecules with antioxidant efficacy to prevent the deleterious effects are an important field of research. The drug molecules that contain a pyrazole core remain a choice in medicinal chemistry towards more practical antioxidant agents [4-7]. The compound pyrazole is classified as heterocyclic since it consists of a five-membered ring with one double bond. It has three carbon atoms and two nitrogen atoms at positions 1 and 2 in a partly saturated non-aromatic ring [8,9]. Among the azole family of chemicals, they are among the most researched classes. Many compounds containing the pyrazole nucleus led to a wide range of uses in fields like technology, medicine, and agriculture [10-14]. In particular, they are described as inhibitors of anticancer [15-17], antimicrobial and antioxidant [18], antipyretic [19-22], antibacterial [23-27], anti-malarial, biodegradable, antileishmanial [28-30], anticonvulsant [31], and inflammatory [32,33]. Finally, have become attractive candidates for the development of new corrosion inhibitors by appropriately substituting them with required functional groups [34,35]. Additionally, they have been successfully developed into commercially viable medications, such as anti-inflammatory celecoxib and the alcohol dehydrogenase inhibitor fomepizole [36]. Heterocyclic compounds containing a pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [37]. This research involves the synthesis of new derivatives for heterocyclic compounds and the evaluation of their antioxidant activities. The structures of newly synthesized compounds were confirmed using FT-IR, ^{1}HNMR and ^{13}CNMR.

2. Materials and methods:

Melting points are uncorrected and were determined using digital melting point equipment. Using DMSO-d6 as an internal standard, all ^{1}H and ^{13}C NMR spectra were captured using a Bruker ultra-shield 400 MHz spectrometer. Potassium bromide discs were used to record the FT-IR spectral data on a Shimadzu FT-IR spectrophotometer. The

chemicals utilized in this investigation were provided by Merck, CDH, BDH, Fluka, and FDC Limited.

2.1 Synthesis of Azo Compounds [S1, S2] [38-41].

Metoclopramide (3g. 0.01mol.) was dissolved in a mixture of 2.0 mL. conc. HCl and 5 mL of H_2O, then cooled to 0-5 ˚C. The aforementioned cold mixture was thoroughly stirred before adding a solution of sodium nitrite (0.69 g., 0.01 mol.) in 3 mL of distilled water. The completion of the diazotization after 30 minutes was determined by adding a 0.01 mol solution of either methyl acetoacetate or acetylacetone. The pH of the reaction mixture was maintained at 8–9 by simultaneous addition of 10 % NaOH aqueous solution. Precipitation occurred, and the product was filtered, washed several times with ethanol: water (1:1) to give the azo compounds [S1, S2]. Physical properties of azo compounds are shown in Table 1.

2.2 Synthesis of Pyrazole Compounds [S3-S8] [34].

A solution containing 80% hydrazine hydrate and its derivatives (0.0013 mol.) in (10 mL.) of absolute ethanol was added with continuous stirring to (0.5 g, 0.0013 mol.) to a solution of compound [S1] in 10 mL of absolute ethanol. The mixture was then refluxed for 8-10 hrs. The reaction was monitored by TLC. The formed precipitate was filtered and purified by ethanol/H_2O (1:1). Physical properties of compounds [S3-S8] are shown in Table 1.

2.3 Synthesis of pyimidline Compounds [S9, S10] [42].

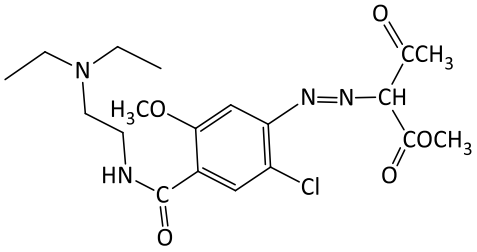
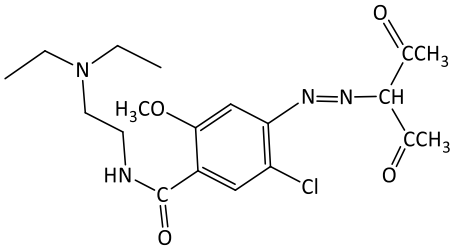
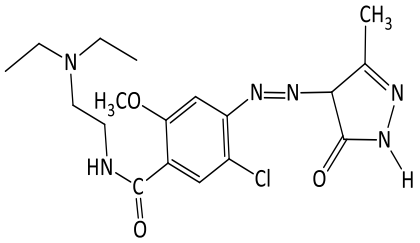
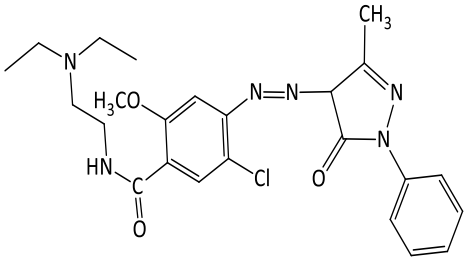
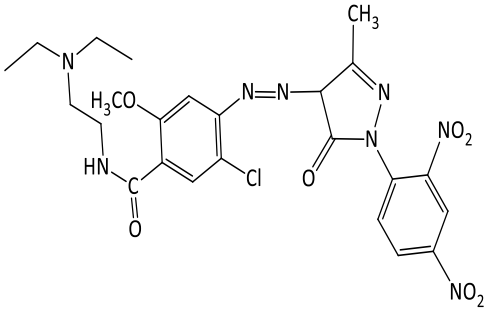
A solution of compound [S2] (0.5 g., 0.0014 mol.) in (3 mL) pyridine, urea or thiourea (0.0014 mol) was added with stirring, then, the mixture was refluxed for (6-8) hrs. The reaction was monitored by TLC and neutralized using cold, diluted hydrochloric acid. The formed precipitate was filtered and recrystallized from acetone. Physical properties of these derivatives are listed in Table 1.

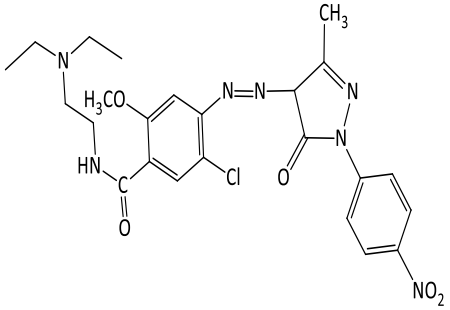
2.4 The Antioxidant Activity by DPPH Method [43-46].

The free radical scavenging activity was evaluated using the DPPH (1,1-diphenyl-2-picrylhydrazyl) assay, following a modified Blois method. A DPPH solution was prepared by dissolving 4 mg of DPPH in 100 mL of ethanol. To prevent photodegradation, the solution was protected from light by wrapping the container in aluminum foil. From [S3-S10], several concentrations (6.25,12.5, 25, 50, 100) ppm were generated. A 100 ppm solution was prepared by dissolving 1 milligram of the chemical with 10 milliliters of ethanol to create 100 parts per million, which was then diluted to (6.25,12.5, 25, and 50) ppm. (1 mL) of the solution (6.25,12.5, 25, 50, or 100) ppm was added to (1 mL) of the DPPH solution in a test tube. Following an hour of incubation at 37 °C, the absorbance of each solution was measured at 517 nm with a spectrophotometer. The reference utilized was ascorbic acid. The following equation was used to compute the percentage of scavenging activity of each extract on DPPH radical as % inhibition of DPPH (I%):

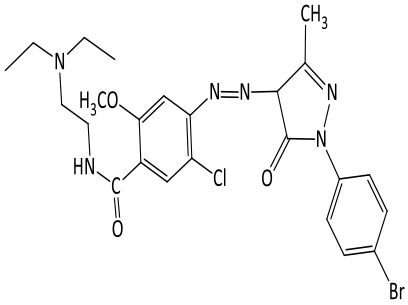
$$I\% = \frac{Abs(blank)}{\text{Abs(sample}} * 100 \quad (1)$$

Table 1: Physical properties of compounds [S1-S10]

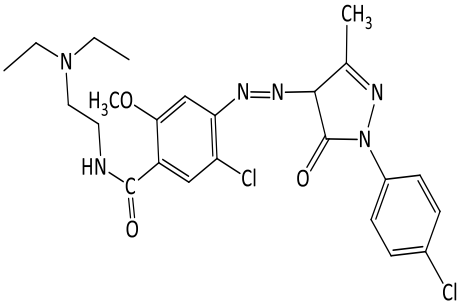
Comp. No	Structure of compounds	Yield %	Color	M.p ̊C
S1	 methyl 2-((2-chloro-4-((2-(diethylamino)ethyl)carbamoyl)-5-methoxyphenyl)diazenyl)-3-oxobutanoate	89	Orange	190-191
S2	 5-chloro-*N*-(2-(diethylamino)ethyl)-4-((2,4-dioxopentan-3-yl) diazenyl)-2-methoxybenzamide	85	Yellow	178-180
S3	 5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxy-4-((3-methyl-5-oxo-4, 5-dihydro-1*H*-pyrazol-4-yl)diazenyl)benzamide	76	Brown	oily
S4	 5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxy-4-((3-methyl-5-oxo-1-phenyl -4,5-dihydro-1*H*-pyrazol-4-yl)diazenyl)benzamide	70	Orange	166-168
S5	 5-chloro-*N*-(2-(diethylamino)ethyl)-4-((1-(2,4-dinitrophenyl)-3-methyl-5-oxo -4,5-dihydro-1*H*-pyrazol-4-yl)diazenyl)-2-methoxybenzamide	78	Dark orange	144-146

S6		73	Red	150-152

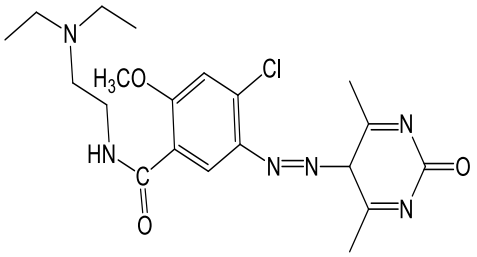
5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxy-4-((3-methyl-1-(4-nitrophenyl)-5-oxo -4,5-dihydro-1*H*-pyrazol-4-yl)diazenyl)benzamide

S7		85	Shine brown	206-208

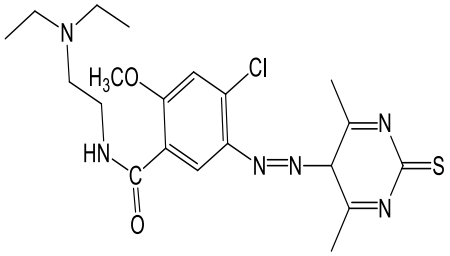
4-((1-(4-bromophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl)-5-chloro-N -(2-(diethylamino)ethyl)-2-methoxybenzamide

S8		75	Deep yellow	180-181

5-chloro-4-((1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)diazenyl) -N-(2-(diethylamino)ethyl)-2-methoxybenzamide

S9		78	white	185-187

4-chloro-N-(2-(diethylamino)ethyl)-5-((4,6-dimethyl-2-oxo-2,5-dihydropyrimidin-5-yl) diazenyl)-2-methoxybenzamide

S10		85	Off white	190-191

4-chloro-N-(2-(diethylamino)ethyl)-5-((4,6-dimethyl-2-thioxo-2,5-dihydropyrimidin -5-yl)diazenyl)-2-methoxybenzamide

3. Results and discussion:

3.1 Chemistry:

Researchers focused on synthesizing heterocyclic compounds due to their broad applications, particularly in biological, industrial, and agricultural fields. Consequently, they developed novel derivatives, including pyrazole and pyrimidine compounds. The structure of the product assignment on the melting point, FT-IR and NMR spectrum. The FT-IR spectrum of compound [S1] showed band at 1766 cm^{-1} due to ester carbonyl group, (1731) cm^{-1} due to ketone carbonyl group, ^{1}HNMR (ppm) of compound [S1]: at 7.91-7.81 aromatic protons, 3.92 CH_3-O-CO, 3.91 CH-N=N, 2.36 CH_3- CO, While the ^{13}C-NMR (ppm) of compound [S1]: 117.82-141.35 aromatic carbons , 99.45 N-**C**H-CO, 70.92 CH_3-O-CO, 32.00 CH_3- CO . The FT-IR spectrum of compound [S2] showed band at 1714 cm^{-1} due to ketone carbonyl group, and at 1458 cm^{-1} due to ν(N=N) , ^{1}HNMR (ppm) of compound [S2]: at 7.93-7.42 aromatic protons, 4.27 CH-N=N, 2.01 CH_3- CO, While the ^{13}C-NMR (ppm) of compound [S1]: 112.00-141.24 aromatic carbons ,99.32 N-**C**H-CO . FT-IR spectral data of Pyrazole compounds [S3, S9] confirms the presence of the NH of the pyrazole ring at 3325-3220 cm^{-1} and its derivatives[A4-S8] confirms the presence of the C=N of the pyrazole ring at 1629-1631 cm^{-1}, ^{1}HNMR (ppm) of compound [S4]: at 7.40-7.97 aromatic protons, 3.01 CH pyrazole ring , while the ^{13}C-NMR (ppm) of compound [S4]: 149.62 C=N pyrazole ring, 116.05 -134.70 aromatic carbons , 66.06 N-**C**H pyrazole ring. ^{1}HNMR (ppm) of compound [S10]: at 7.91 aromatic protons, 3.41 CH_3-, while the ^{13}C-NMR (ppm) of compound [S10]: 145.82 C=N, 190.27 C=S in pyrim.[47,48]. All data are listed in Table 2.

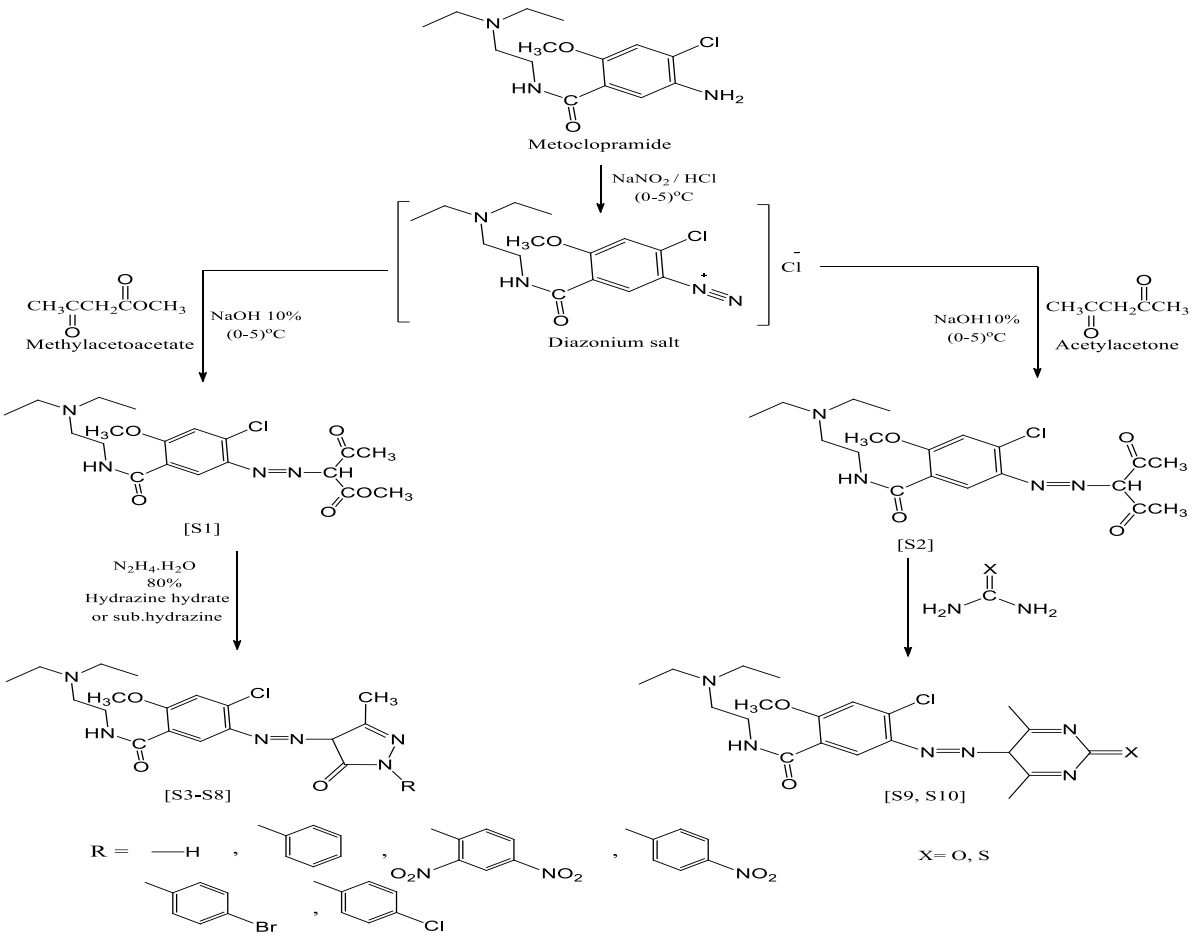


Figure 1: path way synthesis [S1, S2] and pyrazole compounds [S3-S10]

Diazonium salt, a well-known compound, is formed through the reaction between nitrous acid and aromatic primary amine such as Metoclopramide. Since sodium nitrite naturally reacts with excess mineral acid to generate the unstable nitrous acid (HONO), this acid must be freshly prepared in situ. Due to its instability, the formation and handling of the diazonium salt require the reaction to be conducted in a cold solution. In an alkaline solution, the diazonium salt and (Methyl acetoacetate and Acetyl acetone) completed a coupling process to produce the azo compounds [S1, S2]. The proposed mechanism is shown in Figure 2 [49].

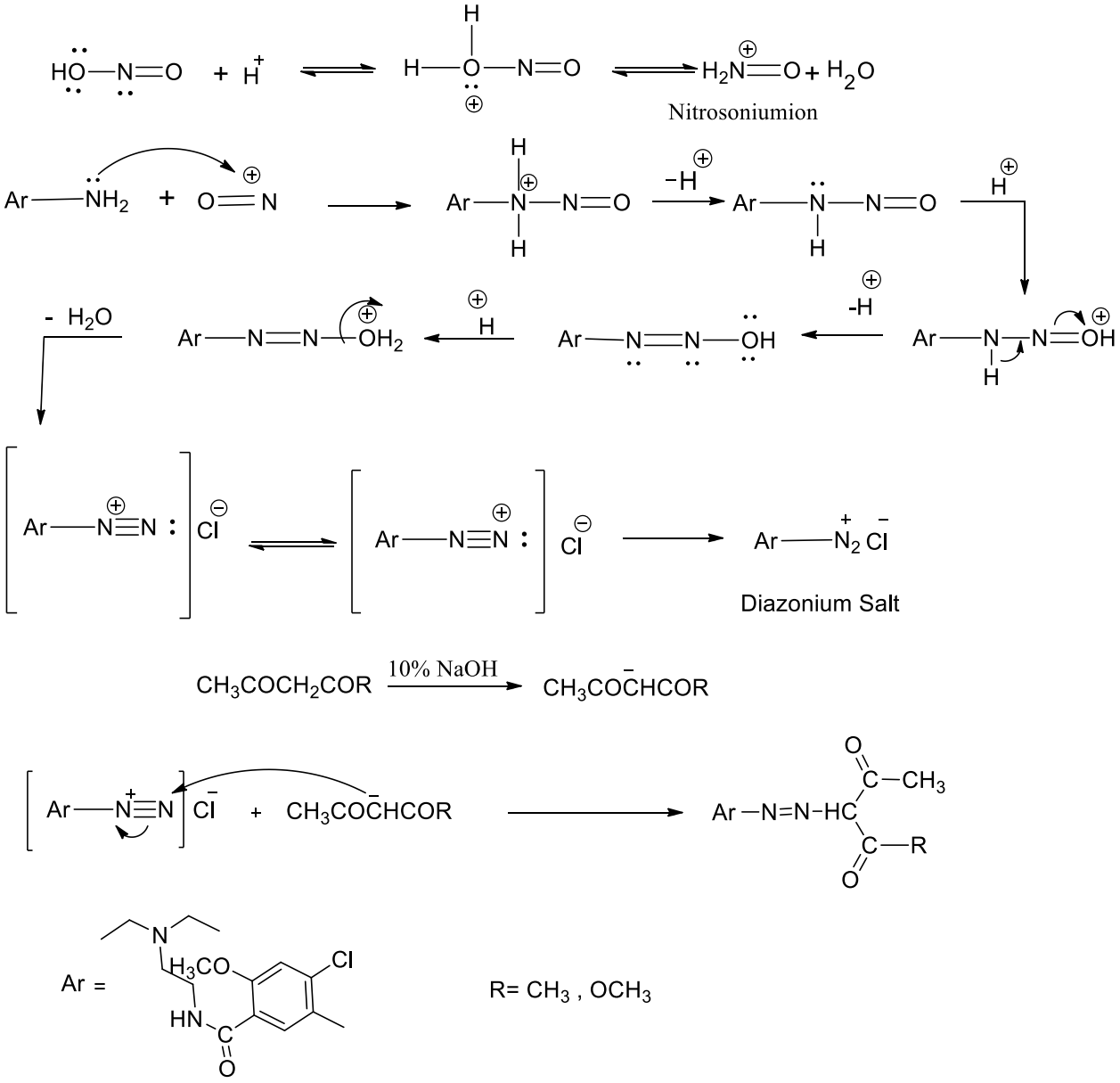


Figure 2: Mechanism steps for the synthesis of compounds [S1, S2]

The compounds [S3- S8] were produced as a result of the reaction between compound [S1] and hydrazine hydrate 80% and its derivatives (phenyl hydrazine, 2,4-dinitrophenyl hydrazine, 4-nitrophenyl hydrazine, 4-bromophenyl hydrazine, 4-chlorophenyl hydrazine), respectively. The suggested mechanism [50] for this reaction represents a nucleophilic substitution reaction through the nucleophilic attack of the amino group of hydrazine and its

derivatives on carbonyl group in the ester, followed by the loss of an ethanol molecule, as shown in Figure -3.

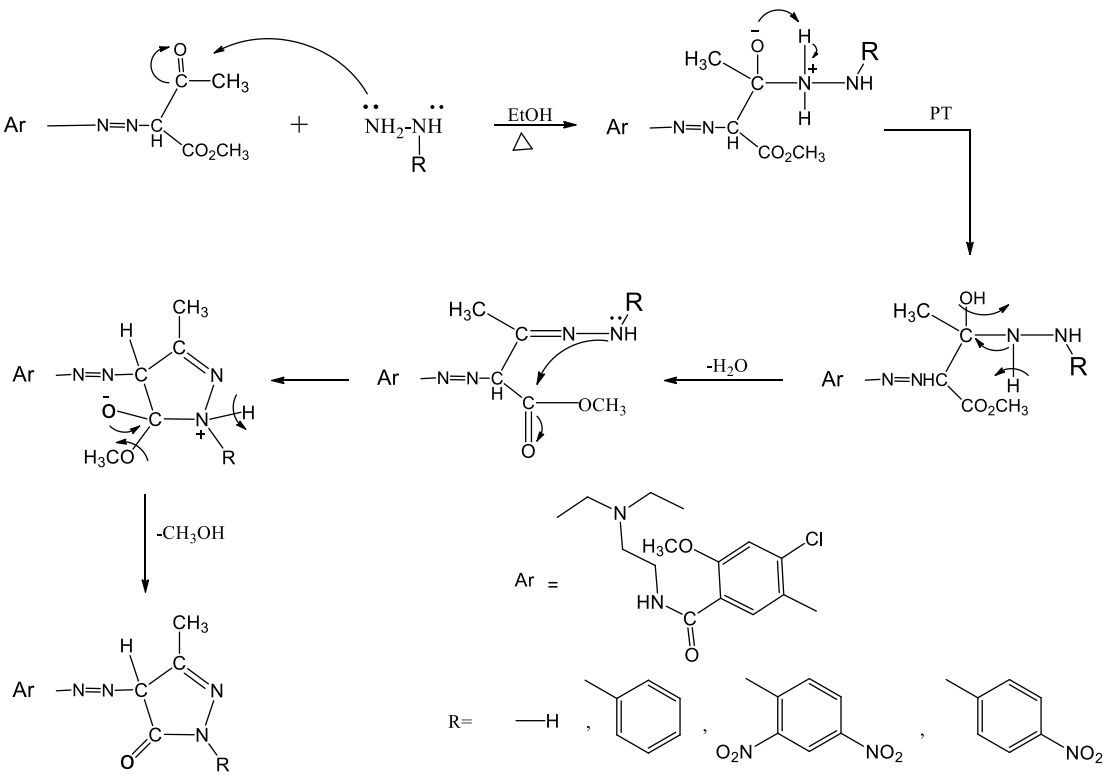


Figure 3: Mechanism steps for the synthesis of compounds [A1-A4]

The treatment of compound [S2] with urea or thiourea produced compound [S9,S10]. The proposed mechanism for these reactions [50], is illustrated in scheme (4), which describes a nucleophilic substitution process by the nucleophilic attack of the amino group of urea or thiourea on the carbonyl group in the ketone, followed by losing H_2O molecules, as shown in Figure 4.

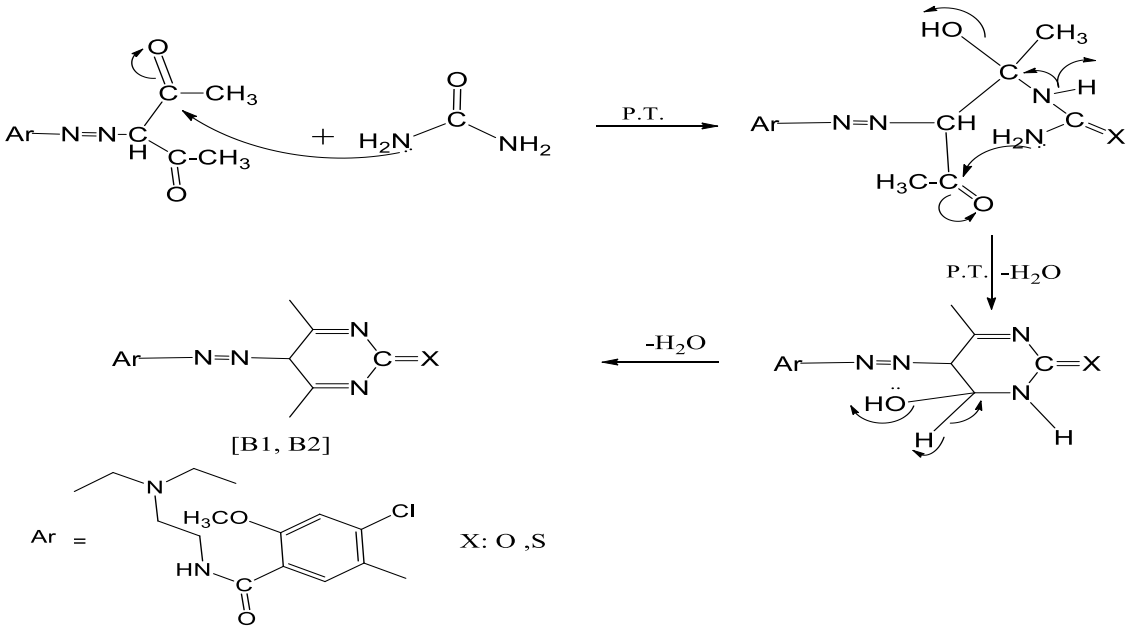
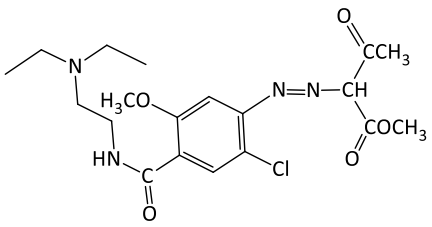


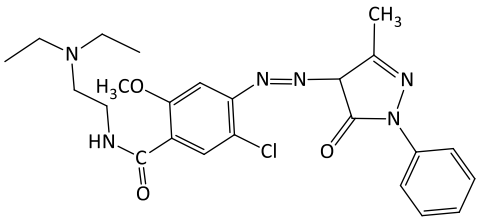
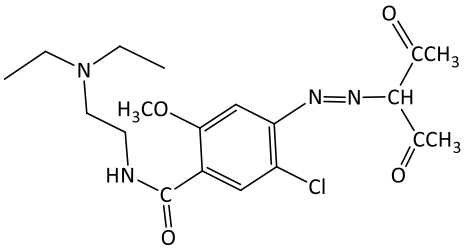
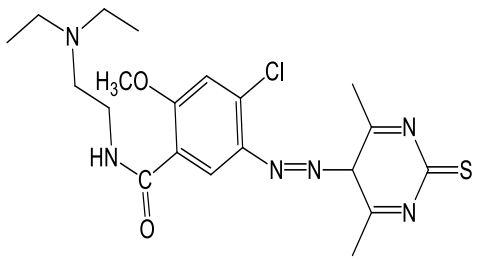
Figure 4: Mechanism steps for the synthesis of compounds [S9, S10]

Table 2: The FT-IR spectral data (cm^{-1}) of all prepared compounds

Comp. NO	ν(NH)	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O) amide	ν(C=N)	ν(C=C)	ν(N=N)	ν(C-N)	ν(C-O)	Others
S1	3379	3072	2935, 2875	1683	-	1600, 1508	1463	1303	1172	ν(C=O): *ester* 1766, ketone 1731 ν(C-Cl): 1043
S2	3382	3004	2970, 2877	1695	-	1569, 1514	1458	1355	1170	ν(C=O): ketone 1714 ν(C-Cl): 1047
S3	3325	3093	2935, 2870	1650	1641	1577, 1515	1415	1373	1130	ν(C-Cl): 1031
S4	3249	3097	2931, 2858	1668	1629	1591, 1550	1434	1311	1137	ν(C-Cl): 1031
S5	3386	3087	2939, 2858	1673	1641	1596, 1504	1415	1330	1134	*ν(C-Cl):* 1062, ν(C-NO_2): 1596,1367
S6	3210	3022	2911, 2867	1670	1629	1559, 1515	1417	1349	1113	ν(C-Cl): 1002, ν(C-NO_2): 1557,1372
S7	3251	3092	2920, 2864	1672	1630	1590, 1560	1420	1372	1132	ν(C-Cl): 1031, ν(C-Br): 671
S8	3280	3081	2924, 2866	1673	1631	1592, 1502	1418	1370	1133	ν(C-Cl): 1041
S9	3255	3075	2920, 2851	1675	1630 1625	1585, 1562	-	1365	1137	ν(C=O): pyrim.ring1692
S10	3350	3071	2995, 2852	1670	1632 1628	1590, 1582	-	1363	1135	ν(C=S): pyrim.ring1487

Table 3: The ^{1}H-NMR and ^{13}C-NMRspectral data (δ, ppm) of compounds [S1,S4,S2,S10]

Comp. NO.	Structure	^{1}H-NMR spectral data (δ, ppm)		^{13}C-NMR spectral data (δ, ppm)	
		δ ppm	*Group*	δ ppm	*Group*
S1		1.00-0.79	t,6H,CH_3-CH_2-N	19.95	**C**H_3-CH_2-N
		2.36	s, 3H, CH_3-CO	32.00	**C**H_3-CO
		2.48-2-49	q, 4H, CH_2-N	50.21	CH_3-**C**H_2-N
		3.83-3.81	t, 2H, CH_2-N	57.80	**C**H_2-CH_2-NH
		3.89	t, 2H, CH_2-NH	65.52	CH_2-**C**H_2-NH
		3.91	s, 1H, CH-N=N	70.92	**C**H_3-O-CO
		3.92	s, 3H, CH_3-O-CO	85.58	**C**H_3-O-Ar
		3.96	s, CH_3-O-Ar	99.45	N-**C**H-CO
		7.19-7.81	m, 2H, Ar-H	117.82-141.35	**C**-Ar
		8.40	s, 1H, NH	166.96	NH-**C**O-Ar

				168.99	O-**C**O-CH
				199.45	CH-**C**O-CH_3
		1.23-1.04	t, 6H, CH_3-CH_2-N	14.34	CH_3-CH_2-N
		2.24	CH_3-C in pyrazole	35.30	CH_3-C in pyrazole
		2.83-2.29	q, 4H, CH_2-N	40.59	CH_2-CH_2-NH
		3.01	s, 1H, CH in pyrazole	48.87	CH_2-CH_2-NH
S4		3.19	t, 2H, CH_2-N	59.07	CH_3-O-Ar
		3.99-3.65	t, 2H, CH_2-NH	66.06	N-CH in pyrazole
		4.00	s, CH_3-O-Ar	116.05-134.70	C-Ar
		7.40-7.97	m, 7H, Ar-H	149.62	C=N in pyrazole
		8.82	s, 1H, NH	167.96	CO in pyrazole
				170.06	NH-CO-Ar
		1.21-1.17	t,6H, CH_3-CH_2-N	13.67	CH_3-CH_2-N
		2.01	s, 6H, CH_3-C=O	27.13	CH_3-CO
		2.03-2.49	q, 4H, CH_2-N	31.87	CH_2-CH_2-NH
		3.66-3.77	t, 2H, CH_2-N	47.26	CH_3-CH_2-N
S2		3.95	s, CH_3-O-Ar	55.20	CH_3-O-Ar
		3.98	t, 2H, CH_2-NH	65.35	CH_2-CH_2-NH
		4.27	s, 1H, CH-N=N	99.32	N-CH-CO
		7.93-7.42	m, 2H, Ar-H	112.00-141.24	C-Ar
		8.56	s, 1H, NH	168.91	NH-CO-Ar
				198.35	CH-CO-CH_3
		1.00-1.02	t,6H, CH_3-CH_2-N	13.23	**C**H_3-CH_2-NH
		2.56-2.57	q, 4H,2-CH_2-N	20.03	**C**H_3-CH_2-NH
		2.60-3.30	t, 2H, CH_2-N	55.00	2CH_3
		3.41	s,6H, CH_3-	59.56	CH_2-N
S10		3.96	s,3H, OCH_3	61.45	O- **C**H_3
		4.09	t, 2H, CH_2-NH	116-129	**C**-Ar
		7.14	s, 1H, NH-N-hydraz.	145.82	C=N
		7.91	m, 2H, Ar-H	165.16	NH-**C**O-Ar
		8.40	s, 1H, NH-C=O	190.27	**C**=S in pyrim.

3.2 Anti-oxidant activities

The free radical scavenging ability of samples (S3-S10) was evaluated by the DPPH scavenging model system using equation (1). The derivatives were produced in a range of

concentrations, and their ability to suppress DPPH free radicals was evaluated by coupling them with their free radicals. Because ascorbic acid has several hydroxyl groups that can be stable free radicals and can capture free radicals of DPPH, it was employed as a reference when assessing absorption for its great efficacy as an antioxidant. After mixing these compounds with DPPH, their absorbance was recorded using spectral methods at a wavelength of 517 nm. This was done while keeping the workspace dark because light affects DPPH and can cause the radicals to replicate. It indicates how much substance is needed to inhibit 50% of the DPPH radicals with IC50; the stronger the substance's ability to inhibit free radicals, the lower the IC50, and vice versa. In general, it is observed in most of the measured compounds to increase the activity increases with increasing concentration of the substance as a result of increasing the percentage of free radicals captured by DPPH. At low concentrations (6.25–12.5 µg/mL), the free radical scavenging capacity of samples S3–S10 remained relatively stable, with minimal variation observed. However, when the concentration was increased (50 -100 µg/mL) all showed a promising radical scavenging ability. The compound [S3] showed radical scavenging ability up to 70% due to the presence of the hydrogen atom that can stabilise free radicals, and additionally, the compounds' derivatives (S3-S10) have good action. Because the compounds (S4-S8) have groups of carbonyl, and the compounds (S9, S10) have a group of thionyl. From these conclusions and the results shown in the table (4), the compounds (S3-S10) show medium-strength activity, and the compound (S3) in the pyrazol ring shows high activity due to its containment of hydrogen atoms that are capable of forming free radicals.

Table 4: DPPH radical scavenging assay of pyrazole compounds [S3-S10].

COMP. NO.	6.25 µg/ml	12.5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	IC50
S3	39.53	41.21	44.34	60.43	63.91	12.61
S4	16.25	25.21	28.69	53.91	63.45	63.72
S5	14.78	26.52	28.29	35.21	55.21	86.04
S6	20.72	28.38	29.16	36.12	57.18	82.41
S7	39.01	40.89	43.75	61.21	63.16	40.18
S8	38.13	40.97	43.8	59.11	62.99	42.37
S9	20.43	23.47	29.13	34.34	51.73	95.14
S10	22.56	25.37	31.18	36.25	53.73	89.02
ascorbic acid	42.92	52.74	65.92	83.07	97.11	5.38

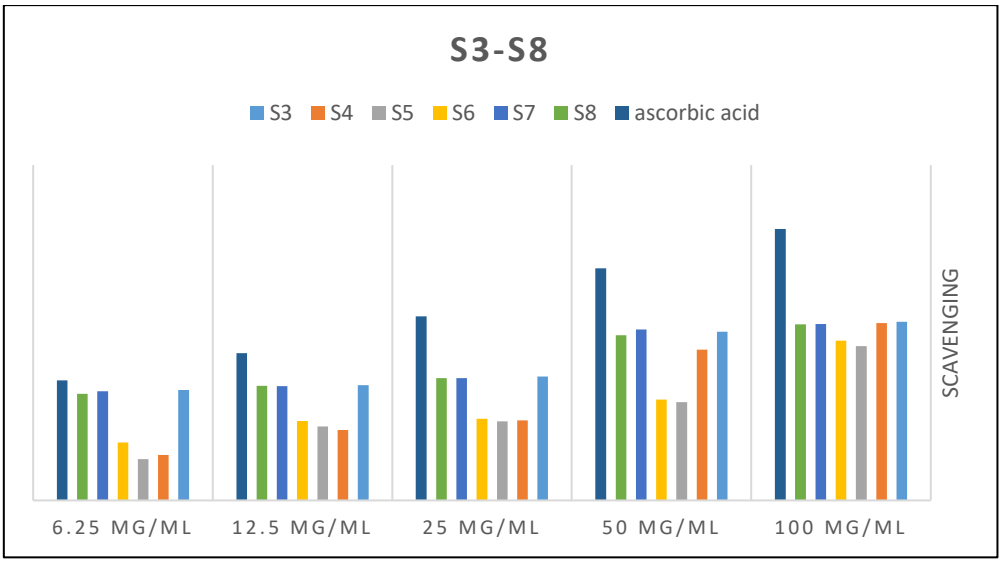


Figure 5: DPPH radical scavenging assay for pyrazole compounds [S3-S8]

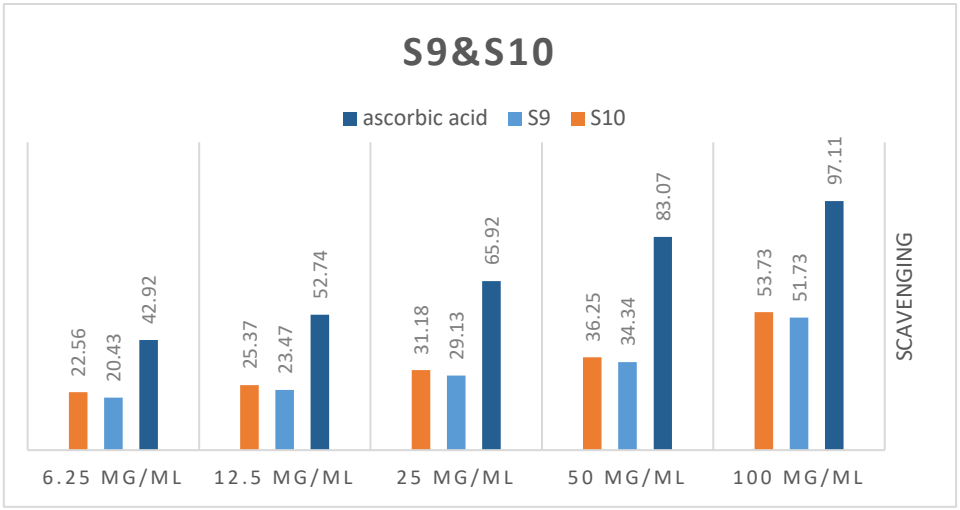


Figure 6: DPPH radical scavenging assay for pyrazole compounds [S9,S10]

Conclusion

This study successfully synthesized and characterized novel Metoclopramide -based derivatives. Structural analysis, confirmed by FT-IR along with ^{1}HNMR and ^{13}CNMR for selected compounds, confirmed the formation of the targeted molecules, demonstrating the effectiveness of the synthetic approach. Additionally, the antioxidant evaluation of these derivatives. The compounds [S3, S4, S7, S8], in particular, exhibited strong antioxidant activity, making them a standout candidate for further development as a multifunctional therapeutic agent. The findings of this study suggest that these novel metoclopramide derivatives hold significant promise in the development of new treatments for infections and oxidative stress-related conditions. Further studies, including in vivo testing and mechanism elucidation, are warranted to fully explore the therapeutic potential of these compounds.

6. Author's Declaration

- Conflicts of Interest: None.
- We hereby attest that every figure and table in the document belongs to us.
- Ethical Clearance: The University of Baghdad's local ethical commission gave its approval to the initiative.

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