Synthesis and characterization of some new thiazolidinone derivatives containing indole ring

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Abstract. Many new heterocyclic compounds including 4-thiazolidinones containing indole with triazole units were described. The new Schiff bases [VII]a, b and [VIII]a,b synthesized by condensation acid hydrazides [II], [VI] with different (aromatic) aldehydes in absolute ethanol. The refluxing equimolar amounts of the Schiff bases ([VII]a,b, [VIII]a,b) with thioglycolic acid in benzene led to get thiazolidin-4-ones derivatives ([IX]a,b and [X]a-d). Finally, the new derivatives [XI]a-c run out via the reacted compound [IX]a with different n-alkyl bromide (methyl bromide, ethyl bromide, and butyl bromide) in alkaline media.

Keywords: Schiff bases, thiazolidinones, Indoles, triazole.

1. Introduction

Indole is a fused ring (pyrrole with benzene to α,β-position) is called bicyclic heterocyclic [1]. The Indol system is the most important heterocyclic available in natural compounds. Because of wide structural diversity, this system becomes an important structural requirement in many pharmaceutical fields [2]. Because of their varied biodynamic, Indoles have occupied a rare place in the chemistry of nitrogen heterocyclic compounds [3]. Many derivatives of Indole have good biological activity exists in plants, animals, and micro-organisms which represents an important class of therapeutic agents in the medicinal chemistry field [4]. The chemistry of 1,2,4-triazole has received great attention due to its synthetic and effective biological importance [5]. Thiazolidinones (containing nitrogen and sulfur in a five-member ring) are an important system in heterocyclic derivatives. Thiazolidinones have sulfur atom at position 1, another hetero atom (nitrogen) at position 3 besides to carbonyl group at position 2, 4, or 5, 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position [6].
There are many bioactive heterocyclic molecules have always attracted the attention of a chemist over the years due to their biological value [7]. Thiazolidin-ones moiety in many compounds have variety of biological activities as: anti-inflammatory [8], antifungal [9], antitubercular [10], Antimicrobial [12], toxicological properties [13], anti-tubercular [14], Antioxidant activities [16], Antihepatotoxic Agent [17].

2. Materials and methods

The chemicals sourced from the GCC, Merck, and Aldrich Co. Techniques: FTIR spectra were implemented by a Shimadzo (Ir prestige-21). ¹HNMR spectra were implemented by the company: Bruker (model: Ultra-shield 300 MHz), Origin: Switzerland (ppm δ), in DMSO and the TMS internal standard. Measurements were implemented in the Department of Chemistry, Al-albyat University / Jordan. By using Hot Stage and Gallen Kam melting point, the uncorrected melting points were determined.

The new compounds were synthesized according to Scheme 1:
Ethyl-2-methyl-1H-indole-3-carboxylate [I]: was prepared were by the literature [18], yield 94%, m.p. (98-100) °C.

2-methyl-1H-indole-3-carboxyhydrazide [II]: was prepared were by the literature [19]. Yield 84%, m.p. = (144-146) °C.

2-(2-methyl-1H-indole-3-carbonyl)hydrazine carbothioamide[III]: was prepared were by the literature [20]. Yield 90 %, m.p.: (200-202) °C.

5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazole-3-thiol [IV]: was prepared were by the literature [21], Yield 88%, m.p. = (234-236) °C.

Synthesis of compounds type [V]

A mixture of compound [IV] (0.01mol), ethyl chloroacetate (0.01 mol, 1.23 g) , (20 mL) from ethanol with sodium acetate (anhydrous) (0.01mol, 0.82g) was refluxed for (6) hrs. Ethanol was
removed after completion of the reaction and the residue crystallized from ether. The physical data are blog in Table (1)

**Synthesis of compounds [VI]**
A mixture of ester-compound [V] (0.006 mol) (in ethanol 2.5) and hydrazine hydrate 1.5 ml were reflux for (3) hrs. To room temperature, the mixture was cooled and the solvent was evaporated to the formed product, recrystallized from ethanol. The physical data are blog in Table (1)

**Synthesis of Schiff bases [VII]a, b and [VIII]a, b**
A mixture of substituted-benzaldehyde (0.01 mol), different acid hydrazide compounds [II] or [VI] (0.01 mol), 2 drops of glacial acetic acid and absolute ethanol (15 mL) was heating for (6) hrs. Under vacuum, the solvent was evaporated; the residue crystallized using chloroform and methanol. The physical data of all Schiff bases are blog in Table (1).

**Synthesis of Thiozoldenones [IX]a, b and [X]a, d**
Schiff bases [VII]a, b or [VIII]a, b (0.001mol) was refluxed with thioglycolic acid (0.001 mol) in dry benzene (3 mL) for (12) hrs. Afterwards, the solvent was evaporated and neutralized the residue with sodium bicarbonate solution. Filtration the precipitate and recrystallized from acetone. The physical properties are blog in Table (1).

**Synthesis of N-(2-(4-alkyloxyphenyl)-4-oxothiazolidin-3-yl)-2-methyl-1H-indole-3-carbo-xamide [XI]a, c**
A mixture of compounds [IX]a (0.0015mol) and anhydrous potassium carbonate (0.012mol, 0.80g) dissolved in acetone 20 mL, was added (methyl bromide, ethyl bromide, and butyl bromide) (0.004 mol), the reaction mixture was refluxed (24 hrs.). The mixture was poured over ice-water the solid was filtered, dried and recrystallized from ethanol. The physical data are blog in Table (1).

Table 1. Physical data of synthesized compounds [V] – [XI]a, c.

| Com. No. | Nomenclature | Structural formula | Molecular formula | M.P◦C | Yield % | Color     |
|----------|--------------|--------------------|-------------------|-------|---------|-----------|
| [V]      | ethyl 2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio) acetate | ![Structure1](image1.png) | C15H16N4O2S | 90-92 | 80      | Dark brown |
| [VI]     | 2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio) acetohydrazide | ![Structure2](image2.png) | C13H14N6OS | 170-172 | 85      | Dark Brown |
| [VII]a   | N’-(4-hydroxybenzylidene) -2-methyl-1H-indole-3-carbohydrazide | ![Structure3](image3.png) | C17H15N3O2 | 296-298 | 80      | Pale yellow |
N’-(4-(dimethylamino) benzylidene)-2-methyl-1H-indole-3-carbohydrazide

C_{19}H_{20}N_{4}O_{2} 248-250 86 Red

2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )-N’ -(4-nitrobenzylidene)aceto hydrazide

C_{20}H_{17}N_{7}O_{3}S 286-288 78 Yellow

2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )-N’ -(3-nitrobenzylidene) acetohydrazide

C_{20}H_{17}N_{7}O_{3}S 204-206 85 Brown

N’-(4-(dimethylamino) benzylidene)-2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )aceto hydrazide

C_{22}H_{23}N_{7}OS 254-256 78 Dark yellow

N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-methyl-1H-indole-3-carboxamide

C_{19}H_{17}N_{3}O_{3}S 128-130 81 pale orange

N-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)-2-methyl-1H-indole-3-carboxamide

C_{21}H_{22}N_{4}O_{2}S 68-70 76 Orange

2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )-N-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide

C_{22}H_{19}N_{7}O_{4}S_{2} 140-142 86 Brown

2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )-N-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)acetamide

C_{22}H_{19}N_{7}O_{4}S_{2} 148-150 77 Yellow

N-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)-2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio)acetamide

C_{24}H_{25}N_{7}O_{2}S_{2} 164-166 70 Yellow

2-(5-(2-methyl-1H-indol-3-yl)-4H-1,2,4-triazol-3-ylthio )-N-(4-oxo-2-p-tolylthiazolidin -3-yl) acetamide

C_{23}H_{22}N_{6}O_{2}S_{2} 119-121 73 Red
3. Results and Discussion

Compound [I], we got it through the reaction of phenylhydrazine with ethyl acetoacetate in glacial acetic acid (Fischer indole synthesis). The FTIR spectrum represent the vanishment of NH bands for phenylhydrazine and (C=O) of ethyl acetoacetate with appearance bands at 1734 cm\(^{-1}\) assignable to C═O of ester, in addition to a new band at 1654 cm\(^{-1}\) due to the C=N group and at 3404 cm\(^{-1}\) for N-H indole ring. Condensation hydrazine hydrate with ester [I] to get the 2-methyl-1H-indole-3-carbohydrazide [II]. FTIR spectrum revealed stretching vibration (N-H, NH\(_2\)) groups as well as stretching absorption at of C═O (amid) group and disappearance of two bands for ester moiety. Nucleophilic addition reaction of acid hydrazide [II] to ammonium thiocyanate in ethanol (using hydrochloric acid as the catalyst to give 2-(2-methyl-1H-indole-3-carbonyl) hydrazine carbothioamide [III]. The FTIR indicated C=S absorption band at 1288 cm\(^{-1}\)[22], in addition, bands which come back to NH\(_2\) stretching vibration (asy. and sy.). Also, shifting of C═O (amid) group to 1637 cm\(^{-1}\).

Thiosemicarbazides [III] was converted to 1,2,4-triazole derivatives [IV] under cyclization reaction in the solution of aqueous sodium hydroxide then acidification with hydrochloric acid to yield, these compounds diagnosed by FTIR spectroscopy. FTIR data represent the S─H absorption band around 2600 cm\(^{-1}\) and vanishment of the band of the (C═O amide) in the starting materials [III]. The compound [V] was identified by FTIR and Mass spectroscopy. The FTIR spectra of this compound showed a significant band at 1743 cm\(^{-1}\) for compound [V] which comes back to C═O stretching vibration of ester group. They also represent the vanishment of stretch the absorption band of S-H group. The FTIR spectral data are blog in Table (2). The mass spectrum of compound [V], revealed several peaks assignable to the presence of triazole and indole derivatives This spectrum showed interesting peaks at m/z = 70(100\%) (base peak) due to the triazole ring. Also, most of the characteristic fragments at m/z =117(74\%) due to indole ring that give good evidence for the presence of indole ring, besides the fragments at m/z =145(27\%) due to 3-methyl-2-methyleneindoline [23]. Acid hydrazide derivatives [VI] was run out by the reaction of ester compound [V] with hydrazine (80\%) in ethanol. The FTIR spectrum represents a shift in the carbonyl stretching band for the ester.
group from 1743 cm\(^{-1}\) to 1672 cm\(^{-1}\) for the amide group of compound [VI]. Also three bands in the range (3420-3184) cm\(^{-1}\) are for asymmetric and symmetric bands of NH and NH\(_2\) groups. The FTIR spectral data for this compound is a blog in Table (2).

**Table 2. FTIR data of new compounds [V] - [VI].**

| Comp.No. | VN-H | VC-H arom. | VC-H alipha. | VC=O amide | VC=O ester | VC=N | VC=C arom. | VC-S-C |
|----------|------|------------|-------------|------------|------------|------|------------|--------|
| [V]      | 3454-3200 | 3064      | 2980-2854 | ---- | 1743 | 1620 | 1595 | 651 |
| [VI]     | 3400-3188 | 3057      | 2954-2852 | 1672 | ---- | 1620 | 1597 | 655 |

The Schiff bases of compounds [VII]\(_{a,b}\) and [VIII]\(_{a,b}\) were run out the refluxing of acid hydrazide derivatives [II] or [VI] or with different aldehyde type aromatic in ethanol. The data of FTIR for series [VII]\(_{a,b}\) and [VIII]\(_{a,b}\), Tables (3) represent the vanishment of two bands for NH\(_2\) (stretch.) of acid hydrazide with the appearance of C=N stretching bands at (1618-1653) cm\(^{-1}\). The \(^1\)HNMR spectrum (in DMSO) for compound [VIII]\(_b\) showed the following signals: signal type singlet in \(\delta(8.87)\)ppm for NH-indole proton, also signal type singlet \(\delta(8.68)\)ppm for of CO-NH-N proton, signals at \(\delta(8.19-8.34)\) ppm that assignable to the N-H triazole ring, signal at \(8.07\) ppm for of N=CH proton, signals at \(\delta(7.56-8.00)\) ppm that could may come back to the aromatic-protons, signal type singlet in \(\delta(3.90)\)ppm for of S-CH\(_2\)-CO protons, finally signal type singlet in \(\delta(1.83)\)ppm for CH\(_3\) protons.

**Table 3. FTIR data of new Schiff bases [VII]\(_{a-d}\).**

| Comp. No. | VN-H | VC-H arom. | VC-H alipha. | VC=O amide | VC=N | VC=C arom. | Other |
|-----------|------|------------|-------------|------------|------|------------|-------|
| [VII]\(_a\) | 3400,3190 | 3040       | 2976-2820   | 1670  | 1645 | 1602       | VO-H: 3211 |
| [VII]\(_b\) | 3442-3250 | 3080       | 2912-2802   | 1665  | 1620 | 1602       | VC-N-C : 1365, 1178, 813 |
| [VIII]\(_a\) | 3423,3290,3203 | 3066 | 2926-2860   | 1670  | 1625 | 1597       | p-NO\(_2\):1510,1328 |
| [VIII]\(_b\) | 3402,3286,3197 | 3074 | 2926-2850   | 1662  | 1618 | 1597       | m-NO\(_2\):1517, 1319 |
| [VIII]\(_c\) | 3400,3304,3192 | 3078 | 2954-2852   | 1668  | 1653 | 1604       | VC-N-C : 1367, 1180, 813 |
| [VIII]\(_d\) | 3392-3196 | 3059       | 2922-2858   | 1674  | 1622 | 1608       | mono-substituted : 692, 758 |

The thiazolidin-4-ones derivatives [IX]\(_{a,b}\) and [X]\(_{a-d}\) were run out by refluxing equimolar amounts of the Schiff bases [VII]\(_{a,b}\) and [VIII]\(_{a-d}\) with thioglycolic acid in dry benzene. These compounds were
diagnosed by 1HNMR and FTIR spectroscopy. The FTIR spectra represent the vanishment of a stretching band of imine bond and appearance of C=O stretching band in (1685-1718) cm⁻¹. This was the most characteristic evidence for the success of the cyclization step. The spectral data from FTIR spectroscopy are blog in Table (4). The 1HNMR spectrum (in DMSO) for compound [X]ₐ represent the following signals: signal type singlet in δ(10.79)ppm for NH-indole proton, also signal type singlet in δ(10.32)ppm for CO-NH proton, signals in region δ(6.63-7.50) ppm that come back to the aromatic-protons, signal in δ(4.05)ppm for CH proton of thiazolidinone rings, signal type singlet in δ(3.93)ppm for S-CH₂-CO protons, signal type singlet in δ(3.51)ppm for protons for CH₂ protons of thiazolidinone ring and CH₃ protons. The 1HNMR spectrum(in DMSO) for compound [IX]ₐ showed the following signals: signal type singlet in δ(10.09)ppm for NH indole proton, also signal type singlet in δ(9.78)ppm for the proton of CO-NH-N group, also signal type singlet in δ(7.99)ppm for O-H proton. Signals in region δ(6.72-7.72) ppm that come back to the aromatic-protons, signal in δ(4.67)ppm for CH proton of thiazolidinone rings, signal type singlet in δ(5.01)ppm for two protons of S-CH₂-CO group, signal type singlet in δ(3.51)ppm for two-protons for CH₂ thiazolidinone ring, finally signal type singlet in δ(2.971)ppm for CH₃ proton.

Table 4. FTIR data of new thiazolidinone compounds[IX]ₐ-[X]ₐ.

| Comp. No. | VN-H | VC-H arom. | VC-H aliph. | VC=O | VC=O amide | VC=N | VC=C arom. | Other |
|-----------|------|------------|-------------|------|-------------|------|-------------|-------|
| [IX]ₐ     |     | 3400-3200  | 3022        | 2983-2810 | 1708 | 1670       | 1610  | 1597       | VO-H :3251 |
| [IX]₉     |     | 3400-2190  | 3012        | 2972-2854 | 1705 | 1668       | 1612  | 1595       | VC-N-C : 1355, 1180, 813 |
| [X]ₐ      |     | 3400-3200  | 3045        | 2924-2848 | 1716 | 1683       | 1620  | 1597       | p-NO₂:1519,1346 |
| [X]₉      |     | 3446, 3304, 3431, 3188 | 3089 | 2924-2852 | 1702 | 1681       | 1625  | 1608       | m-NO₂:1527, 1350 |
| [X]₉      |     | 3290, 3178 | 3040        | 2920-2850 | 1690 | 1668       | 1641  | 1608       | VC-N-C : 1367, 1182, 813 |
| [X]₉      |     | 3400-3200  | 3026        | 2953-2854 | 1699 | 1683       | 1620  | 1604       | mono-substituted: 700, 740 |

The new series compounds of [XI]ₐ-c were run out via reacted compound [IX]ₐ with different n-alkyl bromide in alkaline media. The FTIR spectra of these compounds represent the vanishment of the OH stretching band and the appearance the new C-O bands in (1222-1247)cm⁻¹ for alkoxy groups. The FTIR bands data blog in Table (5).

The 1HNMR spectrum (in DMSO) for compound [XI]ₐ, represent the following signals: signal type singlet at δ(10.85) ppm for NH-indole proton, also signal type singlet appeared at δ(10.26)ppm for proton in CO-NH-N group, signals in region δ(6.76-7.58) ppm that may come back to the aromatic-protons, signal in δ(5.67) ppm for CH proton of thiazolidinone ring, signal type singlet in δ(3.72)ppm for S-CH₂-CO protons, signal type singlet in δ(3.47) ppm for two-protons of CH₂ thiazolidinone ring, signal type singlet in δ(3.51)ppm for OCH₃ protons, finally, a signal type singlet at δ(3.37) ppm for two-protons of -CH₂-CO group.
Table 5. FTIR data of new compounds [XI]a-c.

| Comp.No. | VN-H       | VC-H arom. | VC-H alipha. | VC=O |VC=O amide | VC=O bend | VC=O bend |
|----------|------------|------------|--------------|------|------------|-----------|-----------|
| [XI]a    | 3420-3210  | 3057       | 2950-2854    | 1735 | 1678       | 1610      | 1249      |
| [XI]b    | 3400-3190  | 3057       | 2978-2872    | 1718 | 1670       | 1610      | 1247      |
| [XI]c    | 3400-3200  | 3059       | 2958-2872    | 1716 | 1670       | 1610      | 1246      |

4. Conclusions

In this work new thiazolidin-4-one compounds derived from 2-methyl-1H-indole-3-carbohydrazide using two routes were synthesized in good yields via simple methods. The chemical structures of newly thiazolidinone compounds containing diverse substitution group were in conformity based on their physical properties and spectroscopic data.

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