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# New Derivatives of Thiozolidinone, Synthesis and Characterization

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**Abstract**

The present work involved synthesis of new thiozolidinone derivatives,These derivatives could be divided into three type of compounds; quinolin-2-one[V]$_{a,b}$ ,Schiff bases[VI]$_{a,b}$ and imide compounds[VII]$_{a-d}$. The reaction p-Hydroxyacetophenone with thiosemicarbazide led to formation thiosemicarbazon compound [II], the reacted of thiosemicarbazone with chloro acetic acid in CH3CO2Na led to yield 4- thiazelidinone compound[III] in addition, thiosemicarbazide was $POCl_3$ to [III] give [IV] compound used intermediates to synthesis new compounds of reacted with two type of coumarin in glacial acetic acid to give quinolin-2-one[V]$_{a,b}$, The later compound refluxing with different benzaldehyde in dry benzene and glacial acetic acid give Schiff bases[VI]$_{a,b}$ . While the reaction with four kind acid anhydride using dioxane awarded imid compounds [VII]$_{a-d}$. The synthesized compounds were identified using FTIR and $^1$H NMR spectroscopy.

**Key Words:** thiozolidinone, thiadiazol, quinolin-2-one ,Schiff bases and imid compounds.

## INTRODUCTION

4-Oxothiazoles have a wide range of biological activities depending on their structure, lately, many workers interested by synthesis new 4-oxothiazolidine-2,5-diylidene derivatives containing significant pharmacophore groups, such as thiazole, benzothiazole, benzimidazole [(1)]. Thus, compounds have high anti-malarial [(2)] and antitumor activity [(3)]. Among the heterocyclic compounds, 1,3,4-thiadiazole derivatives have become an important type for the development of new drugs [(4)]. The compounds which containing 1,3,4-thiadiazole appeared good biological activity spectrum [(5)] including anti-microbial [(6)], anti- tuberculosis [(7)], anti-inflammatory [(8)], carbonic anhydrase inhibitors [(9)], anti-convulsants [(10)], anti-hypertensive [(11)], anti-oxidant [(12 )], anti-cancer [(13)] and anti-fungal properties[(14)]. 1,3,4-thiadiazole heterocyclic compounds undergo various chemical reactions has made them important for new molecule planning because of their a lucky structure, which have many biological potential [(15)]. As example, two 1,3,4-thiadiazole compounds currently used in clinical medicine are: acetazolamide and methazolamide as carbonic anhydrase inhibitors [(16)].

The number of scientific studies with imides compounds has highly considerably[(17)]. Taking into account the importance of the imide compounds to both heterocyclic chemistry and medicinal field [(18)]. In recent few years the study of the chemistry of imides has been given specific impacts, because of their pharmacological and other industrial uses. For examples, derivatives of imides have evidenced to be important agent and have been using in the treatment of arthritis, tuberculosis, convulsions and epilepsy [(19)]. Some derivatives of imides can be used to stimulate the growth of plants [(20)]. Other imide derivatives have been used as fungicides and as herbicides [(21)]. While the aromatic imides are used as brightening agent in the laundry and allied industries [(22,23)]. Pyrrolidine-2,5-diones are an important class of heterocyclic compounds with good applications in the organic synthesis and medicinal chemistry [(24,25)].

Among the pharmacologically important of heterocyclic compounds, quinoline and its derivatives have been known to possess various biological activities, [(26,27)] and quinolines are active components in various industrial antioxidants and dyes.[(28 -30)]

The aim of this work its Synthesis and characterization of new thiazolidinone compounds and their derivatives ( Schiff bases, quinoline and imide compounds).

## MATERIALS AND METHODS

**Preparation of 2-(1-(4-hydroxyphenyl)ethylidene)hydrazine-1-carbothioamide[II]**

A mixture of 4- hydroxyacetophenone[I] (1.36g ,0.01mole) , thiosemicarbazide (0.91g , 0.01mole) in ethanol ( 20mL ) was refluxed for 5hrs[(31)], after cooling, the solid was filtered, dried and recrystallized from ethyl acetate .

Color: White; Yield: 78%; M.P:219-221.[(32)]

IR (ν, $cm^{-1}$):3365-3178($NH_2$,NH),3014(CH arom.),2918-2850(CH aliph.),1645(C=N), 1600(C=C),1282(C=S).

**Synthesis of 2-(4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)phenoxy)acetic acid[III]**

Heated a mixture of thiosemicarbazone[II] (2.09g,0.01mol) ,chloroaceticacide (1.88g 0.02mol,) and sodium acetate (fused) (4.92g, 0.06mol) in absolute ethanol(10 mL) for 6 hrs[(33)]. Then, the mixture of reaction was poured onto (100 mL) cold water and the precipitate was filtered, washed with water (for many times), recrystallized from ethanol.

Color: Off white; Yield: 60%; M.P:240-242$^0$C.

IR (ν, $cm^{-1}$ ):3340-2600(OH),3234(NH), 3050( C-Harom.), 2972-2933 (C-H aliph.),
1691(C=O), 1629(C=N), 1600(C=C), 796( C-S).

$^1$H NMR (□ppm):2.32 (s, 5H,$CH_2$ cyclic and $CH_3$), 3.8 (s, 2H,$OCH_2$), 6.78-7.72 (dd, 4H, Ar-H), 9.85(s, 1H,NH), 11.85(s, 1H,OH).

**Synthesis of 2-((1-(4-((5-amino-1,3,4-thiadiazol-2-yl)methoxy)phenyl)ethylidene) hydrazono) thiazolidin-4-one[IV]**

Compound [III] (3.07g,0.01 mol) was mixed with thiosemicarbazide (0.91g, 0.01mol) in phosphorus oxy

chloride (5 mL), afterward the mixture was refluxed softly for 6 hrs[34]. After cooling, was poured onto ice water (50 mL) with stirring. The precipitate was filtered, washed with solution of $NaHCO_3$, then water, dried and recrystallized from ethanol.
Color: Brown; Yield: 80%; M.P:> $300^0$C
IR (ν, $cm^{-1}$ ) :3360-3232( $NH_2$ ), 3020( C-Haromatic) ,2924-2840 (C-H aliphatic), 1697 (C=O), 1660(C=N), 1604( C=C), 777(C-S) .
$^1$H NMR (□ppm): 2.36 (s, 5H,$CH_2$ cyclic and $CH_3$), 3.84 (s, 2H,$OCH_2$), 5.22(broad s, 2H,$NH_2$), 6.8-7.84 (m, 4H, Ar-H),11.7(s, 1H,NH).

**SYNTHESIS OF QUNOLINE DERIVATIVES**
Equimolar amounts of two types from coumarin (0.01 mol) and amine compounds [IV] (3.62g,0.01mol) in glacial acetic acid (10mL) was heated under reflux for 6hrs. After cooling poured onto crushed ice to afford, the resulting was filtered and dried at room temperature. Recrystallization from ethanol.

**2-((1-(4-((5-(2-oxoquinolin-1(2H)-yl)-1,3,4-thiadiazol-2-yl)methoxy)phenyl) ethylidene)hydrazono)thiazolidin-4-one[V]$_a$**
Color: Gray; Yield: 61%; M.P: 238-$240^0$C
IR (ν, $cm^{-1}$ ) :3059( C-Haromatic),2953-2850(C-H aliphatic), 1701,1670 (C=O), 1616(C=N), 1600(C=C),725(C-S).
$^1$H NMR (□ppm):2.31 (s, 5H,$CH_2$ cyclic and $CH_3$), 3.85 (s, 2H,$OCH_2$), 6.48(d,2H,CH of CH=CH),6.78 (m, 8H, Ar-H),11.79(s, 1H,NH) .

**2-((1-(4-((5-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-1,3,4-thiadiazol-2-yl)methoxy)phenyl)ethylidene) hydrazono)thiazolidin-4-one**[V]$_b$
Color:Brown; Yield: 83%; M.P: 190-$192^0$C
IR (ν, $cm^{-1}$ ) :3300(OH), 3100( C-Haromatic),2950-2819(C-H aliphatic), 1700,1666 (C=O), 1620(C=N), 1598(C=C),748(C-S).
$^1$H NMR (□ppm): 2.2(s,3H,$CH_3$at C4 of ring), 2.37 (s, 5H,$CH_2$ cyclic and $CH_3$C=N), 3.85 (s, 2H,$OCH_2$), 6.13(s,1H,OH), 6.41(s,1H,CH=C) 6.65-8.0 (m, 7H, Ar-H),10.56(s, 1H,NH) .

**SYNTHESIS OF SCHIFF BASE DERIVATIVES**
The mixture of amino compound[IV] (0.01 mol) and different aldehyde (0.01 mol) in benzene (5 mL) addition 3 drops of glacial acetic acid was refluxed for 6h. The solvent was evaporated under vaccum and the residue crystallized from ethanol.

**2-((1-(4-((5-(benzylideneamino)-1,3,4-thiadiazol-2-yl)methoxy)phenyl) ethylidene)hydrazono)thiazolidin-4-one[VI]$_a$**
Color:Brown; Yield: 92%; M.P: 153-$155^0$C
IR (ν, $cm^{-1}$ ) :3100( C-Haromatic),2926-2852(C-H aliphatic), 1708 (C=O), 1681(C=N), 1598(C=C) ,754(C-S).
$^1$H NMR (□ppm): 2.35 (s, 3H,$CH_3$),2.48(s,2H, $CH_2$ cyclic), 3.9(s, 2H,$OCH_2$), 6.87-7.94 (m, 9H, Ar-H),8.4(s,1H,CH imine)11.43(s, 1H,NH).

**2-((1-(4-((5-((4-methoxybenzylidene) amino)-1,3,4-thiadiazol-2-yl)methoxy) phenyl)ethylidene)hydrazono)thiazolidin-4-one[VI]$_b$**
Color:Brown; Yield: 96%; M.P: 230-$232^0$C
IR (ν, $cm^{-1}$ ) :3120( C-Haromatic),2929-2839(C-H aliphatic), 1693 (C=O), 1678(C=N), 1595(C=C) ,1247(C-O-C),759(C-S).
$^1$H NMR (□ppm):2.3 (s, 3H,$CH_3$),2.48(s,2H, $CH_2$ cyclic), 3.65(s, 2H,$OCH_2$), 3.88(s, 3H,$OCH_3$),6.87-7.89 (m, 8H, Ar-H),8.34(s,1H,CH imine)9.88(s, 1H,NH).

**SYNTHESIS OF IMIDE DERIVATIVES [VII]$_{A-D}$**
Refluxed a mixture of amine compound [III] (0.001mole) and different anhydride (0.002mole ) in dry dioxane (20 ml) for 5 hrs, the reaction mixture was left overnight for slow evaporation. The product was recrystallized from acetone.

**1-(5-((4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)phenoxy)methyl)-1,3,4-thiadiazol-2-yl)pyrrolidine-2,5-dione[VII]$_a$**
Color:Gray; Yield: 83%; M.P: 170-$172^0$C
IR (ν, $cm^{-1}$ ) :3080 (C-H) aromatic, 2927-2820(C-H aliphatic),1708,1699,1680(C=O),1625(C=N),1598 (C=C) aromatic, 1359(C-N) .
$^1$H NMR (□ppm): 2.31(t,4H,$CH_2$-$CH_2$ cyclic), 2.43(s, 5H,$CH_2$ cyclic and $CH_3$), 3.7 (s, 2H,$OCH_2$), 6.80-7.8 (m, 4H, Ar-H),12(s, 1H,NH).

**2-(5-((4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)phenoxy)methyl)-1,3,4-thiadiazol-2-yl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione[VII]$_b$**
Color:Brown; Yield: 88%; M.P: 185-$187^0$C
IR (ν, $cm^{-1}$ ):3050 (C-H) aromatic, 2927-2820(C-H aliphatic),1700,1699,1680(C=O),1628(C=N),1597(C=C) aromatic, 1355(C-N) .
$^1$H NMR (□ppm): 2.09(d,4H,$CH_2$-$CH_2$ cyclic), 2.46(s, 5H,$CH_2$ cyclic and $CH_3$), 2.8(d,4H,$2CH_2$ cyclic), 3.92(s, 2H,$OCH_2$),5.62(t,2H, CH-CH cyclic),6.75-8.06 (m, 4H, Ar-H),11.8(s, 1H,NH).

**2-(5-((4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)phenoxy)methyl)-1,3,4-thiadiazol-2-yl)isoindoline-1,3-dione[VII]$_c$**
Color:Brown; Yield: 100%; M.P: 160-$162^0$C
IR (ν, $cm^{-1}$ ) :3100 (C-H) aromatic, 2953-2852(C-H aliphatic),1708,1695,1676(C=O),1620(C=N),1595(C=C) aromatic, 1359(C-N) .
$^1$H NMR (□ppm):2.31(s, 5H,$CH_2$ cyclic and $CH_3$), 4.14 (s, 2H,$OCH_2$), 6.86-8.05 (m, 8H, Ar-H),12.1(s, 1H,NH).

**2-(5-((4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)phenoxy)methyl)-1,3,4-thiadiazol-2-yl)-1H-benzo[f]isoindole-1,3(2H)-dione[VII]$_d$**
Color:Brown; Yield: 100%; M.P: 240-$242^0$C
IR (ν, $cm^{-1}$ ):3068 (C-H) aromatic, 2924-2852(C-H aliphatic),1732,1704,1666(C=O),1630(C=N),1600(C=C) aromatic, 1355(C-N) .
$^1$H NMR (□ppm):2.43(s, 5H,$CH_2$ cyclic and $CH_3$), 3.98 (s, 2H,$OCH_2$), 6.85-8.52 (m, 10H, Ar-H),10.3(s, 1H,NH).

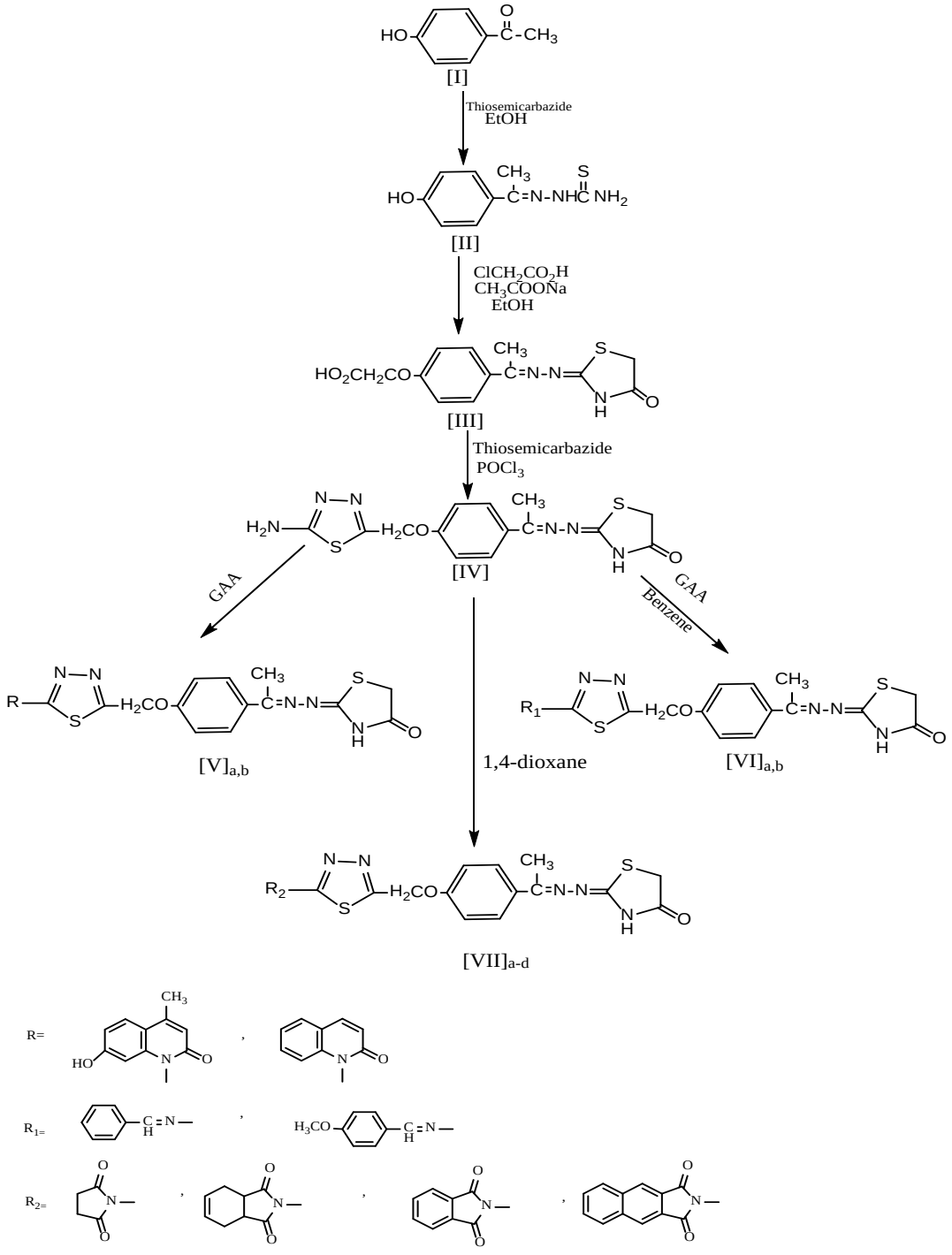



**Figure 1: Synthetic Scheme**

**Analytical Characterization**

FTIR spectra (using KBr disc) were recorded by on a Shimadzo (Ir prestige -21), ¹HNMR spectra were recorded by company : Bruker , model: ultra shield 300 MHz , origin :Switzerland (in DMSO as a solvent), ppm(δ), uses internal standard (TMS), were made at chemistry department , Gazi University, Turkey. Hot-Stage, Gallen Kamp melting point apparatus was used for determined uncorrected melting points.

## RESULTS AND DISCUSSION

The compound [II] was synthesized from condensation of 4-hydroxyacetophenone with thiosemicarbazide. The compounds [II] was characterized using FTIR spectroscopy and melting point. The FTIR spectrum of compound[II]showed disappearance of ketone ν C=O and appearance ν C=N stretching band. While the compound [III] was synthesized from the refluxing compound [II] with chloroaceticacid in presence of sodium acetate. The FTIR spectrum showed the appearance of new stretching band due to a carbonyl group of thiazolidinone [35]and

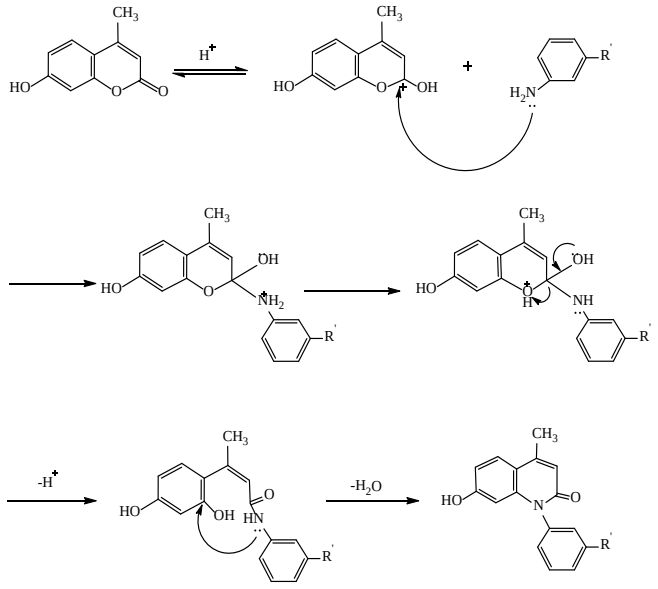
stretching band due to C-S bond, Also appearance a broad stretching band for OH group.

The $^1$HNMR spectrum of compound [III] exhibited the following characteristics chemical shifts: two sharp singlet signal could be attributed to protons of NH group and group(OHacid), respectively. Also the spectrum showed two singlet signals for two protons of CH2 cyclic,and three protons of $CH_3$ group. Also the spectrum exhibited a singlet signal for two protons of OCH2 group.

The reaction of thiazolidenone [III] with thiosemicarbazide in $POCl_3$ yielded a new compound of 1,3,4-thiadiazole [IV].This compound is identified by FTIR spectroscopy. The FTIR spectrum of compound [IV]showed disappearance absorption band due to OH group and the appearance of a new two bands due to stretching vibration of amine group ($NH_2$).

While$^1$HNMR spectrum showed the following signals: singlet signal for one proton of CO- NH (amide) group. Many signals that could be assigned to the Four aromatic protons, also a singlet signal for two protons thiazolidinone ring and $CH_3$ group and single to $OCH_2$ group . Finally a singlet signal appeared for two protons of $NH_2$ group.

The new quinolin-2-one $[V]_{a,b}$, were synthesized by refluxing of coumarin with amino compounds $[IV]_{a,b}$ in glacial acetic acid according to the suggested mechanism.



The characteristic FTIR absorption bands of qunolin-2-one $[V]_{a,b}$, showed a shift in the carbonyl stretching band from lactone group of coumarin to low frequency for lactam group of qunolin-2-one, and disappearance absorption band due to $NH_2$ group.

The $^1$HNMR spectrum of compound [V]a exhibited doublet signal that could be attributed to the CH=CH proton of quinolin-2-one ring, but the $^1$HNMR spectrum of compound [V]b showed another two singlet signals for three protons of $CH_3$ group and a proton of OH group , besides to a singlet signal for CH= proton.

The Schiff bases type $[VI]_{a,b}$ were produced from the refluxing of amino compound [IV]with different aromatic aldehydes in benzene using three drops of glacial acetic acid (GAA) . The FTIR spectra of compounds $[VI]_{a,b}$ showed appearance new absorption band which is assigned to C=N stretching.

The$^1$HNMR spectrum of Schiff base $[VI]_{a,b}$ showed eight aromatic protons appeared and a singlet signal for one proton of CH=N group. when treatment amino compound [IV] with different anhydride in dry 1,4-dioxane under reflux led to produce new imide compounds$[VII]_{a-d}$. Structure of this compound$[VII]_{a-d}$ was confirmed by FTIR, which showed disappearance of absorption bands belong to (-NH2) amine and C=O of acid anhydride with appearance two stretching bands for C=O of imides.

Finlly, the $^1$HNMR spectrum of imide compounds$[VII]_{a,b}$ showed singlet signals due to protons of $CH_2$ or CH groups cyclic moiety for compound$[VII]_a$ and $[VII]_b$ ,respectively while the $^1$HNMR spectrum of compounds $[VII]_{c,d}$ did not showed signils for these groups a proton of $CH_2$ or CH group cyclic anhydride.

## CONCLUSIONS

This work include synthesis new derivatives quinolin-2-one, Schiff bases and imides with good to moderate using easy methods.

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