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A facile synthesis, characterization and biological evaluation of novel spiro-thiazolidinone and quinazolinone-thiazolidine derivatives

Krishna Srivastava*[a], Abhishek Srivastava[b], Ram Prakash Tiwari[a], Amit Tripathi[a], Sreenivasulu Peta[a] & Manoj Verma[c]
[a] Faculty of Chemical Sciences, Shri Ramswaroop Memorial University Lucknow-Dewa Road Barabanki 225 003, Uttar Pradesh, India
[b] Department of Chemistry, GLA University, Mathura 281 406, Uttar Pradesh, India
[c] Forensic Science Laboratory, Mahanagar, Lucknow 226 006, Uttar Pradesh, India
E-mail: krishnajs2063@gmail.com

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The present work aims to synthesize and to perform antibacterial and antifungal screening of some novel spiro-thiazolidinone and quinazolinone-thiazolidine derivatives. The targeted derivatives have been synthesized in four steps. In the first step benzoyl chloride and anthranilic acid react together to form phenyl-4*H*-benzo[d][1,3]oxazin-4-one **(1)**. Step 2 involves the reaction of **1** with thiourea and thiosemicarbazide to produce 4-oxo-2-phenylquinazoline-3(4H)-carbothioamide (**2**) and 1-(4-oxo-2-henylquinazolin-3(4*H*)-yl) thiourea (**3**) respectively. The reaction of synthesized compounds **2** and **3** with substituted isatin and substituted acetophenone yields imine derivatives **4a-c**, **5a-c**, **6a-c**, and **7a-c** respectively in the third step. The cyclization of imine derivatives with thioglycolic acid in the presence of zinc chloride yields the targeted spiro-thiazolidinone (**8a-c**, and **10a-c**) and quinazolinone-thiazolidine (**9a-c**, and **11a-c**) derivatives. Elemental analysis, FTIR, ^{1}H NMR, and mass spectral studies have been used for the characterization of the synthesized compounds. **8b** (MIC 12.5 µg/mL) has been found to be the most effective derivative against *B. subtilis.* Compounds **9c** and **11b**, both with MICs of 12.5 µg/mL, are extremely effective against gram-negative bacterial strains of *P. pneumonia*, whereas compounds **9a** and **11a** have strong antibacterial activity against *E. coli* (MICs 12.5 µg/mL). With an average MIC value of 12.5 µg/mL in each case, compounds **8c**, **9a**, **10a**, and **11a** demonstrate good antifungal activity against *A. niger*, and *C. albicans*. The antifungal activity of compound **11b** is highest against *C. albican* with MIC value of 6.25 µg/mL. The synthesized compounds exhibit strong antibacterial and antifungal activity against distinct pathogens.

Keywords: Spiro-indoline, Thiazolidine, Acetophenone, Thiourea, Isatin, Thioglycolic acid, Antimicrobial activity, Antifungal activity

The majority of heterocyclic scaffolds, whether natural or synthetic, display diverse pharmaceutical and biological activities[1-6]. Currently, entire world is witnessing several new forms of lethal infections such as Corona, Ebola, and other existing microbial diseases along with the constant development of new variants of pathogenic strains. The global outbreak of pandemics has resulted in significant fatalities over the last two years. So, it has become even more important to explore the synthesis of new drug molecules which can be applicable to cure such deathly diseases. Spiro-thiazolidinone and quinazolinone-thiazolidine derivatives are categorized as novel drugs endowed with antimicrobial, antiviral, anticancer, and antidiabetic properties[7-13]. A variety of thiazolidinone-based derivatives can be designed by a comprehensive set of chemical rearrangements/ modifications of the heterocycle scaffold[14-18]. The targeted molecule also contains benzoxazine, which has been shown to be an effective inhibitor of hepatitis C virus and, butyrylcholinesterase[19-23], and also exhibits antiallergic, antitumor, antipsychotic, antileishmanial, anti-inflammatory, antianalgesic, neuroprotective, antagonistic, anti-microbacterial activity, and antibacterial activity[24-35].

The integration of the two aforementioned heterocyclic cores into a single compound results in a unique hybrid pharmacophore that exhibits significant biological activity[36,37]. In the present study, novel spiro-thiazolidinone and quinazolinone-thiazolidine derivatives are successfully designed. These hybrid pharmacophores have a five-membered ring with two heteroatoms, nitrogen and sulphur, linked with quinazoline, and are substituted with isatin or acetophenone. The synthesized hybrid pharmacophores will be biologically active against a wide range of pathogens.

Experimental Section

Analytical grade benzoyl chloride (Merck India), thiourea (CDH), thiosemicarbazide (SD Fine Chem. Limited), isatin (Merck India), acetophenone (CDH), ethanol (CDH), Anthranilic acid (Himedia), pyridine (SD Fine Chem. Limited), sodium bicarbonate (Avarice laboratories), hydrochloric acid (SD Fine Chem. Limited), thioglycolic acid (Merck India), dimethylformamide (Merck India), zinc Chloride (CDH), were used during the synthesis.

The manual melting point apparatus from Thermo Scientific (1201DQ) was used to examine the melting point of synthesized derivatives and was left uncorrected. To check the purity of synthesized derivatives, thin layer chromatographic plates (Merk, 60F-254) were used and visualization was done by I_2 vapors. The values were assessed through R_f values in different solvent conditions (5:2 hexane/ethyl acetate). All new synthesized compounds were characterized by proton nuclear magnetic resonance spectroscopy recorded in deuterated $CDCl_3$ or DMSO-d_6 and TMS as an internal standard using 300 MHz Bruker NMR spectrophotometer. Chemical shift (δ) values were reported as ppm. For other analytical studies, Jasco FTIR-470 spectrophotometer and MS-JEOL SX102 Mass spectroscopy were used. For FT-IR studies KBr plates were used in diffuse reflectance methodology. In mass spectroscopy NBA was used as matrix and Xenon / Argon (10mA, 6Kv) was used as the FAB gas. Elemental analysis were performed at CDRI Lucknow, India on Flash Smart Elemental Analyzer (ThermoFischer Scientific-11206100).

Synthesis of Benzoxazine (1) quinazoline-carbothioamide (2) and quinazoline-thiourea (3)

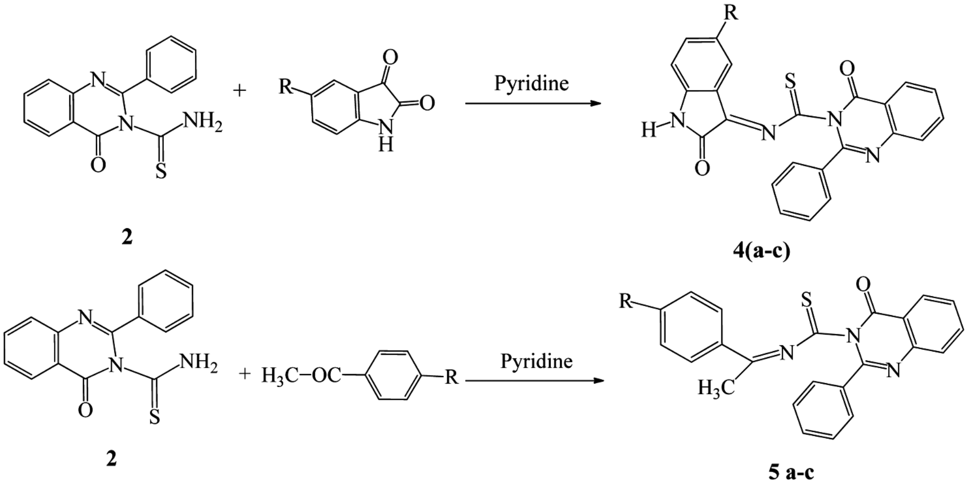
Compound 1, 2, and 3 has been synthesized by the already reported procedure[38-40].

Synthesis of isatin-carbothioamide derivatives 4a-c and actophenone-carbothioamide derivatives, 5a-c

The derivatives **4a-c** and **5a-c** were synthesized by refluxing (11 hrs) 0.02 moles of compound **2** respectively with substituted isatin (0.02 moles) or substituted acetophenone (0.02 moles) in 20 mL of dry pyridine (Scheme 1). The resulting mixture was then transferred into chilled water that contained 10 mL of conc. HCl. A solid mass separates and is allowed to settle for four hours. After repeated filtration and washing with cold water, the solid mass is dried in a vacuum desiccator and recrystallized from ethanol[41-45].

4-Oxo-N-(2-oxoindolin-3-ylidene)-2-phenylquinazoline-3(4*H*)-carbothioamide, 4a: Yield 70%. m.p.107-108°C. Anal. Calcd for $C_{23}H_{14}N_4O_2S$: S, 7.81; N, 13.65; C, 67.30; H, 3.44. Found: S, 7.73; N, 13.61; C, 67.20; H, 3.40%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1350 (C-N, str.), 1015 cm^{-1} (C=S, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 8.02 (s, 1H, free NH).

N-(5-Chloro-2-oxoindolin-3-ylidene)-4-oxo-2-phenylquinazoline-3(4*H*)-carbothioamide, 4b: Yield 73%. m.p.97-98°C. Anal. Calcd for $C_{23}H_{13}ClN_4O_2S$: S, 7.21; N, 12.59; C, 62.09; H, 2.59. Found: S, 7.16; N, 12.56; C, 62.03; H, 2.91%. IR



Scheme 1 — Synthesis of isatin-carbothioamide derivatives **4a-c** and actophenone-carbothioamide derivatives **5a-c**

(KBr): 3455 (N-H, str.), 3090 (C-H, str., Aryl), 1696 (C=O, str.), 1617 (C=N, str.), 1577 (C=C, str., Aryl), 1352 (C-N, str.), 1035 (C=S, str.), 719 cm^{-1} (C-Cl, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, free NH).

N-(5-Bromo-2-oxoindolin-3-ylidene)-4-oxo-2-phenylquinazoline-3(4*H*)-carbothioamide, 4c: Yield 69%. m.p.191-192°C. Anal. Calcd for $C_{23}H_{13}BrN_4O_2S$: S, 6.55; N, 11.45; C, 56.45; H, 2.68. Found: S, 6.50; N, 11.41; C, 56.36; H, 2.63%. IR (KBr): 3455 (N-H, str.), 3076 (C-H, str., Aryl), 1672 (C=O, str.), 1640 (C=N, str.), 1579 (C=C, str., Aryl), 1355 (C-N, str.), 1022 (C=S, str.), 680 cm^{-1} (C-Br, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.11 (m, 12H, Ar-H), 8.02 (s, 1H, free NH).

4-Oxo-2-phenyl-N-(1-phenylethylidene) quinazolin e-3(4*H*)-carbothioamide, 5a: Yield 61%. m.p.187-188°C. Anal. Calcd for $C_{23}H_{17}N_3OS$: S, 8.36; N, 10.96; C, 72.04; H, 2.68. Found: S, 8.30; N, 10.92; C, 72.01; H, 2.63%. IR (KBr): 3080 (C-H, str., Aryl), 2897 (C-H, str.), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1357 (C-N, str.), 1015 cm^{-1} (C=S, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 14H, Ar-H), 1.83 (s, 3H, CH_3).

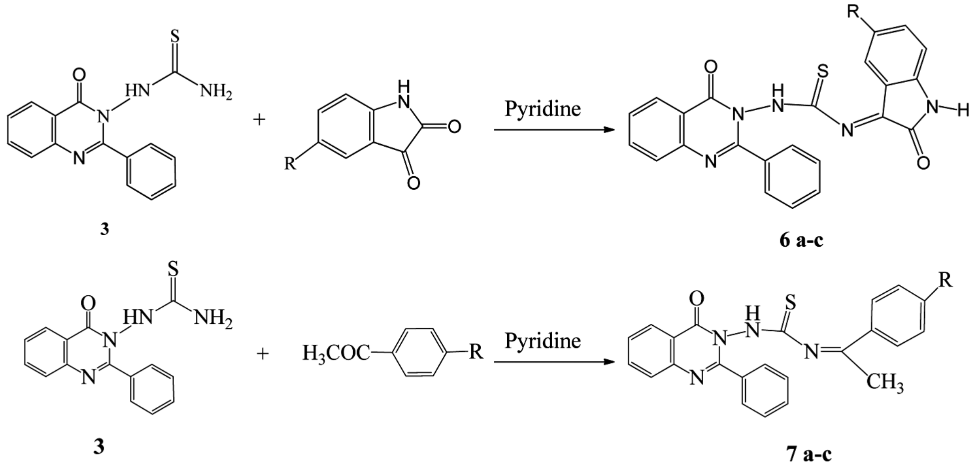
N-(1-(4-Chlorophenyl)ethylidene)-4-oxo-2-phenyl quinazoline-3(4*H*)-carbothioamide, 5b: Yield 63%. m.p.167-168°C. Anal. Calcd for $C_{23}H_{16}ClN_3OS$: S, 7.67, C, 66.10; H, 3.86; 10.05. Found: S, 7.62; C, 66.05; H, 3.82; 10.01%. IR (KBr): 3063 (C-H, str., Aryl), 2867 (C-H, str.), 1675 (C=O, str.), 1643 (C=N, str.), 1560 (C=C, str., Aryl), 1358 (C-N, str.), 1016 (C=S, str.), 723 cm^{-1} (C-Cl, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 1.83 (s, 3H, CH_3).

N-(1-(4-Bromophenyl)ethylidene)-4-oxo-2-phenylquinazoline-3(4*H*)-carbothioamide, 5c: Yield 61%. m.p.161-1621°C. Anal. Calcd for $C_{23}H_{16}BrN_3OS$: S, 6.94; ; N, 9.09; C, 59.75; H, 3.49. Found: S, 6.84; N, 9.02; C, 59.71; H, 3.43%. IR (KBr): 3070 (C-H, str., Aryl), 2885 (C-H, str.), 1646 (C=O, str.), 1640 (C=N, str.), 1572 (C=C, str., Aryl), 1355 (C-N, str.), 1034 (C=S, str.), 643 cm^{-1} (C-Br, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 1.83 (s, 3H, CH_3).

Synthesis of isatin-thiourea derivatives 6a-c and actophenone-thiourea derivatives 7a-c

Compounds **6a-c** and **7a-c** were synthesized (Scheme 2) by refluxing 0.02 moles of compound **3**respectively with substituted isatin (0.02 moles) or acetophenone (0.02 moles) in 20 mL of dry pyridine for 10 hours. Once the reaction was complete, it was poured onto chilled water that contained 10 mL of conc. HCl. A solid mass thus produced is allowed to settle for four hours. The solid mass is dried in a vacuum desiccator and recrystallized from ethanol after being subjected to numerous filtering processes and washings with cold water[41-45].

1-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)-3-(2-oxoin dolin-3-ylidene)thiourea, 6a: Yield 63%. m.p.157-158°C. Anal. Calcd for $C_{23}H_{15}N_5O_2S$: S, 7.54; N, 16.46; C, 64.93; H, 3.55. Found: S, 7.50; N, 16.36; C, 64.85; H, 3.52%. IR (KBr): 3455 (N-H, str.), 3065 (C-H, str., Aryl), 1705 (C=O, str.), 1645 (C=N, str.), 1585 (C=C, str., Aryl), 1360 (C-N, str.), 1034 cm^{-1} (C=S, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 8.02 (s, 1H, NHCO), 2.02 (s, 1H, NHCS).



Scheme 2 — Synthesis of isatin-thiourea derivatives **6a-c** and actophenone-thiourea derivatives **7a-c**

1-(5-Chloro-2-oxoindolin-3-ylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiourea, 6b: Yield 57%. m.p.199-200°C. Anal. Calcd for $C_{23}H_{14}ClN_5O_2S$: S, 6.9; N, 15.23; C, 60.07; H, 3.07. Found: S, 6.89; N, 15.13; C, 60.01; H, 3.04%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1364 (C-N, str.), 1015 (C=S, str.), 713 cm^{-1} (C-Cl, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 2.02 (s, 1H, NHCS).

1-(5-Bromo-2-oxoindolin-3-ylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiourea, 6c: Yield 63%. m.p.154-155°C. Anal. Calcd for $C_{23}H_{14}BrN_5O_2S$: S, 6.36; N, 13.89; C, 54.77; H, 2.80. Found: S, 6.32; N, 13.84; C, 54.71; H, 2.78%. IR (KBr): 3445 (N-H, str.), 3045 (C-H, str., Aryl), 1676 (C=O, str.), 1622 (C=N, str.), 1563 (C=C, str., Aryl), 1356 (C-N, str.), 1035 (C=S, str.), 669 cm^{-1} (C-Br, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 2.02 (s, 1H, NHCS).

1-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)-3-(1-phenylethylidene)thiourea, 7a: Yield 60%. m.p.141-142°C. Anal. Calcd for $C_{23}H_{18}N_4OS$: S, 8.05; N, 14.06; C, 69.32; H, 4.55. Found: S, 8.00; N, 14.01; C, 69.22; H, 4.53%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 2897 (C-H, str.), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1356 (C-N, str.), 1015 cm^{-1} (C=S, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 14H, Ar-H), 2.02 (s, 1H, NHCS), 1.83 (s, 3H, CH_3).

1-(1-(4-Chlorophenyl)ethylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiourea, 7b: Yield 69%. m.p.137-138°C. Anal. Calcd for $C_{23}H_{17}ClN_4OS$: S, 7.41; N, 12.94; C, 63.81; H, 3.96. Found: S, 7.31; C, N, 12.91; 63.72; H, 3.93%. IR (KBr): 3455 (N-H, str.), 3089 (C-H, str., Aryl), 2885 (C-H, str.), 1725 (C=O, str.), 1623 (C=N, str.), 1567 (C=C, str., Aryl), 1354 (C-N, str.), 1028 (C=S, str.), 798 cm^{-1} (C-Cl, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 2.02 (s, 1H, NHCS), 1.83 (s, 3H, CH_3).

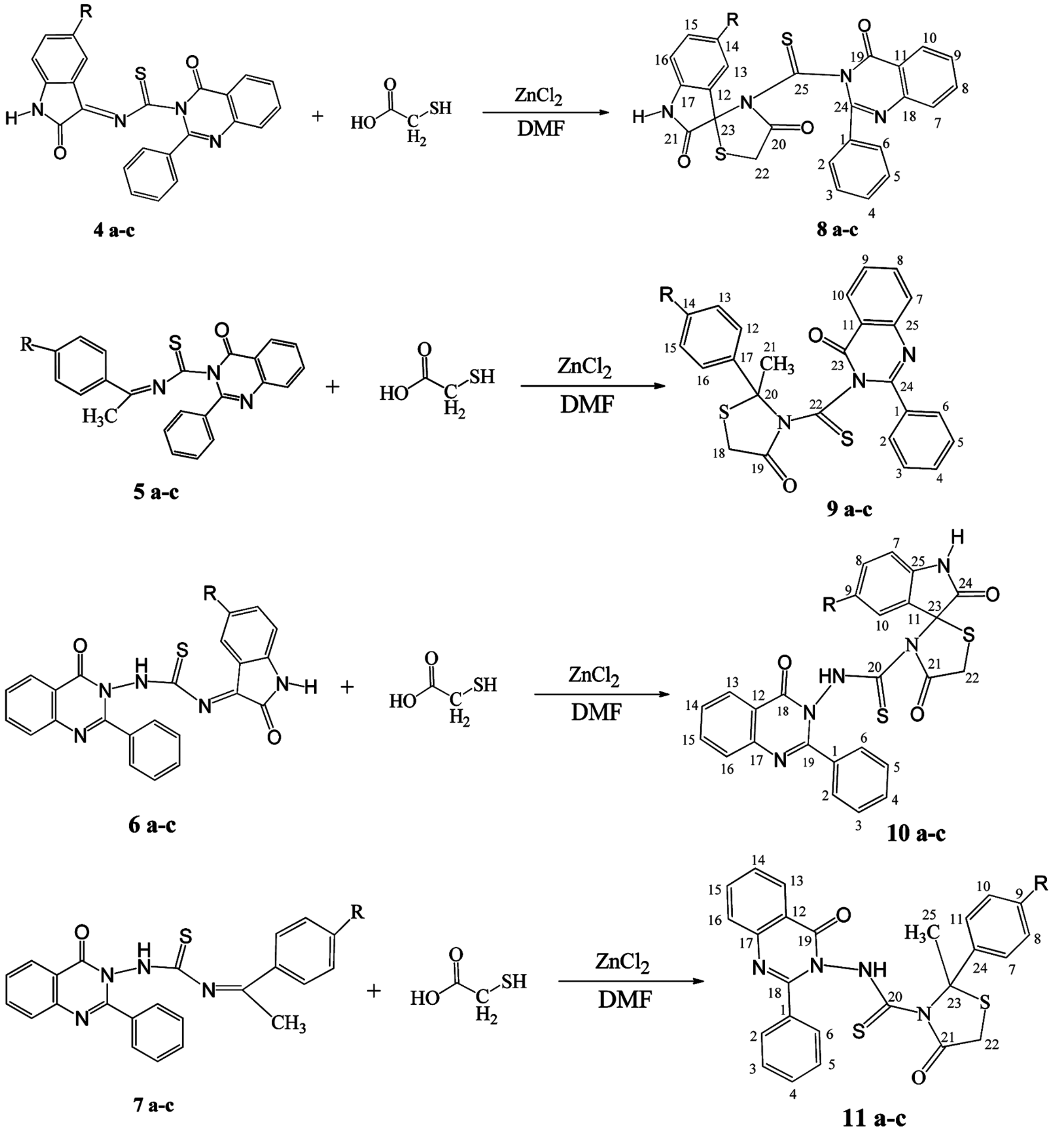
1-(1-(4-Bromophenyl)ethylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiourea, 7c: Yield 64%. m.p.131-132°C. Anal. Calcd for $C_{23}H_{17}BrN_4OS$: S, 6.72; N, 11.74; C, 57.87; H, 3.59. Found: S, 6.62; N, 11.70; C, 57.82; H, 3.54%. IR (KBr): 3455 (N-H, str.), 3075 (C-H, str., Aryl), 2892 (C-H, str.), 1670 (C=O, str.), 1620 (C=N, str.), 1575 (C=C, str., Aryl), 1368 (C-N, str.), 1022 (C=S, str.), 685 cm^{-1} (C-Br, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.53-8.05 (m, 13H, Ar-H), 2.02 (s, 1H, NHCS), 1.83 (s, 3H, CH_3).

Synthesis of spiro-thiazolidinone-dione 8a-c, phenylquinazolinone-thiazolidine9a-c, spiro-thiazo lidinon e-carbothioamide10a-c, andphenylq uinaz olinone-thiazolidine-carbothioamide 11a-c derivatives

The final derivatives **8a-c, 9a-c, 10a-c**, and **11a-c** (Scheme 3) were synthesized by refluxing of 0.01 moles of thioglycolic acid respectively with 0.01 moles of **4a-c, 5a-c, 6a-c**, and **7a-c** and 0.01gm of zinc-chloride as a catalyst in DMF (20 mL) for 14 hours. The resulting mixture was then added to chilled water and stirred vigorously. After 15 minutes, a solid compound was separated and repeatedly washed with cold water before being recrystallized from ethanol. Scheme 3 represents the mechanism of formation of spiro ring and while Scheme S1 shows the possible stereochemistry of spiro compounds 8 and 10 (supporting information).

3'-(4-Oxo-2-phenyl-3,4-dihydroquinazoline-3-carbonothioyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione, 8a: Yield 67%. m.p.127-128°C. Anal. Calcd for $C_{25}H_{16}N_4O_3S_2$: S, 13.23; N, 11.56; C, 61.97; H, 3.33. Found: S, 13.13; N, 11.53; C, 61.92; H, 3.27%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1015 (C=S, str.), 882 cm^{-1} (C-S-C, str.); ^1H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.08-8.05 (m, 13H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, -SCH_2,*J* = 12.3 Hz); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.2 (C22), 84.6 (C23), 114.9 to 133.2 (C1 to C16, of C=C), 139.8 (C17), 148.5 (C18), 155.6 (C24), 168 (C21), 170.4 (C19), 171 (C20), 178.6 (C25). FAB-MS (Argon/Xenon) Mass M^+: 470, 221, 219, 78.

5-Chloro-3'-(4-oxo-2-phenyl-3,4-dihydroquinazoline-3-carbonothioyl) spiro[indo line-3,2'-thiazolidine]-2,4'-dione, 8b: Yield 67%. m.p.124-125°C. Anal. Calcd for $C_{25}H_{15}ClN_4O_3S_2$: S, 12.36; N, 10.80; C, 57.86; H, 2.91. Found: S, 12.31; N, 10.72; C, 57.81; H, 2.85%. IR (KBr): 3445 (N-H, str.), 3072 (C-H, str., Aryl), 1697



Scheme 3 — Synthesis of spiro-thiazolidinone-dione **8a-c**, phenylquinazolinone-thiazolidine **9a-c**, spiro-thiazolidinone-carbothioamide **10a-c**, and phenylquinazolinone-thiazolidine-carbothioamide **11a-c** derivatives

(C=O, str.), 1622 (C=N, str.), (C-Cl, str.), 1568 (C=C, str., Aryl), 1025 (C=S, str.), 884 cm^{-1} (C-S-C, str.); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 7.40-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, -SCH$_2$, J = 12.3 Hz); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 30.2 (C22), 84.2 (C23), 111.9 to 133.2 (C1 to C16, of C=C), 139.6 (C17), 148.3 (C18), 155.5 (C24), 168.2 (C21), 170.2 (C19), 171.2 (C20), 178.2 (C25). FAB-MS (Argon/Xenon) Mass M$^+$: 78, 221, 252, 298, 484.

5-Bromo-3'-(4-oxo-2-phenyl-3,4-dihydroquinazoline-3-carbonothioyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione, 8c: Yield 63%. m.p.118-119°C. Anal. Calcd for $C_{25}H_{15}BrN_4O_3S_2$: S, 11.38; N, 9.94; C, 53.29; H, 2.68. Found: S, 11.34; C, N, 9.84; 53.19; H, 2.62%. IR (KBr): 3458 (N-H, str.), 3075 (C-H, str., Aryl), 1667 (C=O, str.), 1620 (C=N, str.), 1563 (C=C, str., Aryl), 1023 (C=S, str.), 886 (C-S-C, str.), 669 cm^{-1} (C-Br, str.); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 6.80-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, -SCH$_2$, J = 12.3 Hz);

^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.4 (C22), 84.2 (C23), 119.2 to 134.2 (C1 to C16, of C=C), 140.2 (C17), 148.3 (C18), 155.5 (C24), 168.2 (C21), 170.2 (C19), 171.2 (C20), 178.2 (C25). FAB-MS (Argon/Xenon) Mass M$^+$: 484, 341, 297, 221, 78.

3-(2-Methyl-4-oxo-2-phenylthiazolidine-3-carbonothioyl)-2-phenylquinazolin-4(3*H*)-one, 9a: Yield 62%. m.p.111-112°C. Anal. Calcd for $C_{25}H_{19}N_3O_2S_2$: S, 14.02; N, 9.18; C, 65.62; H, 4.19. Found: S, 14.01; N, 9.10; C, 65.56; H, 4.15%. IR (KBr): 3080 (C-H, str., Aryl), 2897 (C-H, str.), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1015 (C=S, str.), 887 cm^{-1} (C-S-C, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.28-8.05 (m, 14H, Ar-H), 3.84 & 3.96 (dd, 2H, -CH_2,*J* = 12.3 Hz), 1.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.9 (C18), 31.1 (C21), 69.6 (C20), 120.5 to 133.2 (C1 to C16, of C=C), 143.2 (C17), 148.5 (C25), 155.6 (C24), 170.4 (C23), 171 (C19), 178.6 (C22). FAB-MS (Argon/Xenon) Mass M$^+$: 343, 266, 195, 182, 78.

3-(2-(4-Chlorophenyl)-2-methyl-4-oxothiazolidine-3-carbonothioyl)-2-phenylquinazolin-4(3*H*)-one, 9b: Yield 68%. m.p.109-110°C. Anal. Calcd for $C_{25}H_{18}ClN_3O_2S_2$: S, 13.03; N, 8.54; C, 61.03; H, 3.69. Found: S, 13.01; N, 8.51; C, 61.02; H, 3.63%. IR (KBr): 3067 (C-H, str., Aryl), 2876 (C-H, str.), 1689 (C=O, str.), 1624 (C=N, str.), 1582 (C=C, str., Aryl), 1034 (C=S, str.), 892 (C-S-C, str.), 778 cm^{-1} (C-Cl, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.24-8.05 (m, 13H, Ar-H), 3.84 & 3.96 (dd, 2H, -CH_2, *J* = 12.3 Hz), 1.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.9 (C18), 31.1 (C21), 69.8 (C20), 120.6 to 133.4 (C1 to C16, of C=C), 141.2 (C17), 148.5 (C25), 155.6 (C24), 170.4 (C23), 171 (C19), 178.6 (C22). FAB-MS (Argon/Xenon) Mass M$^+$: 477, 457, 266, 226, 195, 78.

3-(2-(4-Bromophenyl)-2-methyl-4-oxothiazolidine-3-carbonothioyl)-2-phenylquinazolin-4(3*H*)-one, 9c: Yield 66%. m.p.104-105°C. Anal. Calcd for $C_{25}H_{18}BrN_3O_2S_2$: S, 11.95; N, 7.83; C, 55.97; H, 3.38. Found: S, 11.90; N, 7.81; C, 55.92; H, 3.35,%. IR (KBr): 3073 (C-H, str., Aryl), 2893 (C-H, str.), 1668 (C=O, str.), 1623 (C=N, str.), 1568 (C=C, str., Aryl), 1034 (C=S, str.), 893 (C-S-C, str.), 655 cm^{-1} (C-Br, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.19-8.05 (m, 13H, Ar-H), 3.84 & 3.96 (dd, 2H, -CH_2, *J* = 12.3 Hz), 1.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.9 (C18), 31.1 (C21), 69.6 (C20), 120.5 to 133.2 (C1 to C16, of C=C), 142.2 (C17), 148.3 (C25), 155.4 (C24), 170.4 (C23), 171 (C19), 178.6 (C22). FAB-MS (Argon/Xenon) Mass M$^+$: 522, 457, 269, 266, 195, 78.

2,4'-Dioxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)spiro[indoline-3,2'-thiazolidine]-3'-carbothioamide, 10a: Yield 61%. m.p.111-112°C. Anal. Calcd for $C_{25}H_{17}N_5O_3S_2$: S, 12.84; N, 14.02; C, 60.11; H, 3.43. Found: S, 12.84; N, 14.02; C, 60.11; H, 3.38%. IR (KBr): 3465 (N-H, str.), 3067 (C-H, str., Aryl), 1672 (C=O, str.), 1622 (C=N, str.), 1556 (C=C, str., Aryl), 1378 (C-N, str.), 1123 (N-N, str.), 1023 (C=S, str.), 895 cm^{-1} (C-S-C, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.08-8.05 (m, 13H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, CH_2,*J* = 12.3 Hz), 2.02 (s, 1H, NHCS); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.6 (C22), 84.7 (C23), 115.5 to 133.2 (C1 to C16, of C=C), 141.2 (C25), 148.5 (C17), 155.6 (C19), 160.4 (C18), 168.1 (C24), 171.6 (C21), 179.6 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 457, 253, 167, 146, 112, 78.

5-Chloro-2,4'-dioxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)spiro[indoline-3,2'-thiazolidine]-3'-carbothioamide, 10b: Yield 67%. m.p.87-88°C. Anal. Calcd for $C_{25}H_{16}ClN_5O_3S_2$: S, 12.01; N, 13.11; C, 56.23; H, 3.02. Found: S, 12.01; C, N, 13.11; 56.23; H, 2.96%. IR (KBr): 3465 (N-H, str.), 3075 (C-H, str., Aryl), 1693 (C=O, str.), 1618 (C=N, str.), 1560 (C=C, str., Aryl), 1378 (C-N, str.), 1123 (N-N, str.), 1021 (C=S, str.), 896 (C-S-C, str.), 752 cm^{-1} (C-Cl, str.); ^{1}H NMR ($CDCl_3$/DMSO-d_6) (300 MHz): δ 7.31-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, CH_2,*J* = 12.3 Hz), 2.02 (s, 1H, NHCS); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 30.4 (C22), 84.7 (C23), 111.5 to 133.2 (C1 to C16, of C=C), 139.2 (C25), 148.5 (C17), 156.6 (C19), 160.4 (C18), 168.1 (C24), 171.6 (C21), 179.6 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 457, 253, 167, 146, 112, 78.

5-Bromo-2,4'-dioxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)spiro[indoline-3,2'-thiazolidine]-3'-carbothioamide, 10c: Yield 65%. m.p.81-82°C. Anal. Calcd for $C_{25}H_{16}BrN_5O_3S_2$: S, 11.09; N, 12.11; C, 51.91; H, 2.79. Found: S, 11.02; N, 12.07; C, 51.81; H, 2.76%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 1685 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1385 (C-N, str.), 1130 (N-N, str.), 1015 (C=S, str.), 896 (C-S-C, str.), 660 cm^{-1} (C-Br, str.); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 6.78-8.05 (m, 12H, Ar-H), 8.02 (s, 1H, NHCO), 3.84 & 3.96 (dd, 2H, CH$_2$,J = 12.3 Hz), 2.02 (s, 1H, NHCS); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 30.6 (C22), 84.7 (C23), 119.5 to 133.2 (C1 to C16, of C=C), 140.2 (C25), 148.5 (C17), 156.6 (C19), 160.4 (C18), 168.1 (C24), 171.6 (C21), 179.6 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 502, 299, 210, 155, 146, 78.

2-Methyl-4-oxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)-2-phenylthiazolidine-3-carbothioamide, 11a: Yield 64%. m.p.88-89°C. Anal. Calcd for $C_{25}H_{20}N_4O_2S_2$: S, 13.57; N, 11.86; C, 63.54; H, 4.27. Found: S, 13.51; N, 11.82; C, 63.51; H, 4.23%. IR (KBr): 3475 (N-H, str.), 3070 (C-H, str., Aryl), 1699 (C=O, str.), 1614 (C=N, str.) 1578 (C=C, str., Aryl), 1139 (N-N, str.), 1063 (C-N, str.), 1023 (C=S, str.), 878 cm^{-1} (C-S-C, str.); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 7.30-8.05 (m, 14H, Ar-H), 1.91 (s, 3H, CH$_3$), 3.84 & 3.96 (dd, 2H, CH$_2$,J = 12.3 Hz), 2.02 (s, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 30.8 (C22), 31.0 (C25), 69.8 (C23), 119.5 to 132.1 (C1 to C16, of C=C), 143.2 (C24), 148.1 (C17), 156.2 (C18), 160.2 (C19), 170.4 (C21), 178.1 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 396, 221, 192, 145, 103, 78.

2-(4-Chlorophenyl)-2-methyl-4-oxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidine-3-carbothioamide, 11b: Yield 62%. m.p.194-195°C. Anal. Calcd for $C_{25}H_{19}ClN_4O_2S_2$: S, 12.65; N, 11.05; C, 59.22; H, 3.78. Found: S, 12.65; N, 11.05; C, 59.22; H, 3.76%. IR (KBr): 3459 (N-H, str.), 3067 (C-H, str., Aryl), 1663 (C=O, str.), 1634 (C=N, str.), 1589 (C=C, str., Aryl), 1139 (N-N, str.), 1074 (C-N, str.), 1032 (C=S, str.), 880 (C-S-C, str.), 746 cm^{-1} (C-Cl); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 7.25-8.05 (m, 13H, Ar-H), 1.91 (s, 3H, CH$_3$), 3.84 & 3.96 (dd, 2H, CH$_2$,J = 12.3 Hz), 2.02 (s, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 30.8 (C22), 31.0 (C25), 69.8 (C23), 119.5 to 133.2 (C1 to C16, of C=C), 141.5 (C24), 148.1 (C17), 156.2 (C18), 160.2 (C19), 170.4 (C21), 178.1 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 430, 226, 221, 145, 112, 103.

2-(4-Bromophenyl)-2-methyl-4-oxo-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidine-3-carbothioamide, 11c: Yield 65%. m.p.101-102°C. Anal. Calcd for $C_{25}H_{19}BrN_4O_2S_2$: S, 11.63; N, 10.16; C, 54.45; H, 3.47. Found: S, 11.63; N, 10.16; C, 54.45; H, 3.41%. IR (KBr): 3455 (N-H, str.), 3080 (C-H, str., Aryl), 1683 (C=O, str.), 1610 (C=N, str.), 1575 (C=C, str., Aryl), 1130 (N-N, str.), 1085 (C-N, str.), 1015 (C=S, str.), 880 (C-S-C, str.), 660 cm^{-1} (C-Br, str.); ^{1}H NMR (CDCl$_3$/DMSO-d_6) (300 MHz): δ 7.19-8.05 (m, 13H, Ar-H), 1.91 (s, 3H, CH$_3$), 3.84 & 3.96 (dd, 2H, CH$_2$,J = 12.3 Hz), 2.02 (s, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 30.8 (C22), 31.0 (C25), 69.8 (C23), 120.5 to 133.5 (C1 to C16, of C=C), 142.4 (C24), 148.1 (C17), 156.2 (C18), 160.2 (C19), 170.4 (C21), 178.1 (C20). FAB-MS (Argon/Xenon) Mass M$^+$: 475, 270, 222, 155, 146, 103.

In vitro anti-bacterial and anti-fungal susceptibility test (AST)

The newly designed spiro-thiazolidinone and quinazolinone-thiazolidine derivatives were screened *in vitro* for their bacterial activity against different bacterial species *viz*., *P. aeruginosa*, *B. subtilis*, *S. aureus*, and *E. coli*, while the antifungal activity of the synthesized compounds was tested against *C. albicans*, *A. niger*, and *A clavatus*. The pure isolates of the test microbes were obtained from the Department of Microbiology KGMU Lucknow. To determine the antifungal and antibacterial activity of the synthesized derivatives, serial dilution technique was employed. Initially, the test compound's concentration was taken to be 1 mg/mL in dimethyl sulphoxide (DMSO-d_6). To assess the antibacterial potency, the culture was prepared by mixing 1 mL of anti-bacterial growth containing broth and 20 mL of plane luria-bertani medium. A control tube containing no antibiotic sample was also prepared. Two control tubes containing ampicillin and ketoconazole was prepared at last. All the prepared tube samples were incubated at 37°C (24 hours) for antimicrobial evaluation, while for antifungal testing the tubes were incubated at 28°C for 96 hours. Growth for every conical tube was checked by computing the absorbance value at 600 nm. The plot of compound concentration and absorbance value was used to obtain the MIC (corresponding to the drop in optical density) of the particular derivative.

Results and Discussion

The starting benzoxazine (**1**) was synthesized by a condensation reaction of benzoyl chloride, and anthranilic acid. Pyridine was used as a solvent as it is an effective, basic solvent that is relatively unreactive.

It also acts as an acceptor for the acid by-product formed in the reaction. Thus, helpful in removing the acidic side product and HCl from the reaction mixture. The reaction of synthesized benzoxazine respectively with thiourea and semicarbazide gives primary amines **2**, and **3**. The condensation of **2** with substituted isatin and substituted acetophenone yield imines **4a-c**, and **5a-c** respectively, while **3** on reaction with substituted isatin and substituted acetophenone produces **6a-c**, and **7a-c** respectively. The ^{1}H NMR spectrum of compounds **4a-c/6a-c** and **5a-c/7a-c** exhibit one proton singlet at δ 8.02 ppm (-N-H) and 1.83 ppm ($-CH_3$) respectively, while the two proton singlet ($-NH_2$) that appeared at δ 8.53 ppm in compound **2** and **3** has disappeared (Figures S1, S2, and S3). The final spiro-thiazolidinone (**8a-c,** and **10a-c**) and quinazolinone-thiazolidine (**9a-c** and **11a-c**) derivatives were formed by the cyclization of imine derivatives with thioglycollic acid in presence of catalytic amount of zinc chloride. The characteristic IR peaks for newly synthesized derivatives at 1668 cm^{-1}, 1034 cm^{-1}, 2893 cm^{-1}, and 893 cm^{-1} corresponds to C=O, C=S, C-H, and C-S stretching respectively. All **8a-c - 11a-c** derivative's proton NMR spectra show a new doublet of doublets of 2H ($-CH_2-$) at about δ 3.84 and 3.96 ppm, which is suggestive of the formation of a spiro ring (Figures S4, S5, S6, and S7). The ^{13}C NMR data also supports the proposed structure of the synthesized compounds (Figures S8, S9, S10, and S11). All compounds show an excellent agreement between calculated and experimentally obtained elemental analysis data.

To assess the toxicity of the synthesized compounds against gram-negative (P. aeruginosa, E. coli) and gram-positive (B. subtilis, S. aureus) bacteria, a routine antibacterial susceptibility test (AST) was performed (Fig. 1). Ampicillin was chosen as the control drug because it is effective against both the gram-positive and gram-negative bacterial strains under consideration, indicating a broad spectrum activity against various microbial pathogens regardless of the differences in their cell wall structure. The antibacterial screening outcome of targeted spiro-thiazolidinone, and quinazolinone-thiazolidine derivatives are summarized in Table 1. Derivative **8b** having *p*-chloro substituents shows an excellent MIC value of 12.5 µg/mL against *B. subtilis*. Interestingly, when the chloro group was replaced by bromo (**8c**) MIC value decreased fourfold against *B. subtilis*. Among all synthesized derivatives, compounds **10a, 10b,** and **11b** show good antibacterial activity (MIC value 12.5 µg/mL). Moderate antibacterial activity (MIC value

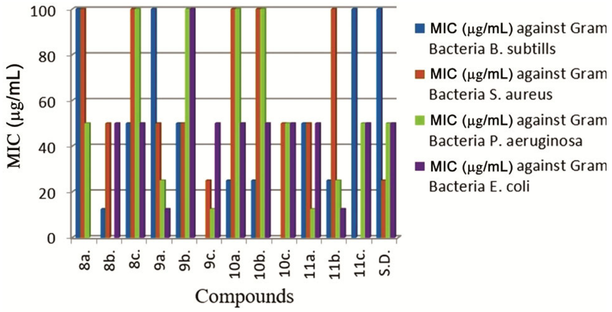


Fig. 1 — Comparison of antibacterial activity of compounds **8a-c** – **11a-c** against Gram negative and Gram positive bacteria

Table 1 — Antibacterial activity of synthesized (**8a-c**, **9a-c**, **10a-c** and **11a-c**) compounds against Gram negative and Gram positive bacteria

Compd	R group with benzene ring	MIC (µg/mL) against Gram +ve Bacteria		MIC (µg/mL) against Gram –ve Bacteria	
		B. subtills	*S. aureus*	*P. aeruginosa*	*E. coli*
8a	H	100	100	50	NA
8b	Cl	*12.5	50	NA	50
8c	Br	50	100	100	50
9a	H	100	50	25	*12.5
9b	Cl	50	50	100	100
9c	Br	NA	25	*12.5	50
10a	H	25	100	100	50
10b	Cl	25	100	100	50
10c	Br	NA	50	50	50
11a	H	50	50	*12.5	50
11b	Cl	25	100	25	*12.5
11c	Br	100	NA	50	50
S.D.	Ampicillin	100	25	50	50

12.5 µg/mL) was noticed for compounds**8c, 9b,** and **11a**. Against *S. aureus*, compound **9c** exhibit good activity (MIC value 12.5 µg/mL), while other derivative shows moderate activity (MIC value25 µg/mL). Two quinazolinone-thiazolidine derivatives **9a,** and **11b** shows strongMIC value of 12.5 µg/mL against *E. coli*. However, the MIC value of other spiro-thiazolidinone, and quinazolinone-thiazolidine derivatives was found 50/100 µg/mL against *E. coli.* Compounds**9c**, and **11a** were found the most active derivative of quinazolinone-thiazolidine series with a MIC value of 12.5 µg/mL against *Paeruginosa*.

The anti-fungal activity of all spiro-thiazolidinone and quinazolinone-thiazolidine were assessed against *A. clavatus*, *A. niger*, and *C. albicans* (Fig. 2). Ketoconazole was used as a control drug for the study. The anti-fungal screening results of final spiro-thiazolidinone and quinazolinone-thiazolidine derivatives are summarized in Table 2. Highest anti-fungal activity with MIC value 6.25 µg/mL against *C. albicans* has been shown by compound **11b**, whereas compound **8c**, and **11a** exhibits excellent antifungal activity (MIC value 12.5 µg/mL) against *C. albicans*. Derivatives **9a**, and **10a** exhibit brilliant activity with MIC value of 12.5 µg/mL against *A. niger*, while moderate antibacterial activity (MIC value 12.5 µg/mL) has been observed for compound **9b, 11a** and **11c**. All synthesized spiro-thiazolidinone and quinazolinone-thiazolidine derivatives show moderate to good anti-fungal activity (MIC value 25-100 µg/mL) against *A. clavatus*. The results demonstrate that the different groups (H, Br, and Cl) attached to the scaffold show a significant effect on antimicrobial activity of the synthesized derivatives.

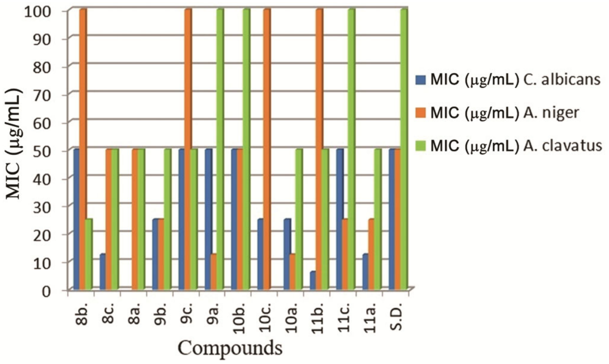


Fig. 2 — Comparison of antifungal activity of compounds **8a-c** – **11a-c**

Conclusions

The current study describes the design and synthesis of novel spiro-thiazolidinone and quinazolinone-thiazolidine derivatives as hybrid pharmacophores having a five-membered ring with two hetero atoms nitrogen and sulphur linked with quinazoline and substituted isatin/acetophenone. The ^{1}H NMR, IR and mass fragmentation data also support the formation of final spiro-thiazolidinone, and quinazolinone-thiazolidine derivatives. The most effective derivative against *B. subtilis* was discovered to be **8b** (MIC 12.5 µg/mL). Compounds **9c** (MIC 12.5 µg/mL) and **11b** (MIC 12.5 µg/mL) were highly effective against gram-negative bacterial strains of *P. pneumonia*, while compound **9a** (MIC 12.5 µg/mL) and **11a** (MIC 12.5 µg/mL) exhibits excellent antibacterial activity against *E. coli*. With an average MIC value of 12.5 µg/mL in each case, the compounds **8c**, **9a**, **10a**, and **11a** demonstrated good antifungal activity against C. albicans, A. niger, and

Table 2 — Antifungal activity of synthesized (**8a-c**, **9a-c**, **10a-c**, and **11a-c**) compounds

Compd	R group with benzene ring	MIC (µg/mL)		
		C. albicans	*A. niger*	*A. clavatus*
8a	H	NA	50	50
8b	Cl	50	100	25
8c	Br	*12.5	50	50
9a	H	50	*12.5	100
9b	Cl	25	25	50
9c	Br	50	100	50
10a	H	25	*12.5	50
10b	Cl	50	50	100
10c	Br	25	100	NA
11a	H	*12.5	25	50
11b	Cl	*6.25	100	50
11c	Br	50	25	100
S.D.	Ketoconazol	50	50	100

C. albicans, respectively. The antifungal activity of compound **11b** against C. albican is at its highest with a MIC value of 6.25 µg/mL.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Conflicts of interest/Competing interests

None of the authors has any potential or actual conflict of interest to disclose in relation to the published article.

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