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Facile synthesis, antimicrobial and antiviral evaluation of novel substituted phenyl 1,3-thiazolidin-4-one sulfonyl derivatives

Milan Kumar Mandal [a], Swagatika Ghosh [b], Lieve Naesens [c], Hans Raj Bhat [d], Udaya Pratap Singh [a,*]

[a] Drug Design & Discovery Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology & Sciences, Allahabad, Uttar Pradesh 211007, India
[b] Food Saftey and Drug Administration, Government of Uttar Pradesh, Lucknow, Uttar Pradesh 226018, India
[c] Rega Institute for Medical Research, KU Leuven, B-3000 Leuven, Belgium
[d] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam 786004, India

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ABSTRACT

A series of novel substituted phenyl 1, 3-thiazolidin-4-one sulfonyl derivatives **5 (a-t)** were synthesized and screened for their *in-vitro* anti-microbial and anti-viral activity. The result of the anti-microbial assay demonstrated compounds **5d, 5f, 5g, 5h, 5i, 5j** showed prominent inhibitory activity against all the tested Gram-positive and Gram-negative bacterial strains, while compounds **5g, 5j, 5o, 5p, 5q** showed significant activity against the entire set of fungal strains as compared to standard drug Ampicillin and Clotrimazole, respectively. The antimicrobial study revealed that compounds having electron-withdrawing groups showed significant antimicrobial potency. The most active antibacterial compound **5j** showed potent inhibition of *S. aureus* DNA Gyrase enzyme as a possible mechanism of action for antimicrobial activity. Moreover, the antiviral testing of selected compounds showed considerable activity against Herpes simplex virus-1(KOS), Herpes simplex virus-2 (G), Herpes simplex virus-1(TK$^-$ KOS ACV^r), Vaccinia virus, Human Coronavirus (229E), Reovirus-1, Sindbis virus, Coxsackie virus B4, Yellow Fever virus and Influenza A, B virus. Compounds **5h** exhibited low anti-viral activity against HIV-1(strain IIIB) and HIV-2 (strain ROD). The study clearly outlined that synthesized compounds endowed with good antimicrobial property together with considerable antiviral activity.

1. Introduction

In the age of dramatic medical advancement, microbial infection is still the leading global killer. Lower respiratory tract infections, diarrhea, HIV/AIDS, tuberculosis, and malaria have become a major threat due to the development of drug-resistant strains [1–3]. Mainly drug resistivity has been evolved due to the irrational use of antibiotics thus, the development of newer analogs is urgently needed [4,5]. European Centre for Disease Prevention and Control (ECDC), the European Union reported that more than 33,000 people die every year due to infections with antibiotic-resistant bacteria. Thiazolidin-4-ones are five-membered heterocyclic compounds, gifted with a wide range of therapeutic properties [6–10]. It offers enormous scope towards the development of new drug candidates and can prove instrumental in the fight against microbial resistance. This ring is also known as wonder nuclei due to their broad range of biological activities *i.e.* antibacterial, antifungal, antioxidant, cytotoxic, analgesic, antiviral, anti-tubercular, anti-inflammatory, and anti-HIV [11–17]. Thiazolidin-4-one biological activity is directly dependent on the type of substitution at C-2 and N-3 positions. The thiazolidine-4-one ring plays an important role in commercially available drugs like Pioglitazone, Teneligliptin, Etozoline, Penicillin G, Cloxacillin, Amoxicillin, Carbenicillin, Piperacillin, and Tazobactam [18,19].

On the contrary, Sulfonamides have significantly contributed to chemotherapy either alone or in combination with other drugs. A literature survey has revealed that sulfonamide derivatives showed multifunctional and multi-targeting action in drug therapy [20]. It also showed significant biological activity such as antibacterial, antifungal, antioxidant, anticancer, antiviral, antitubercular, and diuretics. The versatile range of commercial drugs like antitubercular drug Dapsone, COX-2 inhibitors Celecoxib, uricosurics Probenecid, nonsteroidal antiandrogen Bicalutamide, and antiviral drugs Amprenavir,

* Corresponding author.
E-mail addresses: udaysingh98@gmail.com, udaya.singh@shiats.edu.in (U.P. Singh).

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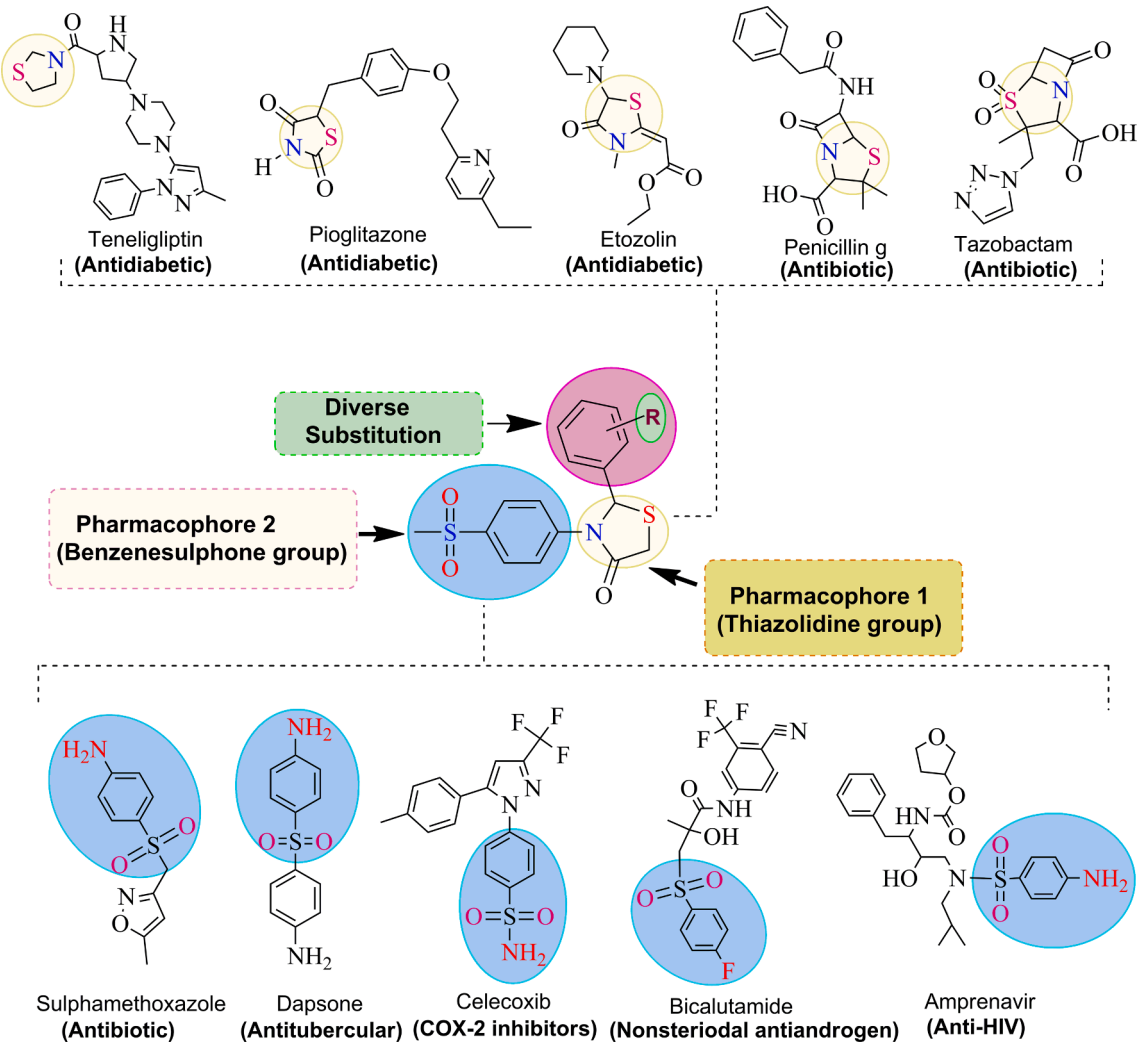


Fig. 1. Chemical structures of commercially available drugs containing Thiazolidine and benzenesulfone moieties.

Fosamprenavir, Darunavir contain benzene sulfonamides (Fig. 1) skeleton [21–25].

Prompted by the above, we hypothesized to develop a single skeleton that comprises thiazolidine-4-one and benzene sulfonyl derivatives in a search of potent anti-infective compounds. It was envisaged that hybridizing these two rings into a single molecule with suitable substitution might give rise to new antibacterial, antifungal, and antiviral scaffold [26,27]. Thus, in the present study, we have synthesized a series of novel 2-(***R***-phenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-thiazolidin-4-one **5 (a-t)** derivatives and subsequently evaluated for inhibitory activity against various human disease-causing bacteria, fungi, and viruses.

2. Materials & method

2.1. Chemistry

All the reagents and solvents used for synthesis and other experimental work were obtained from SD Fine India and Sigma-Aldrich, USA, and were used without purification unless otherwise stated. The melting point was determined in an open capillary tube using a Temp Star Pvt. Ltd. India, apparatus and is uncorrected. The completion of the reaction was monitored by thin-layer chromatography (TLC) performed on Silica gel G plates using appropriate solvents and the spots were visualized by exposure to ultraviolet light or Iodine vapors. Infra-red spectra were recorded by FTIR-8400S, Shimadzu, Japan using KBr pellets, and frequencies are described in wave numbers cm^{-1}. ^1H NMR spectra were recorded by Bruker Avance 400/AvIII HD-300 (FT NMR) with a low and high-temperature facility (−150 °C–+180 °C) in the solvents $CDCl_3$ & DMF using Tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (δ) and the signals are described as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Mass spectra were performed on Agilent 6520 Q-TOF (ESI-MS). Elemental analysis was carried out by Elemental Analyzer: Vario EL-III

2.1.1. General procedure for the synthesis of N-[(*R*-phenyl)methylidene]-4-methylbenzenesulfonamide *3 (a-t)* [28]

An equimolar quantity of corresponding aromatic aldehyde **2 (a-t)** (0.01 mol) and 4-methylbenzenesulfonamide **(1)** (1.12 g, 0.01 mol) in the presence of 20 ml of absolute ethanol was refluxed for 5–6 h. The completion of the reaction was ascertained by TLC (carbon tetrachloride/methanol, 2:1). The whole reaction mixture was transferred into a beaker containing crushed ice in boiling condition and filtered after attaining room temperature. Then the product was kept overnight, dried, and recrystallized using ethanol to get corresponding pure N-[(***R***-phenyl)methylidene]-4-methylbenzenesulfonamide derivatives **3 (a-t)**.

2.1.2. General procedure for the synthesis of 2-(*R*-phenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one *5 (a-t)* [8]

An equimolar quantity of corresponding compounds **3 (a-t)** was

refluxed with thioglycolic acid **(4)** in anhydrous ethanol in the presence of DCC (N,*N*-dicyclohexylcarbodimide) for 9–10 h. The reaction mixture was cooled and poured into ice-cold water. The resultant precipitate was filtered off and washed several times with distilled water, air-dried, and recrystallized from ethanol to obtain final derivatives of 2-(*R*-phenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **5 (a-t)**.

*2.1.2.1. 3-[(4-Methylphenyl)sulfonyl]-2-phenyl-1,3-thiazolidin-4-one **(5a)**.* Yield 69%; white crystals; m.p. 138.9–139.8 °C; IR (KBr, cm^{-1}): 3081(Ar C—H str), 2972(*N*—CH—S str), 2940(CH_2—S str), 1700(C═O str), 1610(C═C str), 1358(C—N str), 1390(—SO_2— str), 690(C—S—C str) ; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 3.50(s, 1H, *N*—CH), 3.75(s, 2H, S—CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.58–7.65(m, 6H, Ar—H), 9.40(s, 1H, —CONH). ESI-MS (*m/z*): 334.81 $[M + H]^+$; anal. calcd. For $C_{16}H_{15}NO_3S_2$: C 57.64, H 4.53, N 4.20; found C 57.63, H 4.56, N 4.21.

*2.1.2.2. 2-(2-Bromophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5b)**.* Yield 61%; brown crystals; m.p. 149.6–150.4 °C; IR (KBr, cm^{-1}): 3092(Ar C—H str), 2954(*N*—CH—S str), 2969(CH_2—S str), 1690(C═O str), 1626(C═C str), 1334(C—N str), 1344(—SO_2— str), 694 (C—S—C str), 540(C-Br str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41(s, 3H, CH_3), 3.52(s, 1H, *N*-CH), 3.80(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.60–7.80(m, 5H, Ar-H), 9.42(s, 1H, –CONH). ESI-MS (*m/z*): 413.18 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}BrNO_3S_2$: C 46.61, H 3.42, N 3.40; found C 46.63, H 3.41, N 3.44.

*2.1.2.3. 2-(3-Bromophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5c)**.* Yield 69%; brown crystals; m.p. 158.2–158.6 °C; IR (KBr, cm^{-1}): 3085(Ar C—H str), 2974(*N*—CH—S str), 2940(CH_2—S str), 1710(C═O str), 1610(C═C str), 1358(C—N str), 1390(—SO_2— str), 689 (C—S—C str), 545(C-Br str) ; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.43(s, 3H, CH_3), 3.49(s, 1H, *N*-CH), 3.78(s, 2H, S-CH_2), 3.99(t, 2H, CH_2, J = 2.5 Hz), 7.53–7.59(m, 5H, Ar-H), 9.44(s, 1H, –CONH). ESI-MS (*m/z*): 413.39 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}BrNO_3S_2$: C 46.61, H 3.42, N 3.40; found C 46.62, H 3.44, N 3.41.

*2.1.2.4. 2-(4-Bromophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5d)**.* Yield 67%; light brown crystals; m.p. 168.6–169.4 °C; IR (KBr, cm^{-1}): 3079(Ar C—H str), 2968(*N*—CH—S str), 2938(CH_2—S str), 1694(C═O str), 1630(C═C str), 1348(C—N str), 1382(—SO_2— str), 710 (C—S—C str), 560(C-Br str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 3.55(s, 1H, *N*-CH), 3.77(s, 2H, S-CH_2), 3.90(t, 2H, CH_2, J = 2.5 Hz), 7.63–7.69(m, 5H, Ar-H), 9.48(s, 1H, –CONH). ESI-MS (*m/z*): 413.32 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}BrNO_3S_2$: C 46.61, H 3.42, N 3.40; found C 46.63, H 3.41, N 3.40.

*2.1.2.5. 2-(2-Chlorophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5e)**.* Yield 62%; white crystals; m.p. 172.3–173.0 °C; IR (KBr, cm^{-1}): 3158(Ar C—H str), 2972(*N*—CH—S str), 2942(CH_2—S str), 1665 (C═O str), 1628(C═C str), 1359(C—N str), 1392(—SO_2— str), 700 (C—S—C str), 650 (C-Cl str) ; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.44(s, 3H, CH_3), 3.48(s, 1H, *N*-CH), 3.82(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.61–7.70(m, 5H, Ar-H), 9.41(s, 1H, –CONH). ESI-MS (*m/z*): 369.36 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}ClNO_3S_2$: C 52.24, H 3.84, N 3.81; found C 52.26, H 3.85, N 3.82.

*2.1.2.6. 2-(3-Chlorophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5f)**.* Yield 60%; white crystals; m.p. 169.9–170.5 °C; IR (KBr, cm-1): 3182(Ar C—H str), 2969(*N*—CH—S str), 2948(CH_2—S str), 1700 (C═O str), 1610(C═C str), 1358(C—N str), 1395(—SO_2— str), 710 (C—S—C str), 668 (C-Cl str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.42(s, 3H, CH_3), 3.50(s, 1H, *N*-CH), 3.81(s, 2H, S-CH_2), 3.94(t, 2H, CH_2, J = 2.5 Hz), 7.59–7.67(m, 5H, Ar-H), 9.41(s, 1H, –CONH). ESI-MS (*m/z*): 369.41 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}ClNO_3S_2$: C 52.24, H 3.84, N 3.81; found C 52.25, H 3.85, N 3.83.

*2.1.2.7. 2-(4-Chlorophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5g)**.* Yield 65%; white crystals; m.p. 174.1–175.1 °C; IR (KBr, cm^{-1}): 3158(Ar C—H str), 2978(*N*—CH—S str), 2942(CH_2—S str), 1695 (C═O str), 1610(C═C str), 1369(C—N str), 1390(—SO_2— str), 690 (C—S—C str), 665 (C-Cl str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.43(s, 3H, CH_3), 3.49 (s, 1H, *N*-CH), 3.74(s, 2H, S-CH_2), 3.91(t, 2H, CH_2, J = 2.5 Hz), 7.50–7.58(m, 5H, Ar-H), 9.45(s, 1H, –CONH). ESI-MS (*m/z*): 368.38 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}ClNO_3S_2$: C 52.24, H 3.84, N 3.81; found C 52.26, H 3.84, N 3.82.

*2.1.2.8. 2-(2-Fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-thiazolidin-4-one **(5h)**.* Yield 59%; white crystals; m.p. 175.6–176.2 °C; IR (KBr, cm-1): 3125(Ar C—H str), 2978(*N*—CH—S str), 2948(CH_2—S str), 1710 (C═O str), 1650(C═C str), 1358(C—N str), 1395(—SO_2— str), 700 (C—S—C str), 590(C-F str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.43(s, 3H, CH_3), 3.55(s, 1H, *N*-CH), 3.75(s, 2H, S-CH_2), 3.91(t, 2H, CH_2, J = 2.5 Hz), 7.55–7.62(m, 5H, Ar-H), 9.41(s, 1H, –CONH). ESI-MS (*m/z*): 352.01 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}FNO_3S_2$: C 54.68, H 4.02, N 3.99; found C 54.69, H 4.05, N 3.99.

*2.1.2.9. 2-(3-Fluorophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5i)**.* Yield 68%; white crystals; m.p. 180.1–180.6 °C; IR (KBr, cm^{-1}): 3142(Ar C—H str), 2962(*N*—CH—S str), 2935(CH_2—S str), 1716 (C═O str), 1653(C═C str), 1346(C—N str), 1389(—SO_2— str), 704 (C—S—C str), 597(C-F str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 3.55(s, 1H, *N*-CH), 3.85(s, 2H, S—CH_2), 3.91(t, 2H, CH_2, J = 2.5 Hz), 7.61–7.69(m, 5H, Ar—H), 9.43(s, 1H, —CONH). ESI-MS (*m/z*): 352.11 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}FNO_3S_2$: C 54.68, H 4.02, N 3.99; found C 54.69, H 4.02, N 3.98.

*2.1.2.10. 2-(4-Fluorophenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5j)**.* Yield 60%; white crystals; m.p. 181.7–182.4 °C; IR (KBr, cm^{-1}): 3151(Ar C—H str), 2966(*N*—CH—S str), 2951(CH_2—S str), 1706 (C═O str), 1652(C═C str), 1346(C—N str), 1391(—SO_2— str), 711 (C—S—C str), 560(C-F str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41(s, 3H, CH_3), 3.52(s, 1H, *N*-CH), 3.80(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.60–7.65(m, 5H, Ar-H), 9.42(s, 1H, —CONH). ESI-MS (*m/z*): 352.16 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}FNO_3S_2$: C 54.68, H 4.02, N 3.99; found C 54.67, H 4.03, N 3.99.

*2.1.2.11. 2-(2-Hydroxyphenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5k)**.* Yield72 %; pale white powder; m.p. 183.2 – 184.1 °C; IR (KBr, cm-1): 3521(Ar-OH str), 3059(Ar C—H str), 2982(*N*—CH—S str), 2940(CH_2—S str), 1695(C═O str), 1640(C═C str), 1358(C—N str), 1395(—SO_2— str), 690(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41(s, 3H, CH_3), 3.52(s, 1H, *N*-CH), 3.80(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.60–7.66(m, 5H, Ar-H), 9.42(s, 1H, —CONH), 10.02(s, 1H, OH). ESI-MS (*m/z*): 350.15 $[M + H]^+$; anal. calcd. for $C_{16}H_{15}NO_4S_2$: C 55.00, H 4.33, N 4.01; found C 55.02, H 4.34, N 4.01.

*2.1.2.12. 2-(3-Hydroxyphenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5l)**.* Yield 76%; pale white powder; m.p. 184.2–184.6 °C; IR (KBr, cm^{-1}): 3516(Ar-OH str), 3128(Ar C—H str), 2992(*N*—CH—S str), 2948(CH_2—S str), 1700(C═O str), 1645(C═C str), 1359(C—N str), 1360(—SO_2— str), 701(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 3.51(s, 1H, *N*-CH), 3.84(s, 2H, S-CH_2), 3.91(t, 2H, CH_2, J = 2.5 Hz), 7.61–7.64(m, 5H, Ar-H), 9.45(s, 1H, —CONH), 10.01(s, 1H, OH). ESI-MS (*m/z*): 350.10 $[M + H]^+$; anal. calcd. for $C_{16}H_{15}NO_4S_2$: C 55.00, H 4.33, N 4.01; found C 55.03, H 4.35, N 4.02.

*2.1.2.13. 2-(4-Hydroxyphenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one **(5m)**.* Yield 75%; pale white powder; m.p. 179.8–180.1 °C; IR (KBr, cm^{-1}): 3552(Ar-OH str), 3165(Ar C—H str), 2995(*N*—CH—S

str), 2936(CH_2—S str), 1686(C═O str), 1643(C═C str), 1366(C—N str), 1392(—SO_2— str), 698(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41(s, 3H, CH_3), 3.52(s, 1H, *N*-CH), 3.80(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.60–7.67(m, 5H, Ar-H), 9.42(s, 1H, –CONH), 10.02(s, 1H, OH). ESI-MS (*m/z*): 350.11 $[M + H]^+$; anal. calcd. for $C_{16}H_{15}NO_4S_2$: C 55.00, H 4.33, N 4.01; found C 55.01, H 4.35, N 4.02.

2.1.2.14. 3-[(4-Methylphenyl)sulfonyl]-2-[4-(propan-2-yl)phenyl]-1,3-thiazolidin-4-one ***(5n)***. Yield 62%; pale white powder; m.p. 181.6 – 182.3 °C; IR (KBr, cm^{-1}): 3080(Ar C—H str), 2900(C—CH_3 str), 2975(*N*—CH—S str), 2940(CH_2—S str), 1665(C═O str), 1620(C═C str), 1358(C—N str), 1395(—SO_2— str), 690(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.32(s, 6H, 2xCH_3), 2.42(s, 3H, CH_3), 3.50(s, 1H, *N*-CH), 3.86(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.60–7.66(m, 6H, Ar-H), 9.42 (s, 1H, —CONH). ESI-MS (*m/z*): 376.02 $[M + H]^+$; anal. calcd. for $C_{19}H_{21}NO_3S_2$: C 60.77, H 5.64, N 3.73; found C 60.75, H 5.63, N 3.74.

2.1.2.15. 3-[(4-Methylphenyl)sulfonyl]-2-(2-nitrophenyl)-1,3-thiazolidin-4-one ***(5o)***. Yield 59%; yellow crystal; m.p. 149.6–150.1 °C; IR (KBr, cm^{-1}): 3100(Ar C—H str), 2972(*N*—CH—S str), 2940(CH_2—S str), 1710(C═O str), 1420(C-NO_2 str), 1626(C═C str), 1360(C—N str), 1395(—SO_2— str), 695(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.45(s, 3H, CH_3), 3.48(s, 1H, *N*-CH), 3.85(s, 2H, S-CH_2), 3.95(t, 2H, CH_2, J = 2.5 Hz), 7.61–7.65(m, 5H, Ar-H), 9.41(s, 1H, –CONH). ESI-MS (*m/z*): 379.11 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}N_2O_5S_2$: C 50.78, H 3.73, N 7.40; found C 50.79, H 3.74, N 7.41.

2.1.2.16. 3-[(4-Methylphenyl)sulfonyl]-2-(3-nitrophenyl)-1,3-thiazolidin-4-one ***(5p)***. Yield 63%; yellow crystal; m.p. 157.6–158.3 °C; IR (KBr, cm^{-1}): 3106(Ar C—H str), 2981(*N*—CH—S str), 2955(CH_2—S str), 1706(C═O str), 1434(C-NO_2 str), 1619(C═C str), 1366(C—N str), 1398(—SO_2— str), 696(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.42(s, 3H, CH_3), 3.51(s, 1H, *N*-CH), 3.81(s, 2H, S-CH_2), 3.94(t, 2H, CH_2, J = 2.5 Hz), 7.54–7.59(m, 5H, Ar-H), 9.46(s, 1H, –CONH). ESI-MS (*m/z*): 379.09 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}N_2O_5S_2$: C 50.78, H 3.73, N 7.40; found C 50.79, H 3.74, N 7.42.

2.1.2.17. 3-[(4-Methylphenyl)sulfonyl]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one ***(5q)***. Yield 56%; yellow crystal; m.p. 168.8–169.2 °C; IR (KBr, cm^{-1}): 3120(Ar C—H str), 2975(*N*—CH—S str), 2938(CH_2—S str), 1700(C═O str), 1451(C-NO_2 str), 1610(C═C str), 1359(C—N str), 1365(—SO_2— str), 690(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 3.49 (s, 1H, *N*-CH), 3.79(s, 2H, S-CH_2), 3.91(t, 2H, CH_2, J = 2.5 Hz), 7.50–7.54(m, 5H, Ar-H), 9.45(s, 1H, —CONH). ESI-MS (*m/z*): 379.14 $[M + H]^+$; anal. calcd. for $C_{16}H_{14}N_2O_5S_2$: C 50.78, H 3.73, N 7.40; found C 50.80, H 3.75, N 7.42.

2.1.2.18. 2-(2-Methylphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-thiazolidin-4-one ***(5r)***. Yield 57%; white powder; m.p. 172.6–173.4 °C; IR (KBr, cm^{-1}): 3080(Ar C—H str), 2920(C—CH_3 str), 2970(*N*—CH—S str), 2945(CH_2—S str), 1700(C═O str), 1625(C═C str), 1380(C—N str), 1390(—SO_2— str), 695(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41(s, 3H, CH_3), 2.44(s, 3H, CH_3), 3.46 (s, 1H, *N*-CH), 3.74(s, 2H, S-CH_2), 3.92(t, 2H, CH_2, J = 2.5 Hz), 7.50–7.56(m, 5H, Ar-H), 9.42(s, 1H, —CONH). ESI-MS (*m/z*): 348.26 $[M + H]^+$; anal. calcd. for $C_{17}H_{17}NO_3S_2$: C 58.77, H 4.93, N 4.03; found C 58.79, H 4.94, N 4.04.

2.1.2.19. 2-(3-Methylphenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one ***(5s)***. Yield 62%; white powder; m.p. 170.3–170.7 °C; IR (KBr, cm^{-1}): 3120(Ar C—H str), 2935(C—CH_3 str), 2980(*N*—CH—S str), 2948(CH_2—S str), 1720(C═O str), 1650(C═C str), 1375(C—N str), 1390(—SO_2— str), 710(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.42(s, 3H, CH_3), 2.43(s, 3H, CH_3), 3.46 (s, 1H, *N*-CH), 3.74(s, 2H, S-CH_2), 3.92(t, 2H, CH_2, J = 2.5 Hz), 7.50–7.55(m, 5H, Ar-H), 9.42(s, 1H, —CONH). ESI-MS (*m/z*): 348.28 $[M + H]^+$; anal. calcd. for $C_{17}H_{17}NO_3S_2$: C 58.77, H 4.93, N 4.03; found C 58.78, H 4.94, N 4.03.

2.1.2.20. 2-(4-Methylphenyl)-3-[(4-methylphenyl) sulfonyl]-1,3-thiazolidin-4-one ***(5t)***. Yield 51%; white powder; m.p. 174.8 – 175.1 °C; IR (KBr, cm^{-1}): 3180(Ar C—H str), 2910(C—CH_3 str), 2976(*N*—CH—S str), 2942(CH_2—S str), 1690(C═O str), 1630(C═C str), 1385(C—N str), 1395(—SO_2— str), 700(C—S—C str); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.40(s, 3H, CH_3), 2.42(s, 3H, CH_3), 3.45 (s, 1H, *N*-CH), 3.73(s, 2H, S-CH_2), 3.94 (t, 2H, CH_2, J = 2.5 Hz), 7.51–7.59(m, 5H, Ar-H), 9.41(s, 1H, —CONH). ESI-MS (*m/z*): 348.30 $[M + H]^+$; anal. calcd. for $C_{17}H_{17}NO_3S_2$: C 58.77, H 4.93, N 4.03; found C 58.77, H 4.95, N 4.04.

2.2. In-vitro antimicrobial screening

2.2.1. Determination of the inhibition zone

The newly synthesized compounds **5 (a-t)** were screened for their antimicrobial potency against pathogenic bacteria and fungi. Gram-negative bacteria *Pseudomonas aeruginosa* (MCCB 0035), *Escherichia coli* (ATCC 8739), *Salmonella typhimurium* (NCIM-2501), *Klebsiella aerogenes* (NCIM-2098) and Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213), *Bacillus cereus* (NCIM-2458), *Lactobacillus casei* (NCIM-2651), and *Streptococcus pneumonia* (ATCC 49619) were used to evaluate antibacterial activity. The antifungal activity was evaluated against fungal strains *Aspergillus fumigatus* (NCIM 2081), *Aspergillus niger* (NCIM 2191), *Candida albicans* (NCIM 2087), and Cryptococcus neoformans (ATCC 9011) [29,30]. The preliminary screening for antibacterial and antifungal activities was carried out by the agar disk diffusion technique. Mueller-Hinton agar (MHA) Petri plates and Whatman filter paper disc (8 mm) were prepared and sterilized. Stock solutions of test compounds and standard compounds (Ampicillin, Clotrimazole) were prepared in DMSO and diluted with distilled water to get a final concentration of 100 μg/mL. The filter paper disks were soaked in standard and test solutions. After this, the disks were placed in MHA Petri plates seeded with standard microbial suspensions in a triplicate manner and were incubated at 35 °C for 24 h for bacterial strains and 48 h for fungal strains. The results were recorded in 'mm' as the average diameter of the inhibition zones of microbial growth around each disk for each test compound.

2.2.2. Determination of MIC

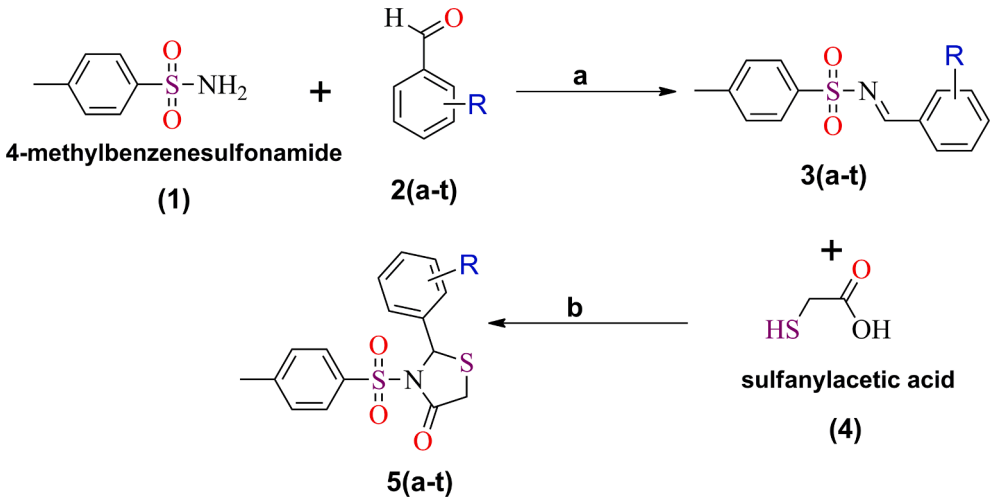
Minimal Inhibitory Concentrations (MICs, μg/mL) were determined by following the Broth Micro dilution procedure as per CLSI. For the growth of bacterial strains and fungal strains, Mueller–Hinton Broth and saboraud liquid medium were used, respectively. Two-fold serial dilution of all synthesized compounds and standard drugs of various concentrations were prepared in a suitable medium ranging from 512 to 0.25 μg/mL. Bacterial broth culture was incubated for 2–6 h, while fungal broth culture was incubated for 24 h at 35 °C to achieve the turbidity of a 0.5 McFarland standard. The bacterial and fungal suspension was adjusted with a sterile solution to obtain a final concentration of $5x10^5$ CFU/mL and 0.5–2.5 × 10^3 CFU/mL, respectively. MIC's were defined as the lowest concentration of the substance that gave no visible turbidity and completely inhibited the microbial growth.

2.2.3. DNA Gyrase inhibition assay

The *S. aureus* DNA gyrase purification, Supercoiling, and decatenation were executed as reported by F. Blanche.[31] The IC_{50} (μM) was determined from the dose response curve.

2.2.4. Antiviral activity assays

Eleven final derivatives were screened for their antiviral activity using a Cytopathic effect (CPE) reduction assay. Antiviral potency was determined against human coronavirus, adeno virus-2, Vaccina virus using Human embryonic lung (HEL) cells and Parainfluenza-3virus, Reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, and



Scheme 1. Scheme for the synthesis of 2-(***R***-phenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-thiazolidin-4-one derivatives **5 (a-t). Reagents and Condition: (a)** C_2H_5OH, reflux, 80 °C, 5–6 h.; **(b)** DCC (N,*N*-dicyclohexylcarbodimide), C_2H_5OH, reflux 120 °C, 9–10 h.

Yellow fever virus using African green monkey kidney Viro cells. Madin-Darby Canine Kidney (MDCK) cells were used to evaluate Influenza A/H1N1A/Ned/378/05, Influenza A/H3N2A/HK/7/87, and Influenza B B/Ned/537/05 viruses. The anti-HIV activity was also performed using MT4 cells against HIV-1 (strain IIIB) virus and HIV-2 (strain ROD) virus.

To evaluate the antiviral activity, the viruses were added to sub-confluent cell cultures in 96 well plates. Two-fold serial dilutions of test compounds were prepared and added to the cell cultures. Virus entry inhibitor dextran sulfate (MW-10000), mycophenolic acid (an inhibitor of cellular IMP dehydrogenase), broad-spectrum antiviral agent Ribavirin, Acyclovir, Amantadine, Rimantadine, antiherpetic agents Ganciclovir and Brivudin were used as reference compounds. The cell cultures were incubated for 3–6 days at 37 °C (35 °C in case of Influenza viruses). Antiviral and cytotoxic effects of test compounds were assessed by light microscopy or by MTS cell viability assay. Antiviral activity was reported as EC_{50} (50% effective concentration) based on the inhibitory effect of test compounds on virus-induced cytopathic effect (CPE). Cytotoxicity was expressed as MCC (Minimal Cytotoxic Concentration) and CC_{50} (Cytotoxic concentration) assessed by colorimetric formazan-based MTS assay.

3. Result & discussion

3.1. Chemistry

The synthetic approach for final derivatives was depicted in Scheme 1. The synthesis was accomplished in two different steps. The first step corresponds to the formation of Schiff's base (reactive imine) by nucleophilic addition of an amine to the carbonyl group of aromatic aldehyde. While in the second step, the Nitrogen atom of Schiff's base

Table 1
Minimum inhibitory concentration (**MIC**) in μg/ml of **5 (a-t)** against pathogenic bacterial and fungal strains.[a]

Comp. Code	*R*	Bacterial Strains[b]								Fungal Strains[c]			
		EC	PA	ST	KA	SA	BC	LC	SP	AN	CA	AF	CN
5a	H	64	128	>256	>256	64	128	64	128	32	64	64	128
5b	2-Br	16	32	32	64	32	64	64	128	64	32	64	128
5c	3-Br	16	16	32	16	32	32	16	64	32	32	32	64
5d	4-Br	4	4	16	8	16	32	8	64	32	16	16	32
5e	2-Cl	16	32	64	32	64	64	16	64	32	32	64	16
5f	3-Cl	8	16	16	8	32	32	16	8	16	16	64	32
5g	4-Cl	4	8	32	32	4	8	16	32	8	8	16	16
5h	2-F	4	8	16	64	8	16	4	64	32	32	16	8
5i	3-F	16	32	64	32	16	16	8	32	32	16	8	16
5j	4-F	2	2	8	16	4	8 s	4	64	8	4	4	4
5k	2-OH	32	32	64	32	64	64	64	128	32	16	32	64
5l	3-OH	16	32	64	16	64	128	32	64	64	16	64	128
5m	4-OH	16	16	32	64	32	64	16	32	64	32	128	64
5n	4-$CH(CH_3)_2$	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>512	>512
5o	2-NO_2	16	32	64	32	16	64	32	64	16	8	16	2
5p	3-NO_2	32	64	32	16	32	64	32	128	8	4	8	2
5q	4-NO_2	16	32	64	32	32	32	16	64	4	4	4	2
5r	2-CH_3	64	64	128	128	64	128	64	128	64	64	128	128
5s	3-CH_3	16	64	64	128	128	64	64	128	128	64	64	128
5t	4-CH_3	64	128	>256	>256	64	>256	>256	>256	128	128	64	>256
AA	Stand. drug	1	4	8	8	2	4	2	8	–	–	–	
CL	Stand. drug	–	–	–	–	–	–	–	–	16	4	1	2

Where AA is Ampicillin and CL is Clotrimazole.

[a] Minimum inhibitory concentration was determined by the micro-broth dilution method.

[b] *Escherichia coli* ***(EC)***, *Pseudomonas aeruginosa* ***(PA)***, *Salmonella typhimurium* ***(ST)***, *Klebsiella aerogenes* ***(KA)***, *Staphylococcus aureus* ***(SA)***, *Bacillus cereus* ***(BC)***, *Lactobacillus casei* ***(LC)***, *Streptococcus pneumonia* ***(SP)***.

[c] *Aspergillus fumigatus* ***(AF)***, *Aspergillus niger* ***(AN)***, *Candida albicans* ***(CA)***, *Cryptococcus neoformans* ***(CN)***.

Table 2
Zone of inhibition of compounds **5 (a-t)** in the concentration of 100 μg/8 mm disc compared with broad-spectrum antibacterial drug Ampicillin (**AA**) and antifungal drug Clotrimazole (**CL**) against pathogenic Bacterial and Fungal strains.

Com. Code[a]	*R*	*Diameter of growth inhibition zone (mm)[a]											
		Bacterial Strains[b]								Fungal Strains[c]			
		EC	PA	ST	KA	SA	BC	LC	SP	AN	CA	AF	CN
5a	H	13.2 ± 1.1	12.5 ± 0.6	07 ± 1.5	07 ± 1.74	13.8 ± 0.9	08 ± 0.4	10 ± 0.4	08 ± 0.8	10.1 ± 1.1	10.8 ± 2.3	10.2 ± 1.2	8.2 ± 0.5
5b	2-Br	14 ± 0.56	15 ± 0.93	12 ± 0.7	10 ± 0.5	16 ± 1.1	10 ± 0.34	10 ± 0.6	08 ± 0.7	10.8 ± 0.51	11.6 ± 0.65	10 ± 0.9	7.2 ± 0.3
5c	3-Br	19 ± 0.53	16 ± 1.5	12 ± 0.32	14 ± 0.6	17 ± 1.2	12 ± 0.32	14 ± 0.43	10 ± 0.9	12 ± 0.6	12.1 ± 0.9	11 ± 1.5	7.5 ± 0.5
5d	4-Br	20 ± 0.9	20 ± 1.1	14 ± 0.6	18 ± 0.3	21 ± 2.3	12 ± 0.4	18 ± 0.44	10 ± 1.6	11.8 ± 0.66	12.9 ± 0.5	9.8 ± 0.5	17 ± 1.0
5e	2-Cl	19 ± 0.69	18 ± 0.55	10 ± 0.72	12 ± 0.5	17 ± 3.6	10 ± 0.7	14 ± 0.3	10 ± 1.32	10.2 ± 0.9	10.8 ± 1.5	9.6 ± 1.2	12 ± 0.9
5f	3-Cl	18 ± 0.23	18 ± 0.56	14 ± 0.2	18 ± 0.23	20 ± 1.2	12 ± 2.2	14 ± 0.6	18 ± 0.7	11.2 ± 0.6	12 ± 0.35	11.8 ± 1.5	10 ± 0.7
5g	4-Cl	23 ± 0.32	24 ± 1.5	12 ± 0.9	12 ± 0.12	22 ± 0.63	18 ± 0.33	14 ± 0.4	12 ± 1.43	18 ± 1.1	20 ± 1.5	13 ± 0.63	12 ± 1.8
5h	2-F	23.8 ± 0.9	20 ± 0.6	14 ± 1.3	10 ± 0.5	19 ± 1.1	14 ± 0.62	19 ± 1.2	10 ± 1.7	12 ± 0.66	15 ± 0.56	15 ± 1.2	19 ± 1.1
5i	3-F	22.8 ± 0.63	18 ± 0.23	10 ± 0.76	12 ± 0.4	17 ± 0.53	14 ± 0.9	18 ± 1.62	12 ± 0.4	11 ± 0.9	15 ± 0.32	15 ± 0.6	14 ± 1.3
5j	4-F	25.9 ± 0.32	25 ± 1.5	18 ± 0.3	14 ± 0.94	23 ± 1.1	18 ± 0.5	19 ± 0.5	10 ± 0.6	19 ± 0.6	21 ± 0.9	19 ± 1.2	13 ± 1.5
5k	2-OH	18.8 ± 0.9	17.5 ± 0.6	10 ± 0.8	12 ± 0.48	16 ± 0.32	10 ± 0.3	10 ± 1.25	08 ± 0.3	15 ± 0.93	16 ± 0.32	13 ± 1.5	11 ± 1.2
5l	3-OH	17.8 ± 1.1	16 ± 1.5	10 ± 0.3	14 ± 0.4	14 ± 1.2	08 ± 0.5	12 ± 1.6	10 ± 0.5	14 ± 1.5	17 ± 0.5	12 ± 2.3	12 ± 1.4
5m	4-OH	15.9 ± 0.23	15.2 ± 0.96	12 ± 0.4	10 ± 0.4	13 ± 0.63	10 ± 0.6	14 ± 0.64	12 ± 2.1	13 ± 0.6	15 ± 0.35	10 ± 1.2	13 ± 1.4
5n	4-$CH(CH_3)_2$	08 ± 0.65	8.5 ± 1.5	07 ± 1.5	07 ± 0.7	0.7 ± 1.2	07 ± 0.1	07 ± 0.30	07 ± 0.6	10 ± 1.2	9 ± 1.5	9.5 ± 0.9	5 ± 0.3
5o	2-NO_2	16 ± 0.9	15 ± 1.1	10 ± 0.8	12 ± 0.34	15 ± 1.5	10 ± 0.6	12 ± 0.66	10 ± 1.5	19 ± 1.5	20 ± 1.1	18 ± 0.9	19 ± 1.2
5p	3-NO_2	16 ± 0.69	14 ± 1.1	12 ± 0.1	14 ± 0.75	16 ± 0.9	10 ± 0.4	12 ± 1.56	08 ± 0.87	20 ± 0.9	22 ± 1.2	20 ± 1.1	19 ± 1.0
5q	4-NO_2	17 ± 1.2	18 ± 1.2	10 ± 1.1	12 ± 0.4	18 ± 1.2	12 ± 0.6	14 ± 0.4	10 ± 0.45	22 ± 0.46	23 ± 1.2	21 ± 0.63	19 ± 1.3
5r	2-CH_3	15 ± 0.69	16 ± 1.9	08 ± 0.6	08 ± 0.3	14 ± 1.1	08 ± 0.4	10 ± 0.7	08 ± 0.8	9.8 ± 0.9	10 ± 0.6	9.6 ± 0.9	11 ± 0.7
5s	3-CH_3	17 ± 1.5	15 ± 0.32	10 ± 0.4	08 ± 1.3	13 ± 1.5	10 ± 0.2	10 ± 0.6	08 ± 0.4	9.6 ± 0.63	10 ± 1.1	9.2 ± 1.5	9 ± 0.5
5t	4-CH_3	12 ± 1.2	11 ± 0.65	07 ± 0.7	07 ± 0.6	12 ± 1.9	07 ± 0.84	08 ± 0.5	07 ± 0.7	9.5 ± 0.9	9.8 ± 0.23	09 ± 1.5	10 ± 0.9
AA	Stand. Drug	18	17	18	17	21	19	20	17	–	–	–	–
CL	Stand. Drug	–	–	–	–	–	–	–	–	23	24	22	19

[a] Agar Disk diffusion assay with standard and test solutions of (100 μg/8mm disk) in triplicate, Mean **(±)** standard deviation.
[b] *Escherichia coli* ***(EC)***, *Pseudomonas aeruginosa* ***(PA)***, *Salmonella typhimurium* ***(ST)***, *Klebsiella aerogenes* ***(KA)***, *Staphylococcus aureus* ***(SA)***, *Bacillus cereus* ***(BC)***, *Lactobacillus casei* ***(LC)***, *Streptococcus pneumonia* ***(SP)***.
[c] *Aspergillus fumigatus* ***(AF)***, *Aspergillus niger* ***(AN)***, *Candida albicans* ***(CA)***, *Cryptococcus neoformans (CN)*.

undergoes attack by a sulfur nucleophile (thioglycolic acid) followed by intramolecular cyclization and elimination of water in the presence of DCC (N,N′-Dicyclohexylcarbodiimide). The DCC is used to accelerate the intramolecular cyclization which results in faster reaction and improved yield [32,33].

The structures of final derivatives **5 (a-t)** were ascertained based on FT-IR, ^{1}H NMR, mass spectra, and elemental analysis. The data found for the title compounds in the elemental analysis (C, H, and N) were found near their calculated values. In IR spectra, significant stretching bands were observed at 1706–1710 cm^{-1}, 689–700 cm^{-1}, and 2954–2982 cm^{-1} due to C═O, C—S—C, and —NH which showed evidence of ring closure. ^{1}H NMR spectra displayed three broad singlets at δ 9.40–9.48 ppm due to —CONH— protons, δ 3.50–3.55 ppm due to *N*-CH protons, and δ 3.74–3.77 ppm for S—CH_2 protons confirming the formation of condensed products, while all other aromatic protons were found in the expected region. Mass spectra of final derivatives showed molecular ion peaks in full agreement with their molecular weight.

3.2. In-vitro antimicrobial activity

The newly synthesized final derivatives were screened for their antimicrobial activity and results are presented in Tables 1 & 2. The entire set of target compounds **5 (a-t)** showed significant inhibitory activities against pathogenic microbes used in the anti-microbial assay as compared to standard drug ampicillin and clotrimazole. It has been found that compounds with halogen substitution, especially Flouro and Chloro substitution at phenyl ring connected to thiazolidine moiety (**5d**, **5f**, **5g**, **5h**, **5j**) exhibited significant to substantial activity against all the tested bacterial strains. Especially compounds **5d**, **5g**, **5h**, and **5j** showed significant activity against gram-negative *E. coli* and gram-positive *L. casei*. In continuation, compounds **5j**, **5g**, and **5d** displayed potent activity against *P. aeruginosa*. Similarly against *S. aureus*, *B. cereus* compound **5g**, **5j,** and against *S. typhimurium* compound **5j** displayed prominent inhibitory activity as compared to ampicillin. Introduction of —NO_2 and —OH group substitution at phenyl ring **(5k, 5l, 5m, 5p, 5q,**

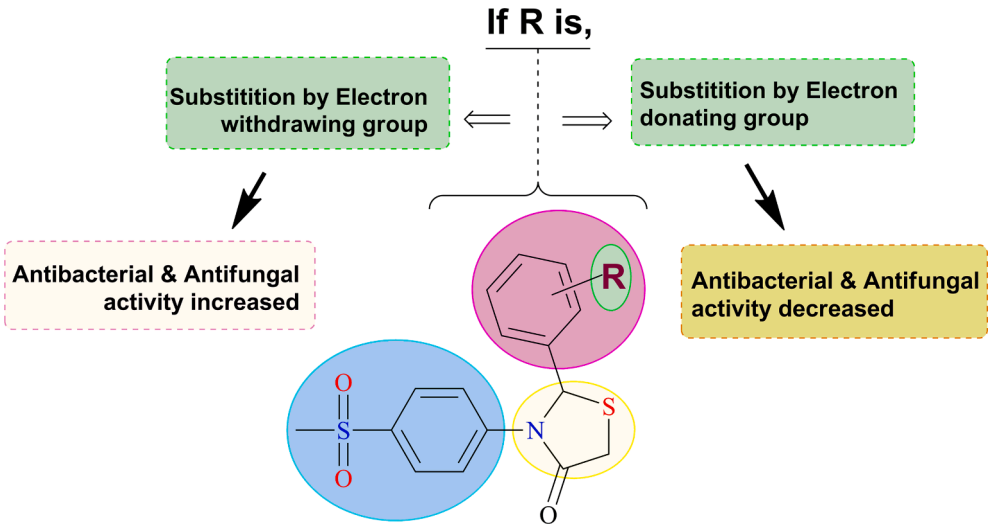


Fig. 2. General prototype structure and structure–activity relationship study of compounds **5 (a-t)** against bacterial and fungal strains.

5r) showed mild to moderate activity against tested pathogenic microbes. Meanwhile, a steep decline in activity was reported by compounds with methyl group substitution **(5r, 5 s, 5 t)** at phenyl ring connected to core 1,3-thiazolidin-4-one moiety. The rest of the compounds were found moderate to weakly active against the same pool of bacterial strains in comparison to standard drug. It has been also noted that analog with bulkier substitution **(5n)** attached to phenyl ring had nil antibacterial activity.

According to the antifungal activity profile, compounds containing nitro substitution (**5o, 5p, 7q**) and halogen substitution (**5g, 5j**) at phenyl ring displayed significant antifungal activity against all the tested fungal strains. Compounds **5q, 5p**, **5g,** and **5j** exhibited more potent activity against *A. niger*, while the compounds **5o**, **5p**, **5q, 5g,** and **5j** showed more prominent activity against *C. albicans*, and compounds **5j, 5p, 5q** displayed significant activity against *A. fumigatus* in comparison to standard drug clotrimazole. Against C. neoformans, compounds **5e**, **5g**, ***5h***, **5j**, **5o**, **5p**, and **5q** showed excellent activity as compared to other compounds. Moreover, compound **5n** showed the least activity against all fungal strains.

3.3. Structure-activity relationship

Structure-activity relationship studies, as shown in Fig. 2 clearly outlined that the presence of electron-withdrawing group on phenyl ring attached to 1,3-thiazolidin-4-one moiety greatly influenced the inhibitory activity against all the tested bacterial strains **(5g, 5j, 5d, 5f, 5p, 5q)** and fungal strains (**5g, 5j, 5o, 5p, 5q)** in comparison to their electron-donating counterparts (**5k, 5l, 5m, 5n, 5r, 5 s, 5 t)**. It is noteworthy to consider that replacement of halogen by non-halogen substituents led to the dramatic reduction in antimicrobial activity. These observations suggest the necessity of an electron-withdrawing group for the generation and escalation of antimicrobial activity. The activity might be influenced may be due to ease of penetration of molecules across the bacterial cell wall resulting in cell wall damage and interrupting cell membrane function with loss of important cellular constituents (potassium ion and amino acids), in the case of fungi, these molecules may cause modulation of steric effect on the phenyl ring.

Table 3
Antiviral activity and cytotoxicity of selected compounds in HEL cell cultures.

Com. Code	Minimum cytotoxic conc.[a] (μM)	Antiviral EC_{50}[b] (μM)					
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Herpes simplex virus-1 TK^- KOS ACV^r	Vaccinia virus	Adeno virus-2	Human Coronavirus (229E)
5a	>100	>100	>100	>100	>100	>100	>100
5c	>100	>100	>100	>100	>100	>100	>100
5e	>100	>100	>100	>100	>100	>100	>100
5g	>100	>100	>100	>100	>100	>100	>100
5h	>100	>100	>100	>100	>100	>100	>100
5k	>100	>100	>100	>100	>100	>100	>100
5m	>100	>100	>100	>100	>100	>100	>100
5n	>100	>100	>100	>100	>100	>100	>100
5o	>100	>100	>100	>100	>100	>100	>100
5p	>100	>100	>100	>100	>100	>100	>100
5q	>100	>100	>100	>100	>100	>100	>100
Brivudin	>250	0.04	>250	0.9	3.5	–	–
Cidofovir	>250	2.8	1.0	3.4	10	7.2	–
Acyclovir	>250	0.1	0.2	22	>250	–	–
Ganciclovir	>100	0.05	0.05	0.4	>100	–	–
Zalcitabine	>250	–	–	–	–	50	–
Alovudine	>250	–	–	–	–	1.4	–
Ribavirin	>250	–	–	–	–	–	>250

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

Table 4
Antiviral activity and cytotoxicity of selected compounds in Vero cell cultures.

Com. Code	Minimum cytotoxic conc.[a] (μM)	Antiviral EC_{50} (μM)					
		Para- influenza-3virus	Reovirus-1	Sindbis virus	CoxsackievirusB4	Punta Torovirus	YellowFevervirus
5a	>100	>100	>100	>100	>100	>100	>100
5c	>100	>100	>100	>100	>100	>100	>100
5e	>100	>100	>100	>100	>100	>100	>100
5g	>100	>100	>100	>100	>100	>100	>100
5h	>100	>100	>100	>100	>100	>100	>100
5k	>100	>100	>100	>100	>100	>100	>100
5m	>100	>100	>100	>100	>100	>100	>100
5n	>100	>100	>100	>100	>100	>100	>100
5o	>100	>100	>100	>100	>100	>100	>100
5p	>100	>100	>100	>100	>100	>100	>100
5q	>100	>100	>100	>100	>100	>100	>100
DS-10.000	>100	>100	>100	38	8.9	20	0.8
Ribavirin	>250	112	>250	>250	>250	126	>250
Mycophenolic acid	>100	0.4	0.4	11.7	>100	1.4	0.8

Required to reduce virus-induced cytopathogenicity by 50%.
[a] Required to cause a microscopically detectable alteration of normal cell morphology.

Table 5
Antiviral activity and cytotoxicity of selected compounds in MDCK cell cultures.

Com. Code			Antiviral EC_{50}[c]					
	Cytotoxicity		Influenza A/H1N1 A/Ned/378/05		Influenza A/H3N2 A/HK/7/87		Influenza B B/Ned/537/05	
	CC50[a] (μM)	Minimum cytotoxic conc.[b] (μM)	visual CPE score	MTS	visual CPE score	MTS	visual CPE score	MTS
5a	>100	>100	>100	>100	>100	>100	>100	>100
5c	>100	>100	>100	>100	>100	>100	>100	>100
5e	>100	>100	>100	>100	>100	>100	>100	>100
5g	>100	>100	>100	>100	>100	>100	>100	>100
5h	>100	>100	>100	>100	>100	>100	>100	>100
5k	>100	>100	>100	>100	>100	>100	>100	>100
5m	>100	>100	>100	>100	>100	>100	>100	>100
5n	>100	>100	>100	>100	>100	>100	>100	>100
5o	>100	>100	>100	>100	>100	>100	>100	>100
5p	>100	>100	>100	>100	>100	>100	>100	>100
5q	>100	>100	>100	>100	>100	>100	>100	>100
Zanamivir	>100	>100	0.8	0.04	1.8	1.2	0.4	0.02
Ribavirin	>100	≥100	8.9	9.8	8.9	1.5	2.1	1.2
Amantadine	>100	>100	>100	>100	0.4	0.3	>100	>100
Rimantadine	>200	>200	0.3	0.1	0.03	0.09	>200	>200

MDCK cells: Madin Darby canine kidney cells.
[a] 50% Cytotoxic concentration, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay.
[b] Minimum compound concentration that causes a microscopically detectable alteration of normal cell morphology.
[c] 50% Effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay.

3.4. DNA Gyrase inhibition study

Impressed by the exceptional antibacterial activity of synthesized compounds, we intend to define the probable mechanism of action of most potent compound **5j**. Thus, the inhibitory activity of compound **5j** was studied against *S. aureus* DNA gyrase enzyme. It has been found that DNA Gyrase responsible for supercoiling into the bacterial DNA, and induces initiation and elongation during replication and transcription stages of the bacterial organisms. Therefore, its inhibition possibly offers selective advantage to limit the bacterial population via introduction of negative supercoils in DNA and traps the chromosome in a positively supercoiled state that may have a downstream impact on cell physiology and division. In the present study, compound **5j** showed IC_{50} of 4.26 μM. Thus, it might be suggested that compound **5j** inhibit the bacterial growth by potent inhibition of DNA Gyrase, and it also be the possible target for other synthesized derivatives due to common structural scaffold.

3.5. Antiviral activity

Some of the synthesized compounds **(5a, 5c, 5e, 5g, 5h, 5k, 5m, 5n, 5o, 5p, 5q)** were evaluated for their antiviral efficacy against a diverse panel of RNA and DNA viruses using cytopathic effect (CPE) reduction assays inappropriate cell cultures (HEL cell, Vero cell, MDCK cells, and MT4 cell lines). From the antiviral data Table 3, 4, 5 & 6, it has been observed that almost all the tested compounds displayed a very marginal level of antiviral activity. However, compounds **5h** exhibited some antiviral potency among all the synthesized compounds in MT4 cell lines against HIV-1(strain IIIB) and HIV-2(strain ROD). In HEL cell cultures against Vaccinia virus and Human Coronavirus (229E), a very low level of activity was observed but no activity was noted in the case of Herpes simplex virus-1 (KOS), Herpes simplex virus-2 (G), and Herpes simplex virus-1 (TKKOS ACVr). In Vero cell cultures, the same set of synthesized compounds displayed negligible activity against Sindbis virus, Coxsackie virus B4, and Yellow Fever virus, but some activity exhibited against Influenza B (B/Ned/537/05) strain in MDCK cell lines.

This antiviral study suggests that a straight forward structure–activity relationship could not be derived as all the synthesized compounds showed the similar intensity of activity. The broad pool of virus testing panels allowed estimating the cytotoxicity of compounds in various mammalian cell lines. All the tested compounds were found non-cytotoxic at 100 μM, the highest concentration tested. Thus, it could be

Table 6
Anti-HIV activity and cytotoxicity of selected compounds in **MT4** cells cultures.

Com. Code	Antiviral EC_{50}		
	Minimum cytotoxic conc.[b] (μM)	HIV-1(strain IIIB)	HIV-2(strain ROD)
5a	>125	>125	>125
5c	>125	>125	>125
5e	>125	>125	>125
5g	>125	>125	>125
5h	111	111	111
5k	>125	>125	>125
5m	>125	>125	>125
5n	>125	>125	>125
5o	>125	>125	>125
5p	>125	>125	>125
5q	>125	>125	>125
Nevirapine	>4	0.075	>4
Lamivudine	>20	0.58	2.3
Azidothymidine	>2	0.0020	0.0022
Didanosine	>50	18	19

Antiviral activity and cytotoxicity were determined by the colorimetric MTT cell viability assay.
The antiviral EC_{50} represents the compound concentration producing 50% inhibition of virus-induced cytopathicity. The CC_{50} represents the compound concentration causing a 50% reduction of cell viability.

suggested that these molecules have the potential to optimize the structures towards the development of antiviral agents due to low toxic potential.

4. Conclusion

The present study demonstrates the utility and synthesis of a series of 1,3-thiazolidin-4-one sulfonyl derivatives **5 (a-t)** using an efficient and simple chemical pathway. The target compounds were evaluated for their antimicrobial and antiviral activities. An antimicrobial study revealed that electron-donating groups were found to be more active than their electron-donating counterparts. The compound **5d, 5f, 5g, 5h, 5i, 5j** showed prominent inhibitory activity against bacterial strains as compared to ampicillin. On the other hand, compound **5g, 5j, 5o, 5p,** and **5q** displayed equipotent activity against the entire tested fungal strains as compared to clotrimazole. Further, by changing the substitution pattern with bulkier group **(5n)** from smaller molecular weight substituents drastically decreased antimicrobial activity. The inhibition of *S. aureus* DNA Gyrase was identified as the probable mechanism of antibacterial activity of most active antibacterial compound **5j**. Eleven final derivatives were screened for the antiviral property, compound **5h** showed antiviral activity against HIV-1(strain IIIB) and HIV-2 (strain ROD) while other compounds possess a very low level of inhibitory activity against various DNA and RNA viruses. The derivatives may be considered as promising antimicrobial analogs whereas further structural modification can lead to the development of potent antiviral agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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References

[1] H. Nikaido, Annu. Rev. Biochem. 78 (2009) 119–146.
[2] A.D. Russell, J. Appl. Microbiol. 92 (2002) 1–3.
[3] X.Z. Li, H. Nikaido, Drugs. 64 (2004) 159–204.
[4] A. Machowska, C.S. Lundborg, Int. J. Environ. Res. Pub. Heal. 16 (2019) 1–14.
[5] C. Buke, M.H. Limoncu, S. Ermertcan, M. Ciceklioglu, M. Tuncel, T. Kose, S. Eren, J. Infec. 51 (2005) 135–139.
[6] V. Ravichandran, A. Jain, K.S. Kumar, H. Rajak, R.K. Agrawal, Chem. Biol. Drug Des. 78 (2011) 464–470.
[7] F.C. Brown, Chem. Rev. 61 (1961) 463–521.
[8] W. Cunico, C.R.B. Gomes, W.T. Vellasco, Mini-Rev. in Org. Chem. 5 (2008) 336–344.
[9] S. Raza, S.P. Srivastava, D.S. Srivastava, A.K. Srivastava, W. Haq, S.B. Katti, Eur. J. Med. Chem. 63 (2013) 611–620.
[10] S.K. Suthar, V. Jaiswal, S. Lohan, S. Bansal, A. Chaudhary, A. Tiwari, A.T. Alex, A. Joesph, Eur. J. Med. Chem. 63 (2013) 589–602.
[11] I. Apostolidis, K. Liaras, A. Geronikaki, D. Hadjipavlou-Litina, A. Gavalas, M. Sokovic, J. Glamoclija, A. Ciric, Bioorg. Med. Chem. 21 (2013) 532–539.
[12] E. Rajanarendar, E. K. Rao, F. P. Shaik, M. N. Reddy, M. Srinivas, J. of Sulfur Chem. 31(2010) 4 263-274.
[13] H. Liu, Z. Li, T. Anthonsen, Molecules. 5 (2000) 1055–1061.
[14] A.M. Isloor, D. Sunil, P. Shetty, S. Malladi, K.S.R. Pai, N. Maliyakkl, Med. Chem. Res. 22 (2013) 758–767.
[15] D. S. Silva, C. E. H. Silva, M. S. P. Soares, J. H. Azambuja, T. R. Carvalho, G. C. Zimmer, C. P. Frizzo, E. Braganhol, R. M. Spanevello, W. Cunico, Eur. J. Med. Chem. 124(2016) 29 574-582.
[16] B. M. Gurupadayya, M. Gopal, B. Padmashali, Y. N. Manohara, Indian J. Pharm. Sci. 70(2008) 5 572-577.
[17] G.K. Verma, G. Shukla, A. Nagaraju, A. Srivastava, K. Raghuvanshib, M.S. Singh, RSC Adv. 4 (2014) 11640–11647.
[18] N. Sahiba, A. Sethiya, J. Soni, D. K. Agarwal, S. Agarwal, Top Curr. Chem. 378 (2020) 34 1-90.
[19] Sucheta, S. Tahlan, P. K. Verma, Chem. Cent. J. 12(2018) 129 1-11.
[20] H.M.A. Ashour, A.E.A. Wahab, Arch. Pharm. Chem. Life Sci. 342 (2009) 238–252.
[21] S. Mahmood, A. Saeed, S. Bua, A. Nocentini, P. Gratteri, C.T. Supuran, Bioorg. Chem. 77 (2018) 381–386.
[22] N.M. Parekh, K.V. Juddhawala, B.M. Rawal, Med. Chem. Res. 22 (2013) 2737–2745.
[23] S.K. Suthar, S. Bansal, S. Lohan, V. Modak, A. Chaudhary, A. Tiwari, Eur. J. Med. Chem. 66 (2013) 372–379.
[24] A. Tacic, V. Nikolic, L. Nikolic, I. Savic, Adv. Tech. 6(2017) 1 58-71.
[25] N.T. Thuan, D.T.M. Dung, D.N. Que, P.T.P. Dung, T.K. Vu, H. Hahn, B.W. Han, Y. Kim, S. Han, N. Nam, D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, Med. Chem. Res. 5 (2015) 3803–3812.
[26] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, A. Gzella, R. Lesyk, J. Med. Chem. 20 (2012) 20 8630-8641.
[27] Q. Zhang, H. Zhou, S. Zhai, B. Yan, Cur. Phar. Design. 16 (2010) 1826–1842.
[28] N. A. A. Elkanzi, World J. Org. Chem. 1(2013) 2, 24-51.
[29] Clinical and Laboratory Standards Institute. 2006; M7-A7. Wayne, Pennsylvania, USA, 1-49.
[30] Clinical and Laboratory Standards Institute. 2002; M27-A2. Wayne, Pennsylvania, USA, 1-29.
[31] F. Blanche, B. Cameron, F.X. Bernard, L. Maton, B. Manse, L. Ferrero, N. Ratet, C. Lecoq, A. Goniot, D. Bisch, J. Crouzet, Antimicrob. Agents Chemother. 40 (1996) 2714–2720.
[32] Z. Turgut, C. Yolacan, F. Aydogan, E. Bagdatli, N. Ocal, Molecules. 12 (2007) 2151–2159.
[33] H.M. Dalloul, J. Chinese Chem. Soc. 56 (2009) 196–201.