Iraqi Journal of Market Research and Consumer Protection
(2024) 16(1): 248-260
DOI: http://dx.doi.org/10.28936/jmracpc16.1.2024.(21)
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المجلة العراقيه لبحوث السوق
وحماية المستهلك

SYNTHESIS AND CHARACTERIZATION OF SOME HETEROCYCLIC COMPOUNDS DERIVED FROM METOCLOPRAMIDE DRUG AND MEASUREMENT of BIOLOGICAL ACTIVITY

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Received 19/ 3/ 2023, Accepted 15/ 8/ 2023, Published 30/ 6/ 2024

ABSTRACT

This study included the synthesis of some new Schiff bases and heterocyclic compounds [1-6] from the reaction of metoclopramide with some aromatic aldehydes by the classical Schiff method, then the Schiff bases were treated with chloroacetyl chloride and thioglycolic acid to obtain cyclic derivatives of beta-lactams [5,6] and 4-thiazolidinone [3,4], respectively. These derivatives were characterized by their melting points by FT IR, 1H NMR. Some compounds prepared were evaluated for their antioxidant activity by oxidation with 2,2-diphenyl-1-picrylhydryl (DPPH). Comparison of the antioxidant activity of the bioactive molecules of the compounds [3–6] with that of the conventional drug metoclopramide showed encouraging results.

Keywords: Thioglycolic acid, Chloroacetyl chloride, Antioxidant, Schiff base.

تحضير وتشخيص بعض المركبات الحلقية غير المتجانسة المشتقة من عقار الميتوكلوبراميد وقياس فعاليتها البايلوجية

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الخلاصة

تضمنت هذه الدراسة تخليق بعض قواعد شيف الجديدة و المركبات الحلقية غير المتجانسة من تفاعل ميتوكلوبراميد مع بعض الألدهيدات العطرية بطريقة شيف الكلاسيكية، ثم تمت معالجة قواعد شيف بكلورو اسيتايل كلورايد وحامض الثايوگلايگولك للحصول على مشتق حلقي من بيتا -لاكتام [5،6] ومشتق 4-ثيازوليدينون [3،4] ،على التوالي. شخصت هذه المشتقات بنقطة انصهار, FT IR، ^{1}H NMR. تم تقييم بعض المركبات المحضرة في المختبر من حيث نشاطها المضاد للأكسدة في المختبر باستخدام (DPPH-2،2 diphenyl-1-picrylhydryl). أظهرت مقارنة النشاط المضاد للأكسدة للجزيئات النشطة بيولوجيًا للمركب [3-6] مع نشاط عقار ميتوكلوبراميد التقليدي نتائج مشجعة.

الكلمات المفتاحية: حامض الثايوكلايكولك، كلورواسيتايل كلورايد، مضادات اكسدة، قواعد شف.

***The research is taken from a master's thesis, the first research.**

INTRODUCTION

The continued existence of humans requires the presence of heterocyclic compounds. The use of synthetic heterocyclic compounds has a substantial influence on a wide variety of goods, including medications, chemotherapy drugs, dyestuffs, photographic chemicals, co-polymers, and a few more **(Al-Adhami & Al-Majidi, 2021)**. In the field of chemistry, a lactam ring that has four members is referred to as a beta-lactam (-lactam) ring.**(Joule et *al.*, 2020**). The term "lactam" refers to a cyclic amide, and beta-lactams get their name from the fact that the nitrogen atom is connected to the beta-carbon atom rather than the carbonyl atom. The 2-azetidinone is the simplest β-lactam that may be created. β-lactams are major structural components of pharmaceuticals**(Fisher *et al.*, 2005)**and have number of pharmacological activities**(Kaur *et al.*, 2020)**, anti-bacterial**(Mishra *et al.*, 2020)**, anti-fungal**(Jarrahpour et *al.*, 2017)**, and anti-inflammatory activities**(Arefi *et al.*, 2020)**. The general structure of 2-Azetidinone, and simplest β-lactam is shown in (Figure, 1).

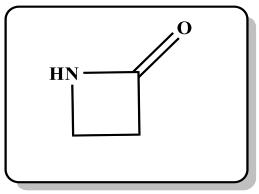


Figure (1): structure of 2-Azetidinone.

Thiazolidinones are derivatives of thiazoles which belong to one of the most intensively investigated classes of five-member heterocyclic compounds having a carbonyl group in addition to nitrogen and sulfur **(Cheddie *et al.*, 2020)**. In the field of medicinal chemistry, these substances are regarded as privileged scaffolds. and pharmacological because of their various biological activities**(Haroon *et al.*, 2021)**. Various isomers of thiazolidinone includes: thiazolidin-2-one, thiazolidin-4-one, thiazolidin-5-one, 2-thioxo-thiazolidin-4- one and thiazolidine-2,4-dione are associated with numerous pharmacological properties**(Nirwan *et al.*, 2019)**,

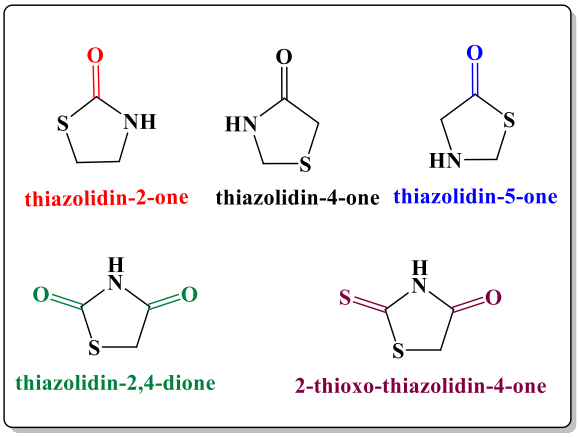


Figure (2): Some different isomers of thiazolidinones.

In particular, thiazolidinone derivatives have attracted interest due to the vast variety of biological features that they possess, in addition to the fact that they are included in the

structural makeup of a great deal of naturally occurring items. They are also the fundamental building blocks of the structures of a wide variety of pharmaceutically active drugs.**(Nirwan *et al.*, 2019)**

EXPERIMENTAL

MATERIALS AND METHODS

The BDH, Fluka, Merck, and Sigma Aldrich firms provide the chemicals that are utilized in this investigation, and those chemicals are used without any additional purification. In addition to this, the melting points that were recorded according to the point of electrothermal melting equipment remained correct. SHIMAZU FTIR-8400 Fourier transform infrared spectrophotometer was used to record FTIR spectra of the produced compounds in the spectral region of (4000-600) cm-1 using KBr discs. The 1H-NMR spectra were obtained by utilizing TMS as an internal reference and DMSO-d6 as a solvent throughout the recording process using a BRUKER 400MHz instrument located in Iraq.

Synthesis of 5-chloro-N-(2-(diethylamino)ethyl)-4-((4-(dimethylamino) benzylidene) amino)-2-methoxybenzamide and (E)-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxy-4-((4-nitrobenzylidene)amino)benzamide (Hamid & Obaid, 2020)

In a (50 mL) round bottom flask, the compound Metoclopramide (0.0044 mol), with equimolar amount of different substituted aromatic aldehydes (0.0044 mol) were added, in (10 mL) absolute ethanol and (2-3) drops of a catalyst glacial acetic acid. The mixture was refluxed in water bath for (6-7) h. The excess solvent was evaporated under reduced pressure. The generate product was dried and further purification was done using recrystallization from dioxan. Some of the physical properties of compounds [1,2] and yield are listed in Table (1.1).

Synthesisof 5-chloro-N-(2-(diethylamino)ethyl)-4-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)-2-methoxybenzamide and 5-chloro-N-(2-(diethylamino)ethyl)-2-methoxy-4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)benzamide [3,4](Ahamad & Hussain, 2015)

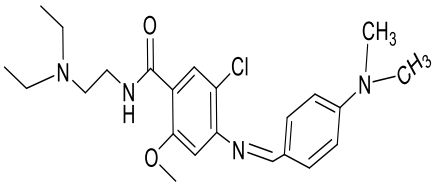
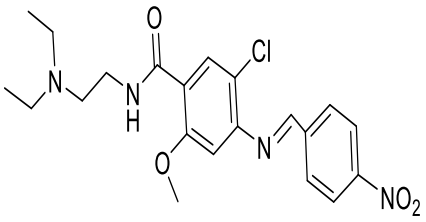
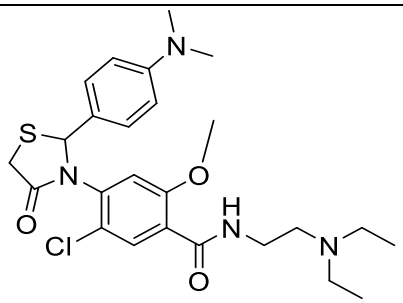
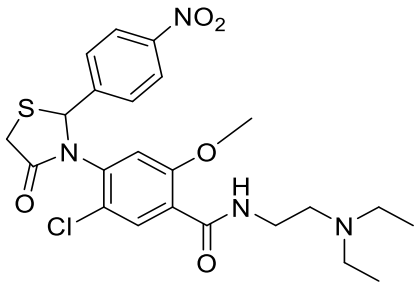
Ethanol with a combination of Schiff bases [1,2] (0.001mol) and an excess of thioglycolic acid (0.002mol). The response was allowed to reflux for a while (18-20h.). After evaporating the solvent, the residue was neutralized with a solution of sodium bicarbonate at a concentration of 5% in order to eliminate any excess thioglycolic acid. After being filtered, the precipitate that had formed was then washed with water many times before being recrystallized from chloroform**(Ali & Hassan, 2022).** Table contains a listing of the compounds' (3, 4) physicochemical features (1.1).

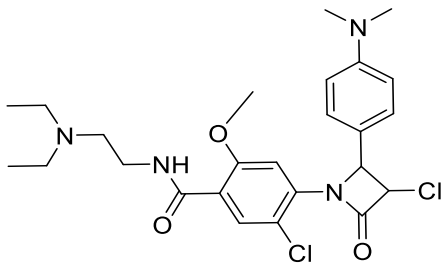
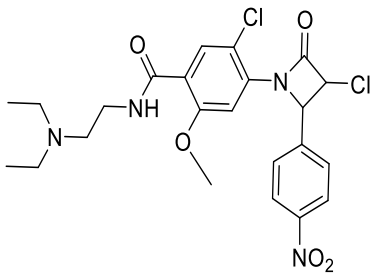
Synthesis of 5-chloro-4-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)-N-(2-(diethylamino)ethyl)-2-methoxybenzamide and 5-chloro-4-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)-N-(2-(diethylamino)ethyl)-2-methoxybenzamide[5,6](Sankar *et al.*, 2019)

After adding a combination of Schiff bases derivatives [1,2] with equimolar volumes of chloroacetyl chloride (0.2 mL, 0.0016 mol) and triethylamine (Et3N) (0.0016 mol) in 10 mL of THF as a solvent, the final product had 0.0016 mol of chloroacetyl chloride and 0.0016 mol of triethylamine. After that, the mixture was heated for (14-16) hours while in a reflux state. The contents were allowed to come down to room temperature, after which the precipitate that was

generated was filtered, washed with cold water, and then subjected to further purification using the recrystallization process with the use of ethanol**(Mousa & Jassim, 2021)**. The table below contains a few examples of the physical characteristics of compounds [5,6]. are listed in Table1.

Table (1): presents a few of the produced compounds' [1-6] observable physical characteristics.

N0.	Structure and Name	Formula and M.wt(g\mol)	M.P °C	Color	Yield (%)	Solvent of Rec
1		$C_{23}H_{31}ClN_4O_2$ 430	107-112	red	95	Ethanol
2		$C_{21}H_{25}ClN_4O_4$ 433	93-103	yellow	91	Ethanol
3		$C_{25}H_{33}ClN_4O_3S$ 505	118-122	yellow	86	Dioxane
4		$C_{23}H_{27}ClN_4O_5S$ 507	180-183	Grey	77	Dioxane

5		$C_{25}H_{32}Cl_2N_4O_3$ 507	135-142	Light Brown	76	THF
6		$C_{23}H_{26}Cl_2N_4O_5$ 509		Light Brown	72	THF

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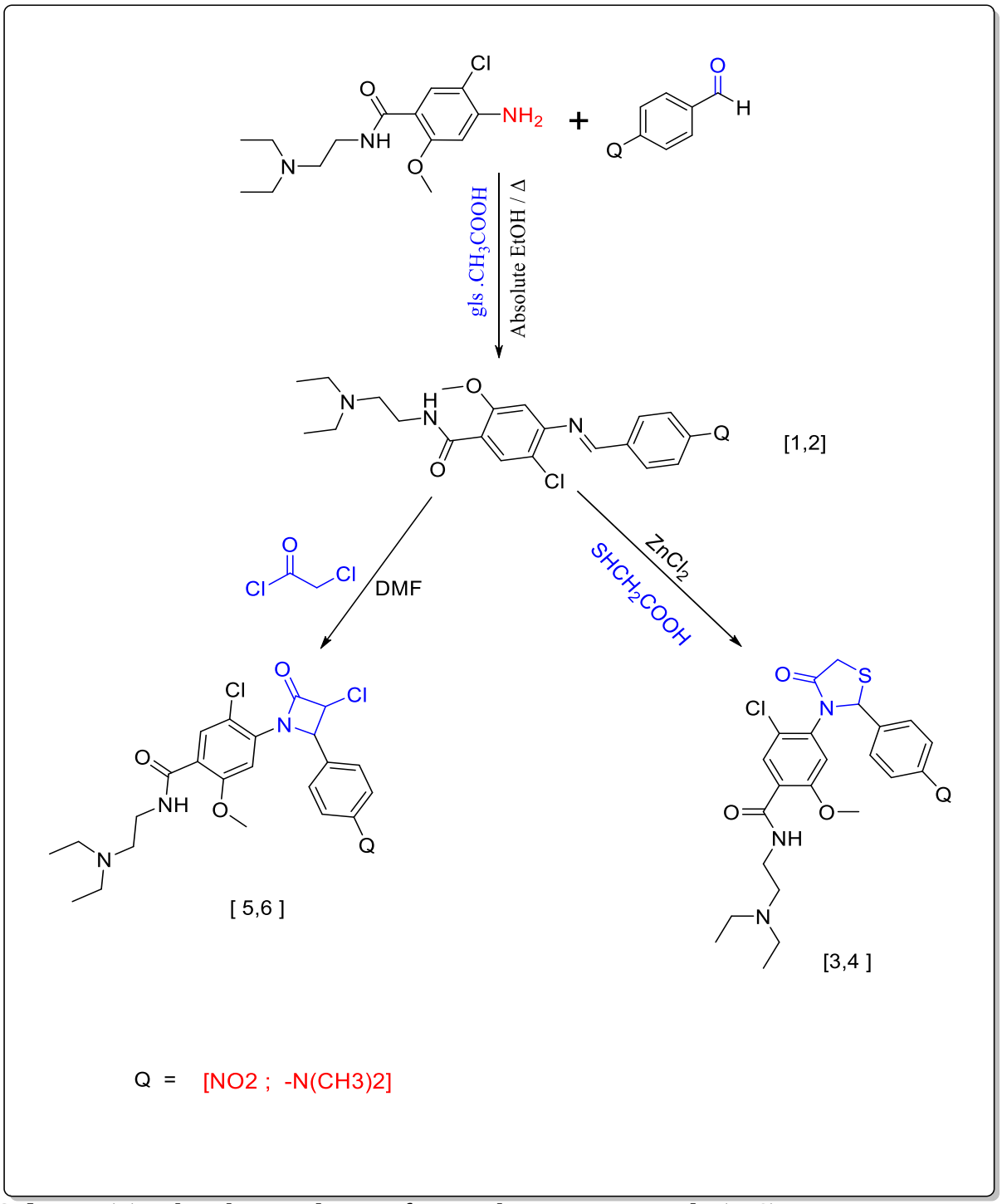
3.RESULTS AND DISCUSSION

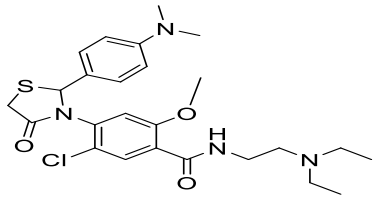
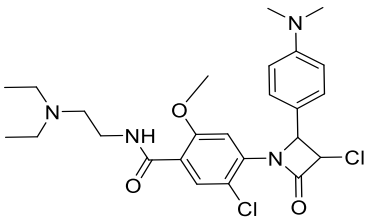


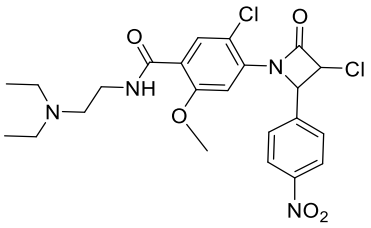
Scheme (1). The chemical steps for synthesis compounds (1-6).

Table (2): FT-IR spectral data (cm^{-1}) for the compounds [1-6]

Comp. No.	νC-H Aromatic	νC-H Aliphatic	νC-O	νC-Cl	C-N	ν C=C Aromatic	νN-H Amide	νC=O Amide	Other bands (ν)cm^{-1}
1	3004	2977 2881	1234	850	1303	1595	3290	1708	1639 (νC=N)Imine
2	3105	2970 2985	1246	856	1344	1604	3221	1693	1647 (νC=N)Imine 1523 Asym. ν (NO2) 1413 Sym.ν (NO_2)
3	3055	2979 2941	1174	821	1305	1579	3220	1716	-
4	3005	2900 2804	1176	813	1251	1604	3221	1678	1523 Asym. (NO_2) 1365 Sym. (NO_2)
5	3109	2931 2868	1245	856	1309	1604	3259	1693	1525 Asym. (NO2) 1344 Sym. (NO_2) 1415 N-N
6	3105	2970 2889	1338	854	1270	1639	3290	1689	-

Table (3): ^{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, 6H, Ar-H), 4.0 (s, 3H, OCH_3), 3.5 (m, 4H, N-$2CH_2$), 2.7 (s, 2H, O=C-CH_2), 2.6 (m, 4H, $2CH_2$), 4.16 (s, 1H, N-CH thiazolidine ring), 1.12-2.3 (m, 12H, 4-CH_3)
2		8.5(s,1H ,NH), 7-8 (m,6H,Ar-H), 5.3(s,1H,N-CH-C=O), 5.44(s,1H,CH-Cl) 4(s,3H,O-CH_3), 3.5 (m , 2H ,NH-CH_2), 2.6(m,4H,N-CH2), 2.2(m, 4H , $2CH_2$), 1.1-2.1(m , 12H , $4CH_3$)

3		8.6(s,1H ,NH), 7-8 (m,6H,Ar-H) 5.16(s,1H,N-CH-C=O), 5.45(s,1H,CH-Cl) 3.90(s,3H,O-CH_3),3.7(m ,2H,N-CH_2), 2.7 (m, 4H , 2CH_2), 1.2(m , 6H , 2-CH_3)

The second part of our work includes the synthesis of Heterocyclic compounds. 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 1309 and 1270 cm^{-1} is due to C-N stretching vibrations, and the range between 1716 and 1689 cm^{-1} is for C=O amid vibrations. The absorptions from 856 cm^{-1} refer to C-Cl vibrations. The ^{1}H NMR spectrum of compound **1** shows signals at 1.12 and 2.3 ppm for the four CH_3 groups. Signals at 2.6, 2.4, 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 7.0-8.0 are 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 7.0-8.0 are 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 of the methoxy group was at 3.90 ppm. Mutilate signals from 7.0-8.0 are belong to the aromatic protons. The singlet signal at 8.6 ppm is for the N-H.

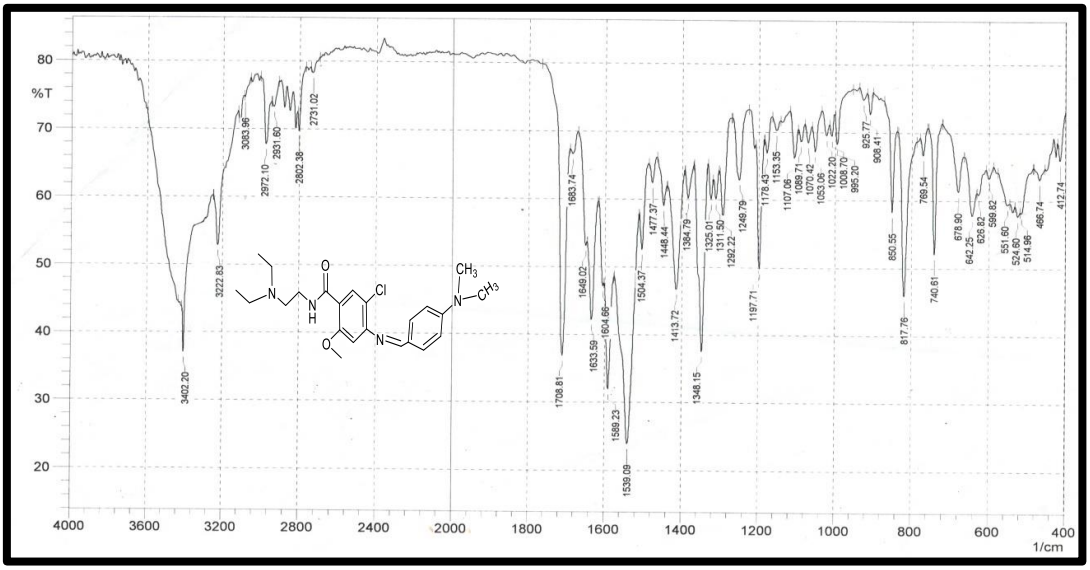


Figure (3). FT-IR spectrum for compound 1.

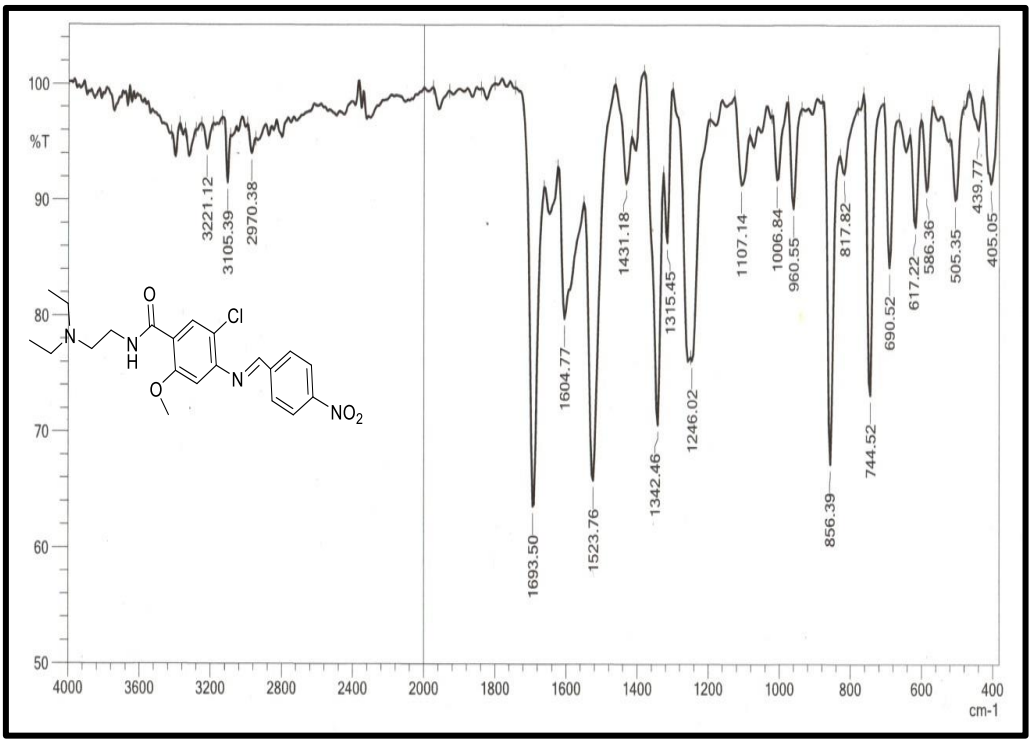


Figure (4): FT-IR spectrum for compound 2.

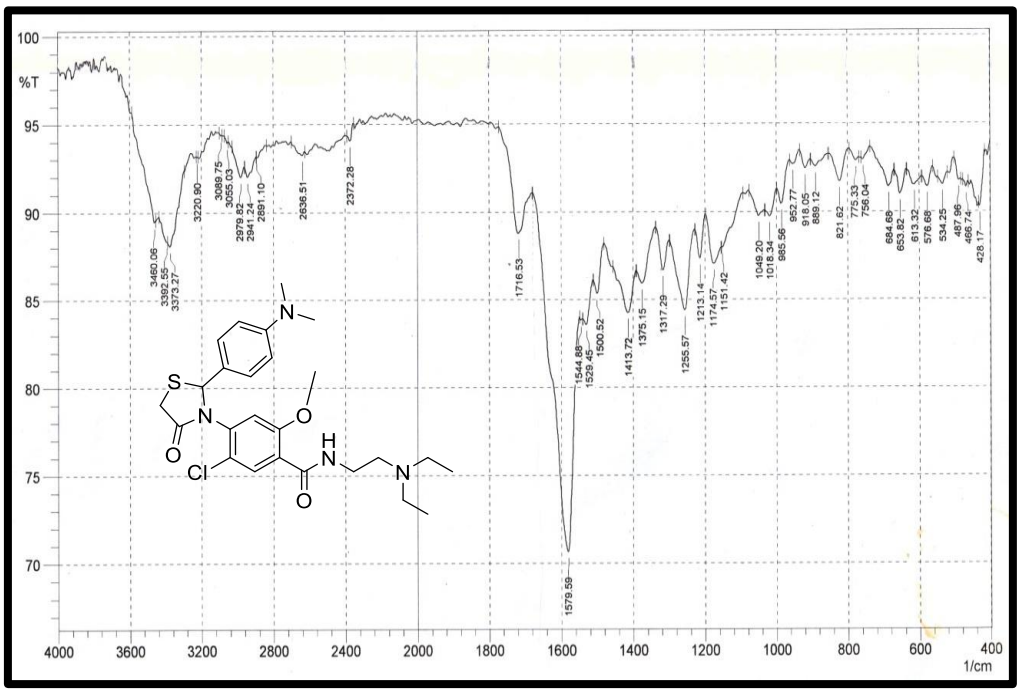


Figure (5). FT-IR spectrum for compound 3.

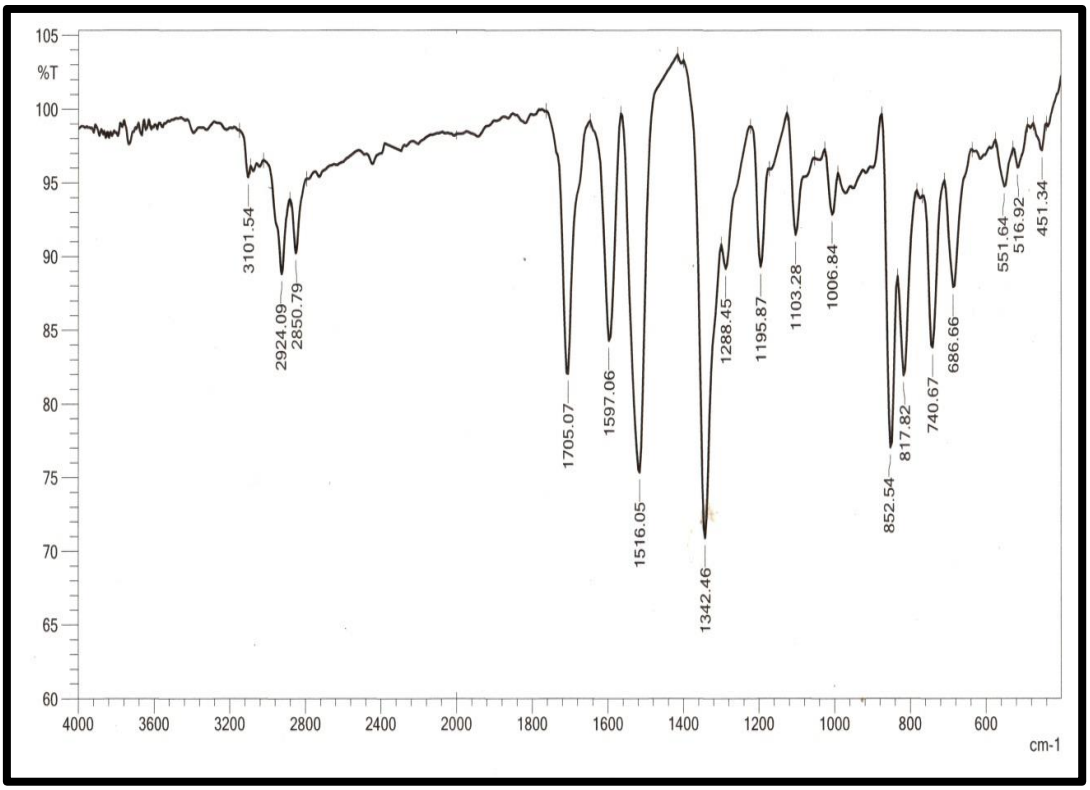


Figure (6): FT-IR spectrum for compound 4.

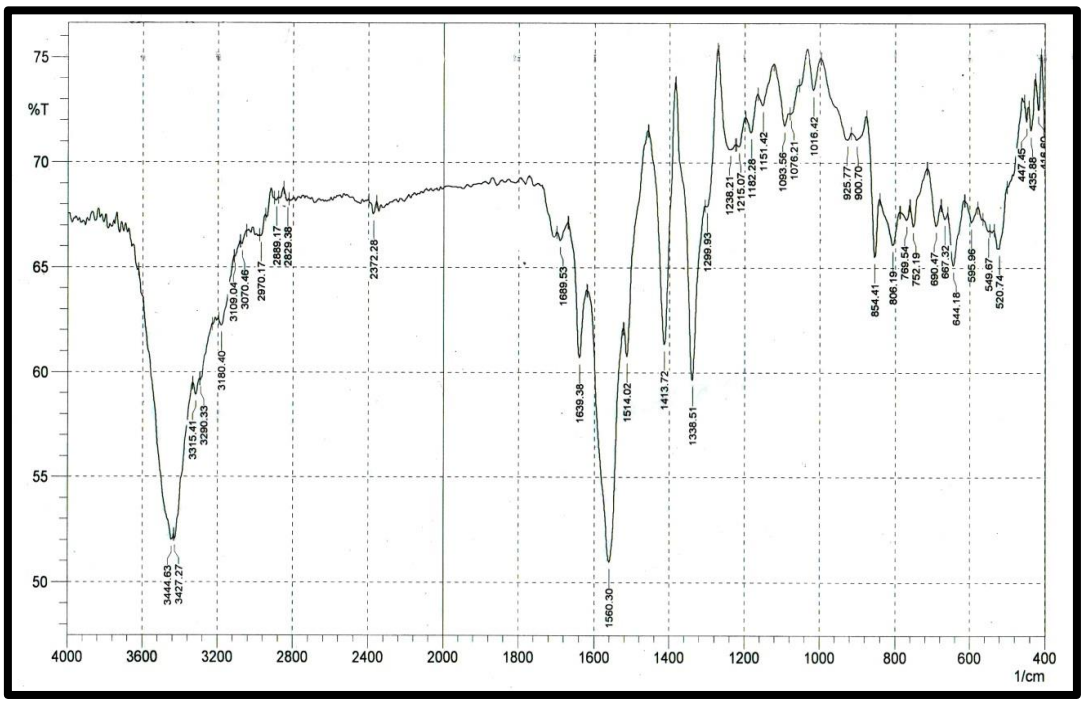


Figure (7): FT-IR spectrum for compound 5.

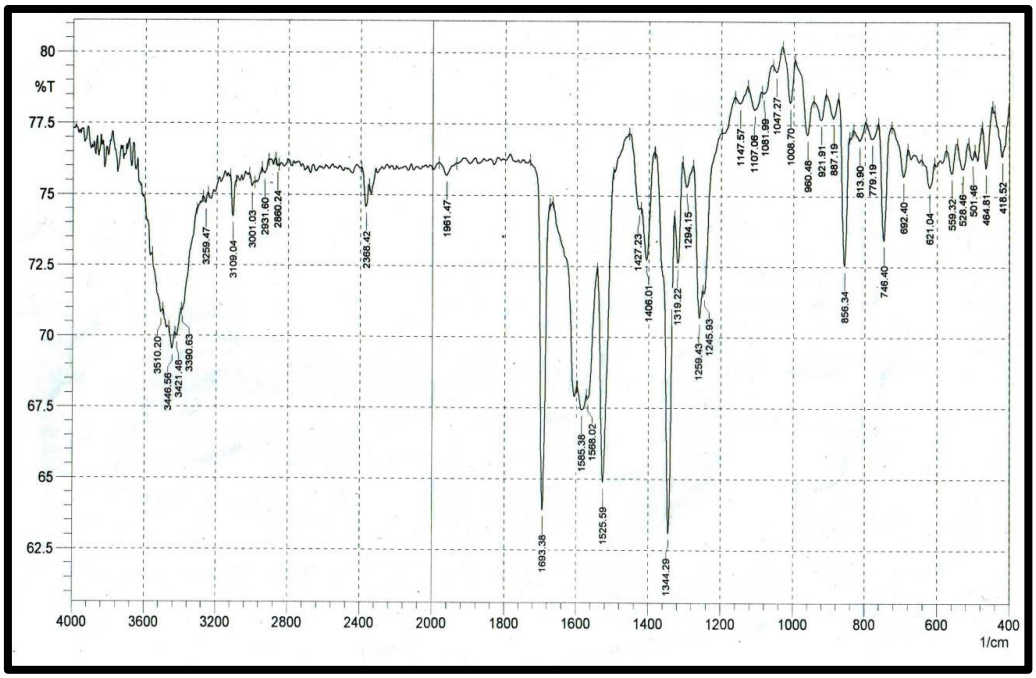


Figure (8): FT-IR spectrum for compound 6.

Antioxidant activity[3,4,5,6] DPPH Radical Detoxificatio Activity(Olszowy & Dawidowicz, 2018):

1- DPPH (1،1-Diphenyl-2-picrylhydrazyl): Re-treated in 100 mL ethanol, keeping solution protected from light..
2- Various concentrations (100, 50, 25)mg/ml from some of the produced chemicals ppm were made. It was made by mixing 1milligram of the compound with10milliliters of ethanol tomake100parts per million, which was then diluted to 50, 25 parts per million, etc.
3- Ascorbic acid (vitamin C): Similar concentrations was prepared.

Table (4): Inhibition percentage (I%) of compounds 3-6.

Compound number	25 (mg/mL)	50 (mg/mL)	100 (mg/mL)
3	71.03	84.29	88.2
4	79.21	77.81	85.17
5	43.18	59.12	78.57
6	54.07	65.82	83.53
Ascorbic acid	80.95	89.25	93.54

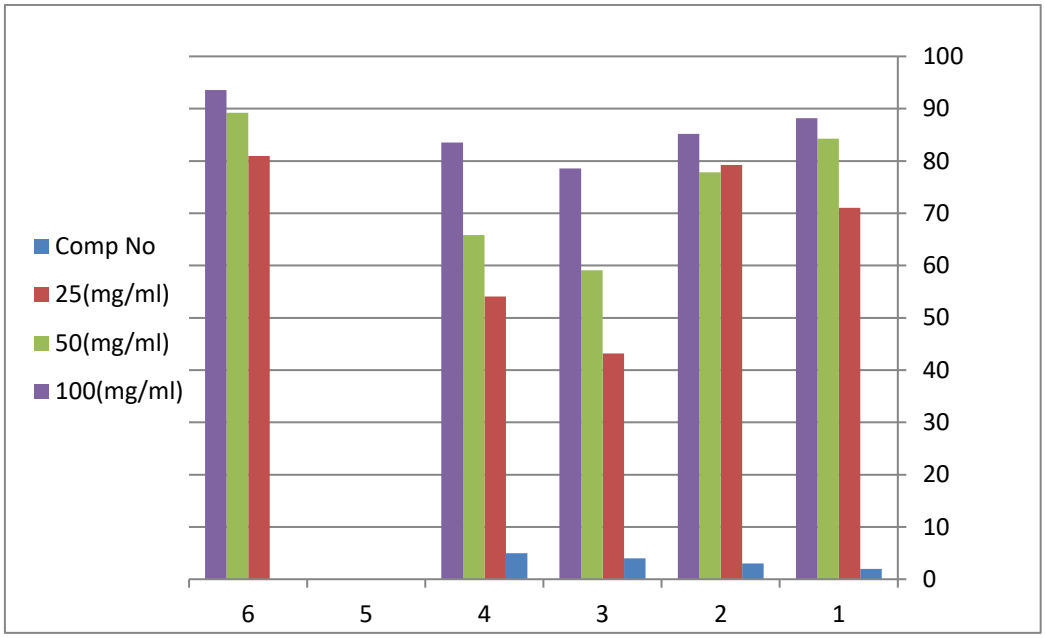


Figure (9): Inhibition percentage (I%) of compounds 3-6.

(DPPH) and a few other methods, all of the compounds were tested to see whether they had the ability to function as antioxidants when the experiment was conducted in vitro. The favorable findings were found when the antioxidant activity of the compound bioactive molecules [3-6] was compared to that of the traditional drug metoclopramide.

CONCLUSION

In this work, some heterocyclic compounds were prepared by the interaction of the drug metoclopramide with some derivatives of aldehydes and ketones, where the antioxidants of these prepared compounds were measured.

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