ISSN 0974-3618 (Print)
0974-360X (Online)
www.rjptonline.org

RESEARCH ARTICLE

Synthesis and Identification of new compounds have Antioxidant activity Beta-carotene, from Natural Auxin Phenyl Acetic Acid

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ABSTRACT:
For the purpose of synthetic compounds active anti-oxidation in plants. At the same time, these synthesized compounds a harmless and not damaged or affect the rapid growth of plants. Phenyl acetic acid was chosen as a nucleus to synthesize compounds used in this study, this compound was chosen because it is considered an important auxin for plant growth. These compounds were tested as antioxidants, and were found to be effective as antioxidants The antioxidant capacity was evaluated by β-carotene/linoleic acid assay. Results showed that 60% of these derivatives have antioxidant activity, exhibiting 50, 57% to 78, 96% inhibitions. Physical characterization of these synthesized compounds, which were established by performing melting point and Rf value. The derivative structures were identified using UV, FT-IR, and HNMR, ^{13}C NM, ^{13}C-DEPT spectral analysis.

KEYWORDS: phenyl acetic acid, Antioxidant.

1. INTRODUCTION:

The importance of antioxidant compounds lies in their ability to be effective against the damage caused by the various types of auxin reactions and free radicals derived from auxin that contribute to the existence of a variety of diseases, such as damage to DNA, cancer and cellular decomposition [1].

Auxin is the first plant hormone to be extracted, and is manufactured in laboratories and is commercially used in agriculture. It was found that the methyl group between the ring and carbonyl is effective in the hormone. Where carbon of methylene and carbon of carbonyl interact with the enzyme to stimulate growth. [2][3].

(Phenyl acetic acid) is one of three important auxins, which are important for the growth of plants; it was proven as natural auxin in plants in 1984 by Wightaman and Lightly. In fact, it is less efficient than natural auxin indole acetic acid, but it has higher concentrations. auxin are naturally created in the developing peaks and elongation areas of the stalk, acid is found in tomato, tobacco, sunflower, barley malt and maize plant [4].

Due to the importance of the oxadiazol compound, many researchers have been interested in preparing different metabolites and studying their biological effect4. They have been used as antimicrobial agents against bacteria, aspergillus niger, food poisoning, varnarium oxani, and fusarium oxysporiumIt also showed an effect on the nervous system as a sedative and anti-inflammatory, and its industrial applications are the manufacture of dyes and polymers resistant to heat and the manufacture of fluorinated (radioactive) and materials that flash [5][7].

Pyrozole aromatic compound aromatic five - ring and three - carbon atoms and two atoms nitrogen. The two nitrogen atoms are adjacent to each other [8][9].

Pyrazole derivatives are found in many vitamins, dyes and in many natural products, extracted from animal or plant sources. It is also found in many enzymes, helper enzymes and polymers, which are part of the important adenosine and guanine molecules, which are involved in building nucleic acids [10][11].

Received on 01.06.2019 Modified on 03.07.2019
Accepted on 31.07.2019 © RJPT All right reserved
Research J. Pharm. and Tech. 2020; 13(1):40-46.
DOI: 10.5958/0974-360X.2020.00007.4

Pyrazole derivatives are very important in the field of pharmaceutical chemistry, because of the multiple areas of therapeutic use. They are used as heat suppressants, anti-inflammatory drugs (phenyl butazone) and anti-heat. It is also used as a medicine for the treatment of neurological disorders, rheumatism and diabetes. It has great effectiveness in resisting toxins and destroying insects. Pyrazole derivatives are used as antimicrobial, fungal and bacterial agents, because they have a wide activity against a large number of microorganisms. [12][13].

In this research we tried to reduce toxicity and at the same time increase the effectiveness of Phenyl acetic acid by converting the acidic side group into derivatives of heterocyclic rings known for their biological activity [14].

2. EXPERIMENTAL:

2.1 Instrumentation:

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification, melting points were recorded on electrothermal melting point apparatus. Thin layer chromatography (TLC) controls were carried out on precoated silica gel plates (F254 Merck). The IR spectra were recorded on (FT-IR Shimazu 4800S) infrared spectrophotometer using KBr pellets. ^{1}H NMR, ^{13}CNMR spectra were recorded on ^{1}H NMR, ^{13}C NMR, ^{13}C-DEPT (Bruker Advance III 600 MHz NMR spectrometer with the cryoprobe).

2.2 Synthesis method:

2.2.1 Synthesis of Phenyl acetic acid hydrazide (z) [15]

A mixture of Phenyl acetic acid (0.03mol) and phosphorus pentachloride (0.07mol) in an hydrous carbon tetrachloride (20ml) were refluxed for 2h at 100 °C, the solvent was distilled off for further reaction without any purification.

To the **Phenyl acetic acid** chloride (0.03mol) was added hydrazine hydrate (0.1mol) dropwise below 5°C and the resultant mixture was stirred for 5h at room temperature. A solid that separated out was washed with aqueous $NaHCO_3$ (10%) and dried in vacuum, it was recrystallized from methanol to obtain pure crystalline solid **z**, yield: 76%, M.p. 188-200°C, IR (KBr, cm^{-1}): ν 3350-3380 (NH-NH2), 1680 (C=O), 1600-1480 (aromatic ring),

2.2.2 Synthesis of derivatives of pyrazol (1-2, 3) [16]–[18].

To a solution of **(z)** (0.001mol) in ethanol (10ml) appropriate diketone (ethyl acetoacetate, acetylacetone, ethylcyanoacetate) (0.002mol) was added and the reaction mixture was reflexed on a water bath for 12h in presence of catalytic amount of glacial acetate acid (2-3 drops), the reaction contents were cooled to room temperature and the obtained product (7,8,9) was filtered, dried and purified by recrystallization from ethanol.

2.2.3 A: Synthesis of 5-[2-(phenyl) ethanone]-3,5-dimethyl-1H-pyrazol (1)

yield 56%, M.p. 265-266ºC; **^{1}H NMR** (600.00 MHz, $CDCl_3$) 2.59 (S, 3H, CH_3), 3.19(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz) 3.97(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz),4.39 (S, 2H, CH_2Ar), δ 7.73 (d, 2H, *J* 7.8 Hz), 7.26 (t, 3H, *J* 6.0 Hz),; **^{13}C NMR** (150.0 MHz, $CDCl_3$) δ 176.14-172.48(2C=O),131.48-128.44(6C, PH+2C=N-pyrazolring), 72.88(CH2,), 40.95(CH2, pyrazol ring), 20.83(CH3), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of two negative signals, the first signal at (-61.26) to (CH2), The second signal at (-40.98) to (CH2, pyrazol ring) the other signals of carbon atoms were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum. (IR (KBr) ν/cm^{-1}, IR (KBr, cm^{-1}): 1683 (C=O), 1622 (C=N), 1350 (C-N).

2.2.4 B: Synthesis of 5-[2-(phenyl) ethanone]-3-methyl-1H-pyrazol-5(4H)-one (2)

yield 43%, M.p. 240-242ºC; ^{1}H NMR (600.00 MHz, $CDCl_3$) δ 2.59 (S, 6H, CH_3), 3.49(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz) 3.97(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz), 4.09 (S, 2H, CH_2Ar) 7.80 (t, 2H, *J* 7.8 Hz), 7.76 (d, 2H, *J* 6.0 Hz), 7.18 (t, 1H, *J* 7.8 Hz),; **^{13}C NMR** (150.0 MHz, $CDCl_3$) δ171.7(C=O),137.7-130.9(6C,PH), 97.34-97.88(2C=Npyrazolring), 67.85(CH2,), 40.13(CH2, pyrazol ring), (21.64-21.040 (2CH3), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of two negative signals, the first signal at (-67.26)to(CH2), The second signal at (-40.28) to (CH2, pyrazol ring) the other signals of carbon atoms were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum; IR (KBr) ν/cm^{-1}: 1683 (C=O), 1622 (C=N), 1350 (C-N).

2.2.5 C: Synthesis of 5-[2-(phenyl) ethanone]-3-amino-1H-pyrazol-5(4H)-one (3)

yield 57%, M.p. 215-216 ºC; ^{1}H NMR (600.00 MHz, $CDCl_3$), 4.69 (s, 2H, CH_2Ar), 3.12(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz), 3.97(d,1H, $J_{Ha\text{-}Hb}$ 17.7 Hz),6.98(s,2H,NH2), 7.79 (d, 2H, *J* 7.8 Hz), 7.36 (t, H, *J* 6.0 Hz), 7.17 (t, 2H, *J* 7.8 Hz), ^{13}C NMR (150.0 MHz, $CDCl_3$) δ δ179.82-172.82(2C=O),155.49(C-NH_2),131.48-128.44(6C,PH+2C=Npyrazolring), 68.64(CH2,), 39.97(CH2, pyrazol ring), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of two negative signals, the first signal at (-68.92) to (CH2) and the second signal at (-40.67)to (CH2, pyrazol ring) the other signals of carbon atoms were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum; IR (KBr) ν / cm^{-1},3502-3425 (NH_2), 1667 (C=O), 1626 (C=N), 1330 (C-N).

2.2.6 Synthesis of 5-[2-phenyl)ethyl]-5-substituted-1,3,4-oxadiazole (4-7) [6], [7], [19], [20].
A mixture of x (0.001mole), substituted aromatic acids (0.002mole) and phosphorus oxychloride (15ml) was reflexed on oil bath at (100-110°C) for 6h, the excess of phosphorus oxychloride was distilled off and cooled residue was poured into ice cold. The contents were neutralized with ammonia to offered crude products[15-18], which were filtered, dried and purified by recrystallization from 1,4-dioxane.

(4) yield 66%, mp 88-90ºC; ^{1}H NMR (600.00 MHz, $CDCl_3$) : δ 4.09 (S, 2H, CH_2Ar), 8.01 (d,2H, *J* 7.8 Hz), 7.76 (t, 2H, *J* 6.0 Hz), 7.67 (t, 4H, *J* 7.8 Hz), 7.34 (d,2H, *J* 7.8 Hz) ^{13}C NMR (150.0 MHz, $CDCl_3$) δ 68.12(CH_2),(122.20-151.91)(Ph+2C oxazol), **^{13}C-DEPT-135** (150.0 MHz, $CDCl_3$) The appearance of one negative signal at (-68.36) to (CH2) the other signals of carbon atoms (Ph+2C oxazol) were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum ; IR (KBr) ν/3; IR (KBr) ν / cm^{-1} 1612 (C=N).

(5) yield 56%, mp 108-110 ºC; ^{1}H NMR (600.00 MHz, $CDCl_3$): δ 4.35 (S, 4H, CH_2Ar), 8.24 (t, H, *J* 7.8 Hz),8.05(t, H, *J* 7.8 Hz), 7.86 (d, 2H, *J* 6.0 Hz), 7.46 (d, 2H, *J* 6.0 Hz) 7.28 (t, 4H, *J* 7.8 Hz); ^{13}C NMR (150.0 MHz, $CDCl_3$) δ (69.62-69.12)($2CH_2$), δ(121.22- 142.17) -14-singnal of (12C-2Ph+2C oxazol), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of tow negative signals at(-69.68,-69.02)to(2CH2) the other signals of carbon atoms (2Ph+2C oxazol) were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum,; IR (KBr) ν / cm^{-1} 1612, 1600-1390, 735, 695;

(6) yield: 49%; mp 218-230 ºC; ^{1}H NMR (400.00 MHz, $CDCl_3$) 4.31 (S, 2H, CH_2Ar), δ 8.42(d,2H, *J* 7.6 Hz), 8.13(d, 2H, *J* 8.0 Hz), 7.81(t, 1H, *J* 8.0 Hz), 7.52 (t, 2H, *J* 6.0 Hz) 7.39(dd, 2H, *J* 8.0, 1.2 Hz); **^{13}**C NMR (150.0 MHz, $CDCl_3$) δ(68.71) to (CH2), (167.98-120.35)-14-singnal of (12C-2Ph+2C-oxazol), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of one negative signal at (-69.23) to (CH2) the other signals of carbon atoms (12C-2Ph+2C -oxazol) were shown with positive values similar to those of carbon atoms in the ^{13}C NMR spectrum; IR (KBr) ν / cm^{-1} 1597, 1543, 1411, 1357, 1087, 833, 740:

(7) yield 42%; mp 223-225 ºC; ^{1}H NMR (400.00 MHz, $CDCl_3$) δ 3.97 (S, 2H, CH_2Ar) 8.21 (d, 2H), 8.08(d, 2H, *J* 8.4 Hz), 7.83 (t, H, *J*8.8 Hz) ,7.43(t, 1H, *J* 8.0 Hz), 7.16 (d, 2H, *J* 6.0 Hz) ; ^{13}C NMR (150.0 MHz, $CDCl_3$) δ 66.12 (CH_2), (154.42-113.10)-14-singnal of (12C-2Ph+2C- oxazol), **^{13}C-DEPT- 135** (150.0 MHz, $CDCl_3$) The appearance of one negative signal at(-66.30)to(CH2) the other signals of carbon atoms , were shown with positive values; IR (KBr) ν/cm^{-1} 1580, 1559, 1519, 1407, 1347, 1091, 840, 742,

2.3. Antioxidant activity study (B-carotène) TEST. [21]
This test demonstrates antioxidant capacity by measuring the inhibition of lipids and conjugated hydro peroxide diene. Which are the products of the process of oxidation of linoleic acid

We take 0.5mg of β-carotène to dissolve in 1 ml of chloroform, add to it a µ25l of linoleic acid and 200 g Tween 40 Mix the mixture and then completely evaporate the chloroform in the evaporator at 40°C. Then add 100ml of distilled oxygenated water and mix well. After that, 2.5 ml of the former mixture is transferred to a test tube and 350µl of compounds prepared at a fixed concentration of 2 mg/ml of ethanol.

The process is repeated with reference material of BHT as positive reference and water and methanol as negative references. The mixture is incubated at room temperature away from light, after which the absorbance is measured at 490 nm at different times (0, 1, 2, 3, 4, 6, 24, 48) hr. The inhibitory ratio of the antioxidant extracts (RAA), is calculated according to the following equation:

RAA% = A sample / ABHT × 100

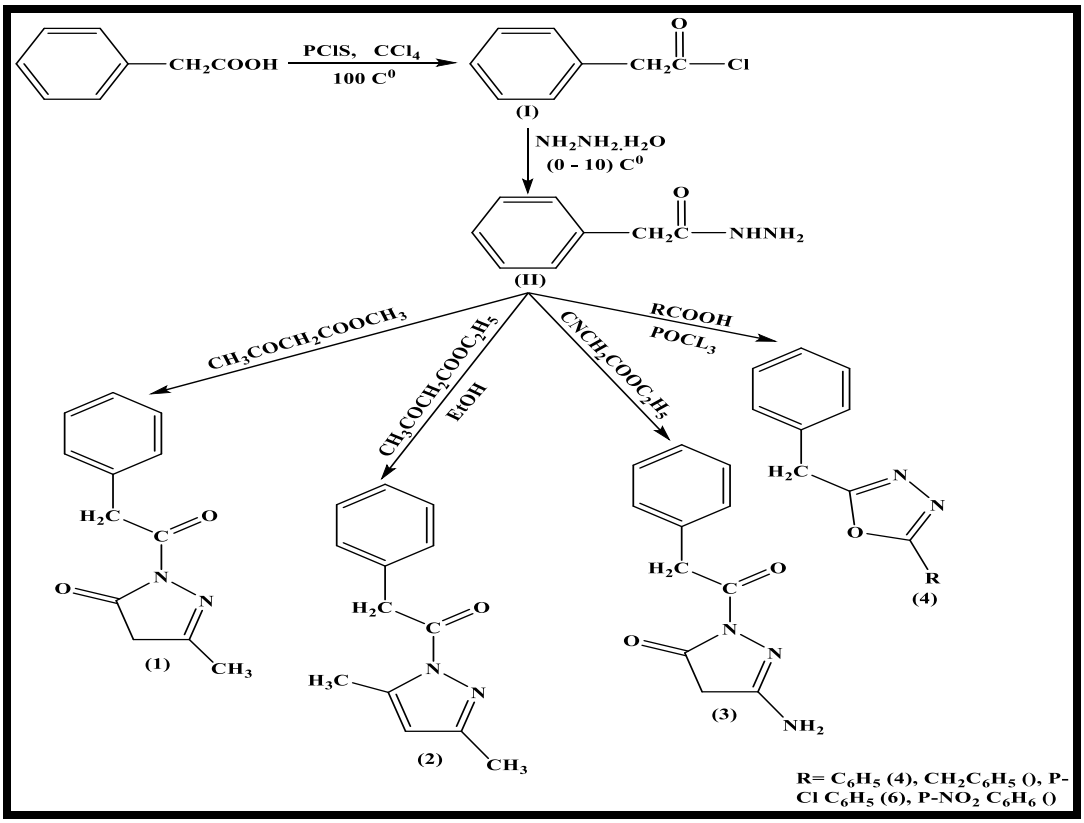
Where:
Sample: A Sample Absorption, A: BHT Absorption BHT

3. RESULTS AND DISCUSSION:

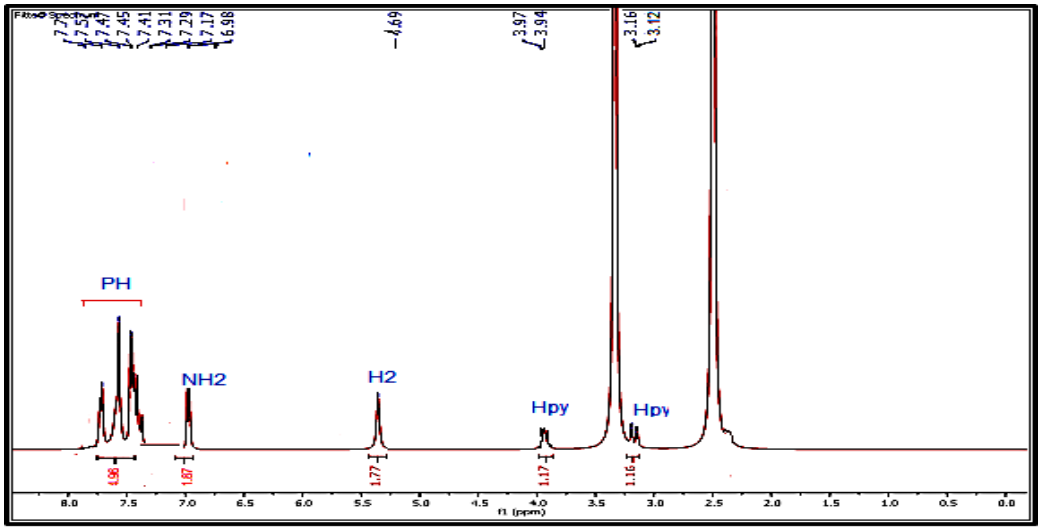
For the synthesis of the compounds **(1-7)**, starting from phenyl acidic acid. Prompted by these results and in continuation of our search for bioactive molecules, we planed to synthesis some pyrazole, pyrazolone, oxadiazol derivatives based on phenyl acidic acid as starting material. The required aryl acid hydrazides (II), were prepared by chloroification of the phenyl acidic acid, followed by treatment with hydrazine hydrate in absolute ethanol. First, the reaction of Phenyl acetic hydrazide (II) with appropriate keto, cyano- ester, di keto in ethanol with presence of glacial acetic acid. The structures of compounds (1-3) were established by many Analytical and spectral data (1H,^{13}C -NMR, IR) of all synthesized compounds were in full agreement with the proposed structures. In general, infrared spectral data (cm–1), display a C=O stretching on at (1668-1665 cm^{-1}) and the presence of bands at (1551-1686 cm^{-1}) for C=N, further more, the ^{1}H NMR spectra showed disappeared NH_2(except compound -3-) and the presence of tow singlet at δ ppm for CH_2(pyrazole) ring. The typical signals on 13C NMR spectrum of dicarbonyl group δ 176.48 ppm, δ 172.48 ppm proved the existence of

pyrazolone ring compounds (1,3). Second, The oxadiazole derivatives **(4-7)** were prepared by reaction of Phenyl acetic hydrazide (II) with appropriate substituted aromatic acids presence of phosphorus oxychloride , theses product proofed by IR which showed absorption peak at (1560 cm^{-1}) due to C=N Stretch vibration and disappeared peak for C=O grope, is structure was further supported by its ^1H NMR spectra, which showed the NH_2 disappeared and multiplet was obtained in the aromatic region for sub. ArH protons.

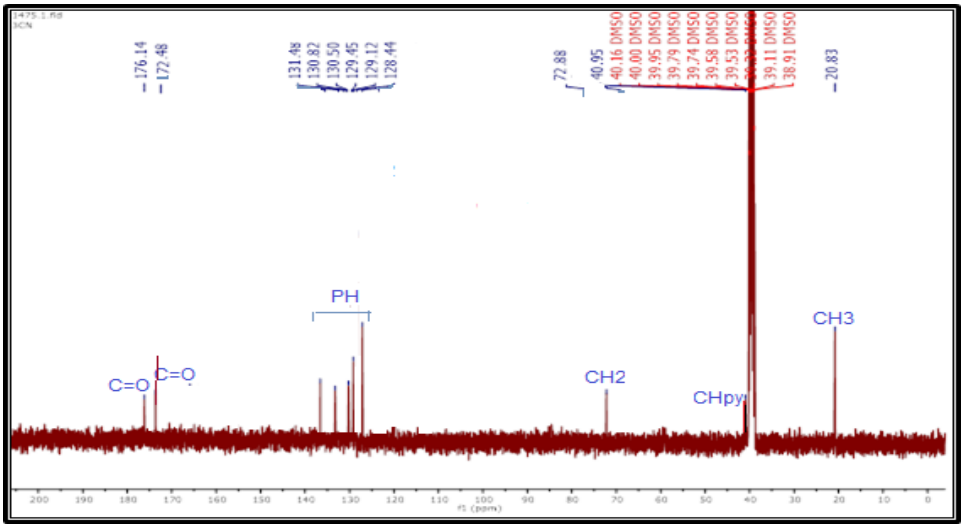
The most important evidence is the spectrum **^{13}C-DEPT- 135, where it showed** appearance negative signals at CH_2 (pyrazole) ring and the other signals of carbon atoms, were shown with positive values in all synthesized compound. The synthesized compounds **(1-7)** were recorded in the scheme **1**.



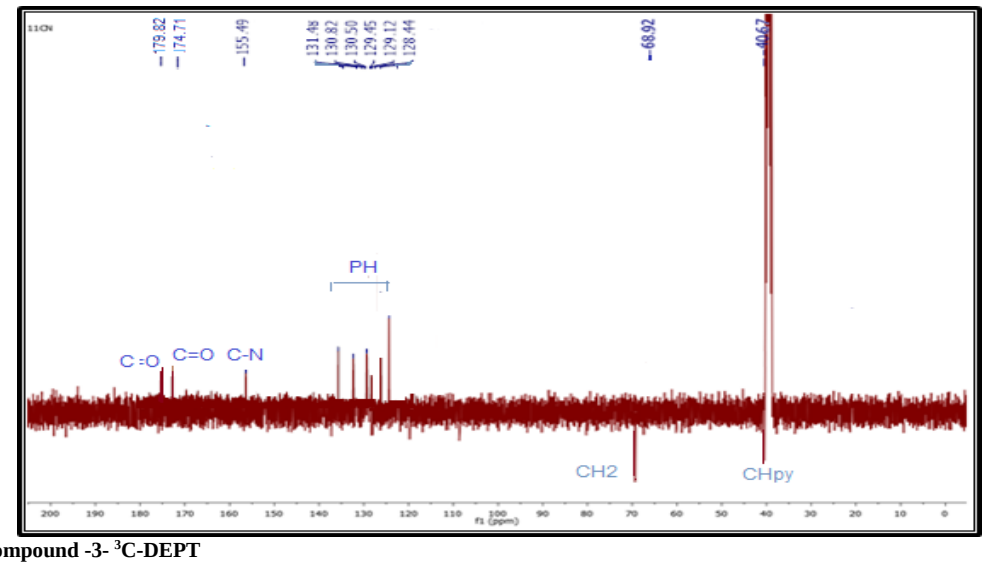
Scheme (1)



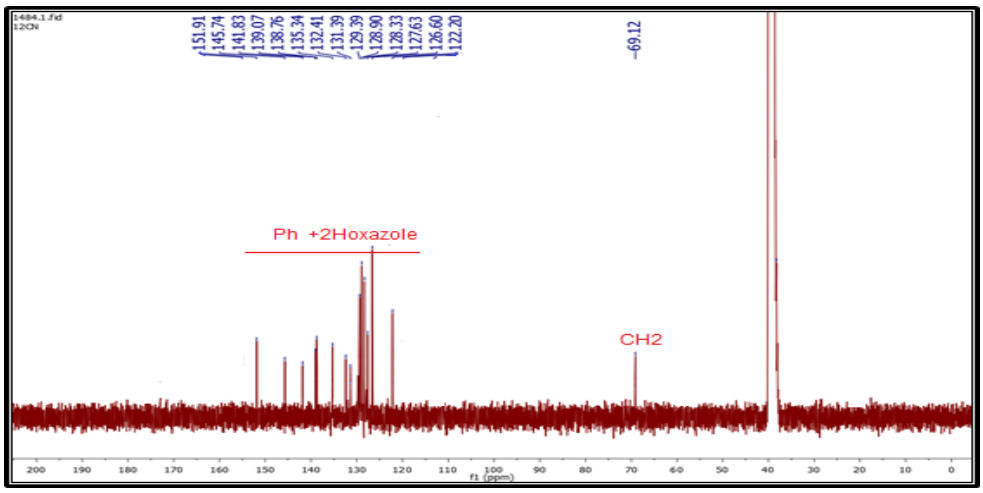
Fieger (1): Compound (3)



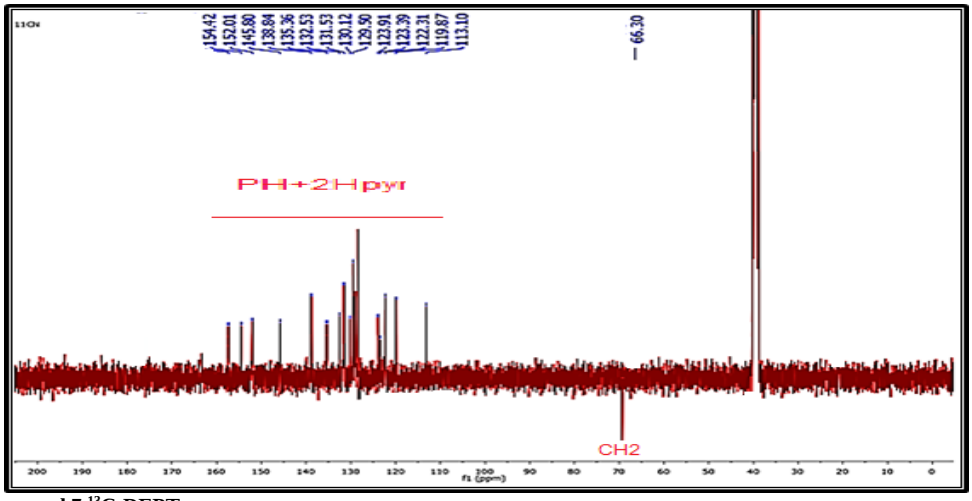
Fieger (2): Compound-1- 13CNMR



Fieger (3): Compound -3- ^{3}C-DEPT



Fieger (4): Compound 4



Fieger (5): Compound 7 ^{13}C-DEPT

Study the antioxidant activity of the compounds prepared by the β-carotene test method. [22]–[25]**.**
The β-carotene / linoleic method is used to measure the inhibition of lipid oxidation or free radical displacement. After the exposure of linoleic acid to the oxidation process, the oxidation products of fatty hydro peroxides, associated products and volatile compounds attack the unsaturated molecules, causing a wavelength reduction at 490 nm while removing the color of β-carotene. Antioxidants modify the free radicals formed during the oxidation reaction that prevents the oxidation and disappearance of β-carotene color. It was noted that some of the prepared compounds inhibit the oxidation of linoleic acid while others leis active. We have noted that each of the compounds has anti-oxidant activity of linoleic acid. The inhibition rates ranged from (78,961 ± 3,183) to (73,977 ± 1,102) Are high ratios compared to BHT (Butylated hydroxytoluene), which is considered to inhibit oxidation of linoleic acid by 100%.While the compounds had a slightly lower inhibition rates (%64,218±7,569c) (%61,868±12,107) (% 56,218± 7,569) respectively.

Table 1: Antioxidant activity of compounds prepared by β-carotene / linoleic test

Samples	Inhibition percentage (mean±SD)
1	56,218±7,569c
2	61,868±12,107de
3	64,218±7,569c
4	78,961±3,183b
5	52,949±2,954e
6	73,977±1,102bc
7	65,740±4,486c
BHT	100,000±2,183a
H20	0,630±0,157f
Methanol	10,651±0,551f

All values followed by letters were not significant (P <0.05) Each value represents the arithmetic mean of three tests ± the standard deviation (M ± SD) Many studies have confirmed the importance of compounds containing heterocyclic rings containing more than one nitrogen atom, such as the carbonyl group, as well as various substituents, and study the effect of these substituents on antioxidant activity. Therefore, we have been interested in the synthesis of some heterocyclic compounds based on phenyl acetic acid (growth hormone) as antioxidant compounds. When examining the synthesized compounds, it was found that the compound 3 is more active than 1,2 possibly due to the dissociation of stable C_6 H_5CH_2CO roots due to the presence of the aromatic ring. Also, because of the presence of the amino group on the pyrozole ring, make this ring more stable. The compound 6, show greater antioxidant more than 4,5,7 due to because it contains heterocyclic systems with halogen substituted.

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