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SYNTHESIS OF NEW AMIDES OF THIAZOLIDINE AND STUDYING THEIR BIOLOGICAL EFFECTIVENESS AGAINST CERVICAL CANCER AND BREAST CANCER IN HUMANS

Ramla Fayiq Ibrahim[1] , D. S. Abid[2]
Department of Chemistry, College of Education for Pure Sciences, University of Basra, Iraq
Emeil: aliali2088h@gmail.com [1], dawodsalim@yahoo.com [2]

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Abstract:

The study included the first reaction of substituted benzaldehyde compounds with cysteine to prepare compound (R). The compound (R) was then reacted with acetic anhydride to prepare the compound (RA) to protect the amine group, which was subsequently reacted with the aromatic amine phenyl hydrazine using the coupling reagents dicyclocardiimide and hydroxybenzotriazole in a solvent containing dichloromethane. This process made it possible to obtain the amide compounds. All synthesized compounds were characterized using Mass-EI NMR {^{1}H, ^{13}C} and FT-IR spectra. Two different cancer cell lines were used to test the effectiveness of the compounds that were synthesized. Human cervical cancer cells and breast cancer cells. Synthetic compounds have shown biological activity against cancer cells. Due to the presence of chiral atoms, substituted thiazolidinedione derivatives have two types of diastereomers that are difficult to separate: cis-(2R,4R) and trans-(28.2R) where the percentage of isomers cis/trans depends on the type of solvent used.

Keywords: Anticancer MCF-7,HeLa,L-Cysteine, Thiazoldines-4- Carboximide.

1. INTRODUCTION

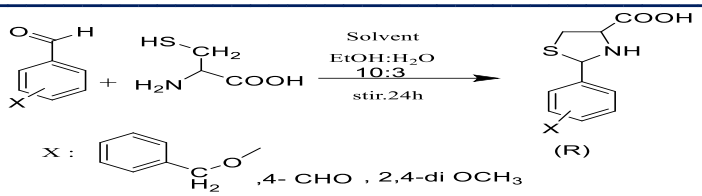
Heterocyclic compounds play an active role in many fields, where Isothiazole, triazole, thiazole (1) and Thiazoldines have received great interest in medicinal, pharmaceutical, chemical and industrial chemistry (2). Thiazolidinedione is an aliphatic cyclic compound found in natural products (3), foodstuffs and antibiotics, which is produced from the reaction of cysteine with aliphatic and aromatic aldehydes or ketones (4). Thiazoldines play a distinctive role in natural products. It is similar to antibiotics, including penicillin and cefasporin. One of the most important thiazolidine derivatives is thiazolidine-4-carboxylic acid [5], which is considered the basis for the production of thiazolidine drugs (6), as is the case against cancer and diabetes (7). Imides are considered active compounds. No matter what, you intervene In the formulation of several biologically active drug derivatives (8), which include anti-inflammatory (9), antifungal, human immunodeficiency (10) creation of pharmaceutical scaffolds, antimicrobial(11), a nticancer, antihypertensive, and cardioprotective—the most popular method. The use of the amide reaction is the reaction of carboxylic acids with the amine. The study aimed to prepare and study the amide derivatives of thiazolidine against two types of cancer cells, the first being human breast cancer and cervical cancer.

2. MATERIALS AND METHODS

Melting points were measured and determined by with ^{1}HNMR spectra were also recorded on a Brucker-400MHz spectrometer in DMSO-d6 in the presence of the TMS compound as an internal reference. Chemical shifts have been reported regarding the residual solvent coupling steady are conveyed in Hertz. The abbreviations for the signs used are as follows: s (single) , d (double) , t (triple), m (multiple) and dd (double doubling). Mass spectra were also recorded on an Agilent mass spectrometer 5975 quadruple analyzer with Electronic Impact Technology (EI) .

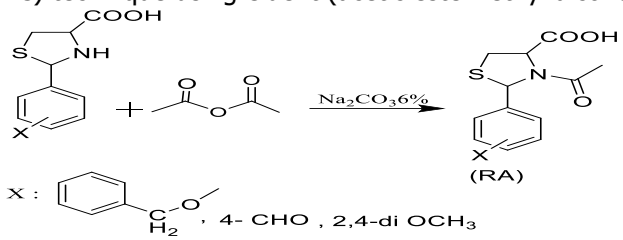
2.1.1General method for preparing compounds [R3,R5,R6]

0.01 mole(1.49g) of L-Cysteine was mixed with an equivalent amount of aromatic aldehyde in a 250ml Erlenmeyer flask in a mixture of ethanol (16ml) and water (5ml) with continuous magnetic shaking at room temperature for 10 hours where a white precipitate was notice. The precipitate was filtered, dried and recrystallized with a mixture of ethanol and water at a percent of (10:3), and the chemical reaction was press by application Thin Layer Chromatography (TLC) using a eluent of (Ethanol: Chloroform) at a ratio of (1:9) [13].



2. 2 General method for preparing compounds [RA3,RA5,RA6]

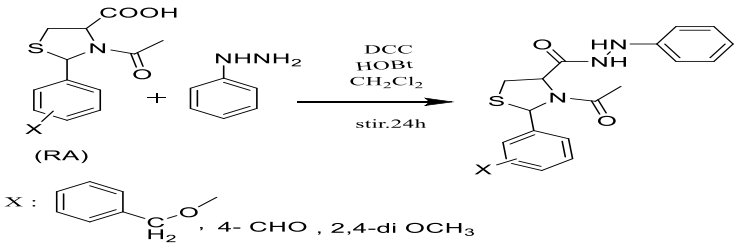
0.01 mole (2.36g) of [R3,R5,R6] was dissolved in a (55 ml) solution of sodium carbonate (Na_2CO_3)%6) in a 150 ml Erlenmeyer bottle, then the reaction was cooled in an integument bath to 0°C percent (1.02mmol)) was added to the reaction mix. (10 m mole) of acetic anhydride in drops over five minutes. The reaction mixture was left on the magnetic shaker for an hour, after stopping the reaction mixture was acidified using a dilute solution of hydrochloric acid (HCl) 5%) and a satiate solution of sodium chloride (NaCl) was added to it for the purpose of equivalence, and the acidified reaction mix was extract by ethyl ethanoate (2x50ml) . The extracted organic layer was rinsed in water while dried exercise no aqueous salt cake (Na_2SO_4) and vaporization the solvent . After that, it formed a white solid.The crystallization mixture of methyl alcohol with distilled water in a ratio of (3:1) . The reaction was followed by Thin Layer of chromatography (TLC) technique using eluent (acetic ester: ethyl alcohol) by amount (6:4) [14].



2 .3 Preparation of 3 -acetyl-N',2-diphenylthiazolidine-4-carbohydrazide

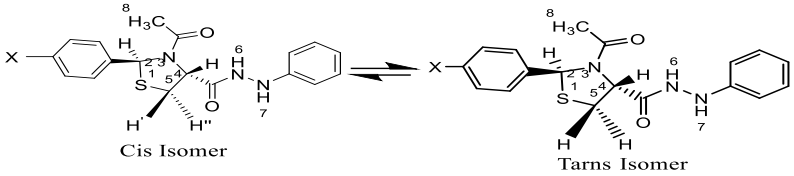
0.004 mole (1.11 g) of [RA3, RA5, RA6] in a circular flask (100 ml) with (0.004 mole) (0.82g) of N,N -′ dicyclohexylcarbodiimide (DCC) and 0.54 g (0.004 mole of 1-Hydroxybenzotriazole (HOBt) in (20 ml) of dichloromethane as a solvent and left the solution with continuous magnetic shaking at zero degrees Celsius for (10) minutes, until the solution became clear, then (0.004) mole of amine(Phenyl Hydrazine) was added to the reaction mix and left under continuous magnetic shaking for 24 hours at room temperature. after that, the formation a white solution be observed and then the reaction mixture was to get rid of the sediment by filtration, which one of them di-cyclohexyl urea (DCU). The filtrate was taken and diluted with dichloromethane (20 ml), then the mixture was washed successively with a solution.

(5%) sodium bicarbonate ($NaHCO_3$) , then with citric acid (10%), then a saturated solution of sodium chloride (NaCl) and finally with distilled water . The solution was dried, and I added anhydrous magnesium sulfate (MgSO4), then filtered and evaporated to make a precipitate recrystallized by a mixture of ethyl alcohol and H2O (1:1) . The chemical reactor was carried out by Thin Layer of Chromatography (TLC) the used a solvents (Formic acid, benzene and tetrahydrofuran) at a ratio of(2:6:) [15].



2.4 Test the effectiveness of some prepared compounds on inhibiting breast cancer cells (MCF7) and cells Cervical cancer(Hela).

The Activity biological of the prepared samples was measured on MCF7 breast cancer line cells and cells Cervical Cancer line (Hela). It was conducted using bromide(3(4,5-dimethyl-2-thiazole-2-yl), 5- diphenyltetrazolium Bromide) (MTT), where the cells were grown in dishes, each dish contained 96 holes, for a full day under ideal conditions of temperature, pressure, and environmental conditions, including At 37 degrees Celsius, in an atmosphere of 5% carbon dioxide, and in a humid atmosphere. After that, the fetal serum media (10% FBS) was removed for cell growth, and the cells were washed twice with phosphate buffer solution (PBS). New culture media was used. It contained diluted concentrations of the compounds to be tested, which were (µg/ml 100), and the cells from the samples were incubated for 48 hours. The gaps in the plate were analyzed for each concentration by adding 10 microliters of freshly prepared 5 MTT in Buffer's phosphate solution and 100 ml of DMSO, then stirring the plates to ensure the crystals dissolved. Each concentration of the prepared compounds was re-measured three times, and the absorbance was measured at a wavelength of 570 nm using BioTak device, and calculated Inhibition percentage (%) of prepared compounds against breast cancer and cervical cancer cell line. [16].



(2S,4R)-3-acetyl-2-(4 (phenoxymethyl)phenyl)-N'-phenylthiazolidine-4-carbohydrazide)trans Isomer(80%)ML3

Yield: 55% m.p: 117-118ºC,[1] HNMR (400 MHz, DMSO-d6) δ, 2.19(dd,3H) (H8), 3.11(t,1H), (H5b), 3.47(t,1H) (H5a), 4.72 (d,1H),(H4),4.98(m,2H) (H9), 5.59(d,1H) (H2), 6.71-8.05(dd, 9H) (HAr), 10.04(s,1H), (H6), 10.22(d,1H) (H7) FT-IR (KBr disk):3325w (NH),3057w (C-H Ar),2927w (C-H),1629 w (C=OAmide), 1577w, Mass spectra (70 ev): M·+ =371.46 m\z

(2R,4R)-3-acetyl-2-(4-(phenoxymethyl)phenyl)-N'-phenylthiazolidine-4-carbohydrazide(Cis Isomer)(20%)ML3

Yield: 55% m.p: 117-118ºC, [1]HNMR (400 MHz, DMSO-d6) δ, 2.09(dd,3H) (H8), 3.05(t,1H), (H5b), 3.32(t,1H) (H5a), 4.68 (d,1H),(H4),4.98(m,2H) (H9), 5.57(d,1H) (H2), 6.71-8.05(dd,9H) (HAr), 10.04(s,1H), (H6), 10.22(d,1H) (H7) FT-IR (KBr disk):3325w (NH),3057w (C-H Ar),2927w (C-H),1629 w (C=OAmide), 1577w, Mass spectra (70 ev): M·+ =371.46 m\z

(2R, 2′R,4S,4′S)-2-2′-(1,4-phenylene)bis (3-acetyle-5,5-dimethyl-N-phenylethiazolidine-4-Carbhydrazide(trans Isomer)(87%)ML5

Yield: 50% m.p: 115-116ºC,[1] HNMR (400 MHz, DMSO-d6) δ, 2.68(s,3H) (H8), 3.15 (m,1H), ((H5b), 3.51(m,1H) (H5a), 4. 99(m,3H) (H4), 5.72(d,3H) (H2), 6.34-7.92 (d,t,14H) (HAr), 10.04(s,1H) (H6), 10.30(s,1H) (H7), FT-IR (KBr disk):3327w (NH),3057w (C-H Ar),2929w,2850(C=O Carboxy Acid) (C-H),1672 w (C=OAmide), 1575w, Mass spectra (70 ev): M·+ =604.79 m\z

(2S,2′S,4S,4′S)-2,2-(1,4-phenyle-5,5-dimethyle-N-phenyle thiazolidine -4-carbohydrazide) (Cis Isomer)(13%)ML5

Yield: 50% m.p: 115-116ºC,[1] HNMR (400 MHz, DMSO-d6) δ, 2.27(s,3H) (H8), 3.04 (s,1H), ((H5b), 3.46(m,1H) (H5a), 4. 71(s,3H) (H4), 5.66(s,3H) (H2), 6.34-7.92 (d,t,14H) (HAr), 10.04(s,1H) (H6), 10.30(s,1H) (H7), FT-IR (KBr disk):3327w (NH),3057w (C-H Ar),2929w,2850(C=O Carboxy Acid) (C-H),1672 w (C=OAmide), 1575w, Mass spectra (70 ev): M·+ =604.79 m\z

(2S,5S)-1-acetyl-5-(2,4- dimethoxyphenyl)- N'-phenylthiazolidine-2-carbohydrazide (trans Isomer)(88%)ML6

Yield: 62% m.p:111-112ºC,[1] HNMR (400 MHz, DMSO-d6) δ, 2.13 (s,3H) (H8), 3.04 (s,1H), (H5b), 3.10(t,1H) (H5a), 3.70(t,3H) (H9), 3.92(t,1H) (H10), 4.83(s,1H)(H4), 6.34(d,1H)(H2) 6.34-7.02 (dd,8H), (HAr), 10.14(s,1H),(H6), 10.35(m,1H) (H7), FT-IR (KBr disk):3329w (NH),3294w (C-H Ar),2929w (C-H),1710w (C=OAmide), 1627w, Mass spectra (70 ev): M·+ =401.48 m\z

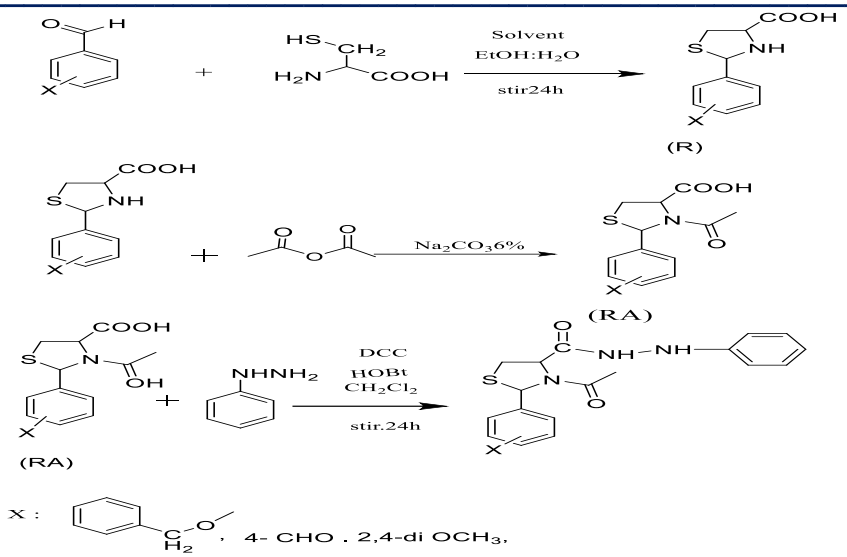
(2S,5S)-1-acetyl-5-(2,4- dimethoxyphenyl)- N'-phenylthiazolidine-2-carbohydrazide (cis Isomer)(12%)ML6

Yield: 62% m.p:111-112ºC,[1] HNMR (400 MHz, DMSO-d6) δ, 2.00 (s,3H) (H8), 3.05 (s,1H), (H5b), 3.51(t,1H) (H5a), 3.65(t,3H) (H9), 3.42(t,1H) (H10), 4.56(s,1H)(H4), 4.72(d,1H)(H2) 6.34-7.02 (dd,8H), (HAr), 10.14(s,1H),(H6), 10.35(m,1H) (H7), FT-IR (KBr disk):3329w (NH),3294w (C-H Ar),2929w (C-H),1710w (C=OAmide), 1627w, Mass spectra (70 ev): M·+ =401.48 m\z

3. RESULTS AND DISCUSSION

3.1 Synthesis of materials

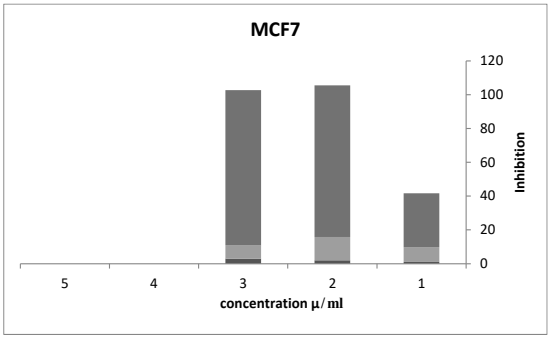
The study involved the synthesis of Thiazolidine derivatives by reacting L-Cysteine with one of its derivatives using ethanol and water (3:1) as a solvent to produce 2-phenylthiazolidine-4-carboxylic acid and its derivatives, (13) and the latter reacts with acetic anhydride to form 3-acetyl -2 -phenylthiazolidine-4-carboxylic acid and its derivatives [14]. with phenyl hydrazine using 1-hydroxybenzotriazole (HOBT) and N,N,N-dicyclohexyl carbodiimide (DCC) as coupling reagents to generate the necessary amides (15). DCC is a low-cost coupling reagent compared to other reagents, however it has a severe drawback that the DCU is weakly soluble.

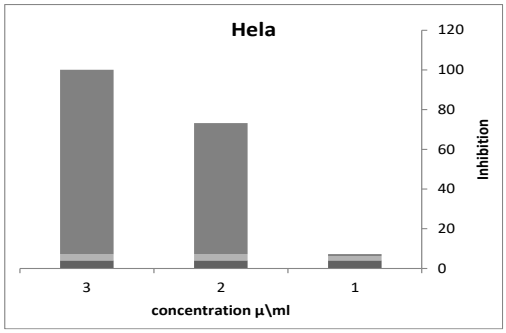


3.2Biological effectiveness against breast cancer and Cervical Cancer

The effectiveness of the prepared compounds (ML3,ML5, ML6) against breast cancer and Cervical Cancer was studied using the method (Dimethyl thiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide [MTT] based on the value. inhibitor(%) of the compounds, as the results showed that the compounds (ML1,ML2,ML3,ML4,ML5,ML6,ML7,ML8,ML9) when treated with cancerous breast cells and Cervical Cancer and had good activity in the death of cancerous breast cells (Michigan Cancer Foundation-7) (MCF) and cancerous Cervical cells. The good activity is due to the compounds ML3,ML7. Compared to the rest of the compounds, it was attributed to the methyl group, while the other compounds, according to the data, did not have anti-breast cancer activity. This noticeable discrepancy in the effectiveness of the compounds on breast cancer lines is due to the difference in the ring substituents. In the prepared series, wi Table (1.1) shows the main inhibitor(%) values for the compounds under study.

Symbol	mean inh(%)breast Cancer cells line	mean inh(%)cervical Cancer cells line	
ML3	31%	0	Inactive
ML5	80%	66%	Active
ML6	62%	93%	Active





4.CONCLUSION

Thiazolidine derivatives were obtained from the reaction of L-Cysteine with benzaldehyde and substituted Benzaldehyde easily and with very good yields, with a percentage ranging between 90- 95% under a few conditions. This intensification gave the product a mix of two isomers, Cis- (2S, 4S) and Trans- (2R, 4S), which could not be segregated. An equilibrium due to desiccation occurred at C(2) between the two isomers. The cis/trans ratios strongly depend on the type of solvent used. The dominant isomer in the DMSO-d6 solvent was the trans isomer while in $CDCl_3$, the main isomer was the cis isomer after complete equilibration, and we concluded from the results that every compound had excellent biologically effective anti-cells lines cancerous Michigan Cancer Foundation (MCF7) and a female cervix carcinoma (Hela).

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