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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antimicrobial activity of thiazolyl benzenesulfonamide-condensed 2,4-thiazolidinediones derivatives

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Abstract A new series of benzoyl chloride-substituted 2,4-thiazolidinedione derivatives have been synthesized by the condensation of 2-amino-4-aryl-thiazole and 4′-chlorosulfonyl benzylidine-2,4-thiazolidinedione. New compounds were evaluated for their in vitro antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas aeruginosa.* Furthermore, new products were tested for in vitro antituberculosis activity against *Mycobacterium tuberculosis* using isoniazid and rifampicin as control drugs. The results of bioassay demonstrated that some of the newly synthesized 2,4-thiazolidinedione derivatives emerged as lead molecules with excellent MIC (mg/mL) values against mentioned organisms compared to standard drugs. The structure of the final analogs has been confirmed on the basis of IR, ^{1}H NMR, mass spectral, and elemental analysis.

Keywords Thiazole · 2,4-Thiazolidinedione · Synthesis · Antibacterial · Antituberculosis

Introduction

Small-ring heterocycles holding nitrogen and sulfur have been under investigation for a long time because of their synthetic diversity and therapeutic relevance. Among the wide range of heterocycles explored to develop privileged candidates in drug discovery, thiazoles have been indentified to play an essential role in medicinal chemistry. Thiazolidinone are the derivatives of thiazolidine which belong to prenominal group of heterocyclic compounds bearing sulfur and nitrogen in a five-member ring (Patel *et al.*, 2011; Desai *et al.*, 2011a, b). Countless research work on thiazolidinones has been accomplished in recent years (Malik *et al.*, 2011; Rekha *et al.*, 2011; Aneja *et al.*, 2011). The nucleus is also well known as wonder nucleus because it gives out different derivatives expressing newer leads for multiple biological activities (Chawla *et al.*, 2011). Over the years, 4-thiazolidinones skeleton has been a fertile source of biopotent heterocycles possessing diverse chemotherapeutic activities (Bhargava and Chaurasia, 1969).

In the recent past, 4-thiazolidinone scaffold and its derivatives have fascinated significant interest of medicinal chemists and have become an important class of heterocyclic compounds because of their utility for miscellaneous biological activities such as anti-inflammatory (Deep *et al.*, 2011; Kumar and Rajput, 2009; Ottana *et al.*, 2005; Geronikaki *et al.*, 2008), analgesic (Tandon *et al.*, 1985; Knutsen *et al.*, 2007), antimycobacterial (Kucukguzel *et al.*, 2002; Srivastav *et al.*, 2005), antimicrobial (Desai *et al.*, 2011a, b; Patel and Patel, 2010; Ozkirimli *et al.*, 2009; Bondock *et al.*, 2007; Madhukar *et al.*, 2009; Fuloria *et al.*, 2009), antiarrhythmic (Amr *et al.*, 2009), anti-HIV activity (Kucukguzel *et al.*, 2006; Barreca *et al.*, 2001), and anticonvulsant (Shiradkar *et al.*, 2007). A crucial component in drug designing program is the construction of new entities with promising bioactivity and lesser side effects. Furthermore, minimal cytotoxic properties have been examined for thiazolidinone derivatives earlier (Alegaon and Alagawadi, 2011), so from all these facts and non-toxic nature of thiazolidinone derivatives, it has been thought of interest to

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synthesize some new benzoyl chloride-substituted 2,4-thiazolidinedione derivatives to furnish a possible antibacterial and antituberculosis agents.

Experimental

Materials and methods

Chemicals and solvents were obtained from commercial sources and used as received throughout the investigation. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. IR spectra (4,000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400-S FT-IR spectrophotometer (Shimadzu India Pvt. Ltd., Mumbai, India) using KBr pellets. Thin layer chromatography was performed on object glass slides (2 × 9 × 7.5 cm) coated with silica gel-G and spots were visualized under UV irradiation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz model spectrometer (Varian India Pvt. Ltd., Mumbai, India) using DMSO as a solvent and TMS as internal standard with ^{1}H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^{1}H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me4Si) and were performed at Centre for Excellence, Vapi, India. The splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All new compounds were subjected to elemental analysis using a Heraeus Carlo Erba 1180 CHN analyzer (Hanau, Germany).

Kirby Bauer disk diffusion method for antibacterial activity

The synthesized benzoyl chloride-substituted 2,4-thiazolidinedione derivatives **6a–6i** were examined for their antimicrobial activity against several bacteria (*Staphyloccoccus aureus* MTCC 96, *Bacillus subtilis* MTCC 619, *Escherichia coli* MTCC 739, and *Pseudomonas aeruginosa* MTCC 741) using the Kirby Bauer disk diffusion method.

The Mueller–Hinton agar media were sterilized (autoclaved at 120 °C for 30 min), poured at uniform depth of 5 mm, and allowed to solidify. The microbial suspension (10^5 CFU/mL) (0.5 McFarland Nephelometery Standards) was streaked over the surface of media using a sterile cotton swab to insure even growth of the organisms. The compounds to be tested were dissolved in dimethylformamide to give solutions of 20–500 μg/mL. Sterile filter paper disks measuring 6.25 mm in diameter (Whatman No. 1 filter paper), previously soaked in a known concentration of the respective test compound in dimethylformamide were placed on the solidified nutrient agar medium that had been inoculated with the respective microorganism and the plates were incubated for 24 h at (37 ± 1) °C. A control disk impregnated with an equivalent amount of dimethylformamide without any sample was also used and did not produce any inhibition. Ciprofloxacin and flucanazole (100 μg/disk) were used as control drugs for antibacterial and antifungal activities, respectively. Each assay was performed in triplicate.

In vitro evaluation of antimycobacterial activity

The preliminary antimycobacterial assessment for the final synthesized compounds was carried out using BACTEC MGIT method. The mycobacterial growth indicator tubes (MGIT) containing 4 mL of modified Middle brook 7H9 Broth Base were numbered as per the title compounds to be tasted for antimycobacterial efficacy by means of various concentrations prepared. The suspension was allowed to stand for 20 min and the tubes were centrifuged at 3,000 rpm for 15 min. After that, prepared suspension of 10^4 to 10^7 CFU/mL of H37Rv *Mycobacterium tuberculosis* strain was added in the medium to be incubated and 0.1 mL of egg-based medium (L. J) was also added. The MGIT tubes were then tightly recapped, mixed well, and incubated into BACTEC MGIT instrument at (37 ± 1) °C until positivity is observed. The readings were measured daily starting from the second day of incubation. Positive cultures were usually detected within 10 days. For reading the actual results, the MGIT tubes were removed from incubator and placed on the UV light next to a positive control tube and an uninoculated tube (negative control). Bright fluorescence detected by the corresponding MGIT tube was noticed in the form of bright orange color in the bottom of the tube and also an orange reflection on the meniscus. The primary screening was conducted at concentration of 6.25 μg/mL against *M. tuberculosis* H37Rv in BACTEC MGIT system. Compounds demonstrating 99 % inhibition in the primary screen were described as most potent compounds. All the other compounds to be tasted were re-examined for their actual MIC using Lowenstein–Jensen MIC method. The MIC was defined as the lowest concentration inhibiting 99 % of the inoculums.

Chemical synthesis

*Synthesis of 2-amino-4-aryl-thiazole (**1**)*

A mixture of acetophenone (0.1 mol), thiourea (0.2 mol), and iodine (0.1 mol) was heated on a steam bath for 4 h. The hydroiodide, thus separated, was filtered, washed with

ether, and dried. It was dissolved in hot water, filtered while hot, and the clear solution neutralized with a strong solution of ammonia. The solid separated was filtered, washed with water, and recrystallized from benzene. Yield: 96 %, m.p. 145–150 °C, IR (KBr disk) 3385–3410 cm^{-1} (NH_2), 1548, 1398 cm^{-1}(C=N, C–N), 635 cm^{-1} (C–S).

*Synthesis of 2,4-thiazolidinedione (**2**)*

In a 250 mL three-necked round-bottomed flask, solution containing (0.6 mol) chloroacetic acid dissolved in 60 mL of water and (0.6 mol) thiourea dissolved in 60 mL of water was added. The mixture was stirred for 15 min to form a white precipitate, accompanied by considerable cooling. To the contents of the flask, 60 mL of concentrated hydrochloric acid was then added slowly from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8–10 h at 100–110 °C. On cooling the contents of the flask solidified to a cluster of white needles, the product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallized from ethyl alcohol. Yield: 85 %, m.p. 122–127 °C, IR (KBr disk) 3387 cm^{-1} (NH), 1684 cm^{-1} (C=O), 622 cm^{-1} (C–S).

*Synthesis of 5-benzylidine 2,4-thiazolidinedione (**3**)*

In a 250 mL three-necked round-bottomed flask provided with a dean-stark apparatus, benzaldehyde (0.188 mol) and 2,4-thiazolidinedione (0.188 mol) were together suspended in ethanol. To this, a catalytic amount of piperidine (1 mL) was added. The mixture was stirred and refluxed. After the complete removal of water and when the temperature reached above 110 °C, the reaction mixture was stirred for a further 1 h. On cooling, the product precipitated out from ethanol. The compound was filtered and washed with cold toluene and dry ethanol. Yield: 93 %, m.p. 238–243 °C, IR (KBr disk) 3360 cm^{-1} (NH), 1684 cm^{-1} (C=O), 628 cm^{-1} (C–S).

*Synthesis of 4′-chlorosulfonyl-5-benzylidine-2,4-thiazolidinedione (**4**)*

5-Benzylidine 2,4-thiazolidinedione (0.04 mol) was placed in a 100 mL round-bottomed flask equipped with a condenser and a dropping funnel. Chlorosulfonic acid (0.16 mol) was added at room temperature using the dropping funnel. The reaction was found to be exothermic. After addition of chlorosulfonic acid completed, the reaction mass was refluxed for 1 h on a water bath. The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a 1 L beaker. The product was filtered and dried. The product was purified by recrystallization from ethanol. Yield: 68 %, m.p. 177–182 °C, IR (KBr disk) 3360 cm^{-1} (NH), 1684 cm^{-1} (C=O), 1120 and 1310 cm^{-1} (SO_2 sym and asym), 763 cm^{-1} (Cl), 628 cm^{-1} (C–S).

*Synthesis of 4-[(z)-2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-N-(4-phenyl-1,3-thiazol-2-yl)benzene sulfonamide (**5**)*

2-Amino-4-aryl-thiazole **(1)** (0.1 mol) and 4′-chlorosulfonyl-5-benzylidine 2,4-thiazolidinedione **(4)** (0.1 mol) were added to a mixture of 4 mL of dry pyridine and 20 mL acetic anhydride. The mixture was refluxed for 2 h, reaction mixture was poured into 20 mL of ice water, and the solid was filtered and purified by recrystallization from ethanol to give product as a white crystalline solid. Yield: 74 %, m.p. 187–192 °C, IR (KBr disk) 3364 cm^{-1} (NH), 1678 cm^{-1} (C=O), 1120 and 1310 cm^{-1} (SO_2 sym and asym), 626 cm^{-1} (C–S).

*Synthesis of 4-(3-benzoyl-2,4-dioxo-thiazolidin-5-ylidenemethyl)-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide (**6**)*

A mixture of 4-[(z)-2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-*N*-(4-ohenyl-1,3-thiazol-2-yl)benzene sulfonamide **(5)** (0.01 mol) and benzoyl chloride derivatives (0.01 mol) in DMF were refluxed for 4 h. Progress of reaction was monitored by TLC using ethanol:toluene (1:4) as eluent. After the completion of reaction, the content was added to cold water. The solid product **(6)** was obtained and filtered, dried, and purified by crystallization from ethanol. Yield: 75 %, m.p. 211 °C, IR (KBr disk) 3375 cm^{-1} (NH), 1678 cm^{-1} (C=O), 764 (Cl). Similarly, other compounds **6a**–**6i** were prepared by above method from intermediate **(5)** and various benzoyl chloride derivatives and purified by recrystallization from ethanol (Table 1).

*4-(3-Benzoyl-2,4-dioxo-thiazolidin-5-ylidenemethyl)-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide (**6a**)* Yield: 75 %; m.p. 211 °C (dec.); IR (KBr, cm^{-1}): 1328 (C–N), 1548 (C=N), 1120 and 1310 (SO_2 sym and asym), 1685 (C=O), 600–800 (C–S), 3198 cm^{-1} (–NH–), 3032–3059 cm^{-1} (–C–H) stretching of aromatic rings, ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.02 (s, 1H, NH), 4.42 (s, 2H, CH_2), 6.64–7.80 (m, 16H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.4–138.1 (18C, –Ar–C), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{26}H_{17}O_5N_3S_3$: C, 56.02 %; H, 3.13 %; N, 7.67 %; found: C, 56.14 %; H, 3.16 %; N, 7.75 %.

Table 1 Physical data of synthesized compounds

Sr. no.	R	Molecular formula	M.P. (°C)	% yield
6a	H	$C_{26}H_{17}O_5N_3S_3$	211	75
6b	2-CH_3	$C_{27}H_{19}O_5N_3S_3$	241	71
6c	3-CH_3	$C_{27}H_{19}O_5N_3S_3$	253	67
6d	4-CH_3	$C_{27}H_{19}O_5N_3S_3$	268	61
6e	2-Cl	$C_{27}H_{16}O_5N_3S_3Cl$	247	59
6f	3-Cl	$C_{27}H_{16}O_5N_3S_3Cl$	260	63
6g	4-Cl	$C_{27}H_{16}O_5N_3S_3Cl$	278	65
6h	2-NO_2	$C_{26}H_{16}O_7N_4S_3$	262	74
6i	4-NO_2	$C_{26}H_{16}O_7N_4S_3$	285	69

4-[3-(2-Methyl-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6b)*** Yield: 71 %; m.p. 241 °C (dec.); IR (KBr, cm^{-1}) : 1330 (C–N), 1558 (C=N), 1124 and 1314 (SO_2 sym and asym), 1678 (C=O), 600–800 (C–S), 3200 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H, CH_3), 4.12 (s, 1H, NH), 4.40 (s, 2H, CH_2), 6.70–7.80 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 13.7 (C-32, C–CH_3 of phenyl ring), 125.4–138.1 (18C, –Ar–C), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{19}O_5N_3S_3$: C, 57.74 %; H, 3.41 %; N, 7.48 %. found: C, 57.88 %; H, 3.34 %; N, 7.55 %.

4-[3-(3-Methyl-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6c)*** Yield: 67 %; m.p. 253 °C (dec.); IR (KBr, cm^{-1}) : 1340 (C–N), 1568 (C=N), 1144 and 1334 (SO_2 sym and asym), 1668 (C=O), 600–800 (C–S), 3210 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (s, 3H, CH_3), 4.18 (s, 1H, NH), 4.47 (s, 2H, CH_2), 6.70–7.80 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 20.4 (C-32, C–CH_3 of phenyl ring), 125.4–138.1 (18C, –Ar–C), 150.7 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.2 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{19}O_5N_3S_3$: C, 57.74 %; H, 3.41 %; N, 7.48 %. found: C, 57.78 %; H, 3.44 %; N, 7.45 %.

4-[3-(4-Methyl-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6d)*** Yield: 61 %; m.p. 268 °C (dec.); IR (KBr, cm^{-1}) : 1340 (C–N), 1568 (C=N), 1144 and 1334 (SO_2 sym and asym), 1668 (C=O), 600–800 (C–S), 3210 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, 752 cm^{-1} (Cl), ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (s, 1H, NH), 4.45 (s, 2H, CH_2), 6.77–7.88 (m, 15H, Ar–H), 8.12 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 20.8 (C-32, C-CH_3 of phenyl ring), 125.4–138.1 (18C, –Ar–C), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{19}O_5N_3S_3$: C, 57.74 %; H, 3.41 %; N, 7.48 %. found: C, 57.70 %; H, 3.37 %; N, 7.50 %.

4-[3-(2-Chloro-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6e)*** Yield: 59 %; m.p. 247 °C (dec.); IR (KBr, cm^{-1}) : 1328 (C–N), 1578 (C=N), 1140 and 1304 (SO_2 sym and asym), 1668 (C=O), 600–800 (C–S), 3200 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, 752 cm^{-1} (Cl), ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.14 (s, 1H, NH), 4.45 (s, 2H, CH_2), 6.70–7.88 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.4–138.1 (18C, –Ar–C), 132.6 (C-26, C–Cl of phenyl ring), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{16}O_5N_3S_3Cl$: C, 53.65; H, 3.41; N, 7.48; found: C, 53.77 %; H, 3.49 %; N, 7.39 %.

4-[3-(3-Chloro-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6f)*** Yield: 63 %; m.p. 260 °C (dec.); IR (KBr, cm^{-1}) : 1326 (C–N), 1588 (C=N), 1140 and 1304 (SO_2 sym and asym), 1670 (C=O), 600–800 (C–S), 3212 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, 752 cm^{-1} (Cl), ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.14 (s, 1H, NH), 4.45 (s, 2H, CH_2), 6.70–7.88 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.5–138.1 (18C, –Ar–C), 133.9 (C-27, C–Cl of phenyl ring), 150.7 and 103.2 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.2 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{16}O_5N_3S_3Cl$: C, 53.65; H, 3.41; N, 7.48; found: C, 53.71 %; H, 3.45 %; N, 7.49 %.

4-[3-(4-Chloro-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6g)*** Yield: 65 %; m.p. 278 °C (dec.); IR (KBr, cm^{-1}) : 1326 (C–N), 1588 (C=N), 1140 and 1304 (SO_2 sym and asym), 1670 (C=O), 600–800 (C–S), 3212 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 1H, NH), 4.40 (s, 2H,

CH_2), 6.77–7.80 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.4–138.1 (18C, –Ar–C), 137.2 (C-28, C–Cl of phenyl ring), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{27}H_{16}O_5N_3S_3Cl$: C, 53.65; H, 3.41; N, 7.48; found: C, 53.62 %; H, 3.43 %; N, 7.53 %.

4-[3-(2-Nitro-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6h)*** Yield: 74 %; m.p. 262 °C (dec.); IR (KBr, cm^{-1}) : 1326 (C–N), 1588 (C=N), 1140 and 1304 (SO_2 sym and asym), 1670 (C=O), 600–800 (C–S), 3212 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, 1036 and 1322 cm^{-1} (NO_2), ^1H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 1H, NH), 4.40 (s, 2H, CH_2), 6.77–7.80 (m, 15H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.4–138.1 (18C, –Ar–C), 147.2 (C-26, C–NO_2 of phenyl ring), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring, respectively, 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{26}H_{16}O_7N_4S_3$: C, 52.69; H, 2.77; N, 9.45; found: C, 52.62 %; H, 2.72 %; N, 9.41 %.

4-[3-(4-Nitro-benzoyl)-2,4-dioxo-thiazolidin-5-ylidenemethyl]-N-(4-phenyl-thiazol-2-yl)-benzenesulfonamide ***(6i)*** Yield: 69 %; m.p. 285 °C (dec.); IR (KBr, cm^{-1}) : 1326 (C–N), 1588 (C=N), 1140 and 1304 (SO_2 sym and asym), 1670 (C=O), 600–800 (C–S), 3212 cm^{-1} (–NH–), 3035–3060 cm^{-1} (–C–H) stretching of aromatic rings, 1036 and 1322 cm^{-1} (NO_2), ^1H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 1H, NH), 4.40 (s, 2H, CH_2), 6.77–7.80 (m, 14H, Ar–H), 8.10 (s, 1H, –NH); ^{13}C NMR (400 MHz, DMSO-d_6) δ 125.4–138.1 (18C, –Ar–C), 150.8 and 103.4 (C-7 and C-8, C of thiazole ring respectively, 151.8 (C-28, C-NO_2 of phenyl ring), 164.3 and 165.1 (C-24 and C-22, –C=O of thiazolidinone ring), 165.7 (C-31, –Ar.-thiazolidinone ring linkage), 173.2 (C-10, C–NH linkage of Ar-thiazole ring; Anal. Calcd. for $C_{26}H_{16}O_7N_4S_3$: C, 52.69; H, 2.77; N, 9.45; found: C, 52.60 %; H, 2.67 %; N, 9.34 %.

Result and discussion

Chemistry

All the reaction was carried out under conventional methods. 4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-*N*-(4-phenyl-thiazol-2-yl)-benzenesulfonamide **(5)** was key intermediate required to synthesized target product. Compound **1** was synthesized by refluxing acetophenone and thiourea. Two stretching bands in the range of 3,200–3,400 cm^{-1} in the FT-IR spectrum of compound **1** confirm the presence of an amino group. Compound **4** was synthesized in three steps and in the first step chloroacetic acid heated with thiourea at reflux temperature to give compound **2** with the removal of 1 mol of water molecule. In the second step, compound **2** was condensed with benzaldehyde in toluene and catalytic amount of piperidine to produce compound **3**. Upon chlorosulfonation of compound **3** in the last step using chlorosulfonic acid, compound **4** was yielded as confirmed by the IR spectrum. The IR spectrum of compound **4** shows stretching band at 1,144 and 1,334 cm^{-1} (symm and asym), respectively, confirms the presence of –SO_3H group. The IR spectra of compound **4** displayed stretching band at 3,335 cm^{-1} indicating the presence of secondary amino group. Compound **5** was produced by the condensation reaction between compounds **1** and **4** in the presence of pyridine and acetic anhydride and the correct synthesis is confirmed by the removal of –SO_3H band from the IR spectrum present in compound **4**. Compound **6** was synthesized by the reaction between various aniline and chloroacetyl chloride in the presence of benzene. Finally, compounds **5** and **6** on condensation in the presence of dimethylformamide gave a series of thiazolidinedione derivatives (**6a**–**6i**). The IR spectra of compounds **6a**–**6i** revealed stretching band at 1,328 and 1,548 cm^{-1}, respectively, confirm the presence of (C–N) and (C=N). Bands at 1,120 and 1,310 cm^{-1} indentified the presence of –SO_2 (sym and asym), while –C=O group demonstrated a sharp band at 1,685 cm^{-1}. The thiazolidinone ring was confirmed by the presence of characteristic –C–S stretching band at 600–800 cm^{-1}. The band at 3,198 cm^{-1} confirms the presence of –NH linkage in the compound. The ^1H NMR spectra of compounds **6a**–**6i** showed the signal at 4.02 ppm due to –NH linkage in the compound. A singlet peak was observed at 4.42 ppm due to the presence of –methylene proton in the compound, while an –NH of thiazolidinone showed peak at 8.10 ppm. All the remaining aromatic proton atoms revealed corresponding peak in the range of 6.64–7.80 ppm. ^{13}C NMR spectral assigned signals in the range between 164.3 and 165.1 due to presence of ketone (–C=O) functional group of thiazolidinone ring, 165.7 range confirmed the –C=O linkage of Ar-thiazolidinone ring, 150.8 and 103.4 ppm range indicates the presence of thiazole ring, 173.2 ppm indicates the presence of –NH linkage of Ar-thiazole ring, 147.2–151.8 range showed the presence of –C–NO_2 functional group, 132.6–137.2 range indicates the presence of –C–Cl group in the compound, 13.7–20.5 range showed the presence of –C–CH_3 group in the molecules, while remaining aromatic carbons resonated in the range of 125.4–138.1.

Antibacterial activity

The antimicrobial bioassay results presented in Table 2 revealed that some of the compounds showed excellent activity against all the mentioned bacteria. Final thiazolidinedione compounds **6d** and **6f** having electron-donating group (–Cl) at C-2 and C-4 positions, respectively, of the phenyl ring exhibited excellent activity (MIC, 6.25 μg/mL, 24 mm zone of inhibition) against Gram-positive bacteria *S. aureus*. Compound **6e** having electron-donating group (–Cl) at C-3 position of the phenyl ring was found half-fold active (MIC, 12.5 μg/mL) against *S. aureus* as compared to most active analogous **6d** and **6e** tested against the same strain. Compound **6i** having two electron-withdrawing group ($–NO_2$) at C-2 and C-4 position of the phenyl ring showed similar inhibitory concentration of 12.5 μg/mL against *S. aureus* with 1 mm lesser zone of inhibition (23 mm). Compound **6h** having electron-withdrawing group ($–NO_2$) at C-4 position was found half-fold active (MIC, 25 μg/mL) against *S. aureus* as compared to compound **6h**. Compound **6c** having electron-donating group ($–CH_3$) at C-4 position of phenyl ring exhibited good activity (MIC, 50 μg/mL, 22 mm zone of inhibition against *S. aureus*). Compound **6b** having electron-donating group ($–CH_3$) at C-3 position of the phenyl ring found half-fold active (MIC, 100 μg/mL) compared to compound **6b**. Final thiazolidinedione compounds **6d** and **6f** having electron-donating group (–Cl) at C-2 and C-4 positions, respectively, of the phenyl ring exhibited excellent activity (MIC, 6.25 μg/mL, 26-mm zone of inhibition) against Gram-positive bacteria *B. subtilis*. Compound **6i** having two electron-withdrawing group ($–NO_2$) at C-2 and C-4 position of the phenyl ring exhibited similar inhibitory concentrations at 6.25 μg/mL against Gram-positive bacteria *B. subtilis* with 4 mm lesser zone of inhibition (22 mm). Compound **6e** having electron-donating group (–Cl) at C-3 position and **6h** having electron-withdrawing group ($–NO_2$) at C-4 position of phenyl ring was found half-fold active (MIC, 12.5 μg/mL) against *B. subtilis* as compared to most active analogs **6d** and **6f** tested against the same strain. Compound **6c** having electron-donating group ($–CH_3$) at C-4 position of phenyl ring showed good activity (MIC, 50 μg/mL, 23-mm zone of inhibition) against *B. subtilis*. Compound **6b** having electron-donating group ($–CH_3$) at C-3 position of the phenyl ring found half-fold active (MIC, 100 μg/mL) as compared to compound **6b**.

Compound **6d** having electron-donating group (–Cl) at C-2 position of phenyl ring was found to contribute

Table 3 Antituberculosis activity of synthesized compounds

	MIC (μg/mL) *M. tuberculosis* (H37RV)
Compounds	MTCC 200
6a	125
6b	125
6c	250
6d	62.5
6e	62.5
6f	62.5
6g	1,000
6h	500
6i	1,000
Standard drugs	
Refampicin	40
Isoniazid	0.2

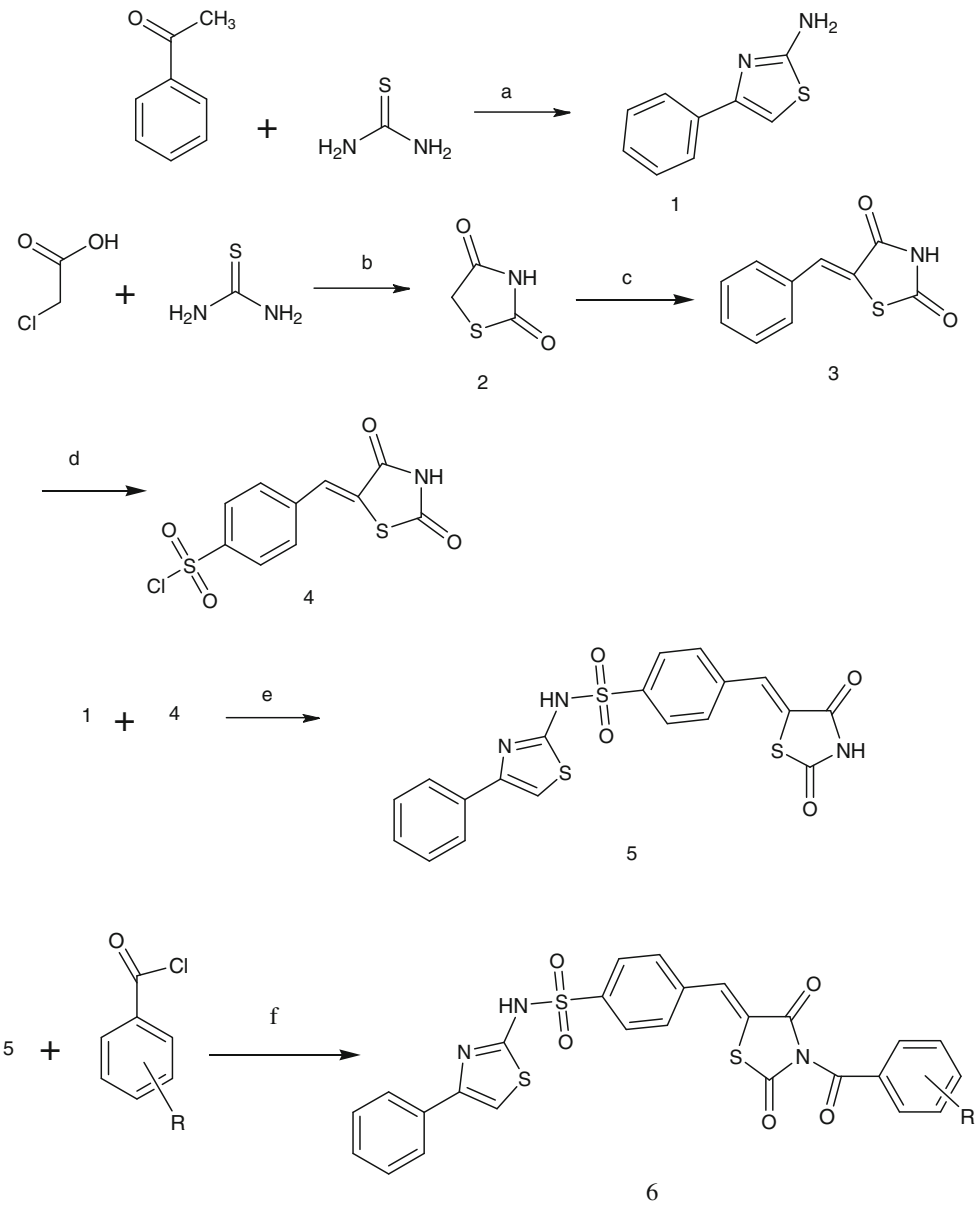
Table 2 Antibacterial activity of synthesized compounds

Comp. nos.	R	Gram negative		Gram positive	
		Zone of inhibition (MIC)		Zone of inhibition (MIC)	
		E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
6a	H	22 (62.5)	22 (62.5)	21 (62.5)	24 (25)
6b	3-CH_3	18 (100)	19 (100)	18 (100)	18 (100)
6c	4-CH_3	22 (50)	22 (50)	22 (50)	23 (50)
6d	2-Cl	**25 (12.5)**	**24 (12.5)**	**24 (6.25)**	**26 (6.25)**
6e	3-Cl	24 (25)	24 (25)	26 (12.5)	25 (12.5)
6f	4-Cl	23 (25)	22 (12.5)	**24 (6.25)**	**26 (6.25)**
6g	3-NO_2	22 (62.5)	22 (62.5)	21 (62.5)	24 (25)
6h	4-NO_2	24 (50)	24 (25)	25 (25)	24 (12.5)
6i	2,4-NO_2	24 (12.5)	22 (100)	23(12.5)	22 (6.25)
Ciprofloxacin (100 μg/disk)		30 (≤1)	31 (≤1)	32 (≤1)	33 (≤1)

The data outside of the bracket shows the zone of inhibition of compound and the data in parenthesis shows the MIC of compounds

The bold entries indicate the best compound of the series display inhibition at lowest minimum inhibition concentration

promising activity (MIC, 12.5 μg/mL, 25-mm zone of inhibition against *E. coli*). Compound **6i** having two electron-withdrawing group (–NO_2) at C-2 and C-4 positions of the phenyl ring exhibited similar inhibitory concentration of 12.5 μg/mL against *E. coli* with 1 mm lesser zone of inhibition (24 mm) than **6d**. Compound **6e** having electron-donating group (–Cl) at C-3 position and **6f** having electron-donating group (–Cl) at C-4 position of the phenyl ring was found half-fold active (MIC, 25 μg/mL) against *E. coli* as compared to most active analogs **6d** tested against the same strain. Compound **6c** having electron-donating group (–CH_3) at C-4 position and **6h** having electron-withdrawing group (–NO_2) at C-4 position of phenyl ring showed good activity (MIC, 50 μg/mL) against Gram-negative bacteria *E. coli* where **6b** having electron-donating group (–CH_3) at C-3 position of the phenyl ring found half-fold active (MIC, 100 μg/mL). Compound **6d** having electron-donating group (–Cl) at C-2 position of phenyl ring appeared with remarkable activity against Gram-negative bacteria *P. aeruginosa* at 12.5 μg/mL of MIC with 25-mm zone of inhibition. Compound **6f** having electron-donating group (–Cl) at C-4 position of the phenyl ring exhibited similar inhibitory concentration of 12.5 μg/mL against *P. aeruginosa* with 2 mm of lesser zone of inhibition (23 mm) than **6d** where the half-fold activity was observed (MIC, 25 μg/mL) for compound **6e** which having electron-donating group (–Cl) at C-3 position and **6h** having electron-withdrawing group (–NO_2) at C-4 position of phenyl ring against the same bacteria. Compound **6c** having electron-donating group (–CH_3) at C-4



Scheme 1 Synthesis of novel 2,4-thiazolidinedione derivatives reagents: *a* I_2, $NH_3{\cdot}H_2O$, reflux 4 h, 80–90 °C; *b* H_2O, Conc. HCl, reflux 8–10 h, 100–110 °C; *c* benzaldehyde, piperidine, toluene, reflux 1 h, 110 °C; *d* chlorosulfonicacid, reflux 1 h, 90–95 °C; *e* dry pyridine, acetic anhydride, reflux 2 h; *f* DMF, reflux 4 h

position showed good activity (MIC, 50 μg/mL), where compound **6b** having electron-donating group ($–CH_3$) at C-3 position and **6i** having two electron-withdrawing group ($–NO_2$) at C-2 and C-4 positions of the phenyl ring found to be half-fold active (MIC, 100 μg/mL) than **6c** against Gram-negative bacteria *P. aeruginosa.*

Antituberculosis activity

In vitro tuberculosis activities of compounds **6a–6i** were assessed against *M. tuberculosis* H37Rv. The results indicated that both thiazolidinedione analogs were active against mycobacteria. Preliminary antituberculosis screening results using BACTEC MGIT method revealed that final thiazolidinedione analogs **6d**, **6e**, and **6f** having electron-donating group at C-2, C-3, and C-4 positions of the phenyl ring displayed highest inhibition at a constant concentration level (62.5 μg/mL) against *M. tuberculosis* H37Rv (Table 3).

Conclusion

The results of study of mycobacterial analysis revealed that the synthesized compounds are promisingly significant and possesses good antibacterial and antituberculosis activity. We have synthesized some benzoyl chloride analogs combining with different substituted thiazole and thiazolidinedione derivative ring systems with a view to get a good antibacterial and antituberculosis agent with less toxic effects Some of the newly synthesized compound containing electron-donating group like mono-chloro on aryl ring **6d**, **6e**, and **6f** showed very good to excellent activity against both the Gram-positive as well as Gram-negative bacteria. Compounds **6h** and **6i** having nitro group as substituents on aryl ring also showed good activity against both bacterial strains (Gram positive and Gram negative). From the antituberculosis result, we found that compounds **6d**, **6e**, and **6f** having electron-donating group at C-2, C-3, and C-4 positions of the phenyl ring showed good antituberculosis activity. The –NH linkage in the compounds increases the activity of compounds. Screening results clearly indicates that compounds of the Scheme 1 exhibit good antimycobacterial activity. This is because of the presence of benzoyl chloride derivatives having electron-donating and electron-withdrawing groups and heterocyclic system attached to thiazole and thiazolidinedione nucleus. Hence, there is enough scope for further study in developing such compounds as a good lead activity. Most of the compounds have shown moderate to promising activity as compared to standard drug against all representative panels of bacterial strains. The compounds having benzoyl chloride derivatives as coupling components could be useful for derivatization to develop more effective antibacterial and antituberculosis agents.

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