Synthesis and Antimicrobial Activity of New Thiazolidinone Derivatives With the use of γ-Ferrite Catalyst

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Abstract: A series of compounds were synthesized from 3,3′-(pyridine-2,6-diyl) bis (2-phenylthiazolidin-4-one) which was prepared from a one-pot three component condensation reaction of 2, 6-diamino pyridine, benzaldehyde and thioglycolic acid in the presence of γ-ferrite as a catalyst. The newly synthesized compounds were characterized by IR, 1HNMR, 13C NMR spectral data. All compounds were tested for anti bacterial and anti fungal activities.

Keywords: Pyridine, Azo derivatives, γ-Ferrite, Arylidene derivatives.

Introduction

During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures1, with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry2. There has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities3. Thiazolidinones and their derivatives are an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture4. Thiazolidinone ring occurs in nature; thus actithiazic acid[(−)2-(5-carboxypentyl)thiazolidin-4-one] isolated from streptomyces strains exhibits highly specific in vitro activity against mycobacterium tuberculosis5. They have found uses, for example, as insecticides, tuberculostatic6-7, anti-inflammatory8, CNS stimulant, anthelmintic9, CO2+ channel blocker10, antiviral11, analgesic12, anticonvulsant13, anti platelet activating factor14, anticancer15, and anti HIV16. 4-Thiazolidinones have also been reported as novel inhibitors of bacterial enzyme17. In view of these above findings it was thought of interest to accommodate thiazolidin-4-one and pyridine in a single molecular frame work and screened for their antimicrobial activity.
Experimental

The NMR (1H & 13C) spectra were recorded at 400 MHz, 100MHz respectively with a Bruker Avance II 400 instrument. NMR spectra were obtained in solutions of DMSO (d6) and chemical shifts reported in parts per million (ppm) and TMS as an internal standard. Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a FT-IR Shimadzu 8400 Spectrophotometer and reported in wave numbers (cm\(^{-1}\)).

3,3′-(Pyridine-2,6-diyl)bis(2-phenylthiazolidin-4-one(1))

To a mixture of 2,6-diamino pyridine (1 equiv.), benzaldehyde (2 equiv), anhydrous γ-ferrite (Fe\(_2\)O\(_3\); 4 equiv) was added and the reaction mixture was refluxed with constant stirring in dry benzene (40ml) for 1/2 h, followed by the addition of thioglycolic acid (2 equiv). The refluxing and stirring were continued for another 10h. The reaction was monitored by TLC. After the completion of the reaction, a reddish brown amorphous solid Fe\(_2\)O\(_3\).2H\(_2\)O/FeO(OH) was removed by filtration, filtrate was concentrated to dryness under reduced pressure to achieve compound.

Dark brown crystals; yield 74%, m.p: 256°-259°C; IR (KBr, vmax, cm\(^{-1}\)) 1698(C=0), 1130(C-N), 672(C=S), 1612(C=N), 1597 (C=O), 132.5, 118.2, 137.02, 114.86, 135.8, 132.5, 122.91, 118.2, 114.86.

General procedure for the Synthesis of 3,3′-(pyridine-2,6-diyl)bis(5-substituted-arylidene-2-phenyl)thiazolidin-4-one derivatives (2a-j)

A mixture of compound 1 (1 equiv.), aromatic aldehyde (2 equiv.), anhydrous sodium acetate (2eqiv.) in glacial acetic acid (50ml) was heated under reflux for 4 h. Concentrated, cooled and poured into the crushed ice. The solid thus separated was filtered, washed with water and recrystallized. All the compounds 2a-j were prepared by the same methodology as mentioned above. The physical and analytical data of compounds were mentioned in Table 1.

General procedure for the synthesis of 3,3′-(pyridine-2,6-diyl)bis(5-(phenyl substituted diazenyl)-2-phenyl)thiazolidin-4-one 3(a-c)

To a solution of aniline (0.01 mol) in glacial acetic acid (5 mL) was added conc. HCl (3 mL) at 0-5°C. A Solution of Sodium nitrite (1 g in 5 mL of water) was then added drop wise. The diazonium salt Solution thus prepared was added to a solution of compound"1" (0.01 mol) in DMF drop wise with stirring below 0°C. The reaction mixture were kept at room temperature for 2-3 days and then poured into to cold water (200 mL). The resulting solids were washed with water and recrystallized from suitable solvents. (viz. Ethanol, methanol). The physical & analytical data of all synthesized compounds were given in Table 1.

3,3′-(Pyridine-2,6-diyl)bis(5-(4-hydroxy arylidene-2-phenyl)thiazolidin-4-one (2a)

IR (KBr, cm\(^{-1}\) ) vmax=3182.65(O-H), 3120.93(CH in ring), 3057.27(Ar), 1653.05(C=O), 1415.80 (C-N), 1600, 1625 (C=C and C=N); 1H NMR (δ ppm, DMSO-d6), 6.25 (s, 2H, N-CH), 6.9 (t, 1H, Pyridine C4), 7.35 (s, 2H, CH), 7.6 (m, 18H, Ar-H), 8.0 (s, 2H, OH), 8.21 (d, 2H, C2-H and C3-H in pyridine); 13C NMR (DMSO) δ: 170.8, 155.08, 137.02, 135.8, 132.5, 122.91, 118.2, 114.86.
3,3'-(Pyridine-2,6-diyl)bis(5-(arylidene-2-phenyl)thiazolidin-4-one (2b)
IR(KBr, cm⁻¹) νmax=3049(Ar-C-H), 1704(C=O), 1625 (C=C), 1620 (C=N), 1515(C=N), 1H NMR (δ ppm, DMSO-d₆) 8.71(m, 20H, Ar-H), 6.20 (s, 2H,N-CH-Ar), 6.92 (t, 1H, C₆-H in Pyridine), 8.19 (d, 2H, C₃-H, C₅-H in pyridine); ¹³C NMR (DMSO) δ: 170.79, 156.2, 136.1, 129.8, 109.12.

3,3'-(Pyridine-2,6-diyl)bis(5-(4-N-dimethylaminoarylidene-2-phenyl)thiazolidin-4-one (2c)
IR (KBr, cm⁻¹) νmax=3423.76(N-H), 3080.42(0), 3030.27(CH in alkene), 2931.90(CH₃), 1683.91(C=O), 1597.11(C=C), 1417.73 (C=N), 1361.79(3° amine).

3,3'-(Pyridine-2,6-diyl)bis(5-(3,4,5-tri methoxy arylidene-2-phenyl)thiazolidin-4-one (2d)
IR(KBr, cm⁻¹) νmax=3080.42(Ar), 3057.27 (C-H in ring), 2937.68(CH₃),1624.12 (C-O), 1388.79(C-N), 1230.63 (C-O-C), 702.11(C-S); ¹H NMR (δ ppm, DMSO-d₆) 3.86(s, 12H, 3.5-OCH₃) 3.79(s, 6H, 4-OCH₃) 7.15-7.25(m, 14H, Ar-H), 7.5(d, 2H, 3,5-Pyridine), 7.96 (s, 2H, CH), 8.07 (s, 2H, C-H), 8.30(t, 1H,C₆-H in pyridine); ¹³C NMR (DMSO) δ: 171.3, 158.9, 153.89, 137.2, 131.9, 124.01, 118.7, 114.2, 65.2.

3,3'-(Pyridine-2,6-diyl)bis(5-(4-methoxy arylidene-2-phenyl)thiazolidin-4-one (2e)
IR (KBr, cm⁻¹) νmax=3057.27(Ar), 3030.27(CH in ring), 2933.83(CH₃), 1584.68(C=O), 1559.17(C=N), 1515(C=N), 1219.05(C=O), 1089.82 (C=O-Chloro), 1059.79(C=O-Nitro), 702.11(C-S). ¹H NMR (δ ppm, DMSO-d₆) 5.91(s, 2H, CH), 8.35(d, 2H, 3,5-Pyridine), 7.25(m, 14H, Ar-H), 7.15-7.19(m, 2H, Ar-N), 7.02(s, 1H, C₆-H in pyridine), 6.20(s, 1H, C₆-H in pyridine), 5.91(s, 2H, CH), 8.02(s, 2H, C-H), 8.35(d, 2H, 3,5-H in pyridine).

3,3'-(Pyridine-2,6-diyl)bis(5-(2-chloro arylidene-2-phenyl)thiazolidin-4-one (2f)
IR(KBr, cm⁻¹) νmax= 3058.91(Ar), 3082.35(CH in heterocyclic ring), 1653.05 (C=O), 1388.79(C-N), 1089.82(C-Cl), 702.11(C-S).

3,3'-(Pyridine-2,6-diyl)bis(5-(2-bromo arylidene-2-phenyl)thiazolidin-4-one (2g)
IR(KBr, cm⁻¹) νmax=3058.91(Ar), 3082.35(CH in heterocyclic ring), 1653.05 (C=O), 1387.12 (C-N), 686.17 (C-S).

3,3'-(Pyridine-2,6-diyl)bis(5-(4-nitro arylidene-2-phenyl)thiazolidin-4-one (2h)
IR(KBr, cm⁻¹) νmax= 3057.93(CH in ring), 3018 (Ar-CH), 1637.11(C=O), 1530.98(N-O), 1387.54(C-N), 701.08(C-S); ¹H NMR (δ ppm, DMSO-d₆) 5.91(s, 2H, CH), 7.1-7.4(m,18H,Ar-H), 7.89(t, 1H, C₆-H in pyridine), 8.02(s, 2H, CH), 8.35(d, 2H, 3,5-H in pyridine).

3,3'-(Pyridine-2,6-diyl)bis(5-(4-chloro arylidene-2-phenyl)thiazolidin-4-one (2i):
IR(KBr, cm⁻¹) νmax= 3082.35(Ar), 3059.20(CH in heterocyclic ring), 1653.05 (C=O), 1388.79(C-N), 1089.82(C-Cl), 702.11(C-S).

3,3'-(Pyridine-2,6-diyl)bis(5-(2-methoxy arylidene-2-phenyl)thiazolidin-4-one (2j)
IR(KBr, cm⁻¹) νmax=3057.27(Ar), 3030.27(CH in ring), 2933.83(CH₃), 1622.19(C=O), 1394.58(C-N), 1219.05(C-O-C), 640.39 (C-S).
3,3′-(Pyridine-2,6-diyil)bis(5-((phenyl) di azenyl)-2-phenyl)thiazolidin-4-one (3a)

Brown colour powder; IR(KBr, cm⁻¹) vmax=3038.76 (C-H in ring), 3019.91 (Ar), 1595.19 (N=N), 1320.22 (C-N), 662.03 (C-O). 1H NMR(δppm, DMSO-d6) 5.92 (s, 2H, CH), 7.05-7.29 (m, 20H, Ar-H), 7.9 (t, 1H, C₄-Pyridine), 8.2 (s, 2H, C₃-H in thiazolidinone), 8.5 (C₂&C₅-H in pyridine).

3,3′-(Pyridine-2,6-diyil)bis(5-((4-nitro phenyl) di azenyl)-2-phenyl)thiazolidin-4-one (3b):

IR(KBr, cm⁻¹) vmax=3047.11 (C-H in ring), 3029.39 (Ar), 1665.82 (C=O), 1602.18 (N=N), 1312.26 (C-N), 1301.03 (C-S); 1H NMR(δppm, DMSO-d6) 6.1 (s, 2H, CH3-Ar), 7.39 (m, 18H, Ar), 7.9 (t, 1H, C₅-H in pyridine), 8.38 (d, 2H, C₃,C₅-H in pyridine); 13CNMR(DMSO) δ: 171.59, 153.35, 148.71, 135.73, 129.8, 124.21, 119.3, 115.27.

3,3′-(Pyridine-2,6-diyil)bis(5-((4-chloro phenyl) diazenyl)-2-phenyl)thiazolidin-4-one (3c)

IR (KBr, cm⁻¹) vmax=3051.26 (C-H in ring), 1705.32 (Ar), 1656.43 (C=O), 1599.14 (N=N), 1307.69 (C-N), 1091.16 (C-Cl), 694.78 (C-S); 1H NMR(δppm, DMSO-d6) 5.82 (s, 2H, CH3-Ar), 7.52 (m, 18H, Ar), 7.85 (t, 1H, C₅-H in pyridine), 8.46 (d, 2H, C₃,C₅-H in pyridine); 13CNMR(DMSO) δ: 170.78, 152.73, 135.2, 130.29, 122.91, 118.2, 116.35.

Table 1. Physical and analytical data of compounds 2a-j & 3a-c.

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<th>Compd</th>
<th>R</th>
<th>Yield</th>
<th>mp</th>
<th>Mol.Formula/Mol.wt</th>
<th>Elementalanalysis (caled/found)</th>
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<td>2b</td>
<td>H</td>
<td>69</td>
<td>338</td>
<td>C₃₂H₂₇N₅O₂S₂/609.76</td>
<td>72.88/72.83, (4.46/4.45)</td>
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<td>293</td>
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Results and Discussion

The key intermediate 1 was prepared by a one pot three component condensation reaction involving 2, 6-di amino pyridine, benzaldehyde, and mercaptoacid in the presence of a γ-ferrite as a catalyst (18). The synthetic route of the compounds is outlined in Scheme-1. This Thiazolidinone(1) reacted with various aldehydes afforded to bis thiazolidinones and
their 5-arylidene derivatives (2a-j) through knoevenagel reaction. In another way Diazotization of compounds with various aromatic amines yielded azo compounds (3a-c). The newly synthesized compounds were characterized by FT-IR, NMR ($^1$H, $^{13}$C) spectral data.

$$\text{NH}_2\text{N}+\text{NH}_2\text{OHC}+\text{SHCH}_2\text{COOH}\rightarrow\text{Gaama-ferrite}$$

Scheme 1. Synthesis of compound 1, 2a-j and 3a-c.

**Anti Microbial Evaluation**

Thirteen of the newly synthesized compounds were evaluated for their in vitro antibacterial activity against *B. subtilis*, *B. thuringiensis*, *E. coli* and *P. aeruginosa*, as well as antifungal activity against *B. fabae*, *F. oxysporam* and *T. viridae* organisms. Agar diffusion method was used for the determination of the preliminary anti bacterial and antifungal activities. Streptomycin, Chloramphenicol and Treflucan were used as reference drugs. The results depicted in Table 2 revealed that most of tested compounds displayed variable inhibitory effects on the growth of the tested organisms. Regarding the activity of the thiazolidinone derivatives against bacteria, the results revealed that compounds 2f-2i, 3b, and 3e exhibited broad spectrum of antibacterial profile against the tested organisms.
Table 2. Antimicrobial activity data of compounds 2a-j & 3a-c (MIC, μg/mL).

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<th>Compd No</th>
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<th>B. thuringiensis</th>
<th>E-Coli</th>
<th>P. aeruginosa</th>
<th>B. fabae</th>
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Regarding the activity of thiazolidinones and their 5-arylidene and their 5-azo derivatives incorporating pyridine moiety against antifungal strains the results revealed that compounds 2e, 2j, 3b, and 3c revealed strong growth inhibitory against the tested fungi.

Conclusion
In conclusion, the objective of the present study was to synthesize and investigate the antimicrobial activities of some new heterocyclic derivatives by the use of γ-ferrite leads serving as potent antimicrobial agents. Our aim has been verified by the synthesis of two different groups of structure hybrids comprising basically the pyridine moiety attached to either arylidene substituted thiazolidinones (or) azo substituted thiazolidinones. The obtained results clearly revealed that some of the newly synthesized compounds exhibited better antimicrobial activity.

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