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Cogent Chemistry (2015), 1: 1048558



Received: 15 January 2015
Accepted: 28 April 2015
Published: 27 May 2015

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Reviewing editor:
George Weaver, University of
Loughborough, UK

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Synthesis and some novel transformations of a spiro 4-thiazolinone derivative and its antimicrobial activities

Paresh N. Patel¹ and Yogesh S. Patel^{2*}

Abstract: Present communication deals with the synthesis and characterization of various spiro thiazolinone heterocyclic compounds. 4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (**5**) was synthesized by facile and fast heterocyclization reaction, which further underwent condensation with 4-chlorobenzaldehyde to afford 2-(4-chlorobenzylidene)-4-(4-(6,7-dihydrothieno[3,2-c]pyridine-5(4H)-ylsulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (**6**). Resultant compound was used as precursor for the preparation of some bioactive fused heterocyclic compounds (**7–10**). All the synthesized compounds were duly characterized by elemental analyses and various spectroscopic techniques. All the synthesized compounds were screened for their antimicrobial activity and it was observed that as the fusion of heterocyclic rings increases its shown higher antimicrobial activities.

Subjects: Bioscience; Environment & Agriculture; Physical Sciences

Keywords: spiro thiazolinone; thiazolopyrimidine pyrazolothiazole

1. Introduction

The last few decades have seen a flurry of activity in the synthesis and development of heterocyclic compounds because of their important biological properties. Heterocyclic compounds containing small rings have been under investigation for a long time because of their important medicinal properties and also contributed to the society from biological and industrial points of view which helps to understand life processes (Yata, Reddy, & Talagadadivi, 2014). Among these types of heterocyclic



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Paresh N. Patel did his PhD in organic synthesis. At present he is doing post doctoral fellowship in India's most reputed Indian Institute of Technology-Madras, Chennai. He is highly engaged in the organic and bio organic research. He published good research articles in the well reputed journals with high impact. He also published few books. The research work incorporated in this article was carried out as a part of his research at one of the most reputed Sardar Patel University, Vallabh Vidyanagar, Gujarat.

Yogesh S. Patel did his PhD in the same university. At present he is head of the department chemistry, Government Science College, Gandhinagar. He is having 17 years of teaching experience. He had published very good articles in the various fields of chemistry and also published books.

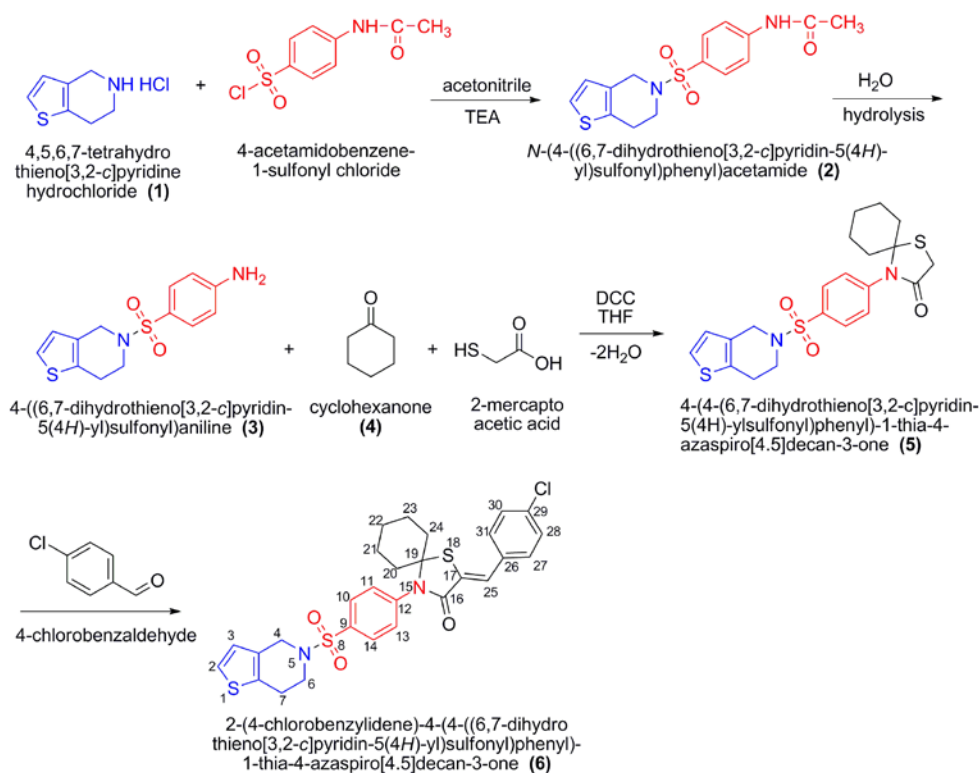
PUBLIC INTEREST STATEMENT

4-Thiazolidinone derivatives exhibit high activity *in vitro* against mycobacterium tuberculosis (TB) and as drugs to treat HIV and cancer. Looking to the better properties of this heterocyclic compound, we have synthesized various spiro heterocyclic derivatives of 4-thiazolidinone for the investigation of an antimicrobial activity profile. Many of the synthesized compounds showed good activity against the test bacteria and fungi. From the results it is observed that as the fusion of heterocyclic rings increases, the antimicrobial activities also increase significantly.

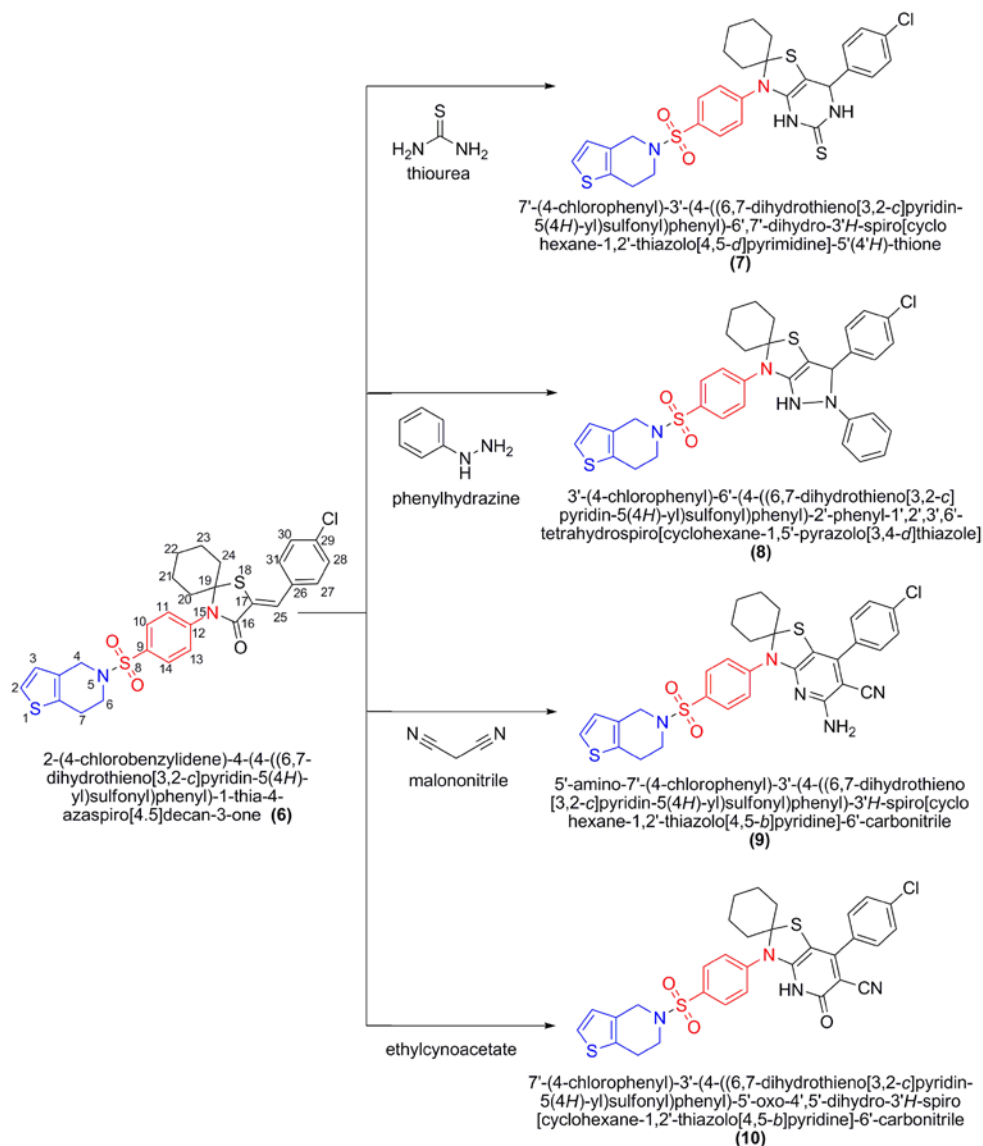
molecules, 4-thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory, and analgesic properties (Hamdi, Al-Ayed, Ben Said, & Fabienne, 2012; Kavitha et al., 2006; Küçükgül, Kocatepe, De Clercq, Şahin, & Güllüce, 2006). 4-Thiazolidinone derivatives exhibit high activity *in vitro* against mycobacterium tuberculosis (TB) and as drugs to treat HIV and cancer (Chen et al., 2009; Küçükgül et al., 2006; Rao et al., 2004). They were also reported as novel inhibitors of the MurB enzyme, integral component in bacterial peptidoglycan biosynthesis, at the low micromolar level (Rubinchik et al., 2011). Recently, 2-aryl-4-thiazolidinone has been synthesized and found to exhibit potent selective antiplatelet-activating factors both *in vitro* and *in vivo* and anti-inflammatory (Bhati & Kumar, 2008), antibacterial (Sayyed et al., 2006), anticancer (Colombo et al., 2008), and anti-HIV-1 activities (Murugesan, Prabhakar, & Katti, 2009). Spiro heterocyclic compounds including thiazolidine moiety have antimicrobial activity (Jain, Sinha, Bhagat, Errington, & Olsen, 2003). Both pyrazolothiazole and thiazolopyrimidine moieties have potent kinase modulators (Lewis et al., 1994), and are used in pharmaceutical compositions (Binnun et al., 2007). This compound has analgesic and anti-Parkinson activities (Amr, Maigali, & Abdulla, 2008) and inhibits the growth of parasite trypanosome cruse (Diego et al., 2001). Such medicinal properties associated with these heterocyclic molecules render them as useful structural units in drug research.

These findings prompted us to synthesize various spiro heterocyclic derivatives of 4-thiazolidinone for the investigation of an antimicrobial activity profile. Our synthetic approach in the different phases of this work, viz.: (1) synthesis of N-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)sulfonyl)phenyl)acetamide, (2) synthesis of 4-((6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl)sulfonyl)aniline, (3) synthesis of 4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)sulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one, (4) synthesis of 2-(4-chlorobenzylidene)-4-(4-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)sulfonyl) phenyl)-1-thia-4-azaspiro[4.5]decan-3-one, and (5) synthesis of bioactive fused heterocyclic compounds. The synthetic approach is summarized in Schemes 1 and 2 and details of the procedures and the results obtained are discussed below.

Scheme 1. Synthesis of compounds 2–6.



Scheme 2. Synthesis of compounds 7–10.



2. Experimental

All common reagents and solvents were used of analytical grade and were used without further purification. Alumina supported pre-coated silica gel 60 F254 thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check the purity of compounds and to study the progress of the reaction whereby TLC plates were illuminated under ultraviolet light (254 nm), evaluated in I_2 vapors and visualized by spraying with Dragendorff's reagent. Infrared spectra (FT-IR) were obtained from KBr pellets in the range of 4,000–400 cm^{-1} with a Perkin Elmer spectrum GX spectrophotometer (FT-IR) instrument. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were acquired at 400 MHz on a Bruker NMR spectrometer using $\text{DMSO-}d_6$ as a solvent as well as TMS an internal reference standard. All melting points were determined on an Electro-thermal IA 9100 apparatus and are uncorrected. Mass spectra (MS) were recorded on EI + Q1 MSLMR UPLR. Microanalytical (C, N, H) data were obtained using Perkin-Elmer 2400 C.H.N elemental analyzer. The initial compound 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (THTP) was synthesized as per the method reported (Hoshang, Shabana, & Krishna, 2008). Required chemicals were purchased from Merck, Fluka, and local market.

2.1. N-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)acetamide (2)

An equimolecular mixture of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (THTP) **1** (0.01 mol, 1.755 g) and 4-acetamidobenzene-1-sulfonylchloride (0.01 mol, 2.335 g) was dissolved in anhydrous acetonitrile (20 mL) using triethylamine (0.01 mol/0.730 g) as base under constant stirring, then the reaction mixture was refluxed for 5 h. After completion of reaction, it was poured in ice-cold water to obtain light yellow colored product **2**, which was filtered and dried. It was purified by column chromatographic technique (petroleum ether: chloroform; 40:60; v/v) and recrystallized from ethanol to give light yellow colored crystalline compound. Yield 87.3%, mp 178–180°C; IR (KBr, ν , cm^{-1}): 3324(-NH, amide, D_2O exchangeable), 1665(>C=O, amide), 1352–1146(SO_2), 1228(C–N, THTP), 724(C–S–C, THTP); $^1\text{H-NMR}$ δ (ppm): 2.42 (t, $J = 6.2$ Hz, 2H, $\text{C}_7\text{-H}$), 2.45 (s, 3H, $-\text{COCH}_3$), 3.07 (t, $J = 6.2$ Hz, 2H, $\text{C}_6\text{-H}$), 3.64 (t, 2H, $\text{C}_4\text{-H}$), 6.28 (s, 1H, $-\text{CONH}$), 6.67 (d, $J = 4.6$ Hz, 1H, $\text{C}_3\text{-H}$), 7.28 (d, $J = 4.8$ Hz, 1H, $\text{C}_2\text{-H}$), 7.42 (d, $J = 8.6$ Hz, 2H, $\text{C}_{11}\text{-H}$, $\text{C}_{13}\text{-H}$), 7.64 (d, $J = 8.6$ Hz, 2H, $\text{C}_{10}\text{-H}$, $\text{C}_{14}\text{-H}$); $^{13}\text{C-NMR}$ δ (ppm): 22.7, 23.8, 24.2, 47.9, 51.4, 117.6, 123.7, 124.2, 132.6, 133.1, 134.6, 142.3, 169.7; ms: m/z 336.18. *Anal. Calcd.* for $\text{C}_{15}\text{H}_{16}\text{O}_3\text{N}_2\text{S}_2$ (336.46): C: 53.57, H: 4.76, N: 8.33, S: 19.02. Found: C: 53.56, H: 4.74, N: 8.32, S: 19.00.

2.2. 4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)aniline (3)

Compound **3** was prepared by base catalyzed hydrolysis of 0.01 mol (3.36 g) N-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)acetamide **2**, using (25 mL) 10% sodium hydroxide solution. The reaction mixture was refluxed for 2 h. The solid compound separated was filtered, dried, and recrystallized from ethanol to give white crystalline compound. Yield 64.9%, mp 171–172°C; IR (KBr, ν , cm^{-1}): 3440(N–H, amine), 1346–1148(SO_2), 1229(C–N, THHP), 728(C–S–C, THTP); $^1\text{H-NMR}$ δ (ppm): 2.47 (t, $J = 6.2$ Hz, 2H, $\text{C}_7\text{-H}$), 3.09 (t, $J = 6.2$ Hz, 2H, $\text{C}_6\text{-H}$), 3.68 (s, 2H, $\text{C}_4\text{-H}$), 6.74 (d, $J = 4.6$ Hz, 1H, $\text{C}_3\text{-H}$), 7.36 (d, $J = 4.8$ Hz, 1H, $\text{C}_2\text{-H}$), 7.42 (d, $J = 8.6$ Hz, 2H, $\text{C}_{11}\text{-H}$, $\text{C}_{13}\text{-H}$), 7.74 (d, $J = 8.6$ Hz, 2H, $\text{C}_{10}\text{-H}$, $\text{C}_{14}\text{-H}$), 11.24 (s, 2H, $-\text{NH}_2$, D_2O exchangeable); $^{13}\text{C-NMR}$ δ (ppm): 22.8, 47.4, 51.6, 123.7, 124.2, 128.6, 129.2, 112.7, 132.4, 133.7, 149.3; ms: m/z 293.70. *Anal. Calcd.* for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}_2\text{S}_2$ (294): C: 53.06, H: 4.76, N: 9.52, S: 21.77. Found: C: 53.04, H: 4.75, N: 9.49, S: 21.74.

2.3. 4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (5)

4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)aniline (1.47 g, 5 mmol) and cyclohexanone (0.98 g, 10 mmol) were stirred in tetrahydrofuran (THF) in an ice bath for 5 min, followed by addition of mercaptoacetic acid (1.38 g, 15 mmol). After 5 min N,N-dicyclohexylcarbodiimide (1.2 mmol) was added to the reaction mixture at 0°C and the reaction mixture stirred for additional 1–3 h at room temperature. Formed dicyclohexylurea was removed by filtration. Filtrate was concentrated to dryness under reduced pressure and the residue was taken up with ethyl acetate. The organic layer was washed with 5% aq. citric acid, water, 5% aq. sodium hydrogen carbonate and then with brine. The organic layer was dried over sodium sulfate and the solvent removed under vacuum to give the crude product, which was purified by recrystallization from 2:1 petroleum ether–diethyl ether to afford compound **5**. Yield 78.4%, mp 166–167°C; IR (KBr, ν , cm^{-1}): 1338–1142(SO_2), 1695(CO, thiozolidinone); $^1\text{H-NMR}$ δ (ppm): 1.34 (brd., 6H, $\text{C}_{21-23}\text{-H}$), 1.78 (t, $J = 2.40$ Hz, 4H, $\text{C}_{20}\text{-H}$, $\text{C}_{24}\text{-H}$), 2.45 (t, $J = 6.2$ Hz, 2H, $\text{C}_7\text{-H}$), 3.12 (t, $J = 6.2$ Hz, 2H, $\text{C}_6\text{-H}$), 3.62 (s, 2H, $\text{C}_{18}\text{-H}$), 3.71 (t, 2H, $\text{C}_4\text{-H}$), 6.72 (d, $J = 4.6$ Hz, 1H, $\text{C}_3\text{-H}$), 7.34 (d, $J = 4.8$ Hz, 1H, $\text{C}_2\text{-H}$), 7.48 (d, $J = 8.6$ Hz, 2H, $\text{C}_{11}\text{-H}$, $\text{C}_{13}\text{-H}$), 7.78 (d, $J = 8.6$ Hz, 2H, $\text{C}_{10}\text{-H}$, $\text{C}_{14}\text{-H}$); $^{13}\text{C-NMR}$ δ (ppm): 23.7, 24.3, 25.4, 32.4, 34.7, 47.9, 52.3, 68.2, 121.5, 124.0, 124.6, 128.7, 132.7, 134.9, 135.3, 143.7, 170.2; ms: m/z 448.24. *Anal. Calcd.* for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3\text{S}_3$ (448.62): C: 56.22; H: 5.39; N: 6.24; S: 21.44. Found: C: 56.23; H: 5.37; N: 6.25; S: 21.47.

2.4. 2-(4-chlorobenzylidene)-4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (6)

A mixture of compound **5** (2.48 g, 5 mmol) and 4-chlorobenzaldehyde (0.7 mL, 5 mmol) was refluxed in a mixture of glacial acetic acid and acetic anhydride (3:1) containing anhydrous sodium acetate (0.36 g, 5 mmol) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cool water (100 mL). The formed solid was filtered off, dried, and recrystallized from methanol to give compound **6**. Yield 68.4%, mp 189–190°C; IR (KBr, ν , cm^{-1}): 1698(CO, thiazolidinone), 1338–1152(SO_2), 1264 and 1077(C–Cl); $^1\text{H-NMR}$ δ (ppm): 1.32 (brd., 6H, $\text{C}_{21-23}\text{-H}$), 1.79 (t, $J = 2.28$ Hz, 4H, $\text{C}_{20}\text{-H}$, $\text{C}_{24}\text{-H}$),

2.47 (t, $J = 6.2$ Hz, 2H, C₇-H), 3.14 (t, $J = 6.2$ Hz, 2H, C₆-H), 3.76 (t, 2H, C₄-H), 6.64 (s, 1H, C₂₅-H), 6.74 (d, $J = 4.6$ Hz, 1H, C₃-H), 7.33 (d, $J = 4.8$ Hz, 1H, C₂-H), 7.42 (d, $J = 8.0$ Hz, 2H, C₂₈-H, C₃₀-H), 7.71 (d, $J = 8.0$ Hz, 2H, C₂₇-H, C₃₁-H), 7.82 (d, $J = 8.6$ Hz, 2H, C₁₀-H, C₁₄-H), 7.98 (d, $J = 8.6$ Hz, 2H, C₁₁-H, C₁₃-H); ¹³C-NMR δ (ppm): 23.5, 24.8, 25.2, 32.7, 47.6, 52.5, 72.4, 121.4, 123.8, 124.2, 124.9, 126.7, 127.2, 128.3, 128.7, 129.2, 132.3, 134.2, 135.3, 138.4, 141.7, 167.2; ms: m/z: 570.68. *Anal. Calcd.* for C₂₈H₂₇ClN₂O₃S₃ (571.17): C: 58.88; H: 4.76; N: 4.90; S: 16.84. Found: C: 58.85; H: 4.77; N: 4.92; S: 16.82.

2.5. 7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-6',7'-dihydro-3'H-spiro[cyclohexane-1,2'-thiazolo[4,5-d]pyrimidine]-5'(4'H)-thione (7)

An equimolar mixture of **6** (3.09 g, 5 mmol) and thiourea (0.35 g, 5 mmol) in absolute ethanol (25 mL)/ anhydrous pyridine (25 mL) was refluxed for 9 h. On cooling, the crude solid appeared which was filtered, washed with ice-cold water containing dil. HCl with constant stirring. The formed solid was filtered off, dried and recrystallized from dioxane to give compound **7**. Yield 62.8%, mp 273–274°C; IR (KBr, ν , cm⁻¹): 3146, 3124(2NH), 1217(CS), 1273 and 1064(C-Cl); ¹H-NMR δ (ppm): 1.30 (brd., 6H, C₂₁₋₂₃-H), 1.77 (t, $J = 2.32$ Hz, 4H, C₂₀-H, C₂₄-H), 2.48 (t, $J = 6.2$ Hz, 2H, C₇-H), 3.14 (t, $J = 6.2$ Hz, 2H, C₆-H), 3.77 (t, 2H, C₄-H), 4.63 (s, 1H, C₂₅-H), 6.78 (d, $J = 4.6$ Hz, 1H, C₃-H), 7.34 (d, $J = 4.8$ Hz, 1H, C₂-H), 7.42 (d, $J = 8.0$ Hz, 2H, C₂₈-H, C₃₀-H), 7.74 (d, $J = 8.0$ Hz, 2H, C₂₇-H, C₃₁-H), 7.83 (d, $J = 8.6$ Hz, 2H, C₁₀-H, C₁₄-H), 7.96 (d, $J = 8.6$ Hz, 2H, C₁₁-H, C₁₃-H), 9.48 (s, 1H, -NH broad, D₂O exchangeable), 10.24 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR δ (ppm): 23.5, 24.8, 25.2, 34.7, 47.6, 52.5, 62.7, 68.4, 117.8, 123.8, 124.2, 124.9, 126.7, 127.2, 127.8, 128.3, 128.7, 129.2, 133.2, 134.2, 141.0, 146.4, 173.2; ms: m/z: 629.12. *Anal. Calcd.* for C₂₉H₂₉ClN₄O₂S₄ (629.28): C: 55.35; H: 4.65; N: 8.90; S: 20.38. Found: C: 55.33; H: 4.67; N: 8.91; S: 20.37.

2.6. 3'-(4-chlorophenyl)-6'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2'-phenyl-1',2',3',6'-tetrahydrospiro[cyclohexane-1,5'-pyrazolo[3,4-d]thiazole] (8)

A mixture of compound **6** (3.09 g, 5 mmol) and phenyl hydrazine (1.06 mL, 10 mmol) was refluxed in absolute ethanol (50 mL) for 4 h. The reaction mixture was cooled, and the solid substance was filtered off, dried, and recrystallized from dioxane to give compound **8**. Yield 80.63%, mp 263–264°C; IR (KBr, ν , cm⁻¹): 3236(NH, pyrazole), 1277 and 1063(C-Cl); ¹H-NMR δ (ppm): 1.29 (brd., 6H, C₂₁₋₂₃-H), 1.76 (t, $J = 2.26$ Hz, 4H, C₂₀-H, C₂₄-H), 2.45 (t, $J = 6.2$ Hz, 2H, C₇-H), 3.18 (t, $J = 6.2$ Hz, 2H, C₆-H), 3.78 (t, 2H, C₄-H), 4.78 (s, 1H, C₂₅-H), 6.74 (d, $J = 4.6$ Hz, 1H, C₃-H), 7.32 (d, $J = 4.8$ Hz, 1H, C₂-H), 7.45–7.98 (m, 13H, Ar-H), 9.87 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR δ (ppm): 23.5, 24.8, 25.2, 35.4, 47.6, 52.5, 67.4, 77.4, 115.7, 117.3, 121.6, 123.8, 124.2, 124.9, 125.4, 126.7, 127.2, 127.8, 128.7, 129.5, 132.3, 134.5, 138.4, 141.7, 146.7, 151.0; ms: m/z: 660.98. *Anal. Calcd.* for C₃₄H₃₃ClN₄O₂S₃ (661.30): C: 61.75; H: 5.03; N: 8.47; S: 14.55. Found: C: 61.73; H: 5.05; N: 8.46; S: 14.53.

2.7. 5'-amino-7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-3'H-spiro[cyclohexane-1,2'-thiazolo[4,5-b]pyridine]-6'-carbonitrile (9)

A mixture of compound **6** (3.09 g, 5 mmol), malononitrile (0.66 g, 10 mmol) and ammonium acetate (1.53 g, 20 mmol) was refluxed in glacial acetic acid (40 mL) for 30 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **9**. Yield 63.42%, mp 222–223°C; IR (KBr, ν , cm⁻¹): 3423–3215(NH₂), 2217(CN), 1275 and 1058(C-Cl); ¹H-NMR δ (ppm): 1.31 (brd., 6H, C₂₁₋₂₃-H), 1.72 (t, $J = 2.60$ Hz, 4H, C₂₀-H, C₂₄-H), 2.46 (t, $J = 6.2$ Hz, 2H, C₇-H), 3.15 (t, $J = 6.2$ Hz, 2H, C₆-H), 3.77 (t, 2H, C₄-H), 6.75 (d, $J = 4.6$ Hz, 1H, C₃-H), 7.34 (d, $J = 4.8$ Hz, 1H, C₂-H), 7.44 (d, $J = 8.0$ Hz, 2H, C₂₈-H, C₃₀-H), 7.78 (d, $J = 8.0$ Hz, 2H, C₂₇-H, C₃₁-H), 7.86 (d, $J = 8.6$ Hz, 2H, C₁₀-H, C₁₄-H), 7.97 (d, $J = 8.6$ Hz, 2H, C₁₁-H, C₁₃-H), 10.28 (s, 2H, NH₂, D₂O exchangeable); ¹³C-NMR δ (ppm): 23.5, 24.8, 25.2, 34.6, 47.6, 52.5, 76.0, 114.2, 117.6, 121.4, 123.8, 124.2, 124.9, 126.7, 127.2, 128.3, 128.7, 129.2, 132.3, 134.2, 138.4, 147.2, 150.7, 151.2, 156.4; ms: m/z: 634.16. *Anal. Calcd.* for C₃₁H₂₈ClN₅O₂S₃ (634.23): C: 58.71; H: 4.45; N: 11.04; S: 15.17. Found: C: 58.73; H: 4.43; N: 11.05; S: 15.19.

2.8. 7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-5'-oxo-4',5'-dihydro-3'H-spiro[cyclohexane-1,2'-thiazolo[4,5-b]pyridine]-6'-carbonitrile (10)

A mixture of compound **6** (3.09 g, 5 mmol), ethyl cyanoacetate (1.13 g, 10 mmol), and anhydrous ammonium acetate (1.60 g, 20 mmol) was refluxed in glacial acetic acid (40 mL) for 20 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from acetic acid to give compound **10**. Yield 63.45%, mp 251–252°C; IR (KBr, ν , cm^{-1}): 3252(NH), 2234(CN), 1687(CO), 1280 and 1063(C–Cl); $^1\text{H-NMR}$ δ (ppm): 1.32 (brd., 6H, $\text{C}_{21-23}\text{-H}$), 1.78 (t, $J = 2.23$ Hz, 4H, $\text{C}_{20}\text{-H}$, $\text{C}_{24}\text{-H}$), 2.47 (t, $J = 6.2$ Hz, 2H, $\text{C}_7\text{-H}$), 3.15 (t, $J = 6.2$ Hz, 2H, $\text{C}_6\text{-H}$), 3.78 (t, 2H, $\text{C}_4\text{-H}$), 6.73 (d, $J = 4.6$ Hz, 1H, $\text{C}_3\text{-H}$), 7.34 (d, $J = 4.8$ Hz, 1H, $\text{C}_2\text{-H}$), 7.43 (d, $J = 8.0$ Hz, 2H, $\text{C}_{28}\text{-H}$, $\text{C}_{30}\text{-H}$), 7.72 (d, $J = 8.0$ Hz, 2H, $\text{C}_{27}\text{-H}$, $\text{C}_{31}\text{-H}$), 7.86 (d, $J = 8.6$ Hz, 2H, $\text{C}_{10}\text{-H}$, $\text{C}_{14}\text{-H}$), 7.98 (d, $J = 8.6$ Hz, 2H, $\text{C}_{11}\text{-H}$, $\text{C}_{13}\text{-H}$), 9.21 (s, 1H, NH, D_2O exchangeable); $^{13}\text{C-NMR}$ δ (ppm): 23.5, 24.8, 25.2, 36.1, 47.6, 52.5, 67.2, 114.8, 118.7, 123.2, 123.8, 124.2, 124.9, 126.7, 127.2, 128.3, 128.7, 129.2, 132.3, 134.2, 138.4, 146.7, 150.2, 152.3, 167.8; ms: m/z : 634.86. *Anal. Calcd.* for $\text{C}_{31}\text{H}_{27}\text{ClN}_4\text{O}_3\text{S}_3$ (635.22): C: 58.61; H: 4.28; N: 8.82; S: 15.14. Found: C: 58.60; H: 4.29; N: 8.85; S: 15.13.

2.9. Antibacterial assay

Selected representative of the synthesized compounds were screened for antimicrobial activity against Gram-positive bacteria viz. *Bacillus subtilis*, *Bacillus sphaericus*, *Staphylococcus aureus*, and Gram-negative bacteria viz. *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Chromobacterium violaceum* by disk diffusion, microdilution/turbidometric methods (Bauer, Kirby, Sherris, & Turck, 1996; Jorgensen & Ferraro, 2009). For the antibacterial assay standard inoculums (1–2; 107 c.f.u mL^{-1} 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6.26 mm in diameter were prepared from Whatman No. 1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37°C. The inhibition zones were measured and compared with the standard. For the determination of MIC, bacteria were grown overnight in Luria Bertani (LB) broth at 37°C harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial twofold dilutions in the range of 50–0.8 $\mu\text{g mL}^{-1}$, 10 mL of the broth containing about 105 c.f.u mL^{-1} of test bacteria was added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37°C, and the growth was monitored visually and spectrometrically. The lowest concentration required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, $\mu\text{g mL}^{-1}$), and mean inhibition zone were also determined and compared with the standard drug streptomycin. The MIC and mean zone inhibition (MZI) data are presented in Table 1.

2.10. Antifungal assay

The selective representative or the series were also screened for their antifungal activity against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* in DMSO by agar diffusion and broth dilution methods (Shorey, Agrawal, Jain, Dwivedi, & Kishore, 2010). For the antifungal assay, Sabourands agar media was prepared in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliter of agar media was poured into each petri dish, excess of suspension was decanted, and the plates were dried by placing in an incubator at 37°C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37°C for 3–4 days. The *C. albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* were plated in potato dextrose agar (Difco) and incubated at 28°C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculums size of 105 spores mL^{-1} . Each test compound was dissolved in DMSO and diluted with potato dextrose broth

Table 1. Antibacterial activity of compounds 5–10

Compounds	Minimal inhibitory concentration (MIC) ($\mu\text{g mL}^{-1}$) ^a						Mean zone inhibition (MZI) (mm) ^a					
	A	B	C	D	E	F	A	B	C	D	E	F
Streptomycin	15 ± 0.5	19 ± 0.8	18 ± 0.8	20 ± 0.5	20 ± 1.0	18 ± 0.5	15 ± 0.5	17 ± 0.5	20 ± 1.0	18 ± 0.6	16 ± 0.8	20 ± 0.5
5	30 ± 0.7	29 ± 1.0	37 ± 1.1	42 ± 0.7	38 ± 1.2	28 ± 0.4	05 ± 0.2	07 ± 0.2	09 ± 0.3	07 ± 0.4	10 ± 0.3	11 ± 0.7
6	27 ± 1.0	25 ± 1.0	34 ± 0.8	36 ± 0.8	32 ± 1.1	25 ± 0.2	09 ± 0.2	10 ± 0.3	12 ± 1.1	09 ± 0.4	11 ± 0.2	13 ± 1.0
7	18 ± 1.1	22 ± 1.1	29 ± 1.0	29 ± 0.4	26 ± 0.5	21 ± 0.8	11 ± 0.5	12 ± 0.7	15 ± 1.0	12 ± 0.5	13 ± 0.8	16 ± 1.0
8	16 ± 0.4	20 ± 0.5	24 ± 0.5	27 ± 0.3	22 ± 1.0	19 ± 0.6	13 ± 1.0	14 ± 1.0	17 ± 1.0	14 ± 1.1	15 ± 1.2	18 ± 0.2
9	17 ± 0.8	21 ± 1.0	26 ± 0.8	30 ± 0.5	27 ± 1.0	22 ± 0.4	12 ± 0.5	13 ± 0.5	16 ± 1.8	11 ± 0.7	12 ± 0.9	14 ± 1.2
10	19 ± 0.4	22 ± 0.4	26 ± 0.4	27 ± 0.4	24 ± 0.8	20 ± 0.9	10 ± 0.8	16 ± 0.5	16 ± 1.4	13 ± 0.8	12 ± 1.0	15 ± 1.2

Notes: A: *Bacillus subtilis*; B: *Bacillus sphaericus*; C: *Staphylococcus aureus*; D: *Pseudomonas aeruginosa*; E: *Klebsiella aerogenes*; F: *Chromobacterium violaceum*. Streptomycin (25 $\mu\text{g/disk}$) and compounds (50 $\mu\text{g/disk}$) were used for the assay.

^aValues are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

Table 2. Antifungal activity of compounds 5–10

Compounds	Minimal inhibitory concentration (MIC) ($\mu\text{g mL}^{-1}$) ^a				Mean zone inhibition (MZI) (mm) ^a			
	G	H	I	J	G	H	I	J
Amphotericin B	15 ± 1.1	20 ± 1.0	22 ± 1.3	18 ± 0.8	20 ± 1.0	19 ± 1.0	18 ± 1.1	22 ± 0.6
5	30 ± 1.1	36 ± 1.2	42 ± 1.4	52 ± 2.0	06 ± 0.4	08 ± 1.2	06 ± 1.1	08 ± 1.2
6	27 ± 1.6	29 ± 1.6	34 ± 1.5	42 ± 0.8	08 ± 0.3	09 ± 1.6	11 ± 0.9	10 ± 0.6
7	24 ± 1.2	26 ± 1.2	28 ± 1.6	30 ± 1.2	14 ± 0.5	12 ± 1.2	14 ± 1.2	19 ± 0.5
8	22 ± 1.0	20 ± 1.2	30 ± 1.4	32 ± 1.6	16 ± 0.8	15 ± 0.6	12 ± 1.0	21 ± 0.7
9	20 ± 0.8	23 ± 0.6	32 ± 1.0	16 ± 0.8	13 ± 0.6	14 ± 1.4	11 ± 1.0	17 ± 0.8
10	23 ± 1.0	21 ± 0.7	29 ± 1.0	26 ± 0.9	14 ± 0.7	14 ± 1.0	13 ± 1.0	18 ± 0.5

Notes: G: *Candida albicans*; H: *Aspergillus fumigatus*; I: *Trichophyton rubrum*; J: *Trichophyton mentagrophytes*. Amphotericin B (75 $\mu\text{g/disk}$) and compounds (100 $\mu\text{g/disk}$) were used for assay.

^aValues are means of three determinations, the ranges of which are less than 5% of the mean in all cases.

(Difco) to prepare serial twofold dilutions in the range 100–0.8 $\mu\text{g mL}^{-1}$. Ten milliliter of the broth containing about 10⁴ (for filamentous fungi) cells mL^{-1} of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for about 48–72 h at 28°C. The lowest concentration required to arrest the growth of fungi was regarded as MIC ($\mu\text{g mL}^{-1}$), and mean inhibition zone were also determined and compared with the standards drug Amphotericin B. The MIC and MZI data are presented in Table 2.

3. Results and discussion

The post reaction products of 4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl) phenyl)-1-thia-4-azaspiro[4.5]decan-3-one **5** were synthesized from 4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl) aniline, in good yield. The assigned structure was proved based on elemental and spectral analysis.

The infrared (IR) spectrum of the isolated product **5** showed absorption bands at 1695 cm^{-1} (thiazolidinone CO) (Hoshang et al., 2008) and 1338–1142 cm^{-1} (SO_2) (Vanparia et al., 2010). The ¹H-NMR spectrum revealed signals at δ 2.45 ppm, δ 3.12 ppm, and δ 3.71 ppm attributed to pi-pyridine protons, signal at δ 3.62 ppm attributed to thiazole ring protons and two doublets at δ 7.48 ppm and δ 7.78 ppm corresponding to aromatic protons. Furthermore, the mass spectra gave a molecular ion peak at m/z 448.24.

Also, compound **5** was confirmed chemically via condensation with p-chlorobenzaldehyde to afford **6**. The structures of the latter compounds were elucidated from their correct data. For example, the IR

spectrum of compound **6** showed an absorption band at 1698 cm^{-1} (thiazolidinone CO) due to conjugation, $^1\text{H-NMR}$ spectrum showed absence of thiazolomethylene protons, and its mass spectrum showed the M^+ peak at m/z 570.68, all of which support its molecular formula. Compound **6** was used as starting material for further synthesis of other heterocyclic compounds. It reacted with thiourea, hydrazine hydrate derivatives, malononitrile, and ethyl cyanoacetate to afford compounds **7–10**, respectively (Scheme 2).

The structures of these compounds were confirmed from their correct data (cf. Section 2). For example, the IR spectrum of compound **7** showed the absence of the band characteristic for (thiazolidinone CO) and the presence of absorption bands at $3,146, 3,124\text{ cm}^{-1}$ (NH), and $1,217\text{ cm}^{-1}$ (CS). Also, its $^1\text{H-NMR}$ spectrum revealed signals at δ 4.63 ppm characteristic of the pyrimidine ring and at δ 9.48 ppm and δ 10.24 ppm for 2NH protons that are D_2O exchangeable. Mass spectra showed M^+ peak at m/z 629.12, which supports its molecular formula.

3.1. Antimicrobial studies

The investigation of antibacterial screening data reveal that, almost all the representative are active and showing moderate to good antibacterial activity. Compounds **7, 8, 9**, and **10** exhibited potent inhibitory activity compared to the standard drug at the tested concentrations, while compound **5** and **6** shows significant antibacterial activity. The obtained results reveal that increasing in fusion of heterocyclic rings with thiazolidine-4-one ring, might be the reason for increasing in significant inhibitory activity. Also, the presence of chlorophenyl in the molecules would enhance the inhibitory activity. The antifungal screening data reveal that, most of the new compounds are active and show moderate to good antifungal activity. Among the screened compounds, the compounds **7, 8, 9**, and **10** with large heterocyclic system on thiazolidine-4-one ring showed highest activity against all the micro-organisms employed. The activity of these compounds is almost equal to the standard. Compounds **5** and **6** also showed good inhibition.

4. Conclusions

A series of novel 4-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-1-thia-4-azaspiro[4.5]decan-3-one derivatives has been synthesized and evaluated for their antibacterial (MIC/MZI) activity and antifungal (MIC/MZI) activity against various bacteria and fungi. Many of the synthesized compounds showed good activity against the test bacteria and fungi. From the results it is observed that as the fusion of heterocyclic rings increase the antimicrobial activities also increase significantly. Based on these results we still continue to synthesis more complex fused heterocyclic rings system.

Funding

The authors received no direct funding for this research.

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Citation information

Cite this article as: Synthesis and some novel transformations of a spiro 4-thiazolinone derivative and its antimicrobial activities, Paresh N. Patel & Yogesh S. Patel, *Cogent Chemistry* (2015), 1: 1048558.

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