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SYNTHESIS OF NEW THIAZOLIDINDIONE AND THIADIAZOLE DERIVATIVES AS ANTICANCER AGENTS

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ABSTRACT

The new series of 5-[(5-{[(E)- (3, 4-substituted-phenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IVa-d) were synthesized by condensation of compound (2, 4-dioxo-1, 3-thiazolidin-5-yl) acetic acid (II) with thiosemicarbazide in phosphorus oxy chloride to afford 5-[(5-amino-1, 3, 4 thiadiazol-2-yl)methyl]-1, 3-thiazolidine-2, 4-dione (III). Treatment of compound (III) with aromatic aldehydes resulted in the formation of (IVa-d) and treatment of compound III with ethyl benzoate resulted in the formation of (Va-e). The synthesized compounds structure were confirmed using (IR) and (^{1}H-NMR). The target compounds were evaluated for their anticancer activities in comparison with doxorubicin as a reference.

KEYWORDS

Thiazolidinedione, Thiadiazole, Anticancer and Doxorubicin.

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INTRODUCTON

There have been many reports in literature depicting that the presence of heterocyclic moieties proves to be more potent and efficacious than a simple aryl group[1-5]. Different possibilities of heterocyclic modifications with a wide spectrum of pharmacological properties are the most important grounds for investigation of this class of compounds. So, design of new substances based on privileged scaffolds is one of the successful directions in drug discovery[1-5]. Thiazolidinedione (TZD) pharmacophore has been the subject of immense research because of its deep involvement in regulation of various physiological processes[6],

including antitumor[7], anti-inflammatory[8,9], analgesic[10], antioxidant[11], antimicrobial activity[12], antibacterial and antifungal[13-16], aldose reductase inhibition[17], anti-diabetic[18] activities. Thiadiazole is a 5-membered ring system exhibit a wide variety of biological activity. 1, 3, 4- Thiadiazole nucleus and its derivatives continue to be of a great interest to a large number of researchers owing to their great pharmaceutical importance[19] and has wide applications in many fields. The earliest uses were in the pharmaceutical area as in anticancer, antimicrobial, antibacterial, antifungal, antiviral, anti-inflammatory and analgesic, antioxidants, antileshmanial, anti-toxoplasma gondii, anti-helicobacter pylori, anti-mycobacterial and anticonvulsant activities[19].

Combination of these two mentioned scaffolds in one molecule according seems to be a promising 'hybrid pharmacophore' approach to new anticancer agents. The aim of the presented work was to synthesize new thiazolidindione and thiadiazole with substituted aromatic Schiff`s base and benzamide and to investigate their anticancer activity.

MATERIAL AND METHODS

Chemistry

All chemicals and reagents used in the reactions were procured from Sigma-Aldrich and Fisher with purity 98% and used without further purification. The purification of the synthesized compounds was performed by recrystallization with appropriate solvent system. Melting points were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK) and are uncorrected. The IR spectra (KBr, cm^{-1}) were recorded on Shimadzu IR 110 spectrophotometer (Shimadzu, Koyoto, Japan). ^{1}H-NMR spectra were recorded on a Bruker proton NMR-300 (300 MHz) (Bruker, Munuch, Germany), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard (chemical shift in ppm). Mass spectra were determined using a GC/MS Mat 112 S at 70ev spectrometer. All reactions were monitored by thin layer chomatograph (TLC) using precoated Aluminum sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Damstadt, Germany).

Synthesis of (2, 4-dioxo-1, 3-thiazolidin-5-yl) acetic acid (II)

A mixture of maleic anhydride (5g, 0.05mol) and thiourea (3.876g, 0.05mol) with distill water (15ml) was refluxed for 3 hat 130-150°C. To the formed intermediate compound (I), sulfuric acid (20ml, 20%) was added was refluxed for 2 h. The resulting mixture was cooled and poured into ice-water to obtain precipitate which is filtered, dried and recrystallized from water to obtain compound (II), mp: 168-169°C, yield: 79% as reported method[20,21].

Synthesis of 5-[(5-amino-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (III)

A mixture of equimolar quantities of compound II (2g, 0.0114mol), thiosemicarbazide (1.04g, 0.0114mol) in phosphorus oxychloride (5ml) and dioxane (10ml) was refluxed for 4 h at 80°C. After cooling the reaction was poured drop wise into beaker contained crushed ice-cold water and sodium bicarbonate with constant stirring, then left standing at room temperature for 30 min. The obtained brown precipitate of compound III that was filtered dried and recrystallized from ethanol. Yield 82%; m.p. 210-215°C; IR (KBr, cm-1): 3442 (OH), 3405 (NH str), 1701(C=O)[22,23].

General Procedure for synthesis of 5-[(5-{[(*E*)-(3, 4-substituted-phenyl) methylidene] amino}-1, 3, 4-thiadiazol- 2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IVa-d)

A mixture of 5-[(5-amino-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (III) (1 g, 0.0043mol) and appropriate aromatic aldehyde derivatives (0.46g, 0.0043mol) was dissolved in absolute ethanol (15-20ml). The mixture was then refluxed for 8 h with stirring. After cooling at room temperature, the reaction was poured drop wise into beaker contained crushed ice cold water with constant stirring, a solid was obtained. The crude product was filtered, dried and recrystallized from ethanol.

5-[(5-{[(*E*)-phenylmethylidene] amino}-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IVa)

Yield: 77%; m.p 200-215°C; Molecular formula - $C_{13}H_{10}O_2N_4S_2$, Molecular weight calculated- 318, MS, m/z: 318 $[M]^+$. IR (KB): 3436 (OH due to resonance of (4-C=O) and (3-NH) of thiazolidinedione ring), 1684 (C=O).^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.12 (s, 1H, NH thiazolidinedione), 8.40-7.20 (m, 6H, 5H ArH, 1H, -N=CH), 4.20 (t, 1H, thiazolidinedione-H), 3.59 (d, 2H, CH_2).

5-[(5-{[(E)-(4-chlorophenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IVb)

Yield: 80%; m.p 199-201°C; Molecular formula - $C_{13}H_9ClO_2N_4S_2$, Molecular weight calculated- 352, MS, m/z: 352 $[M]^+$. IR (KBr, cm^{-1}): 3432 (OH due to resonance of (4- C=O) and (3-NH) of thiazolidinedione ring), 1686 (C=O), 1600-1400 (Aromatic ring). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.02 (s, 1H, NH thiazolidinedione), 8.47-7.53 (m, 5H, 4H ArH, 1H, -N=CH), 4.41 (t, 1H, thiazolidinedione-H), 3.62 (d, 2H, CH_2).

5-{[5-({(E)-[3-(dimethylamino) phenyl] methylidene} amino)-1, 3, 4-thia-diazol-2-yl] methyl}-1, 3-thiazo-lidine-2, 4-dione (IVc)

Yield: 69%; m.p 217-225°C; Molecular formula - $C_{15}H_{15}O_2N_5S_2$, Molecular weight calculated- 361, MS, m/z: 362 $[M+1]^+$. IR (KBr, cm^{-1}): 3369 (-OH due to resonance of (2, 4 C=O) and (3-NH) of thiazolidinedione ring), 1687 (C=O), 1600-1400 (Aromatic ring). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.11 (s, 1H, NH thiazolidinedione), 8.43-7.52 (m, 5H, 4H ArH, 1H, -N=CH), 4.08 (t, H CH thiazolidinedione), 3.52 (d, 2H, CH_2) 2.74 (s, 6H, N $(CH_3)_2$).

5-[(5-{[(E)-(4-methoxyphenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IVd)

[Yield: 75%; m.p 200-220°C; Molecular formula - $C_{14}H_{12}O_3N_4S_2$, Molecular weight calculated- 348, MS, m/z: 348 $[M]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.22 (s, 1H NH thiazolidinedione), 8.40-7.20 (m, 5H, 4H ArH, 1H, -N=CH), 4.20 (t, 1H, CH thiazolidinedione), 3.59 (d, 2H, CH_2), 3.33 (s, 3H, OCH_3).

General Procedure for synthesis of 4-substituted-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Va-e)

A mixture of 5-[(5-amino-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (III) (1g, 0.0043mol) and appropriate ethyl benzoate derivatives (0.46g, 0.0043mol) was dissolved in absolute ethanol (15-20ml). The mixture was then refluxed for 5 h with stirring. After cooling at room temperature, the reaction was poured drop wise into beaker contained crushed ice cold water with constant stirring, a solid was obtained. The crude product was filtered, dried and recrystallized from ethanol.

N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Va)

Yield: 70%; m.p 212-214°C; Molecular formula - $C_{13}H_{10}O_3N_4S_2$, Molecular weight calculated- 334, MS, m/z: 334 $[M]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.12 (s, 1H, NH thiazolidinedione), 8.40-7.20 (m, 6H, 5H ArH, 1H, amideNH), 4.21 (t, 1H, thiazolidinedione-H), 3.59 (d, 2H, CH_2).

4-Methyl-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Vb)

Yield: 58%; m.p 179-182°C; Molecular formula - $C_{14}H_{12}O_4N_3S_2$, Molecular weight calculated- 348, MS, m/z: 349 $[M+1]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^{1}H NMR (300 MHz, DMSO-d_6): δ= 10.12(s, 1H, NH thiazolidinedione), 7.25-8.46 (m, 6H, 5H ArH, 1H, amide NH), 4.25 (t, 1H thiazolidinedione-H), 3.59 (d, 2H, CH_2), 1.7(s, 3H, CH_3).

4-Methoxy-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Vc)

Yield: 61%; m.p 203-206°C; Molecular formula - $C_{14}H_{12}O_4N_4S_2$, Molecular weight calculated- 364, MS, m/z: 364 $[M]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^1H NMR (300 MHz, DMSO-d_6): δ=7.12-8.51 (m, 5H, 4H ArH, 1H, amide NH), 4.20 (t, 1H, thiazolidinedione-H), 3.59 (d, 2H, CH_2), 3.44 (s, 3H, OCH_3).

4-Chloro-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Vd)

Yield: 75%; m.p 198-200°C; Molecular formula - $C_{13}H_9ClO_3N_4S_2$, Molecular weight calculated- 368, MS, m/z: 368 $[M]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^1H NMR (300 MHz, DMSO-d_6): δ=7.54-8.49 (m, 5H, 4H ArH, 1H, amide NH), 4.32 (t, 1H, thiazolidinedione-H), 3.59 (d, 2H, CH_2).

4-Bromo-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Ve)

Yield: 73%; m.p 193-195°C; Molecular formula - $C_{13}H_9BrO_3N_4S_2$, Molecular weight calculated- 413, MS, m/z: 413 $[M]^+$. IR (KBr, cm^{-1}): 3448 (-OH due to resonance of (4 C=O) and (3-NH) of thiazolidinedione ring), 1670 (C=O), 1600-1400 (Aromatic ring). ^1H NMR (300 MHz, DMSO-d_6): δ= 8.40-7.60 (m, 5H, 4H ArH, 1H, amide NH), 4.24 (t, 1H, thiazolidinedione-H).

***In vitro* anticancer activity**

The *in vitro* anticancer activity was measured for the synthesized compounds on mammary carcinoma cell line (MCF7) in the National Cancer Institute, Cairo University. The screening involves calculation of the percentage gusing the Sulfo-Rhoda mine-B stain (SRB) assay[24]. The in vitro anticancer screening was done by the pharmacological unit at the national cancer institute, Cairo University. The screening involves calculation of the percentage growth or surviving fraction of the drug treated cell lines compared by untreated control using Sulforhodamine B (SRB) colorimetric assay. Sulforhodamine B is a bright pink aminoxanthene anionic dye with two sulfonic acid groups that bind electrostatically to protein basic amino acid residue of trichloroacetic acid (TCA) fixed cells under mild acidic condition. Culture fixed with (TCA) were stained for 30 minutes with 0.4% w/v Sulforhodamine B dissolved in 1% acetic acid, and protein bound dye was extracted with 10mM tris base [tris (hydroxymetyl) aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The optical density measured is linear with cell number of the survival fraction. Therefore, the assay is a sensitive measure of drug induced cytotoxicity with the best signal to noise ratio. The assay also, provides a colorimetric end point that is nondestructive, indefinite stable and visible to naked eye.

Procedure

Cells were plated in 96-multiwell plate (104 cells/well) for 24 hours before treatment with the compound (s) to allow attachment of cell to the wall of the plate. Different concentrations of compound under test (0.0, 1.0, 2.5, 5.0 and 10.0µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound (s) for 48 hours at 37ºC and in atmosphere of 5% CO_2. After 48 hours, cells were fixed, washed and stained with Sul-forhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tri EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of the tumor cell line after the specified compound.

RESULTS AND DISCUSSION

Chemistry

The synthetic route employed in the synthesis of the targeted thiazolidindione and thiadiazole derivatives is represented in Scheme No.1 and Scheme No.2.

(2, 4-dioxo-1, 3-thiazolidin-5-yl) acetic acid (II) was prepared by cyclization reaction of equimolar quantities of maleic anhydride and thiourea in

presence of water and sulfuric acid[20,21]. To increase yields in two steps firstly, maleic anhydride and thiourea are refluxed for 3 h with water to form the intermediate then followed by addition of sulfuric acid (10%) and refluxed for 2h.

5-[(5-amino-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (III) was prepared by direct cyclization of compound (II) using thiosemicarbazide in presence of phosphorus oxychloride and refluxed in dioxane for 3-5 hat 70-80^{o}C to improve yield. Alternatively, compound (III) can be obtained by indirect cyclization of the prepared acyl thiosemicarbazide using sulfuric acid as dehydrating agent.

The newly synthesized compounds 5-[(5-{[(E)-(4-substitutedphenyl) methylidene] amino}-1, 3, 4-thiadiazol-2-yl) methyl]-1, 3-thiazolidine-2, 4-dione (IV a-d) were prepared by condensation of a carbonyl compound of aldehyde derivatives with the amine of compound (III) in refluxing ethanol.

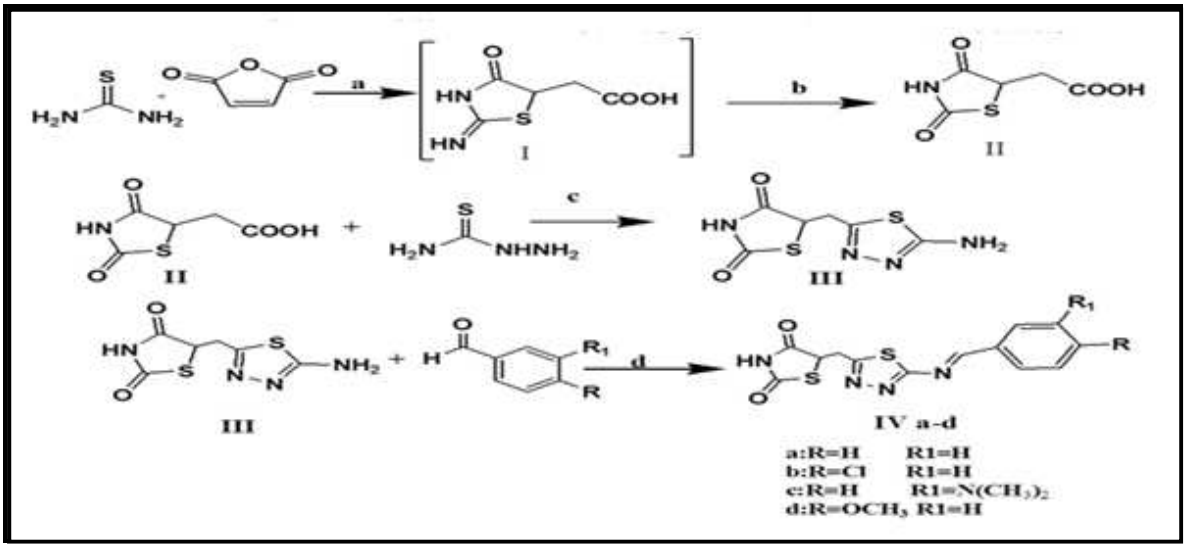
While, 4-substituted-N-[5-(2, 4-Dioxo-thiazolidin-5-ylmethyl) [1, 3, 4] Thiadiazol-2-yl]-benzamide (Va-e) were prepared by condensation of ethyl benzoate derivatives with the amine of compound (III) in presence of ethanol and refluxed 6 h.

***In vitro* anticancer activity**

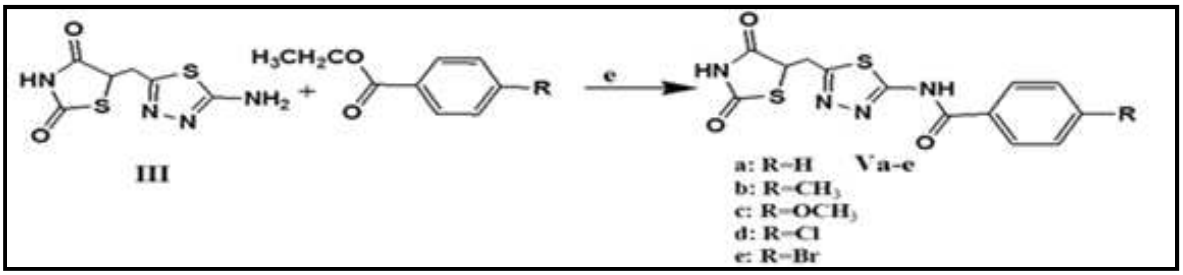
From the results of *in vitro* cytotoxic activity of the target compounds shown in Table No.1, it can be observed that, the compounds Iva and Va showed moderate cytotoxic activity against human carcinoma cell line (MCF7) with IC_{50} values of 5.21 and 6.34μM, respectively. Moreover, the compounds IVb and Vb showed good cytotoxic activity with IC_{50} values 4.33 and 4.36μM respectively. On the other hand, the compounds IVc, IVd, Vc, V e and Vd exhibited promising anticancer activity with IC_{50} values 2.87, 2, 98, 2.60, 2.39 and 2.88μM respectively.

Table No.1: Cytotoxic activity of the newly synthesized compounds

S.No	Compound No	IC_{50}μM	Compound No	IC_{50}μM
1	IVa	5.21	Va	6.34
2	IVb	4.33	Vb	4.36
3	IVc	2.87	Vc	2.60
4	IVd	2.98	Vd	2.39
5	-	-	Ve	2.88
6	Doxorubicin	0.45	Doxorubicin	0.45



Scheme No.1: General procedure for the synthesis of Compounds II, III and IV a-d



Scheme No.2: General procedure for the synthesis of Compounds V a-e

CONCLUSION

The newly synthesized compounds of condensed heterocyclic thiazolidindione and thiadiazole with substituted aromatic aldehyde and ethyl benzoat were evaluated for the cytotoxic activity against human mammary carcinoma cell line (MCF7). The obtained results revealed that, compounds IVc, IVd, Vc, Ve and Vd exhibited anticancer activity with lower IC_{50} values but still higher than that of the reference drug Doxorubicin.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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