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Synthesis, Characterization of Some 1*H*-Tetrazole Derivatives From 3-Aminoacetophene & 3-Amino Phenol

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Abstract. *Tetrazole derivatives a-d have been synthesized in this work. The basic tetrazole aαb were synthesized by cyclization reaction of primary amine (3-aminoacetophenone, 3-aminophenol) with sodium azide and triethyl orthoformate in hot glacial acetic acid. The tetrazole linked pyridine -2-one derivatives c were synthesized by the reaction of compound a with aromatic aldehyde (4-bromobenzaldehyde, 4-methoxy- benzaldehyde), ammonium acetate and ethyl cyanoacetate in ethanol absolute. On the other hand, the alkylation reaction of tetrazole derivatives 2 with alkyl chloride (1-chlorobutane, 1, 4-dichloro butane) in the present of potassium carbonate resulted compounds d. The various spectrum techniques that were available, such as FTIR, 1H-NMR and 13C-NMR spectroscopy, were used to confirm the structures of the produced compounds. Abiological studies were conducted on the prepared compounds 5and 6 to test their effectiveness against bacteria and as anti-cancer agents. It was found that the compounds d were not possess activity against bacteria. While The cytotoxicity study of b, d against Esophageal cancer cells revealed significant cytotoxic effects with an IC_{50} value of 707 µg/mL. The compounds exhibited selective activity, showing a notable difference between its effects on cancerous (SKGT4).*

Keywords: *Tetrazole, pyridine-2-one, 3-amminophenol, Antibacterial activity, Anticancer.*

1. Introduction

Five-membered heterocyclic compounds with one carbon atom and four nitrogen atoms in the ring are called tetrazoles [1]. In medicinal chemistry, tetrazole scaffolds have garnered significant interest for drug design due to their distinct chemical characteristics, such as metabolic stability, the capacity to function as bio isosteres of carboxylic acids, and favorable acidity (Pka) profiles [2]. Enhancing pharmacokinetic characteristics including solubility, membrane permeability, and binding specificity is a common usage for them. [3] The limits of current chemotherapeutic drugs, including toxicity, side effects, and most importantly, the emergence of resistance, make cancer a significant worldwide concern. [4]. Therefore, One of the main objectives of oncological drug research is the creation of novel cytotoxic agents that can target cancer cells specifically while having the least amount of negative effects on healthy tissue. Tetrazole compounds have become viable options for anticancer treatment in this regard. [5]. Tetrazole-containing drugs can exhibit strong in vitro anti-proliferative or cytotoxic action against a variety of cancer cell lines, according to recent investigations. For instance, one study found that indole-tetrazole derivatives were less hazardous to non-cancerous cells and had IC_{50} values in the low micromolar range against breast cancer cell lines (MCF-7, T-47D, and MDA-MB-231) [6]. Similar to this, new tetrazoles containing benzo chromene moieties were created and examined; some of these compounds showed cytotoxicity that was on par with typical drugs like 5-fluorouracil, albeit frequently a little less potent. [7]. The pharmacological effectiveness of tetrazole derivatives against several forms of cancer progression is well recognized[8].

2. Experimental.

2.1 chemical and Instruments

The Fluka, Sigma-Aldrich, and BLD pharmaceutical companies were the suppliers of all chemicals and solvents. Every chemical was used straight away without further purification. Using solvent systems such ethyl acetate: hexane (4:6), thin layer chromatography (TLC) was used to monitor the development of the chemical reactions .A Perkin Elmer Tensor 27 (Bruker) Fourier-transform infrared (FT-IR) spectrophotometer was used to obtain infrared spectra in the 400–4000 cm^{-1} spectral region. The specimens were made into discs of potassium bromide (KBr). A Bruker DRX spectrometer running at 500 MHz was used to record both ^{1}H-NMR and ^{13}C-NMR spectra in order to verify the chemical structures. Tetra methyl silane (TMS) was employed as the internal reference, and deuterated dimethyl sulfoxide (DMSO-d_6) was employed as the solvent. Chemical shifts (δ) are expressed in parts per million, and all NMR measurements were carried out at the University of AL basrah using DMSO as the solvent and TMS as an internal standard.

2.2 procedure of Syntheses.

2.2.1 Syntheses tetrazole derivatives a α b.

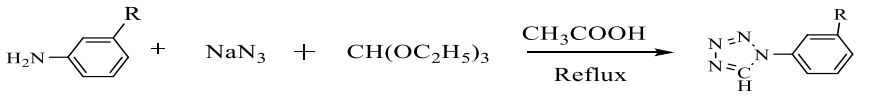
3- amino acetophenone (2. 703 g, 0. 02 m mole), 3–aminophenol (2. 18 g, 0. 02m mole) respectively was dissolved with glacial acetic acid 50 ml and NaN_3 (2. 6 g, 0. 02 m mole) and triethyl ortho formate (10 mL, 0. 02 m mole) were included in round bottom flask. For fifty hours, the resultant mixture was heated under reflux. TLC tracked the reaction's development. After completion of the reaction, the reaction mixture pouring the onto crushed ice, the solid was filtere, cleaned with water, and allowed to crystallize again by ethanol [9].

1-(3-(1*H*- tetrazole-1-yl) phenyl) ethan-1-one (a).

The compound was obtained as pale-brown crystals with a yield of 66%, MP. 166–168°C, Rf= (0. 61): IR (v cm^{-1}) : 3107(C-H of Tetrazole ring), 3061 (C-H Ar.), 1682 (C=O Ketone), 1606 (C=N). ^{1}H-NMR(DMSO-d6) :10. 20 (s, 1H, HC=N tetrazole), 8. 39 -7. 78 aromatic proton), 2. 66 (s, 3H, CH_3). ^{13}C- NMR (101MHz, DMSO-d6: δ ppm) : 196 (C=O), 142 (C =N of tetrazole), 138-120 (Aromatic Carbon), 26 (carbon of CH_3).

3 -(1*H*-tetrazol-1-yl) phenol (b).

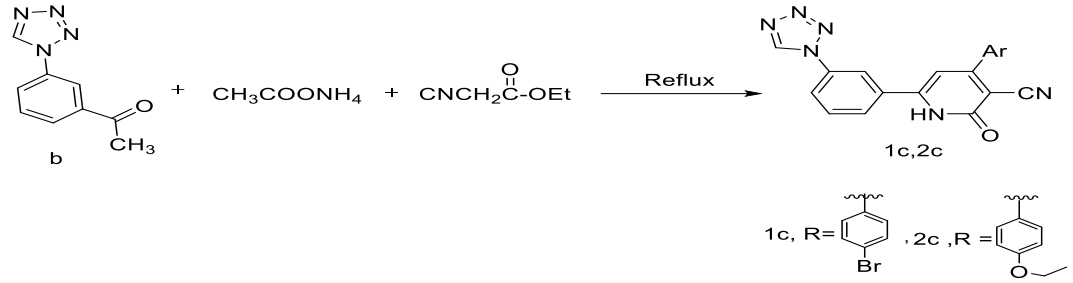
The compound was obtained as brown crystals with a yield of 81%, MP. 166 –168°C, Rf= (0. 5) ; IR (v cm^{-1}) : 3156 (O -H), 3111 (C-H of Tetrazole ring), 3065 (C-H Ar.), 1606 (C=N), ^{1}H-NMR (DMSO-d6) :10. 04 (O- H), 10. 20 (s, 1H, HC=N tetrazole), 7. 43-6. 93 (dd, 4H, aromatic proton). ^{13}C- NMR (101MHz, DMSO-d6: δ ppm) :158 (C-OH), 142 (C=N of tetrazole), 134-107 (aromatic Carbon). [10]



a ,R = $COCH_3$
b, R= OH

2. 2. 2 General procedure for preparation (c).

A mixture of 1-(4-(1*H*- tetrazole-1-yl) phenyl) ethan-1-one (a) (0. 56 gm, 3mmole), ethyl cyanoacetate (0. 319 mL, 3mmole), ammonium acetate (0. 231g, 3mmole) with appropriate aldehyde (4- bromobenzaldehyde, 4- ethoxy benzl aldehyde) 3mmole respectively, in 35mL of ethanol in round bottom flask. The completion of reaction was monitor by TLC. The reaction mixture was heated under reflux. The end point of the reaction was monitor by TLC. Then, the resulted precipitate was filtered, dried and recrystallized from ethanol to obtain the desired chemicals.



6-(3-(1H-tetrazol-1-yl) phenyl) -4-(4-bromophenyl) -2-oxo-1, 2-dihydro- pyridine-3-carbonitrile (1c).

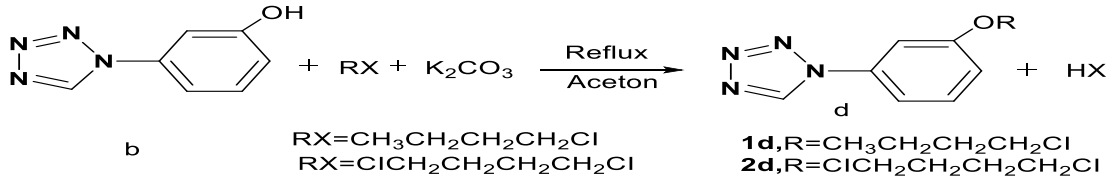
light yellow; m. p 177-179 ℃, Yield (55 %); Rf =0. 32 (hexan: ethyl acetet 6:4); IR (KBr) (cm^{-1}): 3275 (NH), 3143(C-H of tetrazole), 3066, 3008 (C-H of Ar.), 2222(C≡N), 1732 (C=O amide), 1685 (C=N), 968 (C-H out of plane), ^{1}H-NMR (400 MHz, DMSO-d6: δ ppm): 13. 02(s, 1H, NH), 10. 15(s, 1H, CH=N of tetrazole), 8. 48 -7. 73(m, H, aromatic proton), 7. 13 (s, 1H, pyridone (C-H). ^{13}C-NMR (101MHz, DMSO-d6: δ ppm), 162 (C=O of pyridine -2-one), 128(C-H) Pyridonering), 142(C=N of tetrazole), 116 (C≡N), 135, 134, 131, 130, 124, 123, 120 (Carbon of Phenyl ring).

6-(3-(1H-tetrazol-1-yl) phenyl) -4-(4-ethoxyphenyl) -2-oxo-1, 2-dihydropyridine-3-carbonitrile (2c)

Black powder, Yield (73 %); Rf =0. 4 (hexan: ethyl acetet 6:4); M. p 193-195 ℃; IR (KBr) (cm^{-1}): 3116 (NH), 3062 (C-H of tetrazole), 2016 (C-H of Ar.), 2214 (C≡N), 1651 (C=O) amide), 1581 (C=N), 995 (C-H out of plane). ^{1}H- NMR (400 MHz, DMSO-d6: δ ppm): 12. 82 (s, 1H, NH), 10. 15 (s, 1H, CH=N tetrazole) 8. 47 (s, 1H, aromatic proton), 8. 10 (s, 3H, aromatic proton), 7. 12 (s, 1H, pyridone (C-H), 4. 13(q, 2H, OCH_2), 1. 38(s, 3H, CH_3) ^{13}C-NMR (101MHz, DMSO-d6: δppm), 160 (C=O), 142(C=N of tetrazole), 134, 130, 128, 127, 123, 120, 114, 113, 112(aromatic carbons), 116 (C≡N), 63(O-CH_2), 14(CH_3).

2.2.3 General procedure for preparation tetrazole derivatives (d).

A mixture of 4-(1*H*-tetrazol-1-yl) phenol 2 (0. 81 g, 5mmole), Potassium carbonate (0. 69 g, 5mmole), 1-chloro butane, 1, 4-dichlorobutane (10 ml, 10mmole) respectively, in (50 ml) of acetone in round bottom flask. Then, the resultant mixture was heated under refluxed. TLC was used to monitor the reaction. Next, the reaction mixture was cooled to room temperature and poured in cold water, then 50ml of chloroform was added, then separated the organic layer using a separating funnel, dried and evaporated the solvent desired chemicals.



1-(3-butoxyphenyl) -1H-tetrazole (1d).

Pale yellow; mp 75-77 ℃, Yield (63 %); Rf =0. 63 (hexan: ethyl acetet 6:4); IR (KBr) (cm^{-1}): 3143(C-H of tetrazole), 3097 (C-H of Ar.), 2954- 2870 (C-H alphatic), 1203 (C-O), 1597 (C=N), 972 (C-H bending of CH_3), ^{1}H- NMR (400 MHz, DMSO-d6: δ ppm): 10. 11(s, 1H, CH=N tetrazole), 7. 56-7. 46 (m, H, aromatic proton) 4. 07 (t, 2H, O-CH_2), 1. 73(m, 2H, CH_2-CH_2-CH_3), 1. 46 (m, 2H, CH_2-CH_3), 0. 94 (s, 3H, CH_3): ^{13}C NMR (100 MHz, DMSO-*d6*), δ(ppm) :159 (C-O), 142 (C=N of tetrazole), 134, 131, 115, 112, 107 (aromatic carbons), 67(O-CH_2), 30 (O-CH_2-CH_2), 18(CH_2-CH_3), 13 (CH_3).

1-(3-(3-chloropropoxy) phenyl) -1H-tetrazole (2d).

Pale white, Yield (77 %); M. p =84-86 ℃, Rf =0. 28 (hexan: ethylacetet 6:4); IR (KBr) (cm^{-1}): 3140(C-H of tetrazole), 3078 (C-H of Ar.) 2954-2877 (C-H, alphatic protons), 1195 (C-O), 1504 (C=N), 1396 (C-H bending of CH_3). ^{1}H- NMR (400 MHz, DMSO-d6: δ ppm): 10. 11(s, 1H, CH=N tetrazole), 7. 57-7. 13 (m, H, aromatic proton), 4. 17(t, 2H, O-CH_2), 3. 73 (t, 2H, CH_2-Cl), 1. 95(m,

2H, CH_2-CH_2), 1. 88(m, 2H, CH_2-CH_2); ^{13}C NMR (100 MHz, DMSO-*d6*), δ(ppm): 159 (C-O), 142 (C-H of tetrazole), 107-134 (aromatic carbons), 67 (O-CH_2), 45(-CH2-Cl), 28(CH_2-CH_2), 25 (CH_2-CH_2).

2.3 Biological activity study. [11]

2.3.1 -Antibacterial activity of compounds 5and 6.

In this investigation, two different kinds of harmful bacteria used *Escherichia coli*, which is Gram-negative, and *Staphylococcus aureus*, which is Gram-positive. substances that have therapeutic use. Chemical solutions of tetrazole derivatives 5, 6 were produced in concentrations of 500 and 1000 mg/ml using the solvent Dimethyl Sulfoxide DMSO in order to quantify and ascertain the minimum inhibitory concentration [12]. The bacterial isolates' sensitivity test was performed by diffusion method in Mueller-Hinton agar, a transparent food medium that is helpful in figuring at how sensitive microbes are to antibiotics due to the fact that it includes casein and extracted starch [13]. The majority of bacteria and microorganisms can grow in it [14]

After the medium was created and autoclave sterilized, it was divided into plates and allowed to solidify. three tiny pits were then made in each plate [15] After that, it was kept in a for 24 hours at 37^0C. The diameter of the inhibition visible in the dishes surrounding the holes utilized determines the derivatives activity derivatives employed, since the findings were read the following day [16].

When compared to the diameter of inhibition for antibiotics, inhibition refers to the rise in the biological activity of the produced drugs [17]. Where the laboratory results. for compounds 5 and 6 proved that they do not possess antibacterial activity, meaning their inability to inhibit bacterial activity at these concentrations [18]. Figure (1).

Figure (1): Antibacterial activity compounds5, 6 against Escherichia coli and Staphylococcus aureus

2.3.2 Cytotoxic of compounds b, 1d α 2d.

The cytotoxic effect of the compounds b, 1d and 1d were evaluated on the human esophageal cancer cell line SKGT-4 using the MTT assay at a wavelength of 620 nm. Cells were exposed to concentrations of 0, 500, and 1000 µg/mL, with four technical replicates for each concentration .As shown in Figure (2).

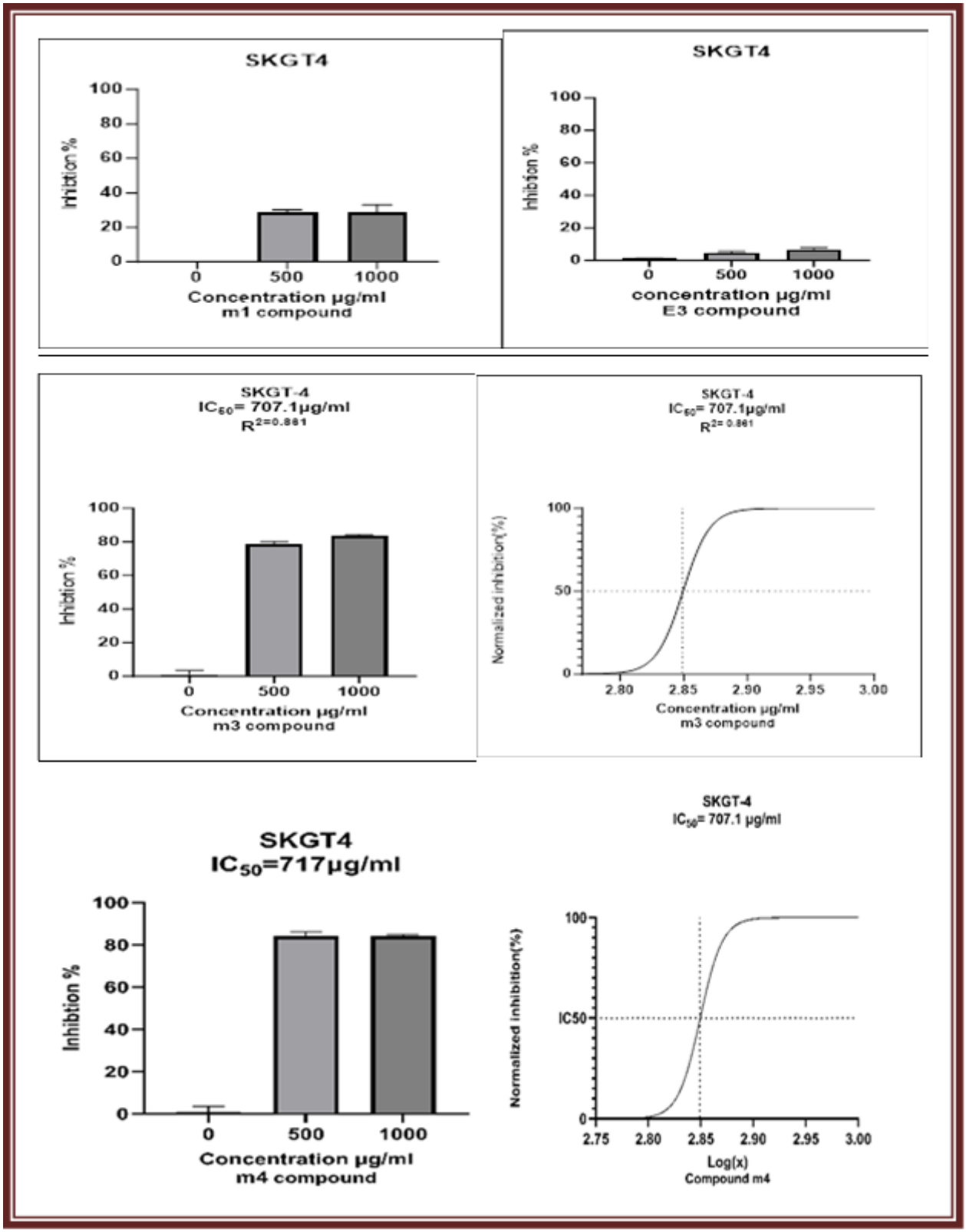


Figure 2: Cytotoxicity Assay for b, 1d, 2d Compound on SKGT-4 cell.

3- Results and discussion.

3.1 Synthesis and Characterization.

Cyclization reaction of primary amine with sodium azid and ethyl orthoformate was using to synthesized tetrazole derivatives 1 and 2. The structures of synthesized compound have been established by spectrum analysis (FT-IR, NMR). FT-IR spectra showed disappearance absorption bands of stretching bands of NH_2 and appearance new absorption band of stretching of C-H of tetrazole at 3107, 3111cm^{-1} respectively. the ^{1}HNMR spectra exhibited singlet signals at 10. 20, 10. 20 ppm because of proton of CH=N in the synthesized tetrazole ring. On the other hand, ^{13}CNMR

displayed signal at 142, 142 ppm respectively, refer to carbon of C=N. The tetrazole derivatives linked pyridine-2-one were synthesized from the cyclization reaction of tetrazole derivative 1 with aromatic aldehyde and ethylcyanoacetate in the present of amoonium acetate to produce compounds 3 and 4. The structure of preparing derivatives have been established by spectra data. The FT-IR showed the departure absorption band of carbonyl group at 1732, 1651 cm^{-1} and appearance anew bands at 3275, 3116 cm^{-1} of stretching vibration of NH, while bands at 2222, 2214 cm^{-1} of stretching vibration of CN. The ^{1}H-NMR spectra showed singlet signal at 13. 02, 12. 82 ppm refer to protons NH in the pyridine -2-one ring. Alternatively, the spectra showed signals at 7. 13, 7. 12 ppm due to protons of pyridine (C-H). On the other hand the ^{13}C-NMR exhibited signals at 162, 160 ppm refer to C=O of the pyridine-2-one ring, signals at 116, 116 due to carbon of CN.

The alkylation reaction of hydroxyl group in the tetrazole derived 2 with alkyl halide in the presence of K_2CO_3 as catalyst produce tetrazole derivatives 5 and 6, the structures of synthesized derivatives exhibited by spectra data. The FT-IR spectrum demonstrated disappearance absorption band at 3156 cm^{-1} which caused by stretching of OH group and appearance anew absorption bands at 2954- 2870, 2954-2877 cm^{-1} of stretching vibration of C-H aliphatic. ^{1}HNMR spectrum for compound 5 showed a new signals at 4. 07, 1. 73-1. 46, 0. 94 ppm refer to aliphatic protons of CH_2 and CH3 groups. A new signals at 30, 18. 13 ppm have been showed in the ^{13} C-NMR. Oppositely, the ^{1}HNMR of compound 6 showed a new signals at 4. 17(t, 2H, O-CH_2), 3. 35(t, 2H, CH_2-Cl), 1. 95(t, 2H, CH_2-CH_2), 1. 87(m, 2H, CH_2-CH_2), 1396(C-H bending of CH_3). Despite the fact that, ^{13}CNMR displayed a new signals at 67ppm (O-CH_2), 45ppm (CH_2-Cl), 28ppm (CH_2-CH_2), 29ppm(CH_2-CH_2).

3.2 Biological Activity

3.2.1 Antibacterial Activity

Most of synthesized tetrazole derivatives 5, 6 were tested against bacteria *(Escherichia coli, Staphylococcus aureus).* As the results of the bioactivity test for compounds 5 and 6 showed no inhibitory effect at concentrations of 500 and 1000 micrograms/ml against the bacterial strains E. coli (Gram-negative) and Stph. aureus (Gram-positive).

2.3.2: Anticancer Activity [19, 20].

The cytotoxic activity of the compounds b, 1d and 2d was evaluated against the human esophageal cancer cell line SKGT-4 using the MTT assay at 620 nm. At the control (0 µg/mL), the mean absorbance of compound 2 was 0. 462, the mean absorbance was 0. 467, with negligible inhibition (1. 07%). At 500 µg/mL, the mean absorbance decreased to 0. 332, with an inhibition ratio of 28. 8% (SD ±1. 53). while at1000 µg/mL, the mean absorbance was 0. 334, with a similar inhibition ratio of 28. 4% (SD ±4. 62). The results indicate that the compound produced only a modest cytotoxic effect on SKGT-4 cells, reaching inhibition levels below 30% even at the highest tested concentration. Due to the plateau in response and absence of a clear dose–response trend beyond 500 µg/mL, it was not possible to determine a reliable IC50 value within the tested concentration range (Figure 2). The mean absorbance of compound 5 was **0. 462**, with a negligible inhibition rate of approximately **1. 1%**. At **500 µg/mL**, the mean absorbance dropped significantly to **0. 101**, corresponding to a strong inhibition rate of approximately **78. 5% (SD ±1. 68).** At **1000 µg/mL**, the absorbance further decreased to **0. 076**, with inhibition increasing slightly to **83. 8% (SD ±0. 44).** Curve fitting analysis revealed an **IC50 707. 1 µg/mL (Log IC50 = 2. 849),** with a steep **Hill Slope of 41. 1** and a correlation coefficient (**R^2 = 0. 861**), confirming a sharp dose–response transition and a relatively strong inhibitory effect at higher concentrations. The results indicate that the m3 compound exerts a pronounced cytotoxic effect on SKGT-4 cells at higher concentrations. Both 500 µg/mL and 1000 µg/mL produced strong inhibition rates of 78. 5% and 83. 8%, respectively, suggesting that the compound reaches its cytotoxic plateau starting from 500 µg/mL. This highlights the potent inhibitory capacity of the compound at elevated doses, while also confirming that increasing the concentration beyond 500 µg/mL does not markedly enhance cytotoxicity, indicating a saturation effect. The mean absorbance of compound 6 was 0. 462, with negligible inhibition. (%1. 1)At 500 µg/mL, absorbance markedly decreased to 0. 074, corresponding to a sharp increase in inhibition (% 84. 2)At 1000 µg/mL, the absorbance remained low (0. 074), with inhibition persisting at 84. 2%, indicating that the plateau of cytotoxic activity was reached at 500 µg/mL .

The curve-fitting analysis showed a LogIC50 = 2. 849, corresponding to an IC50 707 µg/mL, with a steep Hill Slope = 41. 1, indicating a sharp transition between inactive and highly active concentrations. The absence of an R^2 value suggests limitations in regression accuracy, but the data strongly demonstrate that compound m4 exerts a potent cytotoxic effect once the effective dose threshold is reached.

4. Conclusion

In order to obtain new compounds with promising chemical and biological potentials, a group of tetrazole derivatives were successfully generated and described using meticulously explored synthetic pathways at the end of this research. The results of the spectroscopic analysis, which included infrared spectra (FT-IR), proton nuclear magnetic resonance (^{1}H-NMR), and possibly carbon (^{13}C-NMR) spectra, along with other supporting techniques, demonstrated a clear match with the suggested structures of the prepared compounds, confirming the accuracy of the final chemical structures and the success of the preparation steps.

Additionally, the study demonstrated that the addition of the tetrazole group to the organic structure enhances the chemical activity of the resultant compounds and gives them comparatively stable physical properties, making them potential candidates for use in applied chemistry or pharmaceuticals.

For the purpose to create more potent and selective compounds in the future, this study suggests investigating the Structure Activity Relationship and carrying out additional research to assess the biological characteristics of these derivatives, especially in the areas of antibacterial and anti-inflammatory agents.

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