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Synthesis of Some New 1,3,4- Oxadiazole Derivatives and Thiazolidine Derived from Cysteine and Evaluation their Anticancer (MCF7) Activity

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ABSTRACT

The study focused on the preparation of oxadiazole derivatives containing thiazolidine. Thiazolidine firstly was prepared from the reaction of benzaldehyde with L-cysteine with a good yield and then it was reacted with acetic anhydride to prepare acetyl thiazolidine, then with ethanol in the presence of H_2SO_4, then steps were taken to prepare a thiazolidine hydrazide (A_3), which was reacted with aromatic carboxylic acid in presence $POCl_3$ or carbon disulphide and base KOH to obtain oxadiazole derivatives A_{4-8}. These compounds characterized using FT-IR, NMR and Mass (EI) were diagnosed and the synthesized compound were validated. The activity of oxadiazole derivatives were studied against breast cancer cells, the two compound A_8, A_4 showed good activity against the cells as for the compounds A_5, A_6, A_7 it was showed little activity against these cells and the value IC_{50} was calculated.

1. Introduction

Heterocyclic compounds play an effective role in many fields, where the compound of oxadiazole, triazole, thiazole (Guessas, et al., 2007) and thiazolidine have received great attention in medicinal, pharmaceutical and industrial chemistry (Leod & Ames, 1987). Thiazolidine is an aliphatic cyclic compound found in natural produced (Busacca, et al., 1996), foodstuffs and antibiotics, which is produced from the interaction of cysteine or cysteamine (penicillamine) with aliphatic and aromatic aldehydes or ketones (Tawfiq, 2016), thiazolidine plays a distinctive character in natural products similar to antibiotics including penicillin and cevasporine, one of the most important thiazolidine derivatives is thiazolidine-4-carboxlic acid (Šubr & Ulbrich, 2006), which is considered the basis for the basis for the production of thiazolidine drugs (El-Sharkawy, 2011), as it has against cancer, bacteria (Pavin, et al., 2011), fungi, inflammation and diabetes (Da Silva, et al., 2015). Oxadiazole is considered an effective cyclic aromatic compound and is include in the composition of many derivatives of biologically active drugs (Şahin, et al., 2002), which include anti-inflammatory (Guessas, et al., 2007), antifungal, HIV (Wang, et al., 2012) creating pharmaceutical scaffolds, antimicrobials (Bondock, et al., 2012), anticancer, antihypertensive and cardio-tonic. The most famous method used to prepare oxadiazole is a reaction of hydrazide with carboxylic acids in the presence of $POCl_3$ (Gilani, et al., 2010) or it is condensation with carbon disulfide and base (KOH) (Zhang, et al., 2013). The aim of the study was to prepare and study thiazolidine and oxadiazole ring as anti-cancer of type MCF-7.

2. Materials and Methods

Melting points, FT-IR spectra, and ^1H, ^{13}C-NMR spectrum were recorded on Brucker 400MHz in DMSO and $CDCl_3$ solvent. For abbreviation used: s :singlet, d:doublet, t: triplet, dd :doublet of doublets and m: multiblasty. Mass(EI) spectra and spectrophotometry.

2.1. Synthesis the Compound 2-Phenyl thiazolidine-4-carboxylic acid (A).

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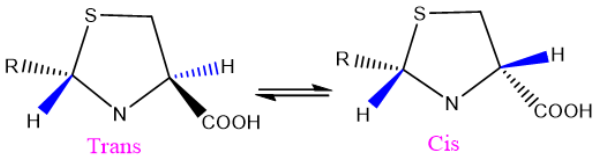
A mix 0.01 mole (1.02 ml) of Benzaldehyde and 0.01 mole (1.21 g) of L-cysteine were mixed in (10 ml) water and (50 ml) ethanol, it was stirred at room temperature for (12 h), the resulting white precipitate formed was filtered, collected, washed, with ether, dried and recrystallized with ethanol; water (1:3) (Nawar, et al., 2020). Structure was showed in Scheme1. This product as a mix of diastereomers, cis-(2R,4R) and trans-(2S,4R) as shown in Equation 1. **(2R, 4R) 2-Phenyl thiazolidine-4-carboxylic acid (A) 61%Cis Isomer (Trans39%)**

Yield: 80%, mp:159-161°C. FT-IR(KBr): 3100-2700(ZwitterionNH_2^+), 1573s (COO^-). ^{1}H NMR(400 MHz, $CDCl_3$): δ2.9 dd, 1H, J=10.28, 8.7 Hz (2.99dd, J=10.51, 5.58Hz) **(H5a)**, δ3.24dd, 1H, J=10.33, 7.25Hz (3.14 dd, J=10.51, 7.51Hz) **(H5b)**, δ3.77 dd, 1H, J=8.36,7.32Hz (3.96t, J=5.91) **(H4)**, δ5.29 s, 1H (5.56s) **(H2)**, 7.00-7.27(5H) **(Har)**.



Equation 1: Cis and Trans diastereomers

2.2. Synthesis the Compound3-Acetyl-2-Phenyl thiazolidine-4-carboxylic acid (A_1).

0.01 mole (2.09 g) was dissolved of (A) in (40 ml) of (6 %) Na_2CO_3 cool in ice bath, followed by the addition 0.04 mole (3.77 ml) of acetic anhydride in the form drops. The mixture was stirred for 1 h and it is acidified by HCl, the mixture was extracted using with ethyl acetate and evaporation leaving the solid white, then washed by water, dried and recrystallized with ethyl alcohol (Majed & Abid, 2015) to give (A_2). **(2R, 4R)-N-Acetyl-2-Phenyl thiazolidine-4-carboxylic acid (A_1) 93%Cis Isomer (Trans7%)**

Yield:85%, mp:147-149°C. FT-IR(KBr): 3327s (OH), 1731m, 1680m(C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ1.98s, 3H (2.19s) **(H7)**, 3.32dd, 1H, J=12.12, 6.66Hz (3.42d, J=6.4Hz) **(H5a)**, δ3.36dd, 1H, J=12.07, 6.98Hz (3.42, d, J=6.4Hz) **(H5b)**, δ5.06t, 1H, J=6.8Hz (4.8s) **(H4)**, δ6.05s, 1H (6.39s) **(H2)**, 7.27-7.35(5H) **(Har)**, δ11.13s, 1H (11.13s) **(H6)(OH)**.

2.3. Synthesis the Compound Ethyl 3-Acetyl-2-Phenyl thiazolidine-4-carboxylate(A_2).

A 0.01 mole of (A1) was mixed with 30ml ethanol and drops of concentrated sulphric acid. The mixture was reflexed for 6 h, then filtered and evaporated to give oily yellow product (Tawfiq, 2016).

2.4. Synthesis the 3-Acetyl-2-Phenyl thiazolidine-4-carbohydrazide(A_3).

Compound A_2 was dissolved in (30 ml) ethanol then (5 ml) of (80%) hydrazine hydrate added. The solutions were reflexed for 24 h, and the solvent evaporated to leave a white precipitate which was recrystallized with water: ethanol (2:8) (Al-Badrany, et al., 2019), to give (A_3) m.p=123-125°C.

2.5. 3-Acetyl-2-Phenyl thiazolidine-4-carbohydrazide (A_3) 75%Trans Isomer (Cis25%)

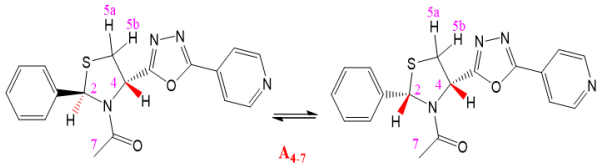
mp:122-125C° FT-IR(KBr): 3317, 3182s (NH_2), 3226w (NH), 1700m, 1662m (C=O). ^{1}HNMR (400MHz, DMSO-d_6): δ1.86s, 3H (2.08s) **(H7)**, 3.1 dd, 1H, J=10,4Hz (3.3m,) **(H5a)**, δ3.46 m, 1H, J=4 Hz (3.37m) **(H5b)**, δ4.21 m, 1H, J=8, 4Hz (4.21s) **(H4)**, δ4.78 d, 2H, J=4 (4.79s) **(H5)**, δ5.3 d, 1H, J=4 (5.3) **(H6)** δ6.43 s,1H (6.22s) **(H2)** 7.22-7.71(5H) **(Har)**. Mass(EI): 265.1 M.Wt, 185.1 peas beak.

2.6. General method for the prepare 2-(2-Phenyl thiazolidine- 4-yl)-5-(aryl)-1,3,4-Oxadiazole (A_{4-7})

Totally compounds are synthesize the same procedure (Husain, et al., 2012). A solution 0.01 mole of compound (A_3) and 0.01 mole of aromatic carboxylic acid in $POCl_3$ (5 ml) was reflex to (90 °C) for 6-8 h on water bath. The reaction was followed using the TLC (ethanol ethyl: acetate 2:8), then evaporated, poured into crushed ice, neutralized using $NaHCO_3$ (10 %) and left to form a precipitate, the result was filtered, washed many step with water, dried and recrystalized from the mixture chloroform: Hexane or ethanol: water. Structures and symbols of prepared compounds are illustrated in Scheme2.Trans and Cis diastereomers of oxadiazole showed in Equation 2 (Jafari, et al., 2017).

2.7. 2-((2R,4S)-N-Acetyl-2-phenylthiazolidine-4-yl)-5-(84hiazoli-4-yl)-1,3,4-oxadiazole (A_4) 85%Trans Isomer (Cis15%)

Yield:20%, mp:187-189°C, FT-IR(KBr disk): 1701s (C=O), 1627m (C=N). ^{1}HNMR(400 MHz, DMSO-d_6): δ1.81s, 3H (2.08s) **(H7)**, 3.13t, 1H, J=8Hz (3.32m, J=4Hz) **(H5a)**, δ3.46m, 1H, J=8 Hz (3.40m, J=4Hz) **(H5b)**, δ4.46t, 1H, J=8Hz (4.45s) **(H4)**, δ6.36 s, 1H (6.16s) **(H2)**, 7.30-8.24(9H) **(Har)**. ^{13}CNMR: δ 22.42**(CH_3)**, 30.44(CH_2)**C_5**, 64.9(CH)**C_4**, 73.3(CH) **C_2,** 121-150 **(CAr)**, 159, 163 (**2C=N**), 170.55 (**C=O**) Mass(EI): 352.2 M.Wt, 180.2 peas beak.



Equation 2: Cis and Trans diastereomers of oxadiazole A4-7

2.8. 2-((2R,4S)N-Acetyl-2-phenylthiazolidin-4-yl)-5-Phenyl-1,3,4-oxadiazole (A_5) 73%Trans Isomer (Cis27%)

Yield:24%, mp:164-167°C**)**. FT-IR(KBr): 1685m (C=O), 1598m (C=N). ^{1}H NMR(400 MHz, DMSO-d_6): δ1.83s, 3H (2.06s) **(H6)**, δ3.1dd, 1H, J=10,4Hz (3.3m) **(H5a)**, δ3.47 m, 1H, J=4Hz (3.41d) **(H5b)**, δ4.21 m, 1H, J=4Hz (4.21m) **(H4)**, δ6.42 s, 1H (6.2s) **(H2)**, 7.23-7.81(10H) **(Har)**. ^{13}CNMR: δ 23.37(**CH_3**), 34.13(CH_2) **C_5**, 67.7(CH)**C_4**, 74.15(CH)**C_2**, 120-140 (**CAr**), 159, 162(**2C=N**), 170 (**C=O).** Mass(EI): 351.2 M.Wt, 180.2 peas beak.

2.9. 2-((2R,4S)-N-Acetyl-2-phenylthiazolidin-4-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (A_6) 91% Trans Isomer (Cis9%)

Yield:22%, mp:191-194°C, FT-IR(KBr disk): 1689s (C=O), 1635m (C=N), 1346, 1540 (NO_2). ^{1}HNMR(400 MHz, DMSO-d_6): δ1.81s, 3H (1.78s) **(H7)**, 3.1m, 1H, J=4Hz (3.3m) **(H5a)**, δ3.37m, 1H, J=8 Hz (3.7m) **(H5b)**, δ4.27m, 1H, J=8Hz

(4.27m) **(H4)**, δ6.38 s, 1H (6.34s) **(H2)**, 7.2-8.1(9H) **(Har)**. Mass(EI): 396 M.Wt, 43.2 peas beak.

2.10. 2-((2R,4S)-N-Acetyl-2-phenylthiazolidine-4-yl)-5-(4-tollyl)-1,3,4-oxadiazole (A_7) 78%Trans Isomer (Cis22%)

Yield:16%, mp:177-179°C, FT-IR(KBr disk): 1741s (C=O), 1627m (C=N). ^{1}HNMR(400 MHz, DMSO-d_6): δ1.85s, 3H (2.05s) **(H7)**, 3.13dd, 1H, J=8,4Hz (3.3m) **(H5a)**, δ3.45m, 1H, J=8 Hz (3.38m) **(H5b)**, δ4.28m, 1H, J=8Hz (4.4m) **(H4)**, δ6.34 s, 1H (6.14s) **(H2)**, 7.2-8.1(9H) **(Har)**. Mass(EI): 362.2 M.Wt, 65.2 peas beak.

2.11. Synthesis the 2-(3-Acetyl-2-Phenyl thiazolidine)-5-mercapto-1,3, 4-oxadiazole (A_8)

A mixture of 0.01mole (A_3) in ethanol, 0.015mole KOH and (5 ml) CS_2 in 0 °C was refluxed for 8 h and followed using TLC(ethanol ethyl: acetate 2:8). The mixtures concentrated and poured in (100 ml) water ice, later acidified by 10 % HCl. The product was filtered, washed, dried (**Pitasse-Santos, et al., 2018**), recrystallized from ethyl alcohol to give (A_7). M.p=163-165°C.

2.12. 2-((2R,4S)-N-Acetyl-2-phenylthiazolidine-4-yl)-5-mercapto-1,3,4-oxadiazole (A_8) 55%Trans Isomer (Trans45%)

Yield:30%, mp:200-202°C. FT-IR(KBr): 3122w (NH), 2626w (SH), 1720 (C=O), 1612s (C=N). ^{1}H NMR(400 MHz, DMSO-d_6): δ1.78s, 3H (1.96s) **(H7)**, δ2.89t, 1H, J=12Hz (3.1m, J=4) **(H5a)**, δ3.4m,1H, J=4 Hz (3.34) **(H5b)**, δ4.24t, 1H, J=4Hz (4.55t) **(H4)**, δ6.42s, 1H (6.54s) **(H2)**, δ6.2s, 1H **(SH)** 7.34-7.84(5H) **(Har)**. Mass(EI):307.1M.Wt, 237.2 peas beak.

2.13. Anticancer Study

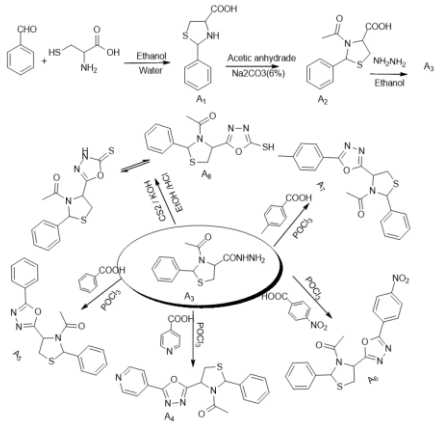
Cell growth and cell viability were quantified using the MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium Bromide) assay. In brief, for monolayer culture, cells (MCF7) were digested with trypsin, harvested, adjusted to a density of 1.4×10^4 cells/well and seeded to 96-well plates filled with 200 µl fresh medium per well for 24 h. When cells formed a monolayer, they were treated with 500-15.62 µg/ml of the compounds for 24 h at 37 °C in 5% CO2. At the end of the treatment (24 h), while the monolayer culture was left untouched in the original plate, the supernatant was removed and 200 µl/well of MTT solution (0.5 mg/ml in phosphate-buffered saline (PBS)) was added and the plate was incubated at 37 °C for an additional 4 h. MTT solution (the supernatant of cells was removed and dimethyl sulfoxide was added (100 µl per well). Cells were incubated on a shaker at 37 °C until crystals were completely dissolved. Cell viability were quantified by measuring absorbance at 570 nm using an ELISA reader (Model wave xs2, Biotek, USA). The concentration of the compounds that resulted in 50% of cell death (IC50) was determined from respective dose-response curves.

MCF7 cancer cells were cultured in a dish containing 96 vacuoles filled with (200 µl) of fresh medium for each holes for (24 h) in optimal conditions (37°C and atmosphere of carbon dioxide at 5% concentration and in a humid atmosphere). After that, serum media (10% FBS was + Antibiotics- penicillin and 100 µg/ml streptomycin) and wash the cells twice with buffer phosphate solution (PBS), Fresh culture media containing dilute concentrations of the compounds to be tested were used, and the cells were then incubated for 48, 72 and 24 hours. Then the prepared compounds were studied in a range of concentrations of 500-15.62 micrograms per liter. Gaps in the plate were analyzed for each concentration by adding 10 µl of 5% of freshly prepared mtt (methanol) in PBS in 100 ml of DMSO, then stirring the plates to facilitate dissolution of the crystals. The absorbance was measured at a wavelength of 570 nm. A Biotek device was used and the half inhibitory concentration was calculated (Ozyazici, 2021) .

3. Results & Discussion

3.1. Organic Synthesis

The amino acid (L-cysteine) attacks the carbonyl group of the benzaldehyde via the NH_2, SH group to product thiazolidine-4-carboxylic acid (A), thiazolidines were easily attained in yields of 80-85%, this product as a mix of diastereomers, Cis-(2R,4R) and Trans-(2S,4R), the couldn't be separated. An equilibrium resulting from epimerization at C(2) occurs between two isomers. The percentage Cis/Trans was strongly dependent on a nature of the solvent. In CDCl3 the major isomer was the Cis isomer while in DMSO-d_6 major isomer was trans isomer. Then protect the amine group will react with acetic anhydride to form 3-Acetyl-2-Phenylthiazolidine-4-carboxylic acid (A_1), the compound (A_1) reacts with ethyl alcohol in the presence H_2SO_4 to synthesis (A_2) (Mohammed, et al., 2021) and before it was condensed with (80%)hydrazine in a presence ethanol solvent to obtain 3-Acetyl-2-Phenylthiazolidine-4-carbohydrazide (A_3), the compound (A_3) goes in two ways, either it was reacted with carboxylic acid in the presence of phosphoryl chloride ($POCl_3$) to obtain 1,3,4-oxadiazole derivatives (A_{4-7}), or condensing it with carbon disulfide and potassium hydroxide KOH to prepare 2-(3-Acetyl-2-Phenylthiazolidine)-5-mercapto-1,3,4-Oxadiazole (A_8), as shown in (Taha, et al., 2016) (scheme 1).



Scheme 1. Compounds prepared in the study A_{1-8}

3.2. Anti-cancer Activity(MCF-7)

The prepared oxadiazole derivatives were studied on breast cancer cells type MCF-7 using five concentrations of each compound, the inhibition activity and IC_{50} value were calculated according to the following relationship:

$$Viability\ \% = \frac{mean\ of\ ODsample}{mean\ of\ OD\ controle} \times 100$$

The Values of the scavenging activity of the synthesis compounds (A_4, A_5, A_6, A_7 and A_8) at concentration(500, 250, 125, 63, 31.5 and 15.5 µg/ml) were measured by the absorbance at 570nm. The inhibition activity was showed that all compounds possess an inhibitory ability at high concentration and gradually decreasing concentration, as compound A_8 showed inhibitory activity towards cancer cells and this may be due to the compound's ability to form hydrogen bonds with the amino acid present in the active center of the cancer cells protein. Through the results IC_{50} shown in Fig.(1), it was observed that the arrangement of a studied compounds according to their ability to inhibit cancer cells is as follows (Ahsan, 2018, Ozyazici, et al., 2021):

$$A_8 > A_4 > A_5 > A_7 .$$

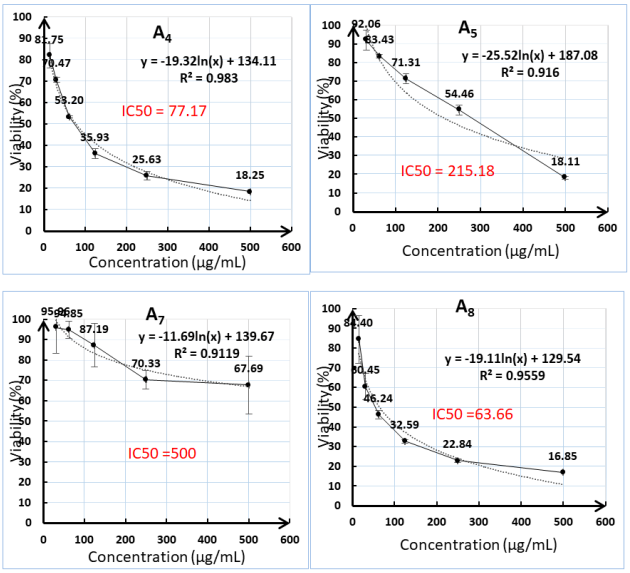


Fig. 1. The relationship of the percentage of inhibition with the concentration and calculate the (IC50) for the studied compounds

4. Conclusions

Thiazolidines were obtained easily in yield of 80-85% from the react of L-cysteine and benzaldehyde under slightly conditions. 1,3,4-oxadiazoles were obtained difficult in low yields 15-30% from the condensate of thiazolidine-4-hydrazides and aromatic carboxylic acid in the presence of $POCl_3$ or reacted with CS_2 and KOH under a little conditions. From the product we conclude that the all compounds oxadiazole and thiazolidine have a biological activities against cancer cells MCF-7, therefore, we recommend the preparation of many thiazolidine and oxadiazole derivatives, and the possibility of studying them on different cancer cells and using them as treatment (drug).

Competing Interests

The authors have declared that no competing interests exist.

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