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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Effect of chloro and fluoro groups on the antimicrobial activity of 2,5-disubstituted 4-thiazolidinones: a comparative study

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**Abstract** The article reports the synthesis of a series comprising of twenty-one 2,5-disubstituted-4-thiazolidinone derivatives, bearing 3-chloro-4-fluorophenyl imino, 4-chlorophenyl imino and 3-chlorophenyl imino groups at position-2 and substituted arylidene groups at position-5. The title compounds were obtained in high yields through Knoevenagel condensation and evaluated for antimicrobial activity against *B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*, and *C. albicans*. Success of the synthesis was confirmed through spectral analysis. The newly synthesized compounds exhibited promising antibacterial activity but no antifungal activity. SAR studies revealed that the presence of a fluoro group in addition to a chloro group had a marked influence on the antibacterial activity.

**Keywords** 4-Thiazolidinones · Arylidene · Spectral analysis · Imino · Knoevenagel condensation · Antimicrobial

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## Introduction

Medicinal chemistry involves the discovery of new chemical entities for the treatment of disease and systematic study of SARs of these compounds. Such studies provide the basis of development of better medicinal agents from lead compounds (Fries, 2008). The nature of these compounds is largely synthetic with some compounds being natural or semi-synthetic. Among the synthetic compounds, only a few qualify to be a "drug." It is an established fact that one drug out of three is a halogenated derivative and halogens are found in drugs belonging to practically all therapeutic classes (Wermuth, 2003). Halogen groups impart different effects on physicochemical and pharmacological activities of drugs.

Antibiotics belong to one of the most prescribed classes of drugs. However, their misuse and evolutionary pressures have led to growing incidences of drug resistant pathogens (Prescott, 2007). This coupled with a decreased pace of discovery of anti-infective agents has aggravated the problem. Thus, there is an urgent need to develop new pharmacophores which not only offer a broad spectrum of activity but also possess a different mechanism of action so as to avoid cross resistance (Chugh, 2008; Williams, 1996).

Heterocyclic compounds present themselves as a group with a plethora of varying biological activities. 4-thiazolidinones are moieties which possess innumerable activities like antimicrobial (Bondock, 2006, 2007; Bonde and Gaikwad 2004; Kavitha *et al.*, 2006; Ronad *et al.*, 2010; Omar *et al.*, 2010; Vicini *et al.*, 2008); anti-convulsant (Shingalapur *et al.*, 2010); anti-diabetic (Faidallah *et al.*, 2011); anti-HIV(Rawal *et al.*, 2005, 2007); cardio-protective (Ozaki and Ohi, 1999); tumor necrosis factor-α antagonist activities (Voss *et al.*, 2003); $Ca^{2+}$ channel blocker (Kato *et al.*, 1999; Hara *et al.*, 1999) and the list is ever

increasing. Various substitutions at this nucleus are possible but greatest difference occurs after making changes at 2 and 5-positions. Compounds with 2-imino-5-arylidene substitutions have been reported to possess various biological activities like anti-inflammatory (Ottana *et al.*, 2005); antimicrobial (Chavan and Rai, 2007); anti-diabetic (Maccari *et al.*, 2011); and anti-arthritic (Ottana *et al.*, 2007). In continuation of the study (Chawla *et al.*, 2011), new substitutions on the imino groups at position-2 and the arylidene ring at position-5 were explored and the synthesized compounds were screened for antimicrobial activity.

## Experimental section

### General

The chemicals and solvents were purchased from Aldrich, Himedia, and SD Fine Chemicals and were used as received. Melting range were determined using open capillary method and are uncorrected. $\lambda_{max}$ were determined using Shimadzu 1700 UV–Visible spectrophotometer. The infra red (IR) spectra were recorded using KBr pellet technique on Shimadzu 8400S FTIR spectrophotometer. $^1$HNMR spectra were obtained on Bruker DRX-300 spectrophotometer using tetramethyl silane (TMS) as internal standard and DMSO-$d_6$ as solvent. Chemical shift ($\delta$) values are reported in ppm. High resolution mass spectra (HRMS) were recorded on JEOL-Accu TOF JMS-T100LC spectrometer. Precoated TLC silica gel-G plates were used for monitoring the progress of reactions.

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

Previously cooled chloro-acetyl chloride (0.46 mol) was added drop-wise to various anilines (**1a**, **1b**, and **1c**) (0.2 mol) under anhydrous conditions. The reaction mixture was stirred at room temperature for 4 h. The residue was neutralized with sodium bicarbonate solution. The contents were filtered off and washed thoroughly with cold water and re-crystallized from ethanol (Scheme 1).

### Synthesis of 2-(substituted phenylimino) thiazolidin-4-one (**3, 4** and **5**)

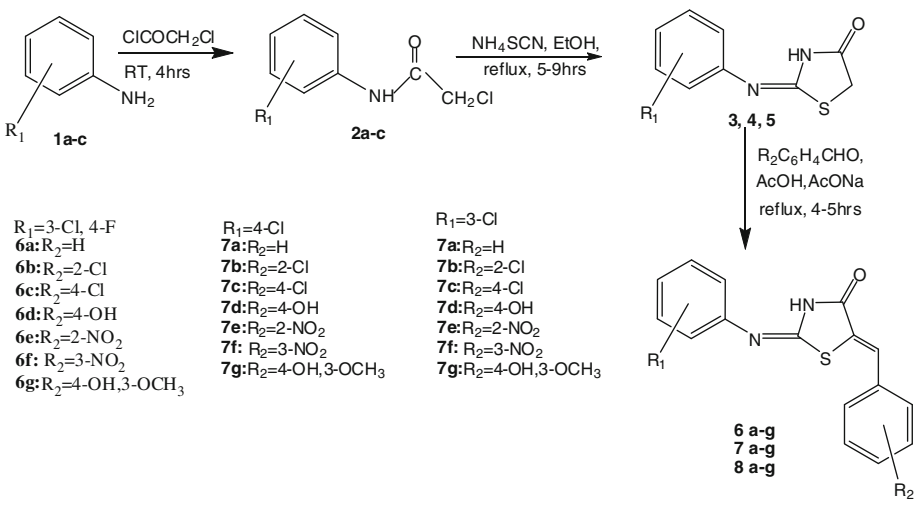
2-chloro-*N*-(substituted phenyl) acetamide (**2a, 2b**, and **2c**) (0.10 mol) was refluxed with ammonium thiocyanate (0.20 mol) for 5–6 h using ethanol as solvent. The reaction mixture was allowed to stand overnight. The contents were filtered off, washed with water, and recrystallized from 1,4-dioxane (Vicini *et al.*, 2006).

#### *2-(3-chloro-4-fluorophenylimino) thiazolidin-4-one (**3**)*

Reaction time 5 h; yield 60%; mp 212–215°C (from dioxane); $R_f$ value 0.72 (Ethyl acetate:chloroform 9:1); IR (KBr) ($\nu$ cm$^{-1}$): –C=O: 1701, –NH– stretch 3400, –NH– bend 1641, C=N 1618, C–N 1248, C–H stretch (aromatic) 2922, C–H bend (aromatic para substituted) 860, C–H bend (aromatic meta substituted) 650, 800, $CH_2$ 1438, Ar–Cl 1060, Ar–F 1191; Mass: M + 1 peak at 245; calculated $C_9H_6ClFN_2OS$ C 44.18, H 2.47, N 11.45.

#### *2-(4-chlorophenylimino) thiazolidin-4-one (**4**)*

Reaction time 5 h; yield 65%; mp 200–203°C (from dioxane); $R_f$ value: 0.81 (Ethyl acetate:Chloroform 9:1); IR (KBr) ($\nu$ cm$^{-1}$): –C=O: 1733; –NH– stretch: 3413; –NH– bend: 1598; C=N: 1637; C–N: 1257; C–H stretch (aromatic): 2921; C–H bend (aromatic para substituted): 862; $CH_2$: 1465 Ar–Cl: 1150; Mass**:** M + 1 peak at 227; calculated $C_9H_7ClN_2OS$ C 47.69, H 3.11, N 12.36.




**Scheme 1** Synthetic route to the title compounds **6a–g**, **7a–g**, and **8a–g**

*2-(3-chlorophenylimino) thiazolidin-4-one (**5**)*

Reaction time 5.5 h; yield 60%; mp 201–208°C (from dioxane); $R_f$ value: 0.74 (Ethyl acetate:Chloroform 9:1); IR (KBr) ($\nu$ $cm^{-1}$): –C=O: 1701; –NH– stretch 3409; –NH– bend 1573; –C–N 1247; C=N 1612; C–H stretch (aromatic) 3062; $CH_2$: 1446 Ar–Cl 1095; C–H bend meta (aromatic) 775, 867; Mass: M + 1 peak at 227; calculated $C_9H_7ClN_2OS$ C 47.69, H 3.11, N 12.36.

General procedure for the synthesis of 2-(substituted phenylimino)-5-(substituted arylidene)-4-thiazolidinones (**6a**–**6g**; **7a**–**7g** and **8a**–**8g**)

2-(substituted phenylimino) thiazolidin-4-one (**3**, **4** and **5**) (0.004 mol) was stirred in acetic acid (35 ml) in the presence of sodium acetate (0.008 mol). Different aryl aldehydes (0.006 mol) were added and the mixture was refluxed for different time periods till the completion of reaction through Knoevenagel reaction. Precipitates were obtained after cooling the reaction mixture to room temperature and subsequently filtered, washed thoroughly with water. 1,4-dioxane was used as solvent for recrystallization from (Vicini *et al.*, 2006).

*2-(3-chloro-4-fluorophenylimino-5-arylidene-4-thiazolidinone) (**6a**)*

Reaction time 4 h; yield 62%; Light Brown crystals; mp 208–210°C (from dioxane); $R_f$ value: 0.69 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 278 nm; IR(KBr,$cm^{-1}$) $\nu$: –C=O 1674; –NH– stretch 3419; –NH-bend 1550; –C–N 1244; C=N 1630; stretch (aromatic) 3001; C=C 1633; Ar–Cl 1050, Ar–F 1164; C–H bend (aromatic ortho) 758; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 12.3 (s, 1H, NH), 8.09 (d, 1H, $J$ = 29.4 Hz, H-5), 7.85 (s, 1H, CH), 7.65 (d, 2H, $J$ = 12.3 Hz, H-3′and 5′), 7.29 (d, 1H, $J$ = 5.1 Hz, H-4′), 7.15 (s, 1H, H-2), 7.07 (d, 2H, $J$ = 3.1 Hz, H-2′and 6′); HRMS calcd for $C_{16}H_{10}ClFN_2OS$: 332.0186, found 333.0165.

*2-(3-chloro-4-fluorophenylimino)-5-(2-chlorobenzylidene)-4-thiazolidinone (**6b**)*

Reaction time 5 h; yield 67%; Off-white crystals; mp 195–200°C (from dioxane); $R_f$ value: 0.69 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 274 nm; IR(KBr,$cm^{-1}$) $\nu$: C=O: 1703; –NH– stretch: 3253; –NH– bend: 1587; C=N: 1616; –C–N: 1242; C–H stretch (aromatic): 3053; C–H bend (aromatic meta substituted): 648, 759; C–H bend (aromatic para substituted):819; C–H bend (aromatic ortho substituted): 750; C=C: 1643; Ar–Cl: 1100; Ar–F: 1242; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.358 (s, 1H, NH); 8.31 (d, 1H, $J$ = 14.1, H-5; 7.8 (s, 1H, CH); 7.269 (t, 1H, $J$ = 2.1, H-4′); 7.156 (d, 1H, $J$ = 4.8, H-6′); 7.04 (m, 2H, J = 5.4, H-3′ and 5′); 6.962 (s, 1H, H-2); HRMS calcd for : $C_{16}H_9Cl_2FN_2OS$: 365.9797, found 366.9628.

*2-(3-chloro-4-fluorophenylimino)-5-(4-chlorobenzylidene)-4-thiazolidinone (**6c**)*

Reaction time 5 h; yield 64%; Light brown crystals; mp 215–220°C (from dioxane); $R_f$ value: 0.71 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 347 nm; IR (KBr,$cm^{-1}$) $\nu$: –C=O: 1690; –NH– stretch: 3137; –NH– bend: 1587; –C–N: 1257; C–H stretch (aromatic): 3053; C–H bend (aromatic para substituted): 879, 817; (aromatic meta substituted): 669, 786; C=C: 1654; Ar–F: 1257; Ar–Cl: 1100; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 12.1 (s, 1H, NH); 8.09 (d, 1H, $J$ = 24, H-5); 7.74 (s, 1H, CH); 7.66 (d, 2H, $J$ = 8.7, H-3′ and 5′); 7.47 (d, 2H, $J$ = 9.3, H-2′ and 6′); 7.29 (d, 1H, $J$ = 5.0, H-5); 7.15 (d, 1H, $J$ = 3.9, H-6); 6.962 (s, 1H, H-2).; HRMS calcd for $C_{16}H_9Cl_2FN_2OS$: 365.9797, found 366.9652.

*2-(3-chloro-4-fluorophenylimino)-5-(4-hydroxybenzylidene)-4-thiazolidinone (**6d**)*

Reaction time 6 h; yield 69%; Yellowish white crystals; mp 210–213°C (from dioxane); $R_f$ value: 0.73 (Toluene: Ethanol, 8:2); $\lambda_{max}$ 267 nm; IR (KBr,$cm^{-1}$) $\nu$: –C=O: 1703; –NH– stretch: 3406; –NH– bend: 1585; –C–N: 1259; C–H stretch (aromatic): 3055; C–H bend (aromatic para substituted): 819, 883; (aromatic meta substituted): 653, 744; Ar–F: 1191; C=C: 1643; Ar–Cl: 1056; Ar-OH: 3500; C–O: 1220; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.8 (s, 1H, NH); 8.0 (s, 1H, CH); 7.15 (d, 2H, $J$ = 4.5, H-3′ and 5′); 6.95 (d, 2H, $J$ = 3.6, H-2′ and 6′); 7.70 (m, 3H, H-2, 5 and 6); HRMS calcd for $C_{16}H_{10}ClFN_2O_2S$: 348.0136, found 349.0015.

*2-(3-chloro-4-fluorophenylimino)-5-(2-nitrobenzylidene)-4-thiazolidinone (**6e**)*

Reaction time 5 h; yield 63%; Rust colored crystals; mp 189–191°C (from dioxane); $R_f$ value: 0.66 (Toluene:Ethanol 8:2); $\lambda_{max}$ 267 nm; IR (KBr,$cm^{-1}$) $\nu$: –C=O: 1703; –NH– stretch: 3436; –NH– bend: 1585; C=N: 1614; –C–N: 1259; C–H stretch (aromatic): 3053; C–H bend (aromatic ortho substituted): 750; C–H bend (aromatic meta substituted): 651, 786; C–H bend (aromatic para substituted): 819; C=C: 1643, Ar-$NO_2$: 1346 (sym), 1504 (asym); Ar–Cl: 1056; Ar–F: 1191; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.9 (s, 1H, NH); 8.268 (s, 1H, CH); 8.234 (d, 1H, $J$ = 4.2, H-5); 7.249 (d, 1H, $J$ = 6.6, H-3′); 6.98 (m, 2H, $J$ = 4.8, H-4′ and 5′); 7.149 (s, 1H, H-2); 8.18 (d, 1H, $J$ = 5.1, H-6′); 8.05 (d, 1H, $J$ = 3.9, H-6); HRMS calcd for $C_{16}H_9ClFN_3O_3S$: 377.7774, found 377.9906.

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

Reaction time 6.5 h; yield 63%; Light brown crystals; mp 240–245°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 339 nm; IR (KBr,$cm^{-1}$) *v*: –C=O: 1681; –NH– stretch: 3421; –NH– bend: 1637; C=N: 1600; –C–N: 1263; C=C: 1637; C–H stretch (aromatic): 3045; C–H bend (aromatic meta substituted): 669, 750; C–H bend (aromatic para substituted): 819; Ar–$NO_2$: 1350 (sym), 1498 (asym); Ar–Cl: 1056; Ar–F: 1184; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 12.4 (s, 1H, NH); 8.39 (d, 1H, $J = 11.4$, H-5); 8.24(d, 1H, $J = 3.3$, H-5′); 8.06 (d, 1H, $J = 8.1$, H-4′); 7.822 (d, 1H, $J = 7.8$, H-6); 7.822 (m, 2H, $J = 14.7$, H-2′ and 6′); 7.575 (s, 1H, CH); HRMS calcd for $C_{16}H_9ClFN_3O_3S$: 377.7774, found 378.0016.

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

Reaction time 7 h; yield 58%; mustard colored crystals; mp 198–201°C (from dioxane); $R_f$ value: 0.77 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 267 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1728, –NH– stretch 3251, –NH– bend 1614, C=N 1585, –C–N 1259, C=C 1650; C–H stretch (aromatic) 3040; 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) ($\delta$, ppm): 12.91 (s, 1H, NH), 7.78 (s, 1H, H-2), 7.40-6.91 (m, 2H, H-5 and 6), 7.781 (s, 1H, CH), 7.67 (s, H-2′), 7.58 (m, 2H, H = 5′ and 6′), 10.20 (s, OH); HRMS calcd for $C_{17}H_{12}ClFN_2O_3S$: 378.0241, found 380.9928.

*2-(4-chlorophenylimino-5-arylidene-4-thiazolidinone) (**7a**)*

Reaction time 5 h; yield 72%; Buff colored crystals; mp 280–283°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 346 nm; IR(KBr,$cm^{-1}$) *v*: –C=O 1674; –NH– stretch 3413; –NH– bend 1564; –C–N 1245; C=N 1564; C–H stretch (aromatic) 2963; C=C 1639; Ar–Cl 1087; C–H bend (aromatic para) 761; $^1$HNMR (DMSO-$d_6$, 300 MHz): ($\delta$, ppm): 11.31 (s, 1H, NH); 7.07 (d, 2H, J 7.5, H-2,6); 7.734(d, 2H, J 8.1, H-3 and 5); 6.985 (s, 1H, CH); 7.218 (d, 2H, J 13.8, H-2′ and 6′); 7.557-7.441 (m, 3H, H = 3′, 4′ and 5′); HRMS calcd for $C_{16}H_{11}ClN_2OS$: 314.0281, found 315.0595.

*2-(4-chlorophenylimino)-5-(2-chlorobenzylidene)-4-thiazolidinone (**7b**)*

Reaction time 5.5 h; yield 62%; Off-white crystals; mp 310–312°C (from dioxane); $R_f$ value: 0.69 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 276 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1724; –NH– stretch 3413; –NH– bend 1490; –C–N 1245; C=N 1606; C–H stretch (aromatic) 2908; C=C 1649; Ar–Cl 1091; C–H bend (aromatic ortho) 756; C–H bend (aromatic para) 825; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.78 (s, 1H, NH); 7.63-7.59 (m, 2H, H-2 and 6); 7.82 (d, 2H, J 6.9, H-3 and 5); 6.99 (s, 1H, CH); 7.60 (d, 1H, J 9.3 H-3′); 7.45 (d, 2H, J 8.4, H = 4′ and 5′); 7.55 (d, 1H, J 9.3, H-6′); HRMS calcd for $C_{16}H_{10}Cl_2N_2OS$: 347.9891, found 349.0129.

*2-(4-chlorophenylimino)-5-(4-chlorobenzylidene)-4-thiazolidinone (**7c**)*

Reaction time 5 h; yield 70%; Off-white crystals; mp 320–325°C (from dioxane); $R_f$ value: 0.90 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 263 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1722; –NH– stretch 3413; –NH– bend 1505; –C–N 1247; C=N 1605; C–H stretch (aromatic) 3051; C=C 1649; Ar–Cl 1091; C–H bend (aromatic ortho) 732; C–H bend (aromatic para) 821; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.908 (s, 1H, NH); 7.063 (d, 2H, J 7.5, H-2 and 6); 7.755(d, 2H, J 17.7, H-3 and 5); 7.633 (s, 1H, CH); 7.542-7.441 (m, 4H, H-2′, 3′, 5′ and 6′); HRMS calcd for $C_{16}H_{10}Cl_2N_2OS$: 347.9891, found 349.0129.

*2-(4-chlorophenylimino)-5-(4-hydroxybenzylidene)-4-thiazolidinone (**7d**)*

Reaction time 9 h; yield 72%; Mud colored crystals; mp 235–240°C (from dioxane); $R_f$ value: 0.71 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 269 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1701; –NH– stretch 3421; –NH– bend 1505; –C–N 1255; C=N 1575; C–H stretch (aromatic) 2979; C=C 1639; Ar–Cl 1080; Ar-OH 3421 (Broad band); C–H bend (aromatic para) 740 and 821; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.268 (s, 1H, NH); 6.977 (d, 2H, J 7.2, H-2 and 6); 7.44(d, 2H, J 8.1, H-3 and 5); 7.897 (s, 1H, CH); 7.06 (d, 2H, J 7.8, H-2′ and 6′); 7.730 (d, 2H, J 6.3, H = 3′ and 5′); 10.288 (s, OH); HRMS calcd for $C_{16}H_{11}ClN_2O_2S$: 330.0230, found 331.0551.

*2-(4-chlorophenylimino)-5-(2-nitrobenzylidene)-4-thiazolidinone (**7e**)*

Reaction time 9 h; yield 63%; Rust crystals; mp 218–220°C (from dioxane); $R_f$ value: 0.79 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 278 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1678; –NH– stretch 3255; –NH– bend 1500; –C–N 1238; C=N 1550; C–H stretch (aromatic) 2983; C=C 1618; Ar–Cl 1083; Ar-$NO_2$ 1338 (Sym) 1517 (Asym); C–H bend (aromatic ortho) 756; C–H bend (aromatic para) 821; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.272 (s, 1H, NH); 7.03 (d, 2H, J 7.8, H-2 and 6); 7.415 (d, 2H, J 7.5, H-3 and 5); 7.927 (s, 1H, CH); 7.797 (d, 1H, J 7.5, H-3′); 7.70 (m, 2H, J

8.7, H = 4′ and 5′); 7.511 (d, 1H, J 8.4, H 6′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.0131, found 360.0568.

*2-(4-chlorophenylimino)-5-(3-nitrobenzylidene)-4-thiazolidinone (**7f**)*

Reaction time 10 h; yield 65%; Buff colored crystals; mp 280–285°C (from dioxane); $R_f$ value: 0.84 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 255 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1681; –NH– stretch 3263; –NH– bend 1500; –C–N 1238; C=N 1512; C–H stretch (aromatic) 2975; C–C 1637; Ar–Cl 1091; Ar-$NO_2$ 1349 (Sym) 1512 (Asym); C–H bend (aromatic meta) 821; C–H bend (aromatic para) 745; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.997 (s, 1H, NH); 7.076 (d, 2H, J 8.1, H-2 and 6); 7.91(d, 2H, J 7.5, H-3 and 5); 7.791 (s, 1H, CH); 8.434 (s, 1H, H-2′); 8.070 (d, 1H, J 7.5, H = 4′); 8.286-8.208 (m, H 5′ and 6′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.0131, found 360.0568.

*2-(4-chlorophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)-4-thiazolidinone (**7g**)*

Reaction time 10 h; yield 65%; Fluorescent yellow crystals; mp 220–228°C (from dioxane); $R_f$ value: 0.79 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 254 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1691; –NH– stretch 3421; –C–N 1263; C=N 1505; C–H stretch (aromatic) 2974; C=C 1647; Ar–Cl 1091; Ar-OH 3473 (Broad band); C; C–H bend (aromatic meta) 823, C–H bend (aromatic para) 756; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.9 (s, 1H, NH); 7.067 (d, 2H, J 8.1, H-2 and 6); 7.44 (d, 2H, J 8.1, H-3 and 5); 7.580 (s, 1H, CH); 7.635 (s, 1H, H-2′); 7.58 (m, 2H, H = 5′ and 6′); 7.176, (d, 1H, J 18.6, H-5′), 7.121 (d, 1H, J 24.3, H-6′) 4.009 (s, 3H, $OCH_3$), 9.770 (s, OH); HRMS calcd for $C_{17}H_{13}ClN_2O_3S$: 360.0335, found 361.0767.

*2-(3-chlorophenylimino-5-arylidene-4-thiazolidinone) (**8a**)*

Reaction time 8 h; yield 72%; Coffee brown crystals; mp 260–262°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 262 nm; IR(KBr,$cm^{-1}$) *v*: –C=O 1679; –NH– stretch 3267; –NH– bend 1504; –C–N 1244; C=N 1595; C–H stretch (aromatic) 3022; C=C 1629; Ar–Cl 1076; C–H bend (aromatic meta) 851 and 875; $^1$HNMR (DMSO-$d_6$, 300 MHz): ($\delta$, ppm): 11.31, (S, 1H, NH), 7.509 (s, 1H, H-2), 7.084-6.985 (m, 3H, H-4,5,6), 7.084 (s, 1H, CH), 7.748-7.509 (m, 5H aromatic); HRMS calcd for $C_{16}H_{11}ClN_2OS$: 314.0281, found 315.0583.

*2-(3-chlorophenylimino)-5-(2-chlorobenzylidene)-4-thiazolidinone (**8b**)*

Reaction time 5 h; yield 60%; Brown crystals; mp 240–242°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 263 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1722; –NH– stretch 3423; –NH– bend 1509; –C–N 1247; C=N 1599; C–H stretch (aromatic) 2966; C=C 1654; Ar–Cl 1039; C–H bend (aromatic meta) 862; C–H bend (aromatic para) 765.; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.7 (s, 1H, NH), 7.593 (s, 1H, H-2), 7.204 (d, 1H, J 28.5, H-4), 7.071-6.985 (m, 2H, H 5 and 6), 7.628 (s, 1H, CH), 7.577 (d, 1H, J 3.9, H-3′), 7.923-7.723 (m, 3H, H-4′, 5′, 6′); HRMS calcd for $C_{16}H_{10}Cl_2N_2OS$: 347.9891, found 349.0123.

*2-(3-chlorophenylimino)-5-(4-chlorobenzylidene)-4-thiazolidinone (**8c**)*

Reaction time 9 h; yield 70%; Brown crystals; mp 240–245°C (from dioxane); $R_f$ value: 0.74 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 348 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1672; –NH– stretch 3265; –NH– bend 1463; –C–N 1251; C=N 1631; C–H stretch (aromatic) 3053; C=C 1631; Ar–Cl 1091; C–H bend (aromatic meta) 821; C–H bend (aromatic para) 763; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.01 (s, 1H, NH), 7.542 (s, 1H, H-2), 7.063 (d, 1H, J 7.5,H-4), 7.45 (d, 2H, J 7.5, H-5 and 6), 7.633 (s, 1H, CH), 7.633-7.441 (m, 4H, H-2′, 3′, 5′ and 6′); HRMS calcd for $C_{16}H_{10}Cl_2N_2OS$: 347.9891, found 349.0103.

*2-(3-chlorophenylimino)-5-(4-hydroxybenzylidene)-4-thiazolidinone (**8d**)*

Reaction time 7 h; yield 72%; Mustard crystals; mp 310–315°C (from dioxane); $R_f$ value: 0.796 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 365 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1677; –NH– stretch 3413; –NH– bend 1500; –C–N 1244; C=N 1564; C–H stretch (aromatic) 3026; C=C 1650; Ar–Cl 1091; Ar-OH 3469 (Broad band); C–H bend (aromatic meta) 825, 850; C–H bend (aromatic para) 764; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.288, (s, 1H, NH), 7.460 (s, 1H, H-2), 7.56 (d, 1H, J 7.5, H-4), 7.258-7.041 (m, 2H, H-5 and 6), 7.433 (s, 1H, CH), 7.741-7.604 (m, 4H, aromatic), 10.181 (s, 1H, OH); HRMS calcd for $C_{16}H_{11}ClN_2O_2S$: 330.0230, found 331.05.

*2-(3-chlorophenylimino)-5-(2-nitrobenzylidene)-4-thiazolidinone (**8e**)*

Reaction time 8.5 h; yield 63%; Dark Brown crystals; mp 200–205°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 274 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1685; –NH– stretch 3265; –NH– bend 1523; –C–N 1236; C=N 1598; C–H stretch (aromatic) 3062; C=C 1639; Ar–Cl 1091; Ar-$NO_2$ 1342(sym) 1523 (asym); C–H bend (aromatic meta) 772 and 857; C–H bend (aromatic ortho) 754; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.05 (s, 1H, NH), 7.716 (s, 1H, H-2), 7.701 (d, 1H, J 8.7, H-4), 7.687-

7.638 (m, 2H, H-5 and 6), 7.497 (s, 1H, CH), 7.762 (d, 1H, J 13.5, H-3′), 7.884-7.785 (m, 3H, aromatic); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.0131, found 360.0572.

*2-(3-chlorophenylimino)-5-(3-nitrobenzylidene)-4-thiazolidinone (**8f**)*

Reaction time 8 h; yield 65%; Coffee brown crystals; mp 275–280°C (from dioxane); $R_f$ value: 0.72 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 342 nm; IR (KBr,$cm^{-1}$) *v*: -C=O 1677; –NH– stretch 3261; -NH– bend 1527; –C–N 1242; C=N 1598; C–H stretch (aromatic) 2964; C=C 1629; Ar–Cl 1114; Ar-$NO_2$ 1352 (sym) 1510 (asym); C–H bend (aromatic meta) 765 and 859; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 11.01 (s, 1H, NH), 7.726 (s, 1H, H-2), 7.611-7.510 (m, 3H, H-4,5 and 6), 7.611 (s, 1H, CH), 7.812 (s, 1H, H-2′), 7.828 (d, 1H, J 3.6 H-, 7.925-7.844 (m, 2H, H-5′ and 6′); HRMS calcd for $C_{16}H_{10}ClN_3O_3S$: 359.0131, found 360.0572.

*2-(3-chlorophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)-4-thiazolidinone (**8g**)*

Reaction time 8 h; yield 60%; Dark brown crystals; mp 225–230°C (from dioxane); $R_f$ value: 0.73 (Toluene:Ethanol, 8:2); $\lambda_{max}$ 375 nm; IR (KBr,$cm^{-1}$) *v*: –C=O 1701; –NH– stretch 3265; –NH– bend 1497; –C–N 1255; C=N 1583; C–H stretch (aromatic) 2905; C=C 1641; Ar–Cl 1033; Ar-OH 3425 (Broad band); C–H bend (aromatic meta) 795, 857; C–H bend (aromatic para) 744; $^1$HNMR (DMSO-$d_6$, 300 MHz) ($\delta$, ppm): 10.9 (s, 1H, NH), 7.253 (s, 1H, H-2), 7.580-7.431 (m, 3H, H-4, 5 and 6), 7.045 (s, 1H, CH), 7.301 (s, 1H, H-2′), 3.839 (s, 3H, $OCH_3$), 9.81 (s, 1H, OH), 7.081-6.966 (d, 2H, H-5′ and 6′); HRMS calcd for $C_{17}H_{13}ClN_2O_3S$: 360.0335, found 361.0759.

Microbiological studies

The antimicrobial activity of the synthesized compounds was evaluated by cup plate method (Indian Pharmacopoeia, 1996) against 24 h old subcultures of two gram positive, two gram negative bacterial strains, and one fungal strain using ciprofloxacin and fluconazole as standard drugs, respectively. Microbial strains viz. *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) for gram positive bacteria; *Escherichia coli* (MTCC 739) and *Pseudomonas aeruginosa* (MTCC 2453) for gram negative bacteria; *Candida albicans* (MTCC 227) for fungus were procured as pure cultures from IMTECH, Chandigarh. Solutions of test compounds at concentrations of 50, 100, 200, and 300 μg/ml were prepared in 8% v/v dimethyl sulfoxide. In all the determinations, tests were performed in triplicate and the values reported are mean of these determinations. The diameters of the circular zones of inhibition were measured and are reported in Table 1.

## Results and discussion

Synthesis

In this study, twenty-one derivatives of 4-thiazolidinone substituted at position-2 and position-5 were synthesized in an attempt to find new molecules as antimicrobial agents. The synthetic pathway leading to the title compounds is given in Scheme 1. All the synthesized compounds were characterized by physicochemical and spectral data (UV, IR, $^1$HNMR, and HRMS).

The probable mechanism of reaction and the theoretically tautomeric forms of key intermediate **3** are shown in Scheme 2 (Vicini *et al.*, 2006). The 3-non substituted 4-thiazolidinones display amino-imino tautomerism. The hydroxyl tautomer was excluded on the basis of spectral studies. In IR spectra, appearence of sharp lactam signal at 3400–3100 and C=N between 1,600 and 1,500 helped in assigning the imino form. Absence of broad band for alcohol further ruled out the possibility of amino form. Occurence of downfield values for NH confirmed the same.

In UV spectra of the final compounds **5a–5g**, **6a–6g**, and **7a–7g**, characteristic K bands arising due to C=N chromophoric group were observed at 267–347 nm. Compounds with nitro and chloro groups showed bathochromic shift. Title compounds can exist as potential E and Z geometrical isomers; Z configuration of 5-exocyclic C=C was assigned 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). In E isomers, due to less deshielding effect of 1-S, such proton resonates at a lower chemical shift value (Momose *et al.*, 1991). The IR spectra showed characteristic peaks ($cm^{-1}$) of lactam –NH at 3400–3100, 1550, C=O at 1,700 and 1,633 for C=C agreed with the structures. In $^1$HNMR spectra, –NH proton observed at 11.8–12.7 ppm shows substitution at 2nd position instead of 3rd position, which is in agreement with a lactam proton since imine proton appears at much higher field (Ishida, 1990). Furthermore, HRMS spectra of the compounds showing corresponding M + 1 peaks confirmed the molecular weights and purity.

## Antimicrobial activity

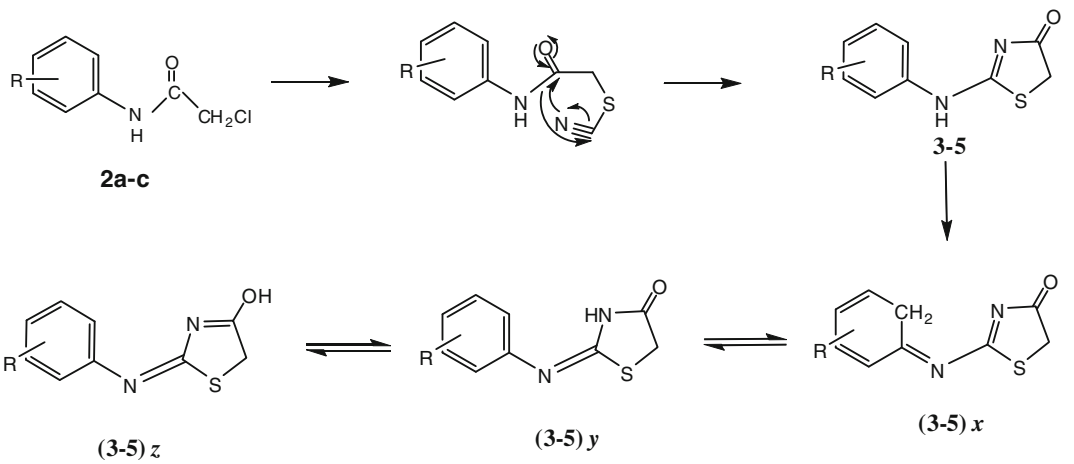
Title compounds were screened for in vitro antimicrobial activity against two gram positive bacteria viz. *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96),

**Table 1** Diameters of zone of inhibition for compounds **5a–5g**, **6a–6g**, and **7a–7g**

| Compound | Diameter of zone of inhibition (mm) ($n = 3$) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* | | | | *B. subtilis* | | | | *P. aeruginosa* | | | | *E. coli* | | | |
| Conc. (μg/ml) | 50 | 100 | 200 | 300 | 50 | 100 | 200 | 300 | 50 | 100 | 200 | 300 | 50 | 100 | 200 | 300 |
| **5a** | 6 | 10 | 10 | 10 | 6 | 6 | 10 | 12 | 8 | 10 | 10 | 12 | 7 | 8 | 11 | 12 |
| **5b** | 10 | 11 | 12 | 14 | 10 | 12 | 14 | 14 | 10 | 10 | 12 | 12 | 8 | 8 | 9 | 10 |
| **5c** | 10 | 12 | 12 | 14 | 8 | 10 | 11 | 13 | 8 | 9 | 11 | 12 | 9 | 12 | 12 | 12 |
| **5d** | 8 | 10 | 10 | 11 | 9 | 10 | 10 | 11 | 8 | 9 | 10 | 10 | 8 | 9 | 10 | 10 |
| **5e** | 10 | 12 | 13 | 14 | 10 | 12 | 13 | 13 | 8 | 9 | 10 | 11 | 8 | 9 | 11 | 12 |
| **5f** | 11 | 12 | 14 | 16 | 12 | 12 | 14 | 15 | 8 | 10 | 11 | 12 | 7 | 8 | 9 | 10 |
| **5g** | 7 | 8 | 9 | 11 | 7 | 8 | 8 | 10 | 7 | 9 | 10 | 10 | 7 | 8 | 8 | 9 |
| **6a** | 5 | 8 | 9 | 10 | 5 | 8 | 9 | 10 | 8 | 8 | 8 | 11 | 7 | 8 | 10 | 12 |
| **6b** | 8 | 8 | 9 | 10 | 8 | 8 | 9 | 10 | 9 | 9 | 9 | 9 | 9 | 9 | 10 | 9 |
| **6c** | 6 | 8 | 9 | 10 | 7 | 8 | 8 | 10 | 6 | 7 | 8 | 10 | 8 | 8 | 7 | 9 |
| **6d** | 6 | 7 | 7 | 8 | 6 | 7 | 7 | 8 | 7 | 8 | 8 | 9 | 7 | 7 | 8 | 8 |
| **6e** | 8 | 9 | 10 | 10 | 8 | 9 | 10 | 11 | 7 | 8 | 8 | 9 | 6 | 8 | 9 | 9 |
| **6f** | 8 | 9 | 9 | 10 | 9 | 10 | 10 | 11 | 8 | 9 | 9 | 11 | 7 | 8 | 9 | 10 |
| **6g** | 6 | 6 | 7 | 8 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 9 | 7 | 8 | 9 | 9 |
| **7a** | 6 | 7 | 8 | 9 | 6 | 7 | 7 | 7 | 6 | 7 | 8 | 9 | 7 | 7 | 7 | 8 |
| **7b** | 7 | 8 | 8 | 9 | 7 | 8 | 8 | 9 | 6 | 7 | 7 | 8 | 7 | 7 | 8 | 8 |
| **7c** | 7 | 8 | 9 | 10 | 7 | 8 | 10 | 10 | 7 | 8 | 8 | 8 | 7 | 9 | 9 | 9 |
| **7d** | 8 | 9 | 9 | 10 | 6 | 7 | 8 | 9 | 7 | 8 | 9 | 10 | 7 | 7 | 8 | 9 |
| **7e** | 8 | 9 | 10 | 10 | 9 | 9 | 9 | 10 | 7 | 8 | 9 | 9 | 6 | 8 | 9 | 9 |
| **7f** | 8 | 9 | 9 | 10 | 8 | 9 | 9 | 10 | 8 | 8 | 9 | 9 | 7 | 7 | 8 | 8 |
| **7g** | 6 | 7 | 8 | 8 | 7 | 8 | 8 | 9 | 6 | 8 | 9 | 9 | 7 | 8 | 9 | 9 |
| Standard | | 14 | | | | 15 | | | | 15 | | | | 17 | | |
| Control | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |

*Standard* Ciprofloxacin; *Control* 8%v/v DMSO

– No activity




**Scheme 2** Mechanism of formation and existence of 3,4, and 5 as tautomers

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. However, none of the compounds showed activity against *Candida albicans*. The activity of the derivatives was found to be concentration dependent (Table 1). Compounds bearing 5-arylidene moeity either as such or substituted with 2-chloro, 2-nitro, and 3-nitro groups were found to be more active against the selected bacterial strains. Unsubstituted arylidene ring showed comparatively lesser activity, which proved that substitution at arylidene moiety affects the activity. The scrutiny of the results revealed that compounds bearing a 4-fluoro group in addition to a 3-chloro group in the phenylimino ring at position-2 of 4-thiazolidinone nucleus were more active against chosen bacterial strains whereas those bearing only 4-chloro or 3-chloro were less active. Significant activity was shown by compounds **5b**, **5c**, **5e**, **5f**, **6b**, **6c**, **6e**, **6f**, **7b**, **7c**, **7e**, and **7f** with electron withdrawing groups like chloro and nitro whereas moderate activity was shown by compounds with electron donating hydroxy group **5d**. However, addition of another electron donating group, i.e., methoxy (**5g**), did not enhance but decreased the activity shown by hydroxyl group alone (**5d**). Presence of a fluoro group in addition to a 3-chloro group enhanced activity against bacteria, as observed for fluoroquinolones where presence of a fluoro group increases spectrum of activity. As a matter of fact, compounds exhibited more or equipotent activity against gram positive organisms when compared to that against gram negative organisms.

## Conclusion

In the present study, twenty-one novel derivatives of 4-thiazolidinone were synthesized and evaluated for activity against selected micro-organisms. Their structures were characterized by UV, IR, $^{1}$HNMR, and HRMS spectroscopy. The derivatives were tested against gram positive organisms, gram negative organisms, and a fungus in the antimicrobial studies by cup-plate method. In the antibacterial studies, compounds bearing a fluoro group in addition to a chloro group exhibited greater activity than those bearing only the chloro group. This observation suggests that di-substitution in the 4-thiazolidinone derivatives by halogens enhanced the antibacterial potential. Interestingly, the compounds exhibited a broad spectrum of activity with similar or more activity against the gram positive organisms than the gram negative ones. However, the compounds were inactive against the fungus. Thus, it can be concluded that 4-thiazolidinones derivatives, with substitutions of chloro and fluoro groups, exhibit potential broad spectrum antibacterial activity.

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## References

Biological Assay, Indian Pharmacopoeia (1996) Govt. of India, Delhi. 2: A100-102

Bonde CG, Gaikwad NJ (2004) Synthesis and preliminary evaluation of some pyrazine containing thiazolines and thiazolidinones as antimicrobial agents. Bioorg Med Chem 12:2151–2161

Bondock S, Khalifa W, Fadda AA (2006) Utility of 1-chloro-3, 4-dihydronaphthalene-2-carboxaldehyde in the synthesis of novel heterocycles with pharmaceutical interest. Synth Commun 36:1601–1612

Bondock S, Khalifa W, Fadda AA (2007) Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde. Eur J Med Chem 42:948–954

Bruno G, Costantino L, Curinga V, Maccari R, Monforte F, Nicolo F, Ottana R, Vigorita MG (2002) Synthesis and aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones. Bioorg Med Chem 10:1077–1084

Chavan AA, Rai NR (2007) Synthesis and antimicrobial screening of 5-arylidene-2-imino-4-thiazolidinones. Arkivoc xvi:148–155

Chawla P, Singh R, Saraf SK (2011) Syntheses and evaluation of 2, 5-disubstituted 4-thiazolidinone analogues as antimicrobial agents Med Chem Res. doi:10.1007/s00044-011-9730-1

Chugh TD (2008) Emerging and re-emerging bacterial diseases in India. J Biosci 33:549–555

Faidallah HM, Khan KA, Asiri AM (2011) Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents. J Flourine Chem 132:131–137

Fries DS (2008) Opioid Analgesics. In: Lemke LT, Williams DA, Roche VF, Zito SN (eds) Foye's principles of medicinal chemistry, 6th edn. Wolter Kluver (India) Pvt. Ltd., New Delhi, pp 652–678

Hara A, Suzuki T, Hashizume H, Shishido N, Nakamura M, Ushikube F, Abiko Y (1999) Effects of CP-060S, a novel $Ca^{2+}$ channel blocker, on oxidative stress in cultured cardiac myocytes. Eur J Pharmacol 385:81–88

Ishida T, In Y, Inoue M, Tanaka C, Hamanaka N (1990) Conformation of (Z)-3-carboxymethyl-[(2E)-2-methyl-3-phenylpropenylidene] rhodanine (epalrestat), a potent aldose reductase inhibitor: X-ray crystallographic, energy calculational, and nuclear magnetic resonance studies. J Chem Soc Perkin Trans 2:1085–1091

Kato T, Ozaki T, Tamura K (1999) Novel calcium antagonists with both calcium overload inhibition and antioxidant activity. 2. Structure–activity relationships of thiazolidinone derivatives. J Med Chem 42:3134–3146

Kavitha CV, Basappa S, Swamy N, Mantelingu K, Doreswamy S, Sridhar MA, Prasad JS, Rangappa KS (2006) Synthesis of new bioactive venlafaxine analogs: novel thiazolidin-4-ones as antimicrobials. Bioorg Med Chem 14:2290–2299

Maccari R, Del Corso A, Giglio M, Moschini R, Mura U, Ottana R (2011) In vitro evaluation of 5-arylidene-2-thioxo-4-thiazolidinones active as aldose reductase inhibitors. Bioorg Med Chem Lett 21:200–203

Macherey AC, Dansette PM (2003) Chemical mechanisms of toxicity: basic knowledge for designing safer drugs. In: Wermuth CG (ed) The practice of medicinal chemistry, 2nd edn. Academic Press, Woburn

Momose Y, Meguro K, Ikeda H, Hatanaka C, Oi S, Sohda T (1991) Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds. Chem Pharm Bull 39:1440–1445

Omar K, Geronikaki A, Zoumpoulakis P, Camoutsis C, Sokovic M, Ciric A, Glamoclija J (2010) Novel 4-thiazolidinone derivatives

as potential antifungal and antibacterial drugs. Bioorg Med Chem 18:426–432

Ottana R, Maccari R, Barreca ML, Bruno G, Rotondo A, Rossi A, Chiricosta G, Di Paola R, Sautebin L, Cuzzocrea SE, Vigorita MG (2005) 5-Arylidene-2-imino-4-thiazolidinones: design and synthesis of novel anti-inflammatory agents. Bioorg Med Chem 13:4243–4252

Ottana R, Maccari R, Ciurleo R, Vigorita MG, Panico AM, Caedile V, Garufi F, Ronsi.svalle S (2007) Synthesis and in vitro evaluation of 5-arylidene-3-hydroxyalkyl-2-phenylimino-4-thiazolidinones with antidegenerative activity on human chondrocyte cultures. Bioorg Med Chem 15:7618–7625

Ozaki T, Ohi N (1999) Improved synthetic methods of CP-060*S*, a novel cardioprotective drug. Tetrahedron 10:3963–3968

Prescott ML, Harley PJ, Klein AD (2007) Microbiology, 6th edn. McGraw-Hill Companies, New York, p 851

Rawal RK, Prabhaka YS, Katti SB, De Clercq E (2005) 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors. Bioorg Med Chem 13:6771–6776

Rawal RK, Tripathi R, Katti SB, Pannecouque C, De Clercq E (2007) Design, synthesis, and evaluation of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones as anti-HIV agents. Bioorg Med Chem 15: 1725–1731

Ronad PM, Noolvi MN, Sapkal S, Dharbhamulla S, Maddi VS (2010) Synthesis and antimicrobial activity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives. Eur J Med Chem 45:85–89

Shingalapur RV, Hosamani KM, Keri RS, Hugar MH (2010) Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem 45:1753–1759

Vicini P, Geronikaki AA, Anastsia K, Incerti M, Zani F (2006) Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-4-thiazolidinones. Bioorg Med Chem 14:3859–3864

Vicini P, Geronikaki AA, Incerti M, Zani F, Dearden J, Hewitt M (2008) 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones with antimicrobial activity: synthesis and structure-activity relationship. Bioorg Med Chem 16:3714–3724

Voss ME, Carter PH, Tebben J, Scherle PA, Brown GD, Thompson LA, Xu M, Lo YC, Yang-Liu RRQ (2003) Both 5-arylidene-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones and 3-thioxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-ones are light-dependent tumor necrosis factor-$\alpha$ antagonists. Bioorg Med Chem Lett 13:533–538

Williams DH (1996) The glycopeptide story: how to kill the deadly 'Superbugs'. Nat Prod Rep 13:469–477