INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL INDOL BASED THIAZOLIDINS WITH ANTIMICROBIAL ACTIVITY

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ABSTRACT

Various {3-[2-(1*H*-indol-3-ylmethoxy)-acetylamino]-4-oxo-2-phenyl-thiazolidin-5-yl}-acetic acids **(5a-f)** have been synthesized from (1*H*-indol-3-ylmethoxy)-acetic acid-benzylidene-hydrazides **(4a-f)** by suing (1*H*-indol-3-yl)-methanol **(1)** as starting material and by involving (1*H*-indol-3-ylmethoxy)-acetic acid ethyl ester **(2)** and (1*H*-indol-3-ylmethoxy)-acetic acid hydrazide **(3)** as intermediates. The chemical structures of these compounds have been established by IR, ^{1}H, ^{13}C-NMR, Mass spectral data and elemental analysis. The newly synthesized compounds were screened for their ability towards antibacterial and antifungal activities.

INTRODUCTION

A literature search revealed that, thiazolidinone derivatives may exhibit antibacterial[1], antituberculosis[2], antiviral[3], and anticancer[4], properties. In addition, some thiazolidinones were recently reported as novel inhibitors of mycobacterial rhamnose synthetic enzymes[5]. Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal and biological properties. Thiazole derivatives are an important class of heterocyclic compounds and they occupy a significant position in medicinal chemistry presenting a wide range of biological activities such as antibacterial[6], antifungal[7], anti-HIV[8], hypertension[9], anti-inflammatory[10], anticancer[11] and anti-convulsant[12] activities.

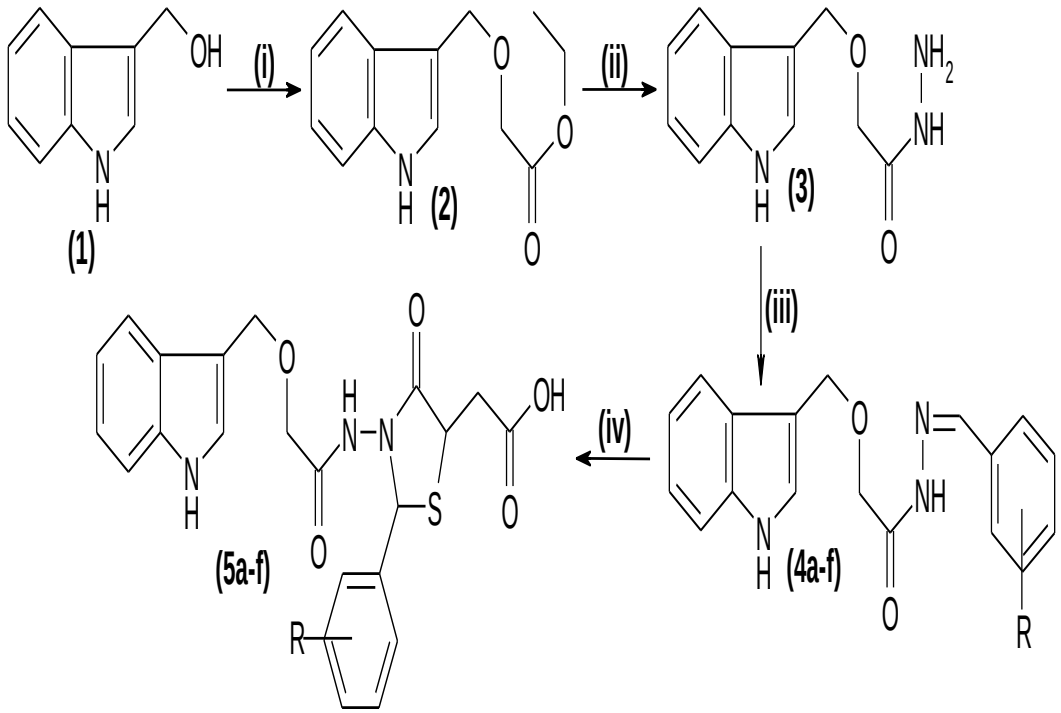
RESULTS AND DISCUSSION

Thus we have designed and synthesized various novel {3-[2-(1*H*-indol-3-ylmethoxy)-acetylamino]-4-oxo-2-phenyl-thiazolidin-5-yl}-acetic acids **(5a-f)**. The target compounds were synthesized by using commercially available (1*H*-indol-3-yl)-methanol **(1)** as starting material. The initial intermediate, (1*H*-indol-3-ylmethoxy)-acetic acid ethyl ester **(2)** has been prepared from compound **1** on reaction with chloro ethylacetate and K_2CO_3 in acetone solvent under reflux for 12 h. The next intermediate, (1*H*-indol-3-ylmethoxy)-acetic acid hydrazide **(3)** was afforded from the reaction between compound **2** and hydrazine hydrate in ethanol solvent on reflux temperature for 4 h. Then compound **3** is turned into final intermediate, (1*H*-indol-3-ylmethoxy)-acetic acid-benzylidene-hydrazides **(4a-f)** on reaction with different aromatic aldehydes in presence of acetic acid in ethanol solvent under reflux for 4-6 h. Finally the target compounds, {3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-4-oxo-2-phenyl-thiazolidin-5-yl}-acetic acids **(5a-f)** were synthesized from the reaction between compounds **4a-f** and mercaptosuccinic acid and $ZnCl_2$ in THF solvent on reflux for 13-15 h. The chemical structures of the newly prepared compounds were confirmed by their IR, ^{1}H & ^{13}C NMR, Mass spectral data and elemental analysis. Further the title compounds have been used to evaluate their anti microbial activity.

ANTIMICRBIAL ACTIVITY

The newly synthesized compounds **5a-f** were screened for their antibacterial activity against two bacterial organisms such as *Staphylococcus aureus* and *Escherichia coli* (106 cell/ml) by the disc-diffusion method[13] in nutrient agar medium, at various concentrations (250, 500 µg/disc) in dimethylformamide (DMF) by using Tetracyclin (250 & 500 µg/disc) as standard drugs. These solutions were added to each filter disc and the plates were incubated at 35 °C and examined for zone of inhibition around each disc after 24 h. The antifungal activity of the

same compounds was also evaluated with same method against two fungal organisms like *Curvularia lunata* and *Aspergillus niger*, at concentrations of 250 and 500 µg/disc. Griseofulvin (250 & 500 µg/disc) was used as the reference compound for this study. Fungal cultures were grown on potato dextrose broth at 25 °C and finally spore suspension was adjusted to 105 spores/ml. The results of the biological screening of these compounds are reported in Table 1. As per the results, most of the compounds showed significant activity against both bacteria and fungi.



Scheme 1: (i) $ClCH_2CO_2Et$, K_2CO_3, Acetone, Reflux, 12 h; (ii) NH_2NH_2, EtOH, Reflux, 4 h; (iii) Ar'-CHO, EtOH, AcOH, Reflux, 4-6 h; (iv) $HOOC-CH_2CH(SH)-COOH$, $ZnCl_2$, THF, Reflux, 13-15 h 4/5 R = (a) = H, (b) = 4-CH_3, (c) = 4-OCH_3, (d) = 4-Cl, (e) = 4-Br, (f) = 4-NO_2

Table 1: The antimicrobial activity of (5a-f) (Zone of inhibition in mm)

S. No	Antibacterial activity				Antifungal activity			
	S. aureus		*E. coli*		*C. lunata*		*A. niger*	
	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
5a	13	19	11	12	08	13	10	12
5b	16	20	13	13	15	21	17	20
5c	10	13	16	15	07	09	11	14
5d	13	14	10	16	09	14	12	10
5e	15	17	13	11	14	10	15	12
5f	12	13	15	14	16	14	13	17
Stnd	18	22	18	22	—	—	—	—
stnd	—	—	—	—	18	25	20	25

EXPERIMENTAL SECTION

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H NMR and 100 MHz spectrometer ^{13}C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

(1*H*-Indol-3-ylmethoxy)-acetic acid ethyl ester (2)

A mixture of (1*H*-indol-3-yl)-methanol **(1)** (0.01 mole), ethyl chloroacetate (0.01 mole) and anhydrous K2CO3 (0.01 mole) in dry acetone was refluxed on a water bath for 12 h. The mixture was then filtered and solvent was removed under reduced pressure. The resulting solid was recrystallised from ethanol to afford compound **2** in pure form.

(1*H*-Indol-3-ylmethoxy)-acetic acid hydrazide (3)

A mixture of compound **2** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol was refluxed on a water bath for 4 h. After cooling, the solid that separated was washed with water, dried and recrystallized from ethanol to get pure compound **3**.

(1*H*-Indol-3-ylmethoxy)-acetic acid benzylidene-hydrazide (4a-f)

A mixture of compound **3** 0.01 mole) in ethanol (20 ml), aromatic aldehyde (0.01 mole) and 1 ml. of glacial acetic acid was refluxed on water bath for 4-6 h. After cooling, the solvent was removed under reduced pressure and the separated solid was crystallized from methanol to achieve **4a-f** in pure form.

{3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-4-oxo-2-phenyl-thiazolidin-5-yl}-acetic acid (5a-f) A

mixture of equimolar amounts of **4a-f** (0.01 mole) and mercaptosuccinic acid (0.01 mole) in THF (20 ml) with a pinch of anhydrous ZnCl2 was refluxed for 13-15 h on a water bath. The reaction mixture was left to cool at room temperature. The solid product so formed was collected and crystallized from methanol to afford pure **5a-f.**

PHYSICAL AND SPECTRAL DATA

(1*H*-Indol-3-ylmethoxy)-acetic acid ethyl ester (2) White solid, Yield: 75 %, M.P: 112-114 °C, IR (KBr): 3224 (N-H), 3035 (C-H, aromatic), 2975 (C-H, CH_3), 1740 (C=O), 1592 (C=C, aromatic), 1210 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.02 (s, 1H, NH), 7.75 (s, 1H, CH), 7.28-7.56 (m, 4H, Ar-H), 4.12 (q, 2H, J = 5.4 Hz, CH_2), 3.45 (s, 2H, CH_2CO), 3.18 (s, 2H, CH_2O), 1.24 (t, 3H, J = 5.4 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 136.5, 131.7, 122.8, 121.7, 120.5, 119.6, 113.0, 112.7, 73.1, 68.8, 59.5, 13.6. MS: *m/z* 233 (M^+). Anal. Calcd. for $C_{13}H_{15}NO_3$: C-66.94, H-6.48, N-6.00, O-20.58. Found: C-65.89, H-6.32, N-5.89, O-19.84.

(1*H*-Indol-3-ylmethoxy)-acetic acid hydrazide (3)

Yellow solid, Yield: 72 %, M.P: 122-124 °C, IR (KBr): 3320 (N-H), 3030 (C-H, aromatic), 2985 (C-H, CH_2), 1670 (C=O), 1585 (C=C, aromatic), 1220 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.98 (s, 1H, NH), 8.04 (s, 1H, NH), 7.68 (s, 1H, CH), 7.28-7.62 (m, 4H, Ar-H), 4.68 (s, 2H, CH_2), 4.42 (s, 2H, NH_2), 3.29 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 135.1, 130.8, 123.4, 120.4, 119.8, 117.6, 110.8, 109.4, 75.5, 69.8. MS: *m/z* 219 (M^+). Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C-60.26, H-5.98, N-19.17, O-14.60. Found: C-59.26, H-5.21, N-18.74, O-13.64.

(1*H*-Indol-3-ylmethoxy)-acetic acid benzylidene-hydrazide (4a)

Pale yellow solid, Yield: 70 %, M.P: 145-147 °C, IR (KBr): 3326 (N-H), 3028 (C-H, aromatic), 2978 (C-H, CH_2), 1672 (C=O), 1630 (C=N), 1575 (C=C, aromatic), 1224 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.08 (s, 1H, NH), 8.15 (s, 1H, NH), 7.65 (s, 1H, CH), 7.41 (s, 1H, CH), 7.32-7.78 (m, 9H, Ar-H), 4.74 (s, 2H, CH_2), 3.32 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 156.7, 137.8, 133.2, 131.5, 130.8, 129.4, 127.4, 124.7, 123.2, 121.4, 117.8, 114.1, 112.3, 73.7, 67.4. MS: *m/z* 307 (M^+). Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C-70.34, H-5.58, N-13.67, O-10.41. Found: C-69.85, H-5288, N-12.89, O-9.84.

(1*H*-Indol-3-ylmethoxy)-acetic acid (4-methyl-benzylidene-hydrazide (4b)

White solid, Yield: 74 %, M.P: 153-155 °C, IR (KBr): 3318 (N-H), 3022 (C-H, aromatic), 2982 (C-H, CH_2), 1674 (C=O), 1634 (C=N), 1590 (C=C, aromatic), 1228 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.12 (s, 1H, NH), 8.07 (s, 1H, NH), 7.78-7.35 (m, 4H, Ar-H), 7.70 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.58 (s, 1H, CH), 7.38 (s, 1H, CH), 7.32 (d, 2H, *J* = 7.4 Hz, Ar-

H), 4.67 (s, 2H, CH_2), 3.18 (s, 2H, CH_2), 2.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 156.7, 143.7, 138.4, 133.6, 131.7, 128.4, 127.2, 125.4, 124.2, 122.4, 117.8, 115.4, 113.0, 73.8, 67.8, 23.4. MS: *m/z* 321 (M^+). Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C-71.01, H-5.96, N-13.08, O-9.96. Found: C-70.12, H-5.52, N-12.48, O-9.24.

(1*H*-Indol-3-ylmethoxy)-acetic acid (4-methoxy-benzylidene-hydrazide (4c)
Brown solid, Yield: 70 %, M.P: 165-167 °C, IR (KBr): 3338 (N-H), 3034 (C-H, aromatic), 2988 (C-H, CH_2), 1676 (C=O), 1642 (C=N), 1610 (C=C, aromatic), 1236 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.14 (s, 1H, NH), 8.10 (s, 1H, NH), 7.65 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.61 (s, 1H, CH), 7.54-7.35 (m, 4H, Ar-H), 7.31 (s, 1H, CH), 7.30 (d, 2H, *J* = 7.1 Hz, Ar-H), 4.58 (s, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.31 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 166.5, 158.4, 138.3, 134.2, 133.7, 127.4, 125.6, 123.7, 122.4, 120.1, 117.4, 113.6, 112.8, 77.4, 70.6, 58.3. MS: *m/z* 337 (M^+); Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C-67.64, H-5.68, N-12.46, O-14.23. Found: C-66.36, H-4.98, N-11.28, O-13.87.

(1*H*-Indol-3-ylmethoxy)-acetic acid (4-chloro-benzylidene-hydrazide (4d)
White solid, Yield: 76 %, M.P: 132-134 °C, IR (KBr): 3340 (N-H), 3036 (C-H, aromatic), 2974 (C-H, CH_2), 1680 (C=O), 1624 (C=N), 1620 (C=C, aromatic), 1242 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.85 (s, 1H, NH), 8.12 (s, 1H, NH), 7.78-7.34 (m, 4H, Ar-H), 7.74 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.48 (s, 1H, CH), 7.36 (s, 1H, CH), 7.35 (d, 2H, *J* = 7.2 Hz, Ar-H), 4.59 (s, 2H, CH_2), 3.29 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.5, 153.6, 139.7, 138.4, 133.2, 131.7, 130.5, 127.6, 124.7, 123.6, 121.0, 117.4, 115.6, 113.4, 77.4, 67.5. MS: *m/z* 341 (M^+); Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C-63.25, H-4.72, Cl-10.37, N-12.29, O-9.36. Found: C-62.74, H-4.21, Cl-9.68, N-11.84, O-8.67.

(1*H*-Indol-3-ylmethoxy)-acetic acid (4-bromo-benzylidene-hydrazide (4e)
Yellow solid, Yield: 69 %, M.P: 125-127 °C, IR (KBr): 3335 (N-H), 3042 (C-H, aromatic), 2980 (C-H, CH_2), 1678 (C=O), 1646 (C=N), 1620 (C=C, aromatic), 1232 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.10 (s, 1H, NH), 8.09 (s, 1H, NH), 7.72 (s, 1H, CH), 7.68 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.54-7.21 (m, 4H, Ar-H), 7.36 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.30 (s, 1H, CH), 4.74 (s, 2H, CH_2), 3.21 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 156.3, 138.7, 134.6, 133.0, 132.7, 131.0, 128.7, 126.4, 123.7, 122.7, 120.4, 118.4, 116.1, 72.7, 68.7. MS: *m/z* 386 (M^+); Anal. Calcd. for $C_{18}H_{16}BrN_3O_2$: C-55.97, H-4.18, Br-20.69, N-10.88, O-8.28. Found: C-54.85, H-4.07, Br-19.86, N-10.21, O-8.03.

(1*H*-Indol-3-ylmethoxy)-acetic acid (4-nitro-benzylidene-hydrazide (4f)
Pale yellow solid, Yield: 71 %, M.P: 140-142 °C, IR (KBr): 3325 (N-H), 3042 (C-H, aromatic), 2990 (C-H, CH_2), 1685 (C=O), 1642 (C=N), 1625 (C=C, aromatic), 1236 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.08 (s, 1H, NH), 8.06 (s, 1H, NH), 7.92 (s, 1H, CH), 7.65 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.54-7.36 (m, 4H, Ar-H), 7.38 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.42 (s, 1H, CH), 4.65 (s, 2H, CH_2), 3.28 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 156.3, 153.4, 138.7, 137.4, 133.1, 132.7, 125.7, 123.7, 124.7, 123.7, 121.4, 114.7, 113.1, 71.7, 68.4. MS: *m/z* 352 (M^+); Anal. Calcd. for $C_{18}H_{16}N_4O_4$: C-61.36, H-4.58, N-15.90, O-18.16. Found: C-60.84, H-4.23, N-15140, O-17.68.

{3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-4-oxo-2-phenyl-thiazolidin-5-yl}-acetic acid (5a)
Yellow solid, Yield: 75 %, M.P: 136-138 °C, IR (KBr): 3040 (C-H, aromatic), 1652 (C=N), 1565, 1545 (C=C, aromatic), 1135 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.12 (s, 1H, NH), 10.61 (s, 1H, COOH), 8.08 (s, 1H, NH), 7.65 (s, 1H, CH), 7.62-7.38 (m, 9H, Ar-H), 4.72 (s, 2H, CH_2), 4.12 (s, 1H, CH), 3.92 (s, 1H, CH), 3.20 (s, 2H, CH_2), 3.08 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.8, 172.8, 171.3, 139.7, 137.6, 133.4, 129.7, 127.2, 125.3, 123.7, 122.4, 121.8, 117.1, 113.6, 112.0, 77.9, 67.5, 56.5, 49.8, 39.1. MS: *m/z* 439 (M^+); Anal. Calcd. for $C_{22}H_{21}N_3O_5S$: C-60.12, H-4.82, N-9.56, O-18.20, S-7.30. Found: C-59.64, H-4.21, N-8.98, O-17.65, S-7.01.

{3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-4-oxo-2-*p*-tolyl-thiazolidin-5-yl}-acetic acid (5b) Brown solid, Yield: 78 %, M.P: 158-160 °C, IR (KBr): 3045 (C-H, aromatic), 1648 (C=N), 1584, 1565 (C=C, aromatic), 1155 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.14 (s, 1H, NH), 10.60 (s, 1H, COOH), 8.11 (s, 1H, NH), 7.69 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.52-7.21 (m, 4H, Ar-H), 7.33 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.62 (s, 1H, CH), 4.75 (s, 2H, CH_2), 4.06 (s, 1H, CH), 3.96 (s, 1H, CH), 3.71 (s, 3H, CH_3), 3.17 (s, 2H, CH_2), 3.01 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.3, 173.1, 172.0, 138.4, 137.2, 135.6, 134.7, 128.7, 126.3, 124.3, 121.8, 120.7, 119.4, 117.4, 115.6, 75.2,

69.4, 58.4, 51.0, 40.2, 21.6. MS: *m/z* 453 (M^+); Anal. Calcd. for $C_{23}H_{23}N_3O_5S$: C-60.91, H-5.11, N-9.27, O-17.64, S-7.07. Found: C-59.87, H-4.98, N-8.87, O-16.84, S-6.92.

[3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-2-(4-methoxy-phenyl)-4-oxo-thiazolidin-5-yl]-acetic acid (5c) Pale yellow solid, Yield: 74 %, M.P: 140-142 °C, IR (KBr): 3025 (C-H, aromatic), 1632 (C=N), 1570, 1555 (C=C, aromatic), 1152 (C-O) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.14 (s, 1H, NH), 10.58 (s, 1H, COOH), 8.13 (s, 1H, NH), 7.74 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.62-7.38 (m, 4H, Ar-H), 7.20 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.65 (s, 1H, CH), 4.62 (s, 2H, CH_2), 4.15 (s, 1H, CH), 3.98 (s, 1H, CH), 3.72 (s, 3H, CH_3), 3.21 (s, 2H, CH_2), 3.06 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3, 172.0, 170.7, 160.4, 139.4, 134.2, 130.6, 128.4, 122.0, 121.7, 120.5, 119.1, 116.2, 115.6, 114.1, 79.4, 65.6, 56.8, 53.1, 47.4, 37.9. MS: *m/z* 469 (M^+); Anal. Calcd. for $C_{23}H_{23}N_3O_6S$: C-58.84, H-4.94, N-8.95, O-20.45, S-6.83. Found: C-57.63, H-4.38, N-8.24, O-19.87, S-6.28.

[3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-2-(4-chloro-phenyl)-4-oxo-thiazolidin-5-yl]-acetic acid (5d) Yellow solid, Yield: 75 %, M.P: 149-151 °C, IR (KBr): 3020 (C-H, aromatic), 1630 (C=N), 1585, 1565 (C=C, aromatic), 1152 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 11.10 (s, 1H, NH), 10.54 (s, 1H, COOH), 8.04 (s, 1H, NH), 7.66 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.51-7.35 (m, 4H, Ar-H), 7.36 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.62 (s, 1H, CH), 4.74 (s, 2H, CH_2), 4.10 (s, 1H, CH), 3.89 (s, 1H, CH), 3.24 (s, 2H, CH_2), 3.04 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.3, 172.8, 170.2, 139.7, 136.2, 134.2, 131.3, 130.8, 128.4, 125.6, 123.2, 120.7, 119.2, 115.3, 114.7, 76.2, 68.3, 57.5, 51.0, 41.0. MS: *m/z* 473 (M^+); Anal. Calcd. for $C_{22}H_{20}ClN_3O_5S$: C-55.75, H-4.25, Cl-7.48, N-8.87, O-16.88, S-6.77. Found: C-54.87, H-3.98, Cl-7.32, N-8.28, O-15.97, S-6.21.

[3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-2-(4-bromo-phenyl)-4-oxo-thiazolidin-5-yl]-acetic acid (5e) Brown solid, Yield: 70 %, M.P: 148-150 °C, IR (KBr): 3015 (C-H, aromatic), 1652 (C=N), 1619, 1582 (C=C, aromatic), 1135 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 11.14 (s, 1H, NH), 10.52 (s, 1H, COOH), 8.09 (s, 1H, NH), 7.68 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.50-7.42 (m, 4H, Ar-H), 7.34 (d, 2H, *J* = 7.1 Hz, Ar-H), 7.58 (s, 1H, CH), 4.68 (s, 2H, CH_2), 4.08 (s, 1H, CH), 3.90 (s, 1H, CH), 3.18 (s, 2H, CH_2), 3.00 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.0, 172.0, 171.7, 136.4, 134.2, 131.2, 130.4, 128.5, 121.4, 120.2, 119.8, 118.7, 116.3, 114.8, 110.1, 75.4, 64.8, 54.6, 52.1, 41.0. MS: *m/z* 518 (M^+); Anal. Calcd. for $C_{22}H_{20}BrN_3O_5S$: C-50.97, H-3.89, Br-15.41, N-8.11, O-15.43, S-6.19. Found: C-49.86, H-3.28, Br-14.87, N-7.84, O-14.98, S-6.02.

[3-[2-(1*H*-Indol-3-ylmethoxy)-acetylamino]-2-(4-nitro-phenyl)-4-oxo-thiazolidin-5-yl]-acetic acid (5f) Yellow solid, Yield: 77 %, M.P: 128-130 °C, IR (KBr): 3020 (C-H, aromatic), 1632 (C=N), 1608, 1585 (C=C, aromatic), 1145 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 11.18 (s, 1H, NH), 10.50 (s, 1H, COOH), 8.10 (s, 1H, NH), 7.67 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.52-7.48 (m, 4H, Ar-H), 7.30 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.57 (s, 1H, CH), 4.75 (s, 2H, CH_2), 4.16 (s, 1H, CH), 3.91 (s, 1H, CH), 3.31 (s, 2H, CH_2), 3.04 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3, 174.1, 173.2, 147.4, 145.6, 139.7, 134.6, 130.2, 125.4, 122.7, 120.3, 119.8, 118.4, 115.6, 110.1, 74.3, 69.7, 57.6, 51.2, 41.0. MS: *m/z* 484 (M^+); Anal. Calcd. for $C_{22}H_{20}N_4O_7S$: C-54.54, H-4.16, N-11.56, O-23.12, S-6.62. Found: C-53.62, H-3.98, N-11.23, O-22.47, S-6.12.

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