Research Article

A Mini Library of Novel Triazolothiadiazepinyndole Analogues: Synthesis, Antioxidant and Antimicrobial Evaluations

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A new series of novel triazolothiadiazepinyndole analogues were synthesized with an aim to examine possible antioxidant and antimicrobial activities. The titled compounds (**3a–z**) were obtained in good yield by reacting 5-(5-substituted-3-phenyl-1H-indol-2-yl)-4-amino-4H-1,2,4-triazole-3-thiols **1a–c** with 3-(2,5-disubstituted-1H-indol-3-yl)-1(4-substituted phenyl)prop-2-en-1-ones **2a–i**. All the newly synthesized compounds were characterized by IR, ¹H NMR, mass spectroscopic and analytical data. The synthesized analogues were tested for antioxidant and antimicrobial potency. Among the tested compounds **3a–c** and **3j–l** have shown very promising free radical scavenging activity and total antioxidant capacity. Compounds **3d–f**, **3m–o**, and **3s–z** have shown excellent ferric reducing antioxidant activity. An outstanding antimicrobial activity is observed with compounds **3a–c** and **3j–l**.

1. Introduction

Antioxidants [1–3] act as “free radical scavengers” hence to prevent or slow the damage done by the free radicals [4–6]. Free-radical-induced oxidative stress associated with several cellular toxic processes including oxidative damage to protein, and DNA, membrane lipid oxidation, enzyme inactivation, and gene mutation leads to carcinogenesis [7]. Antioxidants are involved in processes such as immunity, protection against tissue damage, and reproduction and prevent growth or development caused by free radicals [8–10]. Antioxidants are useful in the prevention and treatment of Parkinson's and Alzheimer's disease [11–13].

Heterocycles constitute one of the major areas of organic chemistry and play important roles in drug discovery. Many of the best selling drugs currently in use contain one or more heterocyclic rings. Several fused heterocycles as well

as biheterocycles are referred to as privileged structures [14]. Among them, sulfur- and nitrogen-containing heterocyclic compounds have maintained the interest of researchers and their unique structures led to several applications in different areas [15]. Triazoles and their derivatives constitute an important class of heterocyclic compounds and their analogues have been reported to possess various biological activities such as antimicrobial [16], anti-inflammatory [17], antihypertensive, anti-HIV [18], anticancer, and antitumor [19, 20]. Several compounds containing 1,2,4-triazole rings known as drugs like fluconazole, posaconazole, alprazolam, [21] and triazolothiadiazepine analogues represent a well-known class of drug substances at different stages of research, which possess antiviral [22] and antimicrobial properties [23].

Indole is a heterocycle of great importance in biological systems [24, 25]. The indole moiety is present in a number

of drugs currently [26] in the market; in our previous approaches, we have described some new indole analogues with highly potent antioxidant, DNA cleavage and antimicrobial activities [27–30].

Interestingly, we have developed a new green protocol for the synthesis of rapid and clean synthetic route towards mini library of triazolothiadiazepinyndole analogues, which showed *in vitro* antioxidant and antimicrobial activities.

2. Materials and Methods

2.1. Chemistry. All chemicals used in this investigation were of analytical grade and were purified whenever necessary. Melting points of the synthesized compounds were measured in open capillaries and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F₂₅₄ aluminium sheets (MERCK). Iodine vapour was used as detecting agent. IR spectra were recorded in KBr on PerkinElmer and FTIR spectrophotometer ($\nu_{\max}$ in cm^{-1}). ^1H NMR and ^{13}C NMR spectra on BRUKER AVANCE II 400-MHz NMR spectrometer and the chemical shifts were expressed in ppm (δ scale) downfield from TMS as an internal reference. The mass spectra were recorded on LC-MSD-Trap-SL instrument. The elemental analysis was performed by using FLASH EA 1112 SERIES instrument.

2.1.1. General Procedure for the Synthesis of Compounds 1a–c. The precursors 5-(5-substituted-3-phenyl-1H-indol-2-yl)-4-amino-4H-1,2,4-triazole-3-thiols (1a–c) were obtained from 3,5-disubstituted indol-2-carboxyhydrazides by reported method [31].

2.1.2. General Procedure for the Synthesis of Compounds 2a–i. 3-(2,5-disubstituted-1H-indol-3-yl)-1(4-substituted phenyl) prop-2-en-1-one 2a–i were prepared by reported method [29] by reacting disubstituted indole aldehydes with substituted acetophenone in the presence of piperidine in good yields.

2.1.3. General Procedure for the Synthesis of Compounds 3a–z

(1) Conventional Method. To a solution of substituted indolyl-triazole 1a–c (0.01 mol) in acetic acid substituted chalcones 2a–i (0.01 mol) were added. The reaction mixture was refluxed 3–4 hrs. The completion of the reaction was monitored by TLC. After the completion, the reaction mixture was poured to a beaker containing 100 mL of ice-cold water. The crude products thus separated were filtered and recrystallized from ethanol to yield target compounds 3a–z.

(2) Microwave Oven Method. A mixture of substituted indolyl triazole 1a–c (0.01 mol) and substituted chalcones 2a–i (0.01 mol) was powdered, mixed, and introduced to borosil sample crucible containing few drops of acetic acid. This was subjected to microwave irradiation for 10 minutes with 70% microwave power. After the completion (TLC), reaction mixture was brought to room temperature, washed with ethanol, and recrystallized to get the title compounds 3a–z

which were found to be in good purity (TLC) and excellent yield.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(5-chloro-3-phenyl-1H-indol-2-yl)-6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3a). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3180, 3090, 1654, 1624, 1546; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 12.47 (s, 1H, indole NH), 11.63 (s, 1H, indole NH), 7.31–8.23 (m, 20H, Ar-H), 5.65 (s, 1H, $-\text{CH}=\text{}$); ^{13}C NMR (DMSO- d_6 + CDCl_3) δ (ppm): 108, 111, 113, 117, 118, 118, 120, 123, 125, 126, 126, 128, 128, 128, 128, 129, 129, 130, 132, 133, 134, 135, 138, 138, 144, 145, 166. MS: m/z = 712 $[\text{M}]^{++}$, 714 $[\text{M}+2]$, 718 $[\text{M}+4]$, 720 $[\text{M}+6]$; Anal. calcd. for ($\text{C}_{39}\text{H}_{23}\text{N}_6\text{Cl}_3\text{S}$): C, 65.60; H, 3.25; N, 11.77%. Found: C, 65.59; H, 3.21; N, 11.75%.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(5-chloro-3-phenyl-1H-indol-2-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3b). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3189, 3049, 1608, 1579, 1553; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.15 (s, 1H, indole NH), 10.25 (s, 1H, indole NH), 7.29–8.72 (m, 21H, Ar-H), 4.95 (s, 1H, $-\text{CH}=\text{}$); MS: m/z = 678 $[\text{M}]^{++}$, 680 $[\text{M}+2]$, 682 $[\text{M}+4]$; Anal. calcd. for ($\text{C}_{39}\text{H}_{24}\text{N}_6\text{Cl}_2\text{S}$): C, 68.92; H, 3.56; N, 12.37%. Found: C, 68.81; H, 3.52; N, 12.31%.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(5-chloro-3-phenyl-1H-indol-2-yl)-6-(4-methylphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3c). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3108, 3053, 1606, 1574, 1553; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.03 (s, 1H, indole NH), 10.03 (s, 1H, indole NH), 7.29–8.14 (m, 20H, Ar-H), 5.35 (s, 1H, $-\text{CH}=\text{}$), 2.44 (s, 3H, CH_3); MS: m/z = 692 $[\text{M}]^{++}$, 694 $[\text{M}+2]$, 696 $[\text{M}+4]$; Anal. calcd. for ($\text{C}_{40}\text{H}_{26}\text{N}_6\text{Cl}_2\text{S}$): C, 69.26; H, 3.78; N, 12.12%. Found: C, 69.15; H, 3.69; N, 12.21%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-6-(4-chlorophenyl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3d). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3391, 3265, 1601, 1540, 1519; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.43 (s, 1H, indole NH), 10.85 (s, 1H, indole NH), 6.40–9.13 (m, 20H, Ar-H), 4.91 (s, 1H, $-\text{CH}=\text{}$), 2.66 (s, 3H, CH_3); MS: m/z = 692 $[\text{M}]^{++}$, 694 $[\text{M}+2]$, 696 $[\text{M}+4]$; Anal. calcd. for ($\text{C}_{40}\text{H}_{26}\text{N}_6\text{Cl}_2\text{S}$): C, 69.26; H, 3.78; N, 12.12%. Found: C, 69.15; H, 3.69; N, 12.21%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3e). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3106, 2996, 1650, 1590, 1560; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.01 (s, 1H, indole NH), 10.12 (s, 1H, indole NH), 6.40–8.58 (m, 21H, Ar-H), 4.91 (s, 1H, $-\text{CH}=\text{}$), 2.55 (s, 3H, CH_3); MS: m/z = 658 $[\text{M}]^{++}$, 660 $[\text{M}+2]$; Anal. calcd. for ($\text{C}_{40}\text{H}_{27}\text{N}_6\text{ClS}$): C, 72.88; H, 4.13; N, 12.75%. Found: C, 72.75; H, 4.09; N, 12.64%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (3f). IR (KBr) $\nu_{\max}$ (cm^{-1}): 3443, 3133, 1602, 1578, 1558; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.31 (s, 1H, indole NH), 10.25 (s, 1H, indole NH), 7.11–8.18 (m, 20H, Ar-H), 5.29 (s, 1H, $-\text{CH}=\text{}$), 2.54 (s, 3H, CH_3), 2.43 (s, 3H,

CH₃); MS: m/z = 672 [M]⁺⁺, 674 [M+2]; Anal. calcd. for (C₄₁H₂₉N₆ClS): C, 73.15; H, 4.34; N, 12.48%. Found: C, 73.02; H, 4.29; N, 12.37%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-6-(4-chlorophenyl)-8-(1H-indol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3g**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3239, 3098, 1607, 1578, 1553; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.78 (s, 1H, indole NH), 10.51 (s, 1H, indole NH), 6.40–8.56 (m, 17H, Ar-H), 4.94 (s, 1H, -CH=); MS: m/z = 602 [M]⁺⁺, 604 [M+2], 606 [M+4]; Anal. calcd. for (C₃₃H₂₀N₆Cl₂S): C, 65.67; H, 3.34; N, 13.92; Found: C, 65.57; H, 3.28; N, 13.85%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-8-(1H-indol-3-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3h**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3404, 3104, 1608, 1558, 1505; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 10.61 (s, 1H, indole NH), 10.01 (s, 1H, indole NH), 6.43–8.91 (m, 18H, Ar-H), 5.15 (s, 1H, -CH=); MS: m/z = 568 [M]⁺⁺, 570 [M+2]; Anal. calcd. for (C₃₃H₂₁N₆ClS): C, 69.65; H, 3.72; N, 14.77%. Found: C, 69.55; H, 3.65; N, 14.71%.

3-(5-Chloro-3-phenyl-1H-indol-2-yl)-8-(1H-indol-3-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3i**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3160, 3096, 1645, 1603; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.97 (s, 1H, indole NH), 11.39 (s, 1H, indole NH), 6.80–7.85 (m, 17H, Ar-H), 5.59 (s, 1H, -CH=), 2.64 (s, 3H, CH₃); MS: m/z = 582 [M]⁺⁺, 584 [M+2]; Anal. calcd. for (C₃₄H₂₃N₆ClS): C, 70.03; H, 3.98; N, 14.41%. Found: C, 69.91; H, 3.95; N, 14.31%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(5-chloro-2-phenyl-1H-indol-3-yl)-6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3j**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3148, 3098, 1643, 1589, 1551; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 12.48 (s, 1H, indole NH), 11.99 (s, 1H, indole NH), 7.07–8.23 (m, 20H, Ar-H), 5.60 (s, 1H, -CH=); MS: m/z = 756 [M]⁺⁺, 758 [M+2], 760 [M+4], 762 [M+6]; Anal. calcd. for (C₃₉H₂₃N₆BrCl₂S): C, 61.75; H, 3.06; N, 11.08%. Found: C, 61.69; H, 3.01; N, 10.91%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(5-chloro-2-phenyl-1H-indol-3-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3k**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3158, 3068, 1590, 1576, 1551; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.15 (s, 1H, indole NH), 10.05 (s, 1H, indole NH), 7.29–8.72 (m, 21H, Ar-H), 5.45 (s, 1H, -CH=); MS: m/z = 722 [M]⁺⁺, 724 [M+2], 726 [M+4]; Anal. calcd. for (C₃₉H₂₄N₆BrClS): C, 64.69; H, 3.34; N, 11.61%. Found: C, 65.21; H, 3.51; N, 11.45%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(5-chloro-2-phenyl-1H-indol-3-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3l**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3108, 3029, 1644, 1606, 1553; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.03 (s, 1H, indole NH), 10.33 (s, 1H, indole NH), 7.2–8.1 (m, 20H, Ar-H), 5.05 (s, 1H, -CH=), 2.44 (s, 3H, CH₃); MS: m/z = 736 [M]⁺⁺, 738 [M+2], 740 [M+4]; Anal. calcd. for (C₄₀H₂₆N₆BrClS): C, 65.09; H, 3.55; N, 11.39%. Found: C, 64.89; H, 3.51; N, 11.28%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-6-(4-chlorophenyl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3m**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3176, 3048, 1623, 1584, 1509; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 12.20 (s, 1H, indole NH), 11.15 (s, 1H, indole NH), 6.32–8.13 (m, 20H, Ar-H), 5.60 (s, 1H, -CH=), 1.74 (s, 3H, CH₃); MS: m/z = 736 [M]⁺⁺, 738 [M+2], 740 [M+4]; Anal. calcd. for (C₄₀H₂₆N₆BrClS): C, 65.09; H, 3.55; N, 11.39%. Found: C, 64.09; H, 3.51; N, 11.28%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3n**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3240, 3198, 1604, 1558, 1553; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.01 (s, 1H, indole NH), 9.90 (s, 1H, indole NH), 6.40–8.58 (m, 21H, Ar-H), 4.31 (s, 1H, -CH=), 2.55 (s, 3H, CH₃); MS: m/z = 702 [M]⁺⁺, 704 [M+2]; Anal. calcd. for (C₄₀H₂₇N₆BrS): C, 68.28; H, 3.87; N, 11.94%. Found: C, 68.18; H, 3.82; N, 11.83%.

3-(5-bromo-3-phenyl-1H-indol-2-yl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3o**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3117, 3047, 1641, 1606, 1573; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 10.25 (s, 1H, indole NH), 9.95 (s, 1H, indole NH), 7.11–8.18 (m, 20H, Ar-H), 5.15 (s, 1H, -CH=), 2.54 (s, 3H, CH₃), 2.43 (s, 3H, CH₃); MS: m/z = 716 [M]⁺⁺, 718 [M+2]; Anal. calcd. for (C₄₁H₂₉N₆BrS): C, 68.62; H, 4.07; N, 11.71%. Found: C, 68.52; H, 4.05; N, 11.59%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-6-(4-chlorophenyl)-8-(1H-indol-3-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3p**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3167, 3047, 1648, 1589, 1558; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 10.61 (s, 1H, indole NH), 10.23 (s, 1H, indole NH), 6.83–8.19 (m, 17H, Ar-H), 5.19 (s, 1H, -CH=); MS: m/z = 646 [M]⁺⁺, 648 [M+2], 650 [M+4]; Anal. calcd. for (C₃₃H₂₀N₆BrClS): C, 61.17; H, 3.11; N, 12.97%. Found: C, 61.12; H, 3.09; N, 12.85%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(1H-indol-3-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3q**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3097, 2998, 1606, 1578, 1551; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.01 (s, 1H, indole NH), 10.01 (s, 1H, indole NH), 6.83–8.91 (m, 18H, Ar-H), 5.15 (s, 1H, -CH=); MS: m/z = 612 [M]⁺⁺, 614 [M+2]; Anal. calcd. For (C₃₃H₂₁N₆BrS): C, 64.60; H, 3.45; N, 13.70%. Found: C, 64.56; H, 3.41; N, 13.51%.

3-(5-Bromo-3-phenyl-1H-indol-2-yl)-8-(1H-indol-3-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3r**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3104, 3049, 1608, 1598, 1558; ¹H NMR (DMSO-d₆+CDCl₃) δ (ppm): 11.07 (s, 1H, indole NH), 10.19 (s, 1H, indole NH), 6.80–7.85 (m, 17H, Ar-H), 5.39 (s, 1H, -CH=), 2.64 (s, 3H, CH₃); MS: m/z = 626 [M]⁺⁺, 628 [M+2]; Anal. calcd. for (C₃₄H₂₃N₆BrS): C, 65.07; H, 3.69; N, 13.39%. Found: C, 64.95; H, 3.65; N, 13.28%.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-6-(4-chlorophenyl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3s**). IR (KBr) $\nu_{\max}$ (cm⁻¹): 3219, 3196, 1641,

1589, 1552; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.01 (s, 1H, indole NH), 10.25 (s, 1H, indole NH), 6.40–8.59 (m, 20H, Ar-H), 4.95 (s, 1H, $-\text{CH}=\text{}$), 2.56 (s, 3H, CH_3); MS: m/z = 692 $[\text{M}]^{++}$, 694 $[\text{M}+2]$, 696 $[\text{M}+4]$; Anal. calcd. for ($\text{C}_{40}\text{H}_{26}\text{N}_6\text{Cl}_2\text{S}$): C, 69.26; H, 3.78; N, 12.12%. Found: C, 69.14; H, 3.72; N, 12.02%.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3t**). IR (KBr) ν_{max} (cm^{-1}): 3244, 3189, 1641, 1604, 1552; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 12.39 (s, 1H, indole NH), 11.09 (s, 1H, indole NH), 6.80–7.85 (m, 21H, Ar-H), 5.15 (s, 1H, $-\text{CH}=\text{}$), 2.76 (s, 3H, CH_3); MS: m/z = 658 $[\text{M}]^{++}$, 660 $[\text{M}+2]$; Anal. calcd. for ($\text{C}_{40}\text{H}_{27}\text{N}_6\text{ClS}$): C, 72.88; H, 4.13; N, 12.75%. Found: C, 72.78; H, 4.10; N, 12.59%.

8-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3u**). IR (KBr) ν_{max} (cm^{-1}): 3248, 3198, 1606, 1579, 1552; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 12.20 (s, 1H, indole NH), 11.98 (s, 1H, indole NH), 7.05–8.13 (m, 20H, Ar-H), 4.37 (s, 1H, $-\text{CH}=\text{}$), 2.57 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); MS: m/z = 672 $[\text{M}]^{++}$, 674 $[\text{M}+2]$; Anal. calcd. for ($\text{C}_{41}\text{H}_{29}\text{N}_6\text{ClS}$): C, 73.15; H, 4.34; N, 12.48%. Found: C, 73.28; H, 4.31; N, 12.36%.

6-(4-Chlorophenyl)-8-(5-methyl-2-phenyl-1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3v**). IR (KBr) ν_{max} (cm^{-1}): 3248, 3198, 1604, 1574, 1552; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.39 (s, 1H, indole NH), 10.39 (s, 1H, indole NH), 6.43–8.91 (m, 20H, Ar-H), 4.55 (s, 1H, $-\text{CH}=\text{}$), 2.58 (s, 3H, CH_3); MS: m/z = 672 $[\text{M}]^{++}$, 674 $[\text{M}+2]$; Anal. calcd. for ($\text{C}_{41}\text{H}_{29}\text{N}_6\text{ClS}$): C, 73.15; H, 4.34; N, 12.48%. Found: C, 73.28; H, 4.31; N, 12.36%.

8-(5-Methyl-2-phenyl-1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3w**). IR (KBr) ν_{max} (cm^{-1}): 3248, 3179, 1604, 1574, 1556; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.05 (s, 1H, indole NH), 10.10 (s, 1H, indole NH), 6.32–8.13 (m, 21H, Ar-H), 5.60 (s, 1H, $-\text{CH}=\text{}$), 2.23 (s, 6H, CH_3); MS: m/z = 638 $[\text{M}]^{++}$; Anal. calcd. For ($\text{C}_{41}\text{H}_{30}\text{N}_6\text{S}$): C, 77.09; H, 4.73; N, 13.16%. Found: C, 77.06; H, 4.68; N, 13.03%.

8-(5-Methyl-2-phenyl-1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-6-(4-methylphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3x**). IR (KBr) ν_{max} (cm^{-1}): 3184, 3148, 1606, 1574, 1553; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 11.05 (s, 1H, indole NH), 10.07 (s, 1H, indole NH), 6.40–8.77 (m, 20H, Ar-H), 4.15 (s, 1H, $-\text{CH}=\text{}$), 2.54 (s, 6H, CH_3), 2.31 (s, 3H, CH_3); MS: m/z = 652 $[\text{M}]^{++}$; Anal. calcd. for ($\text{C}_{42}\text{H}_{32}\text{N}_6\text{S}$): C, 77.27; H, 4.94; N, 12.87%. Found: C, 77.17; H, 4.91; N, 12.96%.

8-(1H-Indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3y**). IR (KBr) ν_{max} (cm^{-1}): 3354, 3258, 1674, 1595, 1554; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 10.61 (s, 1H, indole NH), 10.01 (s, 1H, indole NH), 6.40–8.91 (m, 18H, Ar-H), 4.85 (s, 1H, $-\text{CH}=\text{}$), 2.54 (s, 3H, CH_3); MS: m/z = 548 $[\text{M}]^{++}$; Anal. calcd.

for ($\text{C}_{34}\text{H}_{24}\text{N}_6\text{S}$): C, 74.43; H, 4.41; N, 15.32%. Found: C, 74.39; H, 4.39; N, 15.25%.

6-(4-Chlorophenyl)-8-(1H-indol-3-yl)-3-(5-methyl-3-phenyl-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine (**3z**). IR (KBr) ν_{max} (cm^{-1}): 3391, 3244, 1667, 1601, 1540; ^1H NMR (DMSO- d_6 + CDCl_3) δ (ppm): 12.23 (s, 1H, indole NH), 10.11 (s, 1H, indole NH), 6.76–7.61 (m, 17H, Ar-H), 4.37 (s, 1H, $-\text{CH}=\text{}$), 2.08 (s, 3H, CH_3); MS: m/z = 582 $[\text{M}]^{++}$, 584 $[\text{M}+2]$; Anal. calcd. For ($\text{C}_{34}\text{H}_{25}\text{N}_6\text{S}$): C, 70.03; H, 3.98; N, 14.41%. Found: C, 69.98; H, 3.95; N, 14.35%.

2.2. Biological Activities

2.2.1. Antioxidant Activities

(1) *Free Radical Scavenging Activity*. Free radical scavenging activity was done by DPPH method [32]. Different concentrations (25 μg , 50 μg , and 100 μg) of samples and butylated hydroxy anisole (BHA) were taken in different test tubes. The volume was adjusted to 100 μL by adding MeOH. Five milliliters of 0.1 mM methanolic solution of DPPH was added to these tubes and shaken vigorously. The tubes were allowed to stand at 27°C for 20 min. The control was prepared as above without any samples. The absorbances of samples were measured at 517 nm. Radical scavenging activity was calculated using the following formula:

$$\% \text{ Radical scavenging activity} = \left[\frac{(\text{Control OD} - \text{Sample OD})}{(\text{Control OD})} \right] \times 100. \quad (1)$$

(2) *Total Antioxidant Capacity*. Various concentrations of samples (25 μg , 50 μg , and 100 μg) were taken in a series of test tubes. To this, 1.9 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate) was added. The tubes were incubated at 95°C for 90 min and allowed to cool. The absorbance of each aqueous solution was measured at 695 nm against a blank. Antioxidant capacities are expressed as equivalents of ascorbic acid. Ascorbic acid equivalents were calculated using standard graph of ascorbic acid. The values are expressed as ascorbic acid equivalents in μg per mg of samples.

(3) *Ferric Reducing Antioxidant Power*. Various concentrations of samples (25 μg , 50 μg , and 100 μg) were mixed with 2.5 mL of 200 mmol/L sodium phosphate buffer (pH 6.6) and 2.5 mL of 1% potassium ferricyanide. The mixture was incubated at 50°C for 20 min. Next, 2.5 mL of 10% trichloroacetic acid (w/v) was added. From this solution, 5 mL was mixed with 5 mL of distilled water and 1 mL of 0.1% ferric chloride and absorbance was measured spectrophotometrically at 700 nm. BHA was used as standard.

2.3. *Antimicrobial Activity*. Series of novel indole analogues are tested for *in vitro* antimicrobial activity against gram-negative bacteria *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 33499 and gram-positive bacteria *Staphylococcus aureus* ATCC 6538 and antifungal activity against

Candida tropicalis ATCC 8302 and *Candida albicans* ATCC 60193 by applying the agar plate diffusion technique [33]. Dilution process was adopted at 25 μg , 50 μg , and 100 $\mu\text{g}/\text{mL}$ concentrations, respectively. The activity is compared with reference drugs gentamycin for antibacterial and fluconazole for antifungal activity. The zone of inhibition after 24 hr of incubation at 37°C in case of antibacterial activity and 48 hr in case of antifungal activity was compared with that of standards.

3. Results and Discussion

3.1. Chemistry. Molecules were designed with the aim of exploring their antioxidant and antimicrobial activities. The target compounds were synthesized as outlined in (Scheme 1). 3,5-Disubstitutedindole-2-carboxyhydrazides were reacted with carbon disulphide in the presence of base and hydrazine hydrate to get 5-(5-substituted-3-phenyl-1H-indol-2-yl)-4-amino-4H-1,2,4-triazole-3-thiols **1a-c**. Claisen-Schmidt condensation of 2,5-disubstituted indole-3-carboxaldehydes with substituted acetophenones produced 3-(2,5-disubstituted-1H-indol-3-yl)-1-(4-substituted-phenyl)prop-2-en-1-one **2a-i**. The synthesized compounds **3a-z** were obtained in good yield by cyclocondensation of 5-(5-substituted-3-phenyl-1H-indol-2-yl)-4-amino-4H-1,2,4-triazole-3-thiol **1a-c** with 3-(2,5-disubstituted-1H-indol-3-yl)-1-(4-substituted phenyl)prop-2-en-1-one **2a-i**. The formation of products was monitored by TLC. All the newly synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR, mass spectroscopic and analytical data. The IR spectrum of 8-(5-chloro-2-phenyl-1H-indol-3-yl)-3-(5-chloro-3-phenyl-1H-indol-2-yl)-6-(3-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine **3a** showed a strong absorption at 3180 cm^{-1} and 3090 cm^{-1} corresponding to indole NH, absorption at 1654 and 1624, corresponding to triazole C=N, and absorption at 1546 cm^{-1} corresponding to thiadiazepine C=N stretching, respectively. The ^1H NMR spectrum of **3a** has exhibited a singlet at δ 12.47 ppm due to indole NH and peak at δ 11.63 ppm is due to indole NH which is also D_2O exchangeable. A multiplet between δ 7.31–8.47 ppm corresponds to twenty aromatic protons present in the molecule and a peak at δ 5.65 ppm is assigned for the $-\text{CH}=\text{$ of thiadiazepine ring proton. The ^{13}C NMR spectrum of compound **3a** has shown peaks at δ 108, 111, 113, 117, 118, 118, 120, 123, 125, 126, 126, 126, 128, 128, 128, 128, 129, 129, 129, 130, 132, 133, 134, 135, 138, 138, 144, 145, and 166. The mass spectrum of compound **3a** has shown molecular ion peak at m/z 712 $[\text{M}]^{++}$ which is corresponding to molecular weight of the compound. The above spectral data supports the formation of compound **3a**.

Various new triazolothiadiazepinyndole analogues synthesized during the present investigation are listed in (Table 1).

3.2. Biological Activities. The compounds **3a-z** were screened for their antioxidant (free radical scavenging, total antioxidant capacity, and ferric reducing antioxidant power) and antimicrobial activities.

SCHEME 1: Schematic representation for the formation of novel triazolothiadiazepinyndole **3a-z**.

3.2.1. Antioxidant Activities

(1) Free Radical Scavenging Activity. The target compounds were screened for free radical scavenging activity by DPPH method [32]. The samples were prepared at concentrations of 25, 50, and 100 $\mu\text{g}/100\text{ }\mu\text{L}$ and butylated hydroxy anisole (BHA) was taken as standard. DPPH is a stable free radical in a methanolic solution. Because of the unpaired electron of DPPH, it gives a strong absorption maxima at 517 nm in the visible region (purple color). In addition, the unpaired electron of the radical becomes paired in the presence of a hydrogen donor (a free radical scavenging antioxidant), decreasing the absorption. Among the compounds tested **3a-c** and **3j-l** have shown very promising free radical scavenging activity. The increased activity is due to the existence of halogen substitution at the five positions of both indoles. The hydrogen of indole NH could be donated to the DPPH to form DPPH free radical; by the presence of phenyl ring at the third position of indole, the DPPH free radical will be stabilized by the resonance. Compounds **3d-f**, **3m-o**, and **3s-x** containing halogen atom at five positions of indole and a methyl group at another indole ring have shown moderate activity, whereas compounds **3g-i**, **3p-r**, and **3y-z** have shown the least activity compared with the standard. The bar graph representation of percentage of free radical scavenging activity is displayed in Figures 1 and 2.

TABLE 1: Comparative data of conventional and microwave methods for the synthesis of novel triazolothiadiazepinyndole **3a–z**.

Compd ^a Number	Substituents				Conventional method		Microwave method		m.p. ^c (°C)
	R	R'	R''	R'''	Time (min)	Yield ^b (%)	Time (min)	Yield ^b (%)	
3a	Cl	Cl	Cl	Ph	180–240	85	10	95	200–02
3b	Cl	Cl	H	Ph	180–240	80	10	93	142–43
3c	Cl	Cl	Me	Ph	180–240	75	10	95	194–96
3d	Cl	Me	Cl	Ph	180–240	80	10	95	160–62
3e	Cl	Me	H	Ph	180–240	70	10	93	190–92
3f	Cl	Me	Me	Ph	180–240	65	10	95	158–60
3g	Cl	H	Cl	H	180–240	60	10	85	195–97
3h	Cl	H	H	H	180–240	60	10	80	168–70
3i	Cl	H	Me	H	180–240	70	10	90	155–57
3j	Br	Cl	Cl	Ph	180–240	80	10	98	210–12
3k	Br	Cl	H	Ph	180–240	85	10	96	195–97
3l	Br	Cl	Me	Ph	180–240	85	10	95	140–42
3m	Br	Me	Cl	Ph	180–240	75	10	90	180–82
3n	Br	Me	H	Ph	180–240	65	10	85	165–67
3o	Br	Me	Me	Ph	180–240	60	10	80	168–70
3p	Br	H	Cl	H	180–240	60	10	85	210–12
3q	Br	H	H	H	180–240	60	10	75	218–20
3r	Br	H	Me	H	180–240	60	10	80	120–22
3s	Me	Cl	Cl	Ph	180–240	75	10	85	183–85
3t	Me	Cl	H	Ph	180–240	75	10	85	201–02
3u	Me	Cl	Me	Ph	180–240	80	10	87	181–83
3v	Me	Me	Cl	Ph	180–240	65	10	85	190–92
3w	Me	Me	H	Ph	180–240	60	10	80	161–62
3x	Me	Me	Me	Ph	180–240	65	10	86	172–74
3y	Me	H	H	H	180–240	60	10	75	158–60
3z	Me	H	Cl	H	180–240	60	10	70	149–51

^aProducts were characterized by IR, ¹H NMR, ¹³C NMR, MS, and elemental analysis. ^bIsolated yield. ^cMelting points are uncorrected.

(2) *Total Antioxidant Capacity*. Total antioxidant activity was performed to all the newly synthesized compounds [34]. Antioxidant capacities are expressed as equivalents of ascorbic acid. Among the tested compounds **3a–c** and **3j–l** which are halogen substituted triazolothiadiazepinyndole have shown very strong total antioxidant capacity. Compounds with methyl substitution at the fifth position of the indole ring and no substitution at the second and fifth positions have shown the least total antioxidant capacity compared with the standard. The increased activity is due to the presence of halogen at the fifth position and a phenyl ring at the third position of indole. The results of total antioxidant activity are shown in Figures 3 and 4.

(3) *Ferric Reducing Antioxidant Power Activity*. The novel compounds were screened for ferric reducing antioxidant activity [35]. Butylated hydroxy anisole (BHA) was used as

standard. All the tested compounds have shown positive tendency towards the ferric reducing activity. The presence of reducer (i.e., antioxidant) causes the reduction of the Fe⁺³/ferricyanide complex to the Fe⁺² form after the addition of trichloroacetic acid and ferric chloride. The reducing power of test compounds increases with increase in concentration. Compounds **3d–f**, **3m–o**, and **3s–z** have shown excellent ferric reducing antioxidant activity and other analogues of indole have shown moderate to high activity. The presence of methyl group at the fifth position of the indole ring plays an important role as a better electron donor which enhances reducing power activity of the compounds. The results are presented in Figures 5 and 6.

3.3. Antimicrobial Activity. Applying the agar plate diffusion technique [33], series of novel triazolothiadiazepinyndole

TABLE 2: Zone of inhibition in mm at 25, 50, and 100 $\mu\text{g/mL}$ concentrations.

Compd name	Antibacterial activity									Antifungal activity					
	<i>S. aureus</i>			<i>E. coli</i>			<i>K. pneumoniae</i>			<i>C. tropicalis</i>			<i>C. albicans</i>		
	25	50	100	25	50	100	25	50	100	25	50	100	25	50	100
3a	13	17	20	15	20	22	16	22	25	14	18	20	13	15	18
3b	14	16	20	16	19	24	15	21	24	15	17	21	14	17	19
3c	15	15	19	14	21	25	14	23	26	13	16	20	15	16	20
3d	11	12	17	12	15	16	09	14	15	10	12	15	10	12	14
3e	10	13	15	11	16	17	08	15	18	09	11	14	09	11	12
3f	09	12	16	09	14	16	09	13	14	09	12	13	09	10	10
3g	02	06	08	05	07	08	05	07	09	02	04	06	03	04	05
3h	03	04	09	03	05	07	04	08	10	01	03	05	03	06	09
3i	05	07	08	04	06	08	03	06	08	03	04	06	05	06	08
3j	14	18	21	18	18	23	15	21	23	15	18	21	13	15	17
3k	13	19	20	17	20	22	17	23	24	16	19	21	15	17	18
3l	12	18	21	16	19	25	16	22	26	12	15	21	13	16	19
3m	10	10	15	10	12	15	09	15	16	10	12	15	09	11	12
3n	08	11	14	08	13	14	10	13	18	09	11	14	09	09	11
3o	08	10	14	09	14	16	09	13	19	08	10	12	10	10	12
3p	03	04	09	04	05	08	06	08	12	04	06	08	03	05	07
3q	03	05	07	03	05	08	05	09	11	03	05	07	05	06	08
3r	04	06	08	06	08	09	04	08	10	02	05	06	03	06	07
3s	10	10	15	10	12	15	09	14	15	10	12	14	11	12	13
3t	09	11	13	11	14	17	10	15	18	08	11	15	09	10	12
3u	08	11	14	08	13	14	10	13	14	09	13	13	08	12	14
3v	09	09	16	10	12	15	11	12	17	10	12	15	09	13	15
3w	08	10	14	09	14	16	09	12	15	09	11	16	10	11	12
3x	09	12	12	09	11	14	08	14	16	08	10	17	09	10	12
3y	04	06	09	05	08	10	05	09	10	05	09	10	04	05	06
3z	05	05	08	04	09	11	04	10	12	04	08	11	04	04	05
Std.1	15	19	22	18	21	25	17	23	27	—	—	—	—	—	—
Std.2	—	—	—	—	—	—	—	—	—	15	19	22	16	19	21

Std.1: gentamycin, Std.2: fluconazole.

The bold font refers to the compounds which have shown more potent antimicrobial activities.

analogues were screened for *in vitro* antibacterial activity against (Table 2) gram-negative bacteria *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) and gram-positive bacteria *Staphylococcus aureus* (*S. aureus*) at 25 $\mu\text{g/mL}$, 50 $\mu\text{g/mL}$, and 100 $\mu\text{g/mL}$ concentrations, respectively. Gentamycin was used as standard. The zone of inhibitions was measured in mm for each concentration. Most of the screened compounds were found to have significant antibacterial activity. Compounds **3a–c** and **3j–l** have shown very good activity against all the three bacterial strains. Compounds **3d–f**, **3m–o**, and **3s–x** have shown moderate activity and compounds **3g–i**, **3p–r**, and **3y–z** have shown the least activity. Antifungal screening of the compounds was carried out *in vitro* against two fungi strains *Candida tropicalis* and *Candida albicans* at 25 $\mu\text{g/mL}$, 50 $\mu\text{g/mL}$, and 100 $\mu\text{g/mL}$

concentrations using fluconazole as standard. Among the tested indole analogues the majority of compounds exhibited moderate to significant antifungal activity.

4. Conclusions

We have synthesized titled compounds **3a–z** by economic, better yield, and safer methods through the formation of compounds **1a–c** and **2a–i** under thermal and microwave condition. The compounds **3a–z** were subjected for their antioxidant and antimicrobial screening. Very potent antimicrobial, scavenging and antioxidant activity was observed with compounds containing halogens at the fifth position of indoles. Excellent ferric reducing activity was observed with compounds containing electron donor group at five positions

FIGURE 1: Free radical scavenging activity of 3a-m.

FIGURE 4: Total antioxidant capacity of 3n-z.

FIGURE 2: Free radical scavenging activity of 3n-z.

FIGURE 5: Ferric reducing antioxidant power activity of 3a-m.

FIGURE 3: Total antioxidant capacity of 3a-m.

FIGURE 6: Ferric reducing antioxidant power activity of 3n-z.

of one/both indoles. Therefore, the findings will provide a great impact on chemists and biochemists for further investigations in the indole field in search of molecules possessing potent antioxidant and antimicrobial activities.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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