Preparation, Investigation and Study of Biological Applications of Tyrosine Derivatives against Breast Cancer Cells

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Abstract

Cancerous tumors are considered a serious and fatal diseases for both sexes and for all ages, even fetuses before their birth. Therefore, it has become necessary to find an alternative treatment for radiation to be safer and less dangerous than chemical treatments. Therefore, derivatives of one of the amino acids, such as tyrosine, were prepared. Tyrosine or tyrosine is one of the well-known and important amino acids for humans, and it is present in most proteins; The human body uses it to produce several types of hormones such as noradrenaline and adrenaline. In this paper, we prepared new derivatives of tyrosine represented by (four, five, six)-membered ring, then all these new tyrosine derivatives investigated by several techniques (FT.IR, H.NMR)–spectrophotometric, other physical and chemical properties, with assaying for some new created derivatives as anti-cancer.

Key Words: Tetrazole, Anticancer, Heterocyclic, Tyrosine, Thiazine, Azitidine, Lactam.

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Introduction

Tyrosine is a white, non-essential crystalline amino acid, Tyrosine is one of the important amino acids, is naturally produced by the body from another amino acid (Pisarewicz K, et al 2005) called phenylalanine, and the brain uses it to manufacture some neurotransmitters such as dopamine and adrenaline (S. Pradhan 2007.; Thomas L. 1997). Dopamine is known to regulate pleasure centers in the brain, and is important for movement skills and memory, and adrenaline is a hormone responsible for responding to sudden and stressful situations (*Edon Vitaku* 2014; *Wang, Cuiling 2017*). Tyrosine helps produce thyroid hormones, which are formed when iodine molecules are added to tyrosine. Changes in plasma tyrosine or iodine levels directly affect thyroid levels (S. Pradhan, et al 2007.; *Wang, Cuiling 2017*). Therefore, tyrosine levels can cause hyperthyroidism or hypothyroidism. Tyrosine is a precursor to major neurotransmitters such as epinephrine, norepinephrine, dopamine and other catecholamines (Matheus ME et al 2007; A. Perro et al 2006). These hormones control the brain's oxygen consumption and maintain blood pressure and blood sugar levels. Indirectly, these catecholamines control the way your body responds to stress and anxiety. Any changes in the levels of these neurotransmitters (particularly dopamine) lead to ADHD, anxiety and depression (M. Pera-Titus et al 2015.; C. Casagrande et al 2015).

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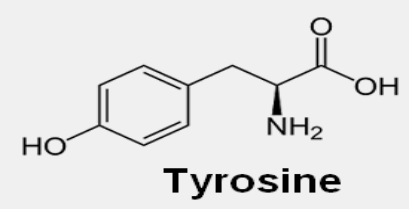
The body may have a genetic disorder that leads to the breakdown of the cellular mechanism that makes tyrosine (Nagham Aljamali 2015), and symptoms of infection can be observed in infants and young children (W.-J. Zhou et al 2014), and these symptoms are decreased growth rate (Mehta SL et al 2007), diarrhea, vomiting, jaundice (jaundice) (Y. Liu, J. et al 2017), mental retardation, and photophobia (Z.W. Seh., et al 2011). Unfortunately, if the cause is genetic, the affected children will not be able to survive, but if it is not genetic, intensive care, low-protein diets (*Shafiq et al 2020)*, and possibly a liver transplant may help (*Wei. Hui et al 2013)*. Combining tyrosine with antidepressant medicines (Nagham Aljamali 2020) known as monoamine oxidase inhibitors (MAOIs) can increase blood pressure to dangerous levels. Also, tyrosine may affect thyroid hormones, raising them to very high levels. How much tyrosine in the body may cause nitrogen imbalance, kidney problems, and hypersensitivity to high-protein diets (*Naumann d. et al 2014)*). L-Tyrosine is a conditionally essential amino acid, which is found naturally in foods, primarily as part of proteins (*Dub, Pavel* et al 2018). It is one of the 22 types of amino acids that cells use to make proteins. L-Tyrosine is provided by taking mixed dietary protein from various sources and can also be consumed in supplement form (*Clark, Jim 2013*). It's common for athletes to take pure L-Tyrosine before workouts, especially with caffeine.



Experimental Part

Amino acids are among the compounds with high sensitivity when stored, so the chemical companies that supply the materials with high accuracy, purity and quality were selected in storage at appropriate temperatures for the purpose of preparing important derivatives and used for therapeutic purposes to reduce the percentage of cancerous tumors and reduce their spread in the body. While the measurements were identified via the following technical represented by ((FT-IR spectra)), ^{1}H NMR_Spectra, in addition to anti-cancer estimation.

Synthesis Procedures

Preparation Procedure of Tyrosine-Derivative {1}

Compound {1} prepared by reaction of tyrosine (0.01 mole) with semicarbazide (0.01 mole) in presence of (H_2SO_4) in cyclization step for (22 hrs) in absolute ethanol flowed with mentioned methods (Nagham Aljamali 2021. Nagham Aljamali 2019) to produce precipitation that acts compound{1} through flowing with mentioned mechanism (Nagham Aljamali 2018),,the latter step, filtered, dried, then recrystallized to give tyrosine Derivative.

Preparation Procedure of Tyrosine-Derivative {2}

Compound {2} prepared by reaction of tyrosine derivative {1} (0.01 mole) with benzaldehyde (0.02 mole) and (drops of glacial acetic acid) in refluxing step for (4 hrs) in absolute ethanol according to mentioned methods (Nagham Aljamali 2021., Nagham Aljamali 2019) to produce precipitation that acts compound{2} through flowing with mentioned mechanism (Nagham Aljamali 2018), the latter step, filtered, dried, then recrystallized to give other tyrosine Derivative.

Preparation Procedure of Tyrosine-Derivative {3}

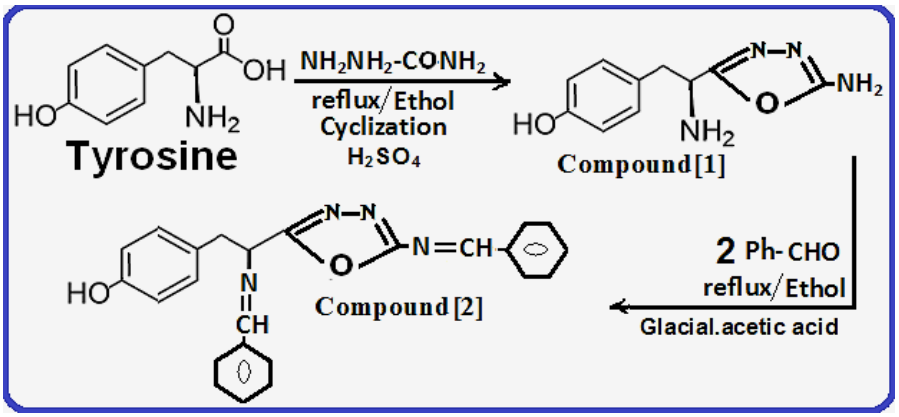
Compound {3} prepared by reaction of tyrosine derivative {2} (0.01 mole) with chloroacetoylchloride (0.02 mole) with trimethylamine flowed with mentioned methods (Nagham Aljamali 2021., Nagham Aljamali 2019) to produce precipitation that acts compound{3} through flowing with mentioned mechanism (Nagham Aljamali 2018), the latter step, filtered, dried, then recrystallized to give cyclic tyrosine Derivative (four membered ring).

Preparation Procedure of Tyrosine-Derivative {4}

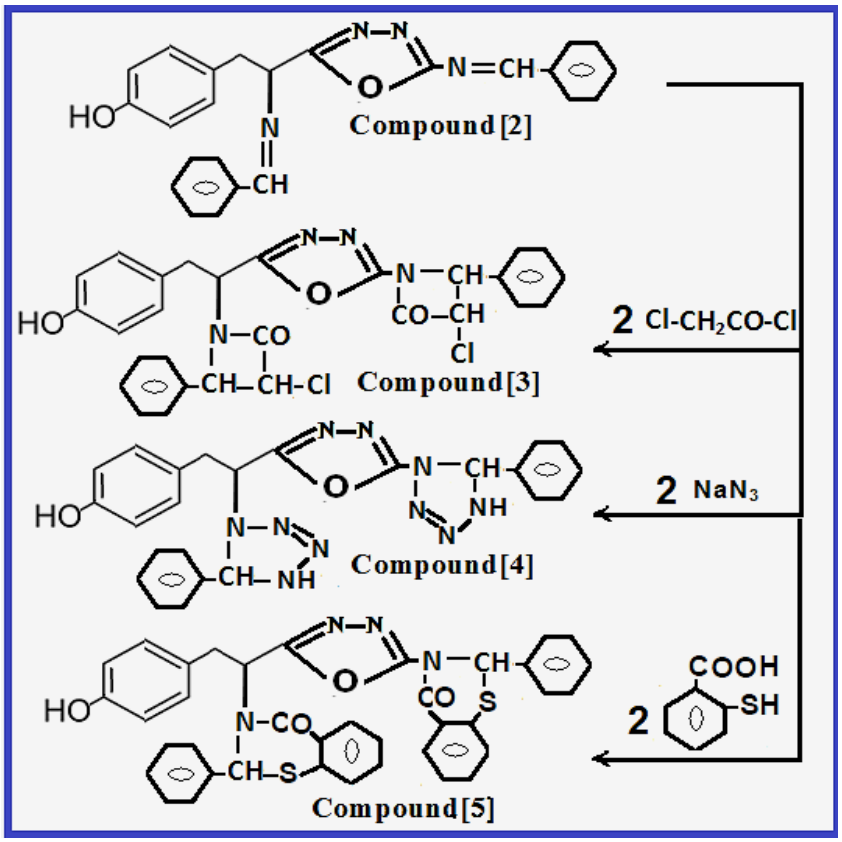
Compound {4} prepared by reaction of tyrosine derivative {2} (0.01 mole) with (NaN_3) (0.02 mole) trendy refluxing step for (4 hrs) flowed with mentioned methods (Nagham Aljamali 2021., Nagham Aljamali 2019) to produce precipitation that acts compound{4} through flowing with mentioned mechanism (Nagham Aljamali 2018), the latter step, filtered, dried, then recrystallized to give cyclic tyrosine Derivative (five membered ring).

Preparation Procedure of Tyrosine-Derivative {5}

Compound {5} prepared by reaction of tyrosine derivative {2} (0.01 mole) with mercaptobenzoic acid (0.02 mole) in (Eth-OH) solvent flowed with mentioned methods (Nagham Aljamali 2021., Nagham Aljamali 2019) to produce precipitation that acts compound{5} through flowing with mentioned mechanism (Nagham Aljamali 2018), the latter step, filtered, dried, then recrystallized to give new cyclic tyrosine Derivative (six membered ring).



Outline 1. Production of Compounds{1, 2 }



Outline 2. Production of Compounds {3, 4, 5}

Results with Discussion

The synthesized tyrosine-derivatives have been studied by many chemical techniques and chemical methods in addition to their studying against cancerous cells:

Spectral Investigation of prepared Compounds

FT.IR- Investigation of tyrosine-Derivatives: The frequency s of important groups in spectra provided strong evidences for new synthesized compound via disappearance of frequency s and

appearance other new frequency s that point to formation of the new derivatives that represented by:

Compound **{1}:** appearance frequency s at (3180, 3200)Cm^{-1} down to (NH_2) of amine group, frequency at (3444)Cm^{-1} down to (OH) of hydroxyl group, frequency at (1666)Cm^{-1} down to (C=N) of endocycle of oxadiazole, frequency at (1176)Cm^{-1} down to (C-O-C) of oxadiazole, frequency at (2976)Cm^{-1} down to (CH) aliphatic according to literature (Nagham Aljamali 2021).

Compound **{2}:** appearance frequency s at (3434)Cm^{-1} down to (OH) of hydroxyl group, frequency at (1662)Cm^{-1} down to (C=N) of endocycle of oxadiazole, frequency at (1156)Cm^{-1} down to (C-O-C) of oxadiazole, frequency at (1624)Cm^{-1} down to (CH=N) of imine group, frequency at (2951)Cm^{-1} down to (CH) aliphatic according to literature (Nagham Aljamali 2021).

Compound **{3}:** appearance frequency s at (3369)Cm^{-1} down to (OH) of hydroxyl group, frequency at (1176)Cm^{-1} down to (C-O-C) of oxadiazole, frequency at (1688)Cm^{-1} down to (CO-N) carbonyl of amide group, frequency at (771)Cm^{-1} down to (C-Cl), frequency at (2956)Cm^{-1} down to (CH) aliphatic according to literature (Nagham Aljamali 2021).

Compound **{4}:** appearance frequency s at (3380)Cm^{-1} down to (OH) of hydroxyl group, frequency at (1134)Cm^{-1} down to (C-O-C) of oxadiazole, frequency at (1289, 1478, 1500)Cm^{-1} down to (N-N=N-) group in tetrazole, frequency at (3310)Cm^{-1} down to (NH) of tetrazole ring, frequency at (2921)Cm^{-1} down to (CH) aliphatic according to literature (Nagham Aljamali 2021).

Compound **{5}:** appearance frequency s at (3395)Cm^{-1} down to (OH) of hydroxyl group, frequency at (1171)Cm^{-1} down to (C-O-C) of oxadiazole, frequency at (1693)Cm^{-1} down to (CO-N) carbonyl of amide group in lactam, frequency at (699)Cm^{-1} down to (C-S), frequency at (2903)Cm^{-1} down to (CH) aliphatic according to literature (Nagham Aljamali 2021)., Other frequencies summarized in some figures (1, 2).

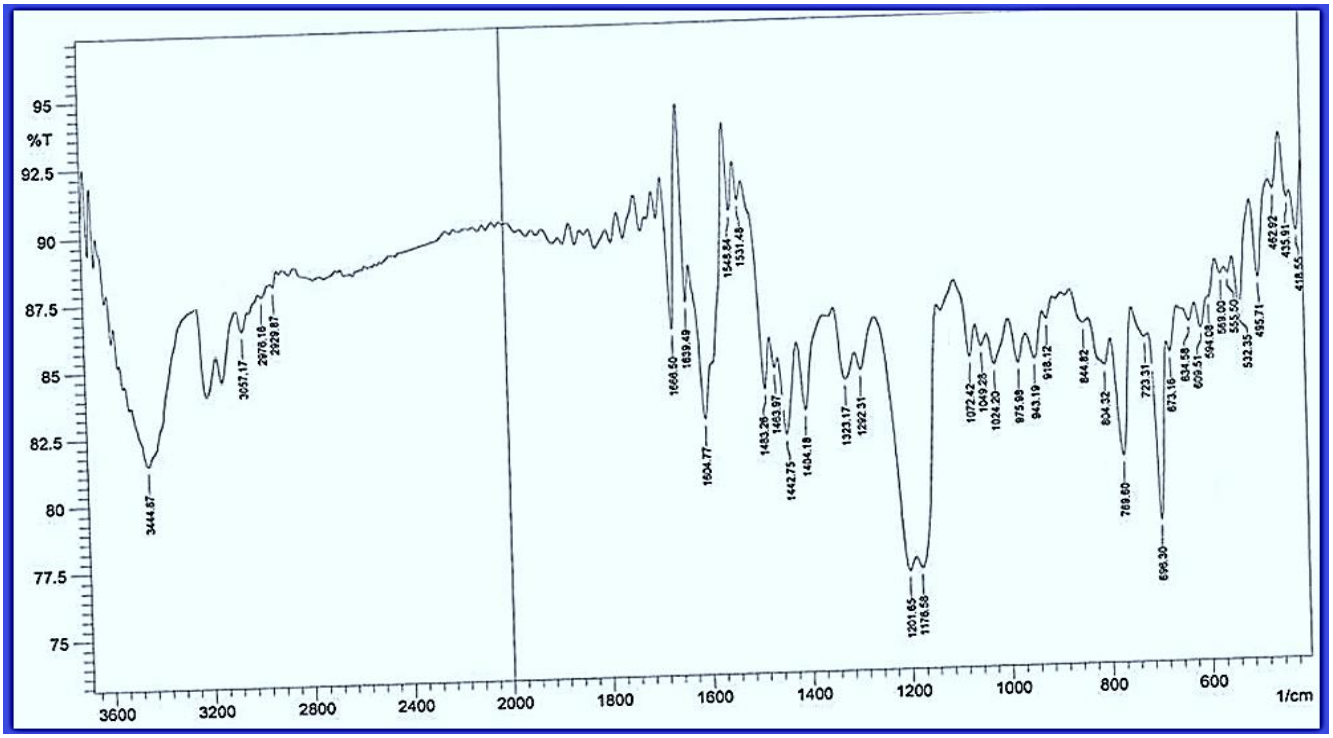


Fig. 1. I.R Spectrum of Tyrosine-Derivative {1}

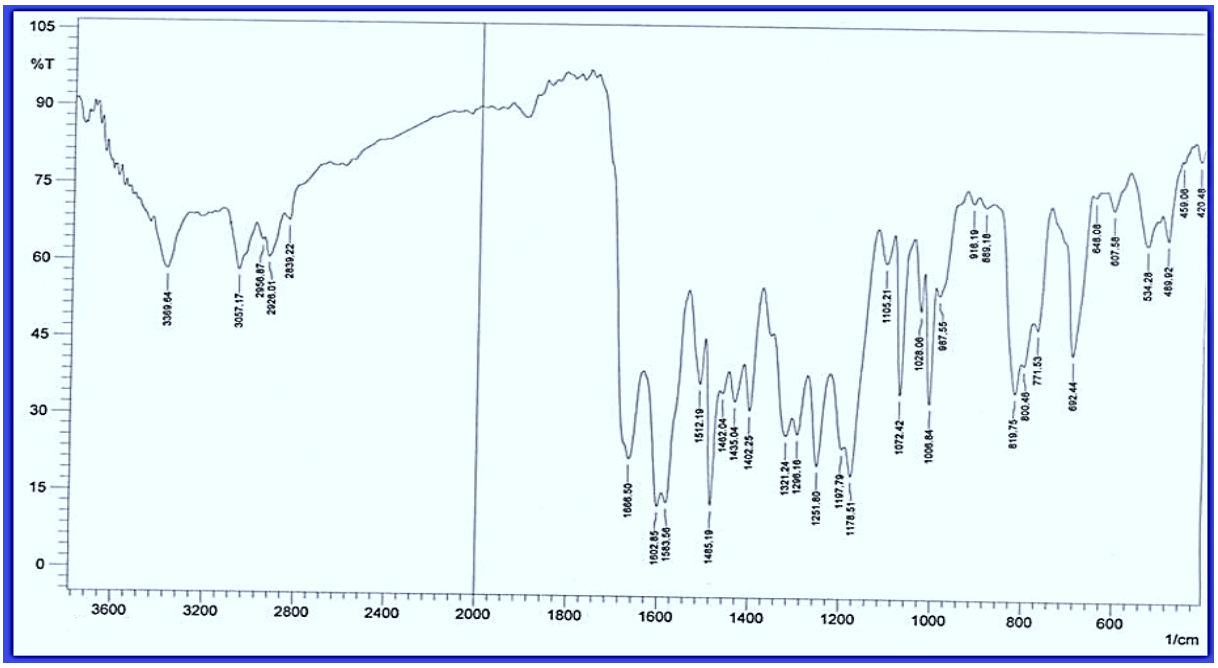


Fig. 2. I.R -Spectrum of The formatted Compound {3}

^{1}H.NMR- Investigation of tyrosine- Derivatives: The peaks of important groups in spectra gave strong indications for new tyrosine-derivatives via disappearance of peaks while appearance other new peaks that point to synthesis of the new tyrosine-derivatives that represented by: signals between (10. 08 to 10.37) down to proton of phenol group (OH) in all compounds, signals at (4.85) down to protons of amine (NH_2) in compound{1}, signals between (6. 80-7. 90) down to protons of phenyl ring in all compounds respectively, signal at (8.74) down to proton of (CH=N) down to proton of imine group in compound{2}, signal at (2.83) down to proton of (N-CO-CH-Cl) in compounds {3} according to literature (Nagham Aljamali 2021)., Some peaks in some figures (3, 4, 5).

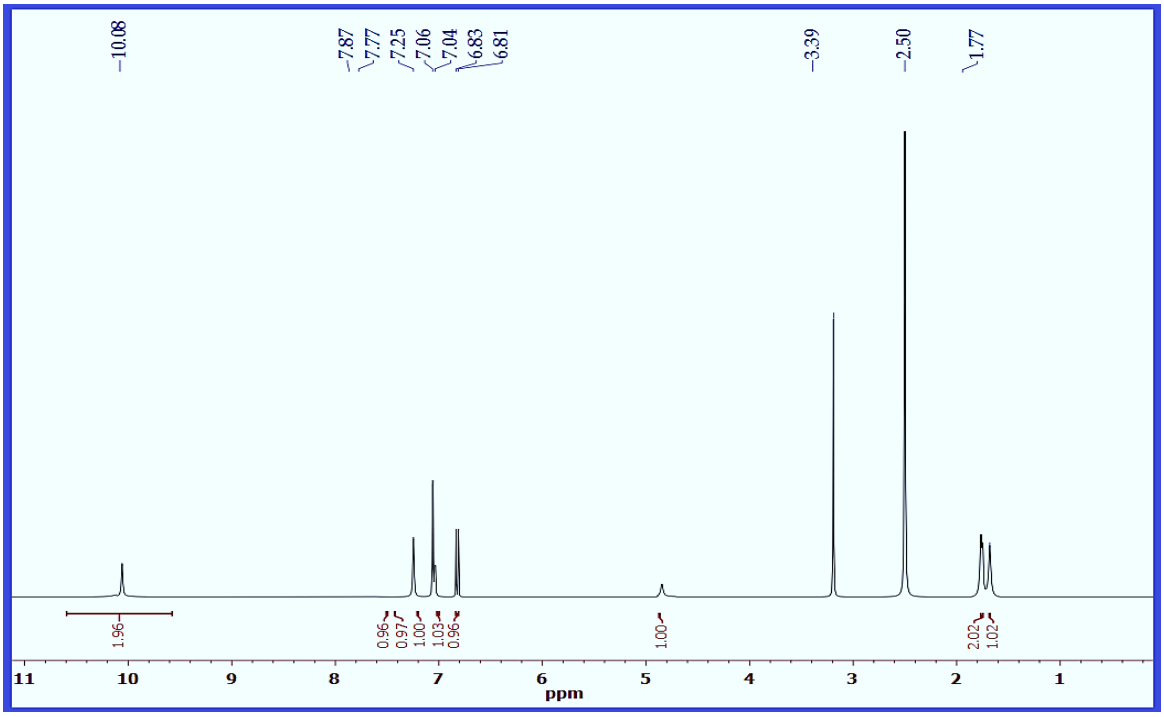


Fig. 3. H.NMR-Spectrum of tyrosine-Derivative {1}

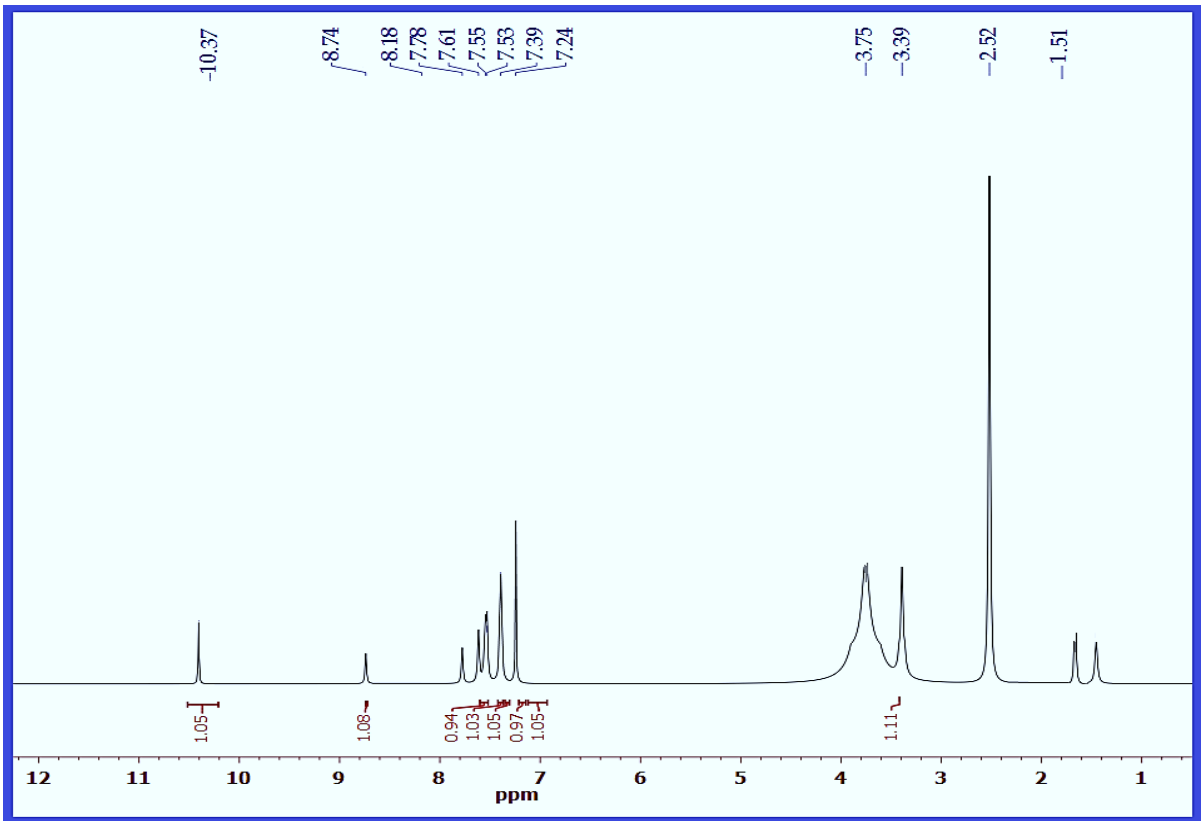


Fig. 4. H.NMR-Spectrum of tyrosine-Derivative {2}

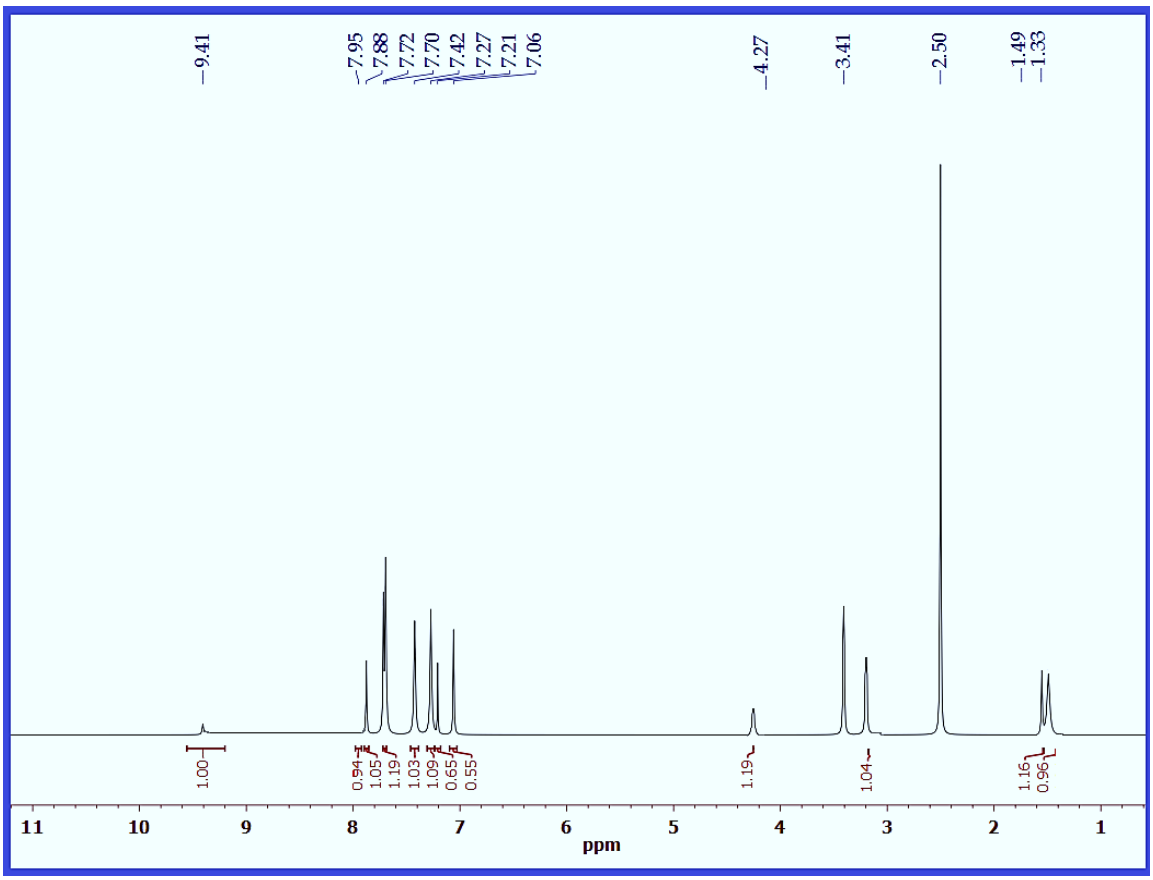


Fig. 5. H.NMR-Spectrum of tyrosine-Derivative {4}

Some physical and Chemical Characterization

All other physical and chemical analysis besides to some description in Table (1):

Table 1. Some Physical Properties of New Tyrosine-Derivatives

Comps	*Product %*	*Color*	*M.P (C°)*	*Rf*	*Solvents (TLC)*
{1}	74	Reddish Yellow	168	0.60	Ethanol: Hexane
{2}	72	orange	174	0.62	Ethanol: Hexane
{3}	78	Yellowish Green	198	0.56	Ethanol: Hexane
{4}	74	Yellowish Orange	204	0.60	Ethanol: Hexane
{5}	80	Deep Orange	211	0.64	Ethanol: Hexane

Investigation for Breast Tumor

Flowed with mentioned methods (Nagham Aljamali and Asma, K 2021., Nagham Aljamali Hussein M. 2021):

Procedure of Breast Cancer -Test:

MTT was rummage to limit cell viability by chromatic investigation flowed with mentioned methods ((Nagham Aljamali and Asma. K 2021., Nagham Aljamali Hussein M. 2021) of two types from cells (MCF-7 and WRL cell lines) for Tyrosine-Derivative [3] figure (6) and table (2):

1. Cell interruption (100 µL) was further to the wells of a small flat plate bottom.
2. The solution was equipped through dissolving the crystals of 5 mg MTT in 1 ml of PBS solution (phosphate buffer solution).
3. The concentrations of all new derivative of the equipped derivatives were castoff in this study (6.15, 12.5, 25, 50, 100, 200, 40) µg/ml of methanol, which were added to each well (three replicates per concentration).
4. A 10 ml MTT solution was added to each well of a plate containing 96 wells and then incubated for 4 hours with a test sample at 37 °C (the solution converted to yellow), according to literatures (Nagham Aljamali and Asma.K 2021., Nagham Aljamali and Hussein M. 2021):

Cell Vitality% = [(Absorption from the treated sample /Absorption from the untreated sample) X 100

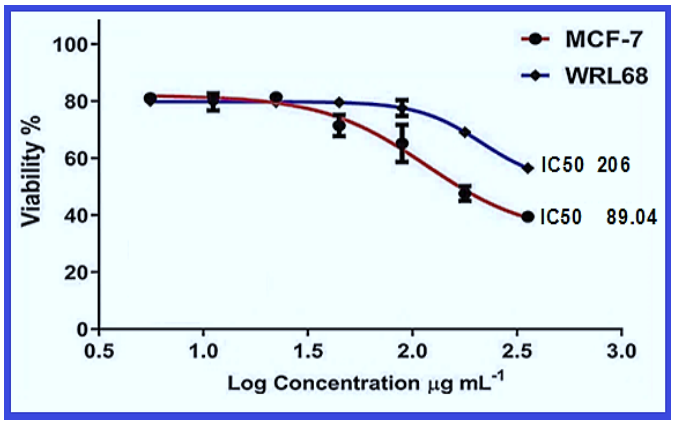


Fig. 6. Effect of Tyrosine-Derivative [3] on Breast Cancer Cells

Table 2. Mean Percentage (%) for each cell line (Respond to Treatment) for Derivative{3}

Concentration of Tyrosine-Derivative [3] (µ g/Ml-1)	MCF-7		WRL	
	Mean	SD	Mean	SD
400	48.16	1.20	51.77	1.01
200	59.04	1.38	41.13	0.33
100	70.35	3.23	29.41	1.87
50	72.28	3.70	27.12	1.75
25	78.83	1.22	23.76	1.43
12.5	80.97	1.65	19.22	1.21
6.25	84.24	0.90	15.10	1.09

Conclusion

The manufactured of Tyrosine-Derivative [3] appeared strong evidences about structures of new tyrosine-derivatives were stable, and all Tyrosine-Derivatives have high solubility in polar solvents such as ethanol, DMSO, Methanol and other solvents. And have decent activity contrary to breast cancer cells.

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Ethical clearance: Ethics committee refer that there is no plagiarism and there is no mistakes or wrong results in this work.

Conflict of interest: The authors declare that there is no conflict of interest.

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