Med Chem Res (2012) 21:2064–2071
DOI 10.1007/s00044-011-9730-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Syntheses and evaluation of 2,5-disubstituted 4-thiazolidinone analogues as antimicrobial agents

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Received: 3 March 2011 / Accepted: 21 June 2011 / Published online: 10 July 2011

Abstract Two novel series of 4-thiazolidinone derivatives, bearing 2-nitrophenyl imino and 4-nitrophenyl imino groups at position-2 and substituted arylidene groups at position-5, have been synthesized and evaluated for antimicrobial activity against four bacterial and one fungal strain. The success of the synthesis of compounds was confirmed on the basis of spectral analysis. All the newly synthesized compounds were obtained in high yields and exhibited good antibacterial activity; however, the antifungal potential was limited to a few agents.

Keywords 4-Thiazolidinones · Arylidene · Spectral analysis · Antimicrobial

Introduction

Diseases caused by microbial infections are very common worldwide. In the past few decades, the development of microbial resistance has led to an increase in the number and severity of infections. Hence, there is a continuous need to explore broad spectrum antimicrobials (Chugh, 2008). Structure–activity relationship between pharmacophore and heterocyclic backbone also need to be emphasized. Novel potent antimicrobial agents with different modes of action have to be developed so as to avoid problems of cross resistance (Williams, 1996; Khan *et al.*, 2005). Researchers across the world are synthesizing new drugs against pathogenic microorganisms. The 4-thiazolidinones are well-known heterocyclic compounds with tremendous structural as well as pharmacological importance. The wonder nucleus is well reputed for a spectrum of biological activities, such as antimicrobial (Ronad *et al.*, 2010; Omar *et al.*, 2010; Mehta *et al.*, 2006; Sattigeri *et al.*, 2005; Liu *et al.*, 2000; Sharma and Kumar, 2000), antitubercular (Kukukguzel *et al.*, 2002), anthelmintic (Choudhari *et al.*, 1995), anti-inflammatory (Goel *et al.*, 1999), etc. Some researchers have reported that 2-arylimino-4-thiazolidinone derivatives possess diverse pharmacological activities (Ottana *et al.*, 2005, 2007, 2009; Chavan and Rai, 2007; Vicini *et al.*, 2008; Geronikaki *et al.*, 2008). Halogenated and nitro substituents can affect the biological activity of the basic nucleus. Thus, an attempt was made to synthesize 2-substituted arylimino-5-substituted arylidene thiazolidine-4-one derivatives with 2-nitroimino and 4-nitroimino groups at position-2 and substituted arylidene groups at position-5 of 4-thiazolidinone, and evaluate them against bacterial and fungal strains.

Experimental section

General

Synthetic starting material, reagents, and solvents were procured from Aldrich, Himedia and SD Fine Chemicals. The reacting materials were used as received. Melting points were

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determined using open capillary method and are uncorrected. The λ_{max} were recorded on Shimadzu 1700 UV–Visible spectrophotometer. The infra red (IR) spectra were recorded on Shimadzu 8400S FTIR spectrophotometer using KBr pellet technique. ^{1}HNMR spectra were recorded on Bruker DRX-300 spectrophotometer using tetramethyl silane (TMS) as internal standard and DMSO-d_6 as solvent. Chemical shift (δ) values are reported in ppm. Splitting patterns were designated as follows: s(singlet), d(doublet); and m(multiplet). High-Resolution Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC spectrometer. Progress of the reactions was monitored by precoated TLC silica gel-G plates and spots were detected in iodine chamber.

Synthesis of 2-chloro-*N*-(substituted phenyl) acetamide (**2a** and **2b**)

Ice cold chloroacetyl chloride (0.46 mol) was added dropwise to substituted aniline (**1a** and **1b**) (0.2 mol) under anhydrous conditions till the addition was complete followed by stirring at room temperature for 4 h. The semi-solid residue was neutralized with sodium bicarbonate solution. The contents were filtered off and washed thoroughly with cold water. The crude mass was air dried and recrystallized from ethanol (Scheme 1).

Synthesis of 2-(substituted phenylimino) thiazolidin-4-one (**3** and **4**)

A solution of 0.10 mol 2-chloro-*N*-(substituted phenyl) acetamide and 0.20 mol of ammonium thiocyanate was refluxed in ethanol for 5 h and allowed to stand overnight. The precipitate was filtered, washed with water, and recrystallized from 1,4-dioxane (Vicini *et al.*, 2006).

*2-(2-Nitrophenylimino) thiazolidin-4-one (**3**)*

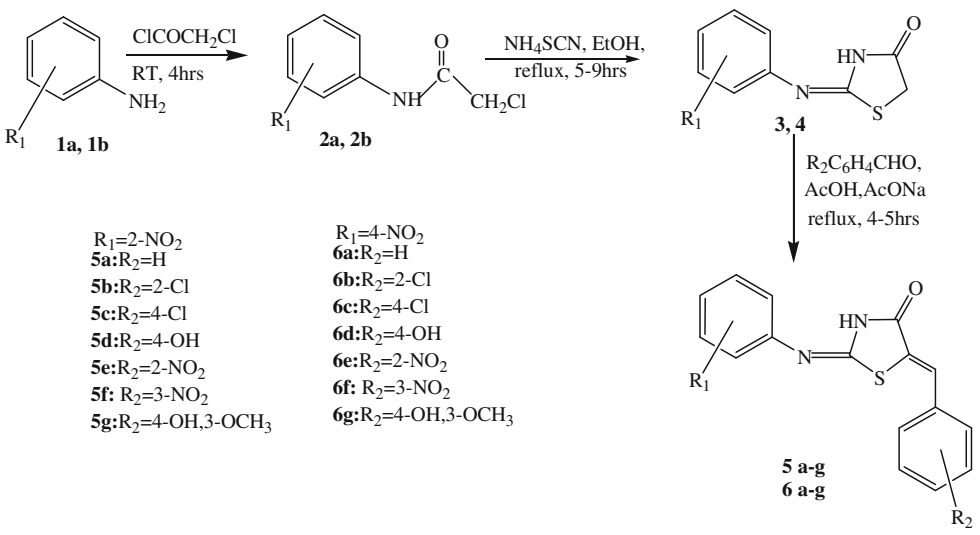
Bright shining orange crystals; Reaction time 4 h; yield 68%; mp 161–164°C (from dioxane); R_f value 0.87 (Ethyl acetate: Chloroform, 9:1); IR (KBr,cm^{-1}) *v*: –C=O: 1731; –NH stretch 3463; –NH– bend 1593; C=N 1639; C–N 1257; C–H stretch (aromatic) 3001; Ar–NO_2 1342(Sym), 1514(Asym); C–H bend (aromatic ortho substituted) 765; Mass: M+1 peak at 238.

*2-(4-Nitrophenylimino) thiazolidin-4-one (**4**)*

Yellowish orange crystals; Reaction time 5 h; yield 70%; mp 230–233°C (from dioxane); R_f value 0.72 (Ethyl acetate: Chloroform, 9:1); IR (KBr,cm^{-1}) *v*: –C=O: 1677; –NH stretch 3260; –NH– bend 1510; C=N 1643; C–N 1245; C–H stretch (aromatic) 2968; Ar–NO_2 1342(Sym), 1413(Asym); C–H bend (aromatic para substituted) 746; Mass: M+1 peak at 238.

General procedure for the synthesis of 2-(substituted phenylimino)-5-(substituted arylidene)-4-thiazolidinones (**5a–5g**; **6a–6g**)

0.004 mol of 2-(substituted phenylimino) thiazolidin-4-one (**3** and **4**) in 35 ml of acetic acid was stirred, followed by buffering with 0.008 mol sodium acetate. Knoevenagel reaction was carried out by addition of different aryl aldehydes (0.006 mol) and refluxing for different time periods till the completion of reaction. The reaction mixture was cooled to room temperature, and the precipitated solid was filtered, washed thoroughly with water, and recrystallized from dioxane (Vicini *et al.*, 2006).



Scheme 1 Synthetic route to the title compounds **5a–5g** and **6a–6g**

*2-(2-Nitrophenylimino-5-arylidene-4-thiazolidinone) (**5a**)*

Reaction time 4 h; yield 69%; Light Brown crystals; mp 238–240°C (from dioxane); R_f value: 0.69 (Toluene: Ethanol, 8:2); λ_{max} 285 nm; IR(KBr,cm^{-1}) *v*: C=O 1726; –NH– stretch 3423; –NH-bend 1593; –C–N 1251; C=N 1643; C–H stretch (aromatic) 300; C=C 1633; Ar–NO_2 1344 (Sym), 1519 (Asym); C–H bend (aromatic ortho) 761; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.74 (s, 1H, NH); 8.04 (d, 1H, $J = 8.1$ Hz, H-3); 7.51(s, 1H, CH); 7.73–7.64 (m, 2H, H-4 and 5); 7.30 (d, 1H, $J = 7.5$ Hz, H-6); 7.30-7.18 (m, 2H, H-2′ and 6′); 7.44–7.31 (m, 2H, H-3′ and 5′); 7.39 (m, 1H, $J = 7.2$ Hz, H-4′); HRMS calcd for $C_{16}H_{11}N_3O_3S$: 325.3418, found 326.0326.

*2-(2-Nitrophenylimino)-5-(2-chlorobenzylidene)-4-thiazolidinone (**5b**)*

Reaction time 9 h; yield 65%; Rust colored crystals; mp 242–247°C (from dioxane); R_f value: 0.69 (Toluene: Ethanol, 8:2); λ_{max} 331 nm; IR (KBr,cm^{-1}) *v*: –C=O 1720; –NH stretch 3423; NH bend 1562; C=N 1658; –C–N 1253; C=C 1643; Ar–NO_2 1342 (Sym), 1517 (Asym); Ar–Cl 1041; C–H bend (aromatic ortho) 761, 779; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.9 (s, 1H, NH); 8.04 (d, 1H, $J = 8.1$ Hz, H-3); 7.85 (s, 1H, CH); 7.72–7.60 (m, 2H, H-4 and 5); 7.97 (d, 1H, $J = 7.8$ Hz, H-6); 7.28 (d, 1H, J = 7.8 Hz, H-3′); 7.61–7.46 (m, 2H, H-4′ and 5′); 7.17 (d, 1H, $J = 7.5$ Hz, H-6′). HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.7869, found 360.2831.

*2-(2-Nitrophenylimino)-5-(4-chlorobenzylidene)-4-thiazolidinone (**5c**)*

Reaction time 8 h; yield 69%; Buff colored powder; mp 205–210°C (from dioxane); R_f value: 0.84 (Toluene: Ethanol, 8:2); λ_{max} 285 nm; IR (KBr,cm^{-1}) *v*: –C=O 1722; –NH stretch 3450; –C–N 1255; C–H stretch (aromatic) 2997; C=C 1643; Ar–NO_2 1344 (Sym), 1519 (Asym); Ar–Cl 1057; C–H bend (aromatic ortho) 757; C–H bend (aromatic para) 800; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.79 (s, 1H, NH); 8.04 (d, 1H, $J = 8.1$ Hz, H-3); 7.54 (s, 1H, CH); 7.97–7.67 (m, 2H, $J = 7.5$ Hz, H-4 and 5); 7.97 (d, 1H, $J = 8.1$ Hz, H-6); 7.40–7.38 (m, 2H, H-2′ and 6′); 7.35–7.16 (m, 2H, H-3′ and 4′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.7869, found 360.0325.

*2-(2-Nitrophenylimino)-5-(4-hydroxybenzylidene)-4-thiazolidinone (**5d**)*

Reaction time 8.5 h; yield 72%; Brown colored crystals; mp 210–215°C (from dioxane); R_f value: 0.67 (Toluene: Ethanol, 8:2); λ_{max} 280 nm; IR (KBr,cm^{-1}) *v*: –C=O 1703; –NH stretch 3338; –C–N 1276; C=N 1600; C–H stretch (aromatic) 3026; C=C 1656; Ar–NO_2 1342 (Sym), 1514 (Asym); Ar–OH 3326 (Broad band); C–H bend (aromatic ortho) 765; C–H bend (aromatic para) 805; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.34 (s, 1H, NH); 8.01 (d, 1H, H-3); 7.59 (s, 1H, CH); 7.81–7.67 (m, 3H, H-4, 5, 6); 7.37–7.19 (m, 2H, H-2′ and 6′); 7.17–6.85 (m, 2H, H-3′ and 5′); 10.18 (s, OH); HRMS calcd for $C_{16}H_{11}N_3O_4S$: 341.3412, found 342.0561.

*2-(2-Nitrophenylimino)-5-(2-nitrobenzylidene)-4-thiazolidinone (**5e**)*

Reaction time 9 h; yield 60%; Light Brown crystals; mp 230–235°C (from dioxane); R_f value: 0.81 (Toluene: Ethanol 8:2); λ_{max} 284 nm; IR (KBr,cm^{-1}) *v*: –C=O 1726; –NH stretch 3415; –C–N 1257; C=N 1600; C–H stretch (aromatic) 3001; C=C 1643; Ar–NO_2 1342 (Sym), 1514 (Asym); C–H bend (aromatic ortho) 763, 801; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.88 (s, 1H, NH); 8.16 (d, 1H, $J = 8.1$ Hz H-3); 8.15–7.95 (m, 2H, H-4 and 5); 8.01 (d, 1H, $J = 8.1$ Hz, H-6); 7.92 (s, 1H, CH); 7.25 (d, 1H, $J = 7.8$ Hz, H-3′); 7.71–7.61 (m, 2H, H-4′ and 5′); 7.79 (d, 1H, $J = 7.5$ Hz, H-6′); HRMS calcd for $C_{16}H_{10}N_4O_5S$: 370.3394, found 371.0268.

*2-(2-Nitrophenylimino)-5-(3-nitrobenzylidene)-4-thiazolidinone (**5f**)*

Reaction time 9 h; yield 63%; Light Orange colored powder crystals; mp 230–235°C (from dioxane); R_f value: 0.71 (Toluene: Ethanol, 8:2); λ_{max} 284 nm; IR (KBr,cm^{-1}) *v*: –C=O 1726; NH stretch 3452; –C–N 1253; C=N 1600; C–H stretch (aromatic) 3060; C=C 1665; Ar–NO_2 1350 (Sym), 1519 (Asym); C–H bend (aromatic ortho) 745, C–H bend (aromatic meta) 795, 821; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.91 (s, 1H, NH); 8.24 (d, 1H, $J = 7.8$ Hz, H-3); 7.78–7.73 (m, 2H, H-4 and 5); 8.05 (d, 1H, $J = 7.5$ Hz, H-6); 7.88 (s, 1H, CH); 8.39 (s, 1H, H-2′); 7.93 (d, 1H, $J = 7.5$ Hz, H-4′); 7.42 (t, 1H, $J = 7.8$ Hz, H-5′); 7.32 (d, 1H, $J = 7.5$ Hz, H-6′); HRMS calcd for $C_{16}H_{10}N_4O_5S$: 370.3394, found 371.2654.

*2-(2-nitrophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)-4-thiazolidinone (**5g**)*

Reaction time 10 h; yield 63%; mustard colored crystals; mp 245–250°C (from dioxane); R_f value: 0.73 (Toluene: Ethanol, 8:2); λ_{max} 283 nm; IR (KBr,cm^{-1}) *v*: –C=O 1726; NH stretch 3452; –C–N 1253; C=N 1600; C–H stretch (aromatic) 3060; C=C 1665; Ar–NO_2 1342 (Sym), 1514 (Asym); Ar–OH 3452 (Broad band); C–H bend (aromatic

ortho) 765; C–H bend (aromatic meta) 821 and 871, C–H bend (aromatic para) 805; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.12 (s, 1H, NH); 7.83 (d, 1H, $J = 3.9$ Hz, H-3); 8.30–8.01(m, 3H, H-4, 5 and 6); 7.25(s, 1H, CH); 6.93 (s, 1H, H-2); 7.43–7.39 (m, 2H, H-5′ and 6′); 9.85 (s, OH), 4.009 (s, 3H, OCH_3); HRMS calcd for $C_{17}H_{13}N_3O_5S$: 371.3672, found 372.1055.

*2-(4-Nitrophenylimino-5-arylidene-4-thiazolidinone) (**6a**)*

Reaction time 7 h; yield 72%; Light Brown crystals; mp 280–283°C (from dioxane); R_f value: 0.72 (Toluene: Ethanol, 8:2); λ_{max} 285 nm; IR(KBr,cm^{-1}) *v*: –C=O 1665; –NH stretch 3269; –NH bend 1565; –C–N 1244; C=N 1631; C–H stretch (aromatic) 3016; C=C 1631; Ar–NO_2 1342 (Sym), 1519 (Asym); C–H bend (aromatic para) 748; ^{1}HNMR (DMSO-d_6, 300 MHz): (δ, ppm): 12.74 (s, 1H, NH); 7.40 (d, 1H, $J = 8.1$ Hz, H-2); 7.95 (d, 1H, $J = 6.9$ Hz, H-3); 7.45–7.40 (m, 2H, H-5 and 6); 7.51 (s, 1H, CH); 7.18–7.15 (m, 2H, H-2′ and 6′); 7.76–7.71 (m, 3H, H-4′, 3′ and 5′); HRMS calcd for $C_{16}H_{11}N_3O_3S$: 325.3418, found 326.0695.

*2-(4-Nitrophenylimino)-5-(2-chlorobenzylidene)-4-thiazolidinone (**6b**)*

Reaction time 7 h; yield 65%; Light Rust (Coffee) colored crystals; mp 250–255°C (from dioxane); R_f value: 0.69 (Toluene: Ethanol, 8:2); λ_{max} 255 nm; IR (KBr,cm^{-1}) *v*: –C=O 1665; NH stretch 3270; –C–N 1244; C=N 1631; C–H stretch (aromatic) 3014; C=C 1631; Ar–NO_2 1342 (Sym), 1517 (Asym); Ar–Cl 1114; C–H bend (aromatic ortho) 748, C–H bend (aromatic para) 794; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.90, (s, 1H, NH); 7.46, (s, 1H, H-2); 8.04 (d, 1H, $J = 8.1$ Hz, H-3); 7.72–7.96 (m, 2H, H-5 and 6); 7.86(s, 1H, CH); 7.71–7.29 (d, 2H, H-3′ and 6′); 7.43 (t, 2H, $J = 9.6$ Hz, H-4′ and 5′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.7869, found 360.5326.

*2-(4-Nitrophenylimino)-5-(4-chlorobenzylidene)-4-thiazolidinone (**6c**)*

Reaction time 8 h; yield 69%; Light yellow crystals; mp 245–250°C (from dioxane); R_f value: 0.85 (Toluene: Ethanol, 8:2); λ_{max} 254 nm; IR (KBr,cm^{-1}) *v*: –C=O 1665; –NH stretch 3274; –C–N 1244; C=N 1565; C–H stretch (aromatic) 3018; C=C 1643; Ar–NO_2 1344 (Sym), 1517 (Asym); Ar–Cl 1114; C–H bend (aromatic para) 817 and 854; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.79 (s, 1H, NH); 7.71 (s, 1H, H-2); 8.04 (d, 1H, $J = 8.1$ Hz, H-3); 7.40 (t, 1H, $J = 7.5$ Hz, H-5); 7.30 (d, 1H, $J = 7.8$ Hz, H-6); 7.54 (s, 1H, CH); 7.31–7.16 (m, 2H, H-2′ and 6′); 7.96–7.71 (d, 2H, H-3′ and 5′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.7869, found 360.0356.

*2-(4-nitrophenylimino)-5-(4-hydroxybenzylidene)-4-thiazolidinone (**6d**)*

Reaction time 8 h; yield 72%; Light yellow crystals; mp >320°C (from dioxane); R_f value: 0.70 (Toluene: Ethanol, 8:2); λ_{max} 254 nm; IR (KBr,cm^{-1}) *v*: –C=O 1665; NH stretch 3272; –C–N 1244; C=N 1565; C–H stretch (aromatic) 3014; C=C 1631; Ar–NO_2 1340 (Sym), 1517 (Asym); Ar–OH 3413 (Broad band); C–H bend (aromatic para) 794 and 856; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.34 (s, 1H, NH); 7.38 (s, 1H, H-2); 8.03–7.77 (m, 3H, H-3,5,6); 7.60(s, 1H, CH); 7.38–7.17 (m, 2H, H-2′ and 6′); 7.71–7.59 (m, 2H, H-3′ and 5′); 10.18 (s, OH); HRMS calcd for $C_{16}H_{11}N_3O_4S$: 341.3412, found 342.0532.

*2-(4-nitrophenylimino)-5-(2-nitrobenzylidene)-4-thiazolidinone (**6e**)*

Reaction time 9 h; yield 60%; Light Brown crystals; mp 250–252°C (from dioxane); R_f value: 0.76 (Toluene: Ethanol, 8:2); λ_{max} 255 nm; IR (KBr,cm^{-1}) *v*: –C=O 1677; NH– stretch 3278; –C–N 1244; C=N 1599; C–H stretch (aromatic) 2983; C=C 1643; Ar–NO_2 1385(Sym), 1510 (Asym); C–H bend (aromatic ortho) 745, C–H bend (aromatic para) 800; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.88 (s,1H, NH); 7.96 (s, 1H, H-2); 8.16 (d, 1H, $J = 8.1$ Hz, H-3); 7.80 (t, 1H, $J = 7.2$ Hz, H-5); 7.26 (d, 1H, $J = 7.8$ Hz, H-6); 7.92 (s, 1H, CH); 8.01 (d, 1H, $J = 8.01$ Hz, H-3′); 7.80 (t, 1H, $J = 7.2$ Hz, H-4′); 7.69 (t, 1H, $J = 7.8$ Hz, H-5′); 7.26 (d, 1H, $J = 7.8$ Hz, H-6′); HRMS calcd for $C_{16}H_{10}N_4O_5S$: 370.3394, found 371.0649.

*2-(4-Nitrophenylimino)-5-(3-nitrobenzylidene)-4-thiazolidinone (**6f**)*

Reaction time 9 h; yield 63%; Light Brown (clay) colored crystals; mp >310°C (from dioxane); R_f value: 0.80 (Toluene: Ethanol, 8:2); λ_{max} 255 nm; IR (KBr,cm^{-1}) *v*: –C=O 1677; NH stretch 3278; –C–N 1242; C=N 1596; C–H stretch (aromatic) 2945; C=C 1643; Ar–NO_2 1344 (Sym), 1514 (Asym); C–H bend (aromatic para) 748, C–H bend (aromatic meta) 808, 845; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.91 (s, 1H, NH); 8.39 (s, 1H, H-2); 8.24 (d, 1H, $J = 7.8$ Hz, H-3); 7.75 (t, 1H, $J = 6.6$ Hz, H-5); 7.32 (d, 1H, $J = 7.5$ Hz, H-6); 7.88 (s, 1H, CH); 8.39 (s, 1H, H-2′); 8.05 (d, 1H, $J = 7.5$ Hz, H-4′); 7.42 (t, 1H, $J = 7.8$ Hz, H-5′); 7.93 (d, 1H, $J = 7.5$ Hz, H-6′); HRMS calcd for $C_{16}H_{10}N_4O_5S$: 370.3394, found 371.3654.

*2-(4-Nitrophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)-4-thiazolidinone (**6g**)*

Reaction time 10 h; yield 63%; mustard colored crystals; mp 270–275°C (from dioxane); R_f value: 0.78 (Toluene: Ethanol, 8:2); λ_{max} 254 nm; IR (KBr,cm^{-1}) *v*: –C=O 1665; NH stretch 3271; –C–N 1244; C=N 1565; C–H stretch (aromatic) 3016; C=C 1631; Ar–NO_2 1340 (Sym), 1517 (Asym); Ar–OH 3423 (Broad band); C–H bend (aromatic ortho) 745; C–H bend (aromatic meta) 856 and 871, C–H bend (aromatic para) 795; ^{1}HNMR (DMSO-d_6, 300 MHz) (δ, ppm): 12.00 (s, 1H, NH); 7.48 (s, 1H, H-2); 7.40–6.91(m, 3H, H-3, 5 and 6); 7.82 (s, 1H, CH); 7.67 (s, 1H, H-2′); 7.58 (m, 2H, H = 5′ and 6′); 9.85 (s, OH), 4.066 (s, 3H, OCH_3); HRMS calcd for $C_{17}H_{13}N_3O_5S$: 371.3672, found 372.3265.

Microbiological studies

Antimicrobial assay of the synthesized compounds was carried out using standard cup plate method (Indian Pharmacopoeia 1996). Twenty-four-hour-old subcultures were used. *Bacillus subtilis* and *Staphylococcus aureus* were used as Gram positive bacterial strains whereas *Escherichia coli* and *Pseudomonas aeruginosa* served as Gram negative strains. One fungal strain viz. *Candida albicans* was chosen for the activity. Ciprofloxacin and fluconazole (100 μg/ml) were taken as standard drugs for antibacterial and antifungal activities, respectively. Pure strains were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The compounds were dissolved in 8% v/v dimethyl sulfoxide and dilutions were made as 50, 100, 200, and

Table 1 Antimicrobial activity of the synthesised compounds (**5a–5g**)

Compound code	Conc. (μg/ml)	Zone of Inhibition (mm) ($n = 3$)				
		Gram +ve bacteria		Gram-ve bacteria		Fungus
		SA	BS	PA	EC	CA
5a	50	10	8	6	7	10
	100	11	10	6	8	11
	200	12	11	8	10	13
	300	15	13	10	12	18
5b	50	11	11	8	9	10
	100	12	13	10	10	16
	200	14	15	12	10	18
	300	15	18	15	12	19
5c	50	14	13	14	10	–
	100	15	14	15	11	–
	200	16	15	17	11	–
	300	18	16	18	11	–
5d	50	10	10	–	–	–
	100	10	10	–	–	–
	200	10	10	–	–	–
	300	11	11	–	–	–
5e	50	10	9	10	8	10
	100	10	9	10	8	16
	200	13	10	13	10	23
	300	14	10	13	11	26
5f	50	8	7	10	10	10
	100	10	15	11	8	12
	200	14	20	15	13	14
	300	16	22	16	15	16
5g	50	7	8	–	–	–
	100	8	8	–	–	–
	200	8	10	–	–	–
	300	8	12	–	–	–
Ciprofloxacin	100	16	27	18	15	–
Fluconazole	100	–	–	–	–	35
Control (8%v/v DMSO)	–	–	–	–	–	–

– no measurable zone of inhibition

Table 2 Antimicrobial activity of the synthesised compounds (**6a–6g**)

Compound code	Conc. (μg/ml)	Zone of Inhibition (mm) ($n = 3$)				
		Gram +ve bacteria		Gram −ve bacteria		Fungus
		SA	BS	PA	EC	CA
6a	50	12	11	10	11	–
	100	13	12	10	12	–
	200	14	13	11	13	–
	300	16	15	13	15	–
6b	50	15	13	13	13	–
	100	16	14	14	14	–
	200	17	15	16	15	–
	300	19	17	17	16	–
6c	50	13	15	11	15	–
	100	14	16	12	16	–
	200	15	17	13	16	–
	300	17	18	14	18	–
6d	50	11	11	10	11	–
	100	12	12	11	12	–
	200	13	14	11	13	–
	300	15	15	12	15	–
6e	50	11	11	10	11	–
	100	15	12	11	11	–
	200	16	13	12	12	–
	300	17	15	12	12	–
6f	50	11	11	10	11	–
	100	15	12	11	11	–
	200	16	13	12	12	–
	300	17	15	12	12	–
6g	50	14	11	14	11	–
	100	15	12	15	12	–
	200	16	14	15	12	–
	300	17	15	17	13	–
Ciprofloxacin	100	19	22	28	18	–
Fluconazole	100	–	–	–	–	35
Control (8%v/v DMSO)	–	–	–	–	–	–

– no measurable zone of inhibition

300 μg/ml. An 8% v/v solution of dimethyl sulfoxide was used as control. In all determinations, tests were performed in triplicates, and the results were taken as mean of the three findings. The diameters of the circular zones of inhibition were measured and are reported in the Tables 1 and 2.

Results and discussion

Synthesis

In the present study, two series of 2,5-disubstituted 4-thiazolidinone (**5a–5g** and **6a–6g**) derivatives were synthesized in an attempt to find new candidates for antimicrobial activity. The synthetic pathway leading to the title compounds is given in Scheme 1. The title compounds were synthesized through a three-step reaction starting from chloroacetylation of 2-nitro and 4-nitro aniline (**1a** and **1b)** to give 2-chloro-*N*-(substituted phenyl) acetamides (**2a** and **2b**). Intermediate acetamides were heterocyclized with ammonium thiocyanate to yield 2-(substituted phenylimino) thiazolidin-4-one (**3** and **4**). The title compounds were obtained by condensing **3** and **4** with various aryl aldehydes through Knoevenagel reaction. Compounds were characterized by physicochemical and spectral techniques (UV, IR, ^{1}HNMR and Mass).

UV spectra of the synthesized compounds showed characteristic K bands arising due to C=N chromophoric group at 267–347 nm justifying the bathochromic shift attributable to nitro and chloro groups. The peaks observed

in IR spectra (cm^{-1}) of lactam NH at 3200, 1550, C=O at 1670 and C=C at 1633 agreed with the structures. Synthesized compounds can exist as potential E and Z geometrical isomers; 5-exocyclic C=C was assigned Z configuration on the basis of NMR spectra. The methine proton deshielded by adjacent C=O was detected at 7.70–7.75 in ^{1}HNMR spectra as observed for analogous arylidene 2,4 thiazolidinedione (Bruno *et al.*, 2002). Owing to less deshielding effect of 1-S, such protons resonate at a lower chemical shift value and were assigned E configuration (Momose *et al.*, 1991). In ^{1}HNMR spectra, NH proton observed at 11.8–12.7 ppm shows substitution at 2nd position instead of 3rd position, which indicates a lactam proton, since imine proton appears at much higher field (Ispida *et al.*, 1990). The presence of M^++1 peaks with 100% abundance in HRMS (high-resolution mass spectrometry) further confirmed the synthesis and purity of compounds.

Antimicrobial activity

All the compounds were screened for in vitro antimicrobial activity against two Gram positive bacteria viz. *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96), two Gram negative bacteria viz. *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 2453), and one fungal strain viz. *Candida albicans* (MTCC 227) using cup plate method (Indian Pharmacopoeia 1996). Compounds were used at concentrations of 50, 100, 200, and 300 μg/ml. The derivatives showed significant activity against the chosen bacteria with more pronounced activity against the Gram positive strains. Compounds **5a**, **5b**, **5e,** and **5f** also showed remarkable activity against *Candida albicans*. The activity of the derivatives was found to be concentration dependent (Tables 1, 2). A close look at the results revealed that compounds bearing 4-nitrophenylimino group at position-2 were more active against bacterial strains, whereas those bearing 2-nitrophenylimino group at position-2 showed activity against *Candida albicans,* in addition to their antibacterial activity. Compounds bearing 5-arylidene moeity either as such or as substituted with 2-chloro, 2-nitro, and 3-nitro groups were found to be active against the selected fungus.

Conclusion

In the present study, two series of novel 4-thiazolidinone derivatives were designed and synthesized. Their structures were characterized by UV, IR, Mass and ^{1}HNMR spectroscopy. The novel compounds were evaluated for antimicrobial activity. The activity of the derivatives was more pronounced against Gram positive organisms than Gram negative organisms. Some of the compounds among 2-nitro imino series (**5a**–**5g**) showed activity against *Candida albicans*. Thus, 4-thiazolidinone analogues exhibit promising antimicrobial activity which could lead to discovery of some promising agents.

Acknowledgments The authors are thankful to Central Drug Research Institute, Lucknow, India for the library facility and spectral characterization.

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