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SYNTHESIS OF SOME NEW THIAZOLIDINE DERIVATIVES AND THEIR BIOLOGICAL SIGNIFICANCE

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An efficient route for the synthesis of new series of N-[3-(1H-1,2,3-benzotriazol-1-yl)-propyl]-2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-1,3-thiazolidine carboxamide, compounds **5** (**a**–**j**) has been elaborated. The compounds **5** (**a**–**j**) have been synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, FAB Mass spectra and chemical analysis. All final compounds were screened for their antimicrobial activity against some selected bacteria, fungi, antituberculosis (against *M. tuberculosis*) and antiinflammatory activity on albino rats.

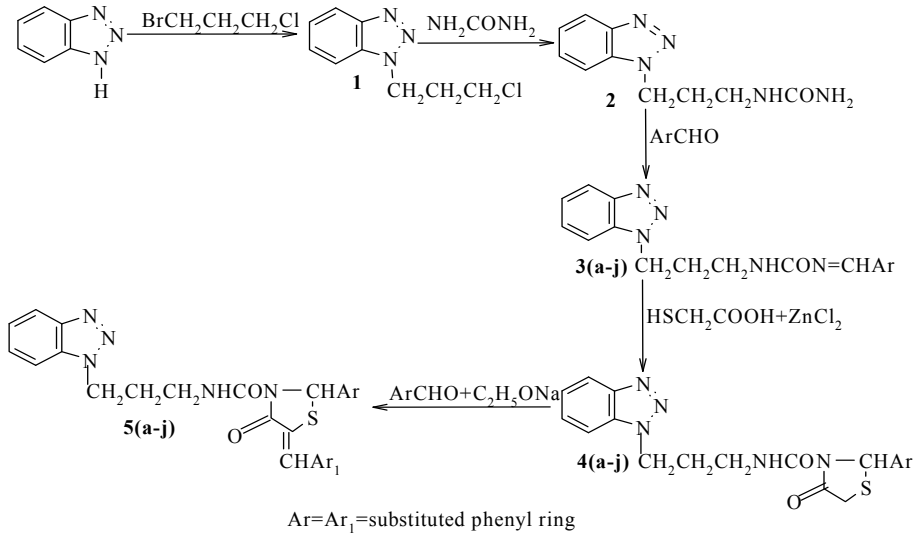
Key words: *synthesis, benzotriazolo-4-oxothiazolidine, antimicrobial, antitubercular activity.*

INTRODUCTION

Heterocyclic compounds have been under investigation for a long time because of their important pharmacological properties. Thiazolidine possess various remarkable biological activities such as antimicrobial [1], antibacterial [2,3], antifungal [4], antipsychotic [5], antiviral [6], antitubercular [7], anticancer [8] and anti HIV [9] activity. 1,2,3-Benzotriazole derivatives have been a topic of interest of a substantial research and continue to be one of the most active areas of the heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities. The large number of benzotriazole derivatives are pharmacologically active lead compounds for drug development. Benzotriazole derivatives also occur widely in many natural products such as those from plants, fungi and marine organisms. The biological and chemical properties of the benzotriazole derivatives have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacologists. Chemical and biological research has also presented a great challenge to synthesize and optimize highly efficient and economical synthetic route to novel biologically active substances.

At present there are thousands of compounds described, including simple and more complex factionalized benzotriazole derivatives. The simple benzotriazole derivatives are comprised of triazole ring fused with the benzene ring and more complex benzotriazole derivatives usually contain the additional fused rings. The benzotriazole nucleus is a pharmaceutically important and emerging heterocycle with a broad spectrum of activities including antibacterial [10–12], antifungal [13, 14], antitubercular [15] and anticancer [16] activity. We have decided to synthesize a new series of N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-

2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-1,3-thiazolidine carboxamide, compounds **5** (**a**–**j**) (see the Scheme).

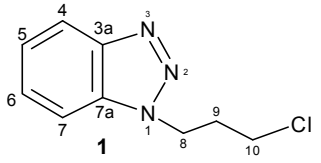


Scheme. Synthesis of compounds **5(a–j).**

EXPERIMENTAL

Melting points were determined using open capillaries and are uncorrected. Progress of reaction was monitored by silica gel G-coated TLC plates in the MeOH: $CHCl_3$ (1:9) system. The spots were visualized by exposing dry plate in iodine vapours. IR spectra were recorded in KBr discs on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz, respectively, using TMS as an internal standard. All chemical shifts were reportted on δ scale. The FAB-Mass spectra were recorded on a Jeol SX-102 mass spectrometer. Elemental analyses were performed on Carlo Erba-1108 analyzer. The analytical data for all the compounds were highly satisfactory. For column chromatographic purification of the products, Merck silica gel 60 (230–400 mesh) was used. The reagent grade chemicals were purchased from the commercial sources and further purified before use.

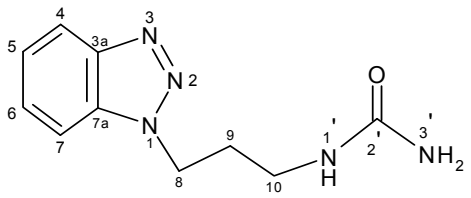
Synthesis of 1-(3-chloropropyl)-1H-1,2,3-benzotriazole (compound 1). 1,2,3-Benzotriazole (0.420 mol) and 1-bromo-3-chloropropane (0.420 mol) in methanol (100 ml) were stirred on a magnetic stirrer for about 6.00 hours at room temperature. The completion of the reaction was monitored by TLC plates coated with silica gel-G. The product was filtered and purified by chromatography over a column packed with silica gel using the system $CHCl_3$: CH_3OH (8:2 v/v) as eluent (150 ml). The purified product was dried under vacuum and recrystallized from ethanol to yield the compound **1**.



1

1-(3-Chloropropyl)-1*H*-1,2,3-benzotriazole (1). Yield: 62%; m.p. 77–79 ºC; IR spectrum (cm^{-1}): 749 (C–Cl), 1324 (N–C), 1463 (C=C), 1542 (N=N), 1430, 2836, 2893 (CH_2), 3021 (CH–Ar); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.13–2.15 (m, 2H, H-9); 3.49 (t, 2H, J = 7.45 Hz, H-10); 4.17 (t, 2H, J = 7.45 Hz, H-8); 7.29–7.96 (m, 4H ArH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 36.2 (C-9); 40.7 (C-10); 46.3 (C-8); 118.5 (C-6); 120.2 (C-4); 128.4 (C-7); 128.9 (C-5); 145.5 (C-3a); 147.9 (C-7a); FAB Mass (*m/z*): 195 [M^+]. Elemental analisys data for $C_9H_{10}N_3Cl$: calculated, %: C, 55.25; H, 5.15; N, 21.47; found, %: C, 55.21; H, 5.13; N, 21.41.

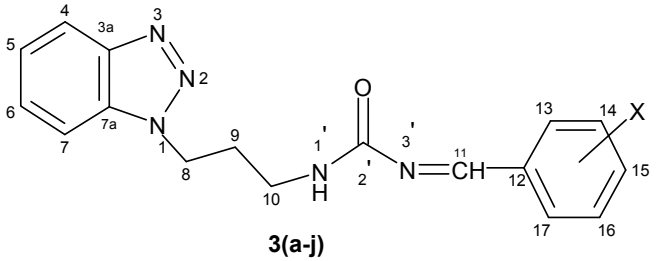
Synthesis of N-[3-(1H-1,2,3-benzotriazol-1-yl)-propyl]urea (compound 2). The compound **1** (0.273 mol) and urea (0.273 mol) were stirred on a magnetic stirrer for about 4.00 hours. The completion of the reaction was monitored by TLC plates coated with silica gel-G. After the completion of the reaction the product was filtered and purified chromatographically on a silica gel packed column using chloroform : methanol (8:2 v/v) as eluent (150 ml). The purified product was recrystallized from ethanol to yield compound **2**.



2

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]urea (2). Yield: 70%; m.p. 60–63 ºC; IR spectrum (cm^{-1}): 1330 (N–C), 1464 (C=C), 1543 (N=N), 1662 (CO), 1431, 2835, 2894 (CH_2), 3022 (CH–Ar), 3365 (NH), 3415 (NH_2); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.15–2.20 (m, 2H, H-9); 3.38–3.42 (m, 2H, H-10); 4.17 (t, 2H, J = 7.40 Hz, H-8); 5.69 (s, 1H, H-1′); 5.96 (s, 2H, H-3′); 7.32–7.94 (m, 4H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 35.5 (C-9); 41.2 (C-10); 48.2 (C-8); 117.6 (C-4); 121.3 (C-7); 127.8 (C-5); 128.2 (C-6); 144.7 (C-3a); 146.7 (C-7a); 163.3 (C-2′); FAB Mass (*m/z*): 219 [M^+]. Elemental analysis data for $C_{10}H_{13}N_5O$: calculated, %: C, 54.78; H, 5.97; N, 31.94; found, %: C, 54.79; H, 5.90; N, 31.88.

Synthesis of N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-N′-[(phenyl)methylidene]urea (compound 3a). The compound **2** (0.036 mol) and benzaldehyde (0.036 mol) in methanol (100 ml) in the presence of 2–4 drops of glacial acetic acid were first stirred on a magnetic stirrer for about 2.00 hours at room temperature followed by reflux on a steam bath for about 3.00 hours. The completion of the reaction was monitored by TLC plates coated with silica gel-G. The product was filtered, cooled and purified on silica gel using CH_3OH : $CHCl_3$ (7:3 v/v) system as eluent (80 ml). The purified product was dried under vacuum and recrystallized from ethanol at room temperature to furnish the compound **3a.**

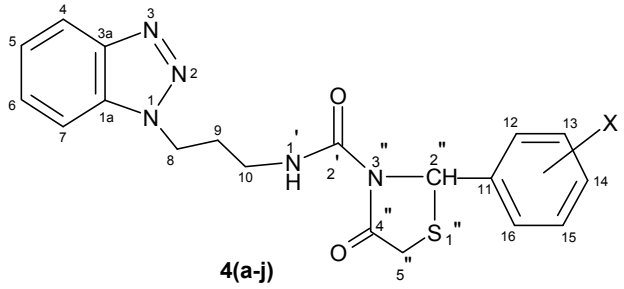


3(a-j)

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-N′-[(phenyl)methylidene]urea (3a). Yield: 60%; m.p. 80–83 ºC; IR spectrum (cm^{-1}): 1301 (N–C), 1462 (C=C), 1541 (N=N), 1550 (N=CH), 1661 (CO), 1429, 2834, 2892 (CH_2), 3020 (CH–Ar), 3361 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.04–2.09 (m, 2H, H-9); 3.28–3.34 (m, 2H, H-10); 4.19 (t, 2H, *J* = 7.35 Hz, H-8); 5.76 (s, 1H, H-1′); 7.94 (s, 1H, H-11); 7.15–7.85 (m, 9H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 38.4 (C-9); 42.3 (C-10); 47.3 (C-8); 115.3 (C-4); 120.0 (C-7); 125.8 (C-5); 126.3 (C-13 and C-17); 127.5 (C-14 and C-16); 128.5 (C-6); 129.2 (C-15); 131.2 (C-12); 136.2 (C-3a); 145.2 (C-11); 146.1 (C-7a); 162.6 (C-2′); FAB Mass (*m/z*): 307 [M^+]. Elemental analysis data for $C_{17}H_{17}N_5O$: calculated, %: C, 66.43; H, 5.57; N, 22.78; found, %: C, 66.40; H, 5.48; N, 22.72.

Compounds **3** (**b**–**j**) have also been synthesized using similar method.

Synthesis of N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(phenyl)-4-oxo-1,3-thiazolidine carboxamide (compound 4a). The compound **3a** (0.016 mol) and thioglycolic acid (0.016 mol) in methanol (50 ml) in the presence of $ZnCl_2$ were first stirred on a magnetic stirrer for about 2.30 hours at room temperature followed by reflux on a steam bath for about 6.00 hours. The completion of the reaction was monitored by TLC plates coated with silica gel-G. The product was filtered, cooled and purified on a column packed with silica gel using the system CH_3OH : $CHCl_3$ (7:3 v/v) as eluent (70 ml). The purified product was dried under vacuum and recrystallized from ethanol at room temperature to furnish compound **4a.**



4(a-j)

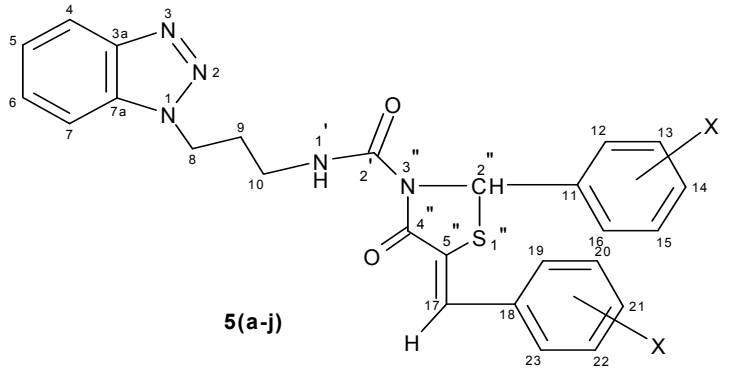
N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(phenyl)-4-oxo-1,3-thiazolidine carboxamide (4a). Yield: 62%; m.p. 81–82 ^{o}C; IR spectrum (cm^{-1}): 668 (C–S–C), 1332 (C–N), 1478 (C=C), 1571 (N=N), 1672 (CO), 1740 (CO cyclic), 1438, 2843, 2903 (CH_2), 2940 (S–CH_2), 3032 (CH–Ar), 3373 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.18–2.22 (m, 2H, H-9); 3.37 (s, 2H, H-5″); 3.40–3.44 (m, 2H, H-10); 4.10 (t, 2H, *J* = 7.35 Hz, H-8); 5.15 (s, 1H, H-2″); 5.80 (s, 1H, H-1′); 6.72–8.09 (m, 9H, Ar–H); ^{13}C NMR spectrum

(75 MHz, $CDCl_3$, TMS), δ: 33.5 (C-5″); 36.6 (C-9); 45.1 (C-10); 47.3 (C-8); 61.7 (C-2″); 110.3 (C-4); 118.9 (C-7); 125.7 (C-5); 126.4 (C-12 and C-16); 128.4 (C-6); 129.8 (C-14); 130.1 (C-13 and C-15); 132.6 (C-3a); 136.4 (C-11); 145.9 (C-7a); 161.1 (C-2′); 168.7 (C-4″); FAB Mass (*m/z*): 381 [M^+]. Elemental analysis data for $C_{19}H_{19}N_5O_2S$: calculated, %: C, 59.82; H, 5.02; N, 18.35; found, %: C, 59.74; H, 4.97; N, 18.29.

Compounds **4** (**b**–**j**) have also been synthesized using the similar method.

Synthesis of N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(phenyl)-4-oxo-5-(benzylidene)-1,3-thiazolidine carboxamides (compound 5a). The compound **4a** (0.010 mol) and benzaldehyde (0.010 mol) in methanol (50 ml) in the presence of CH_3CH_2ONa were first stirred on a magnetic stirrer for about 2.00 hours at room temperature followed by reflux on a steam bath for about 4.00 hours. The completion of the reaction was monitored by TLC plates coated with silica gel-G. The product was filtered, cooled and purified on silica gel using the system CH_3OH : $CHCl_3$ (7:3 v/v) as eluent (90 ml). The purified product was dried under vacuum and recrystallized from ethanol at room temperature to furnish compound **5a.**

Compounds **5 (b-j)** have also been synthesized by using the similar method.



5(a-j)

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(phenyl)-4-oxo-5-(benzylidene)-1,3-thiazolidine carboxamide (5a). Yield: 57%; m.p. 79–81 °C; IR spectrum (cm^{-1}): 1560 (C=CH), 1336 (C–N), 1477 (C=C), 1544 (N=N), 1674 (CO), 1737 (CO cyclic), 1445, 2842, 2903 (CH_2), 3034 (CH–Ar), 3375 (NH), 2850 (C=CH), 3339 (NH); ^1H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.24–2.29 (m, 2H, H-9); 3.48–3.53 (m, 2H, H-10); 4.37 (t, 2H, *J* = 7.50 Hz, H-8); 5.72 (s, 1H, H-1′); 5.27(s, 1H, H-2″); 6.52 (H-17); 6.86–7.72 (m, 14H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 38.2 (C-9); 45.2 (C-10); 51.1 (C-8); 63.7 (C-2″); 110.3 (C-4); 118.9 (C-7); 125.7 (C-5); 126.4 (C-12 and C-16); 126.4 (C-19 and C-23); 128.4 (C-6); 129.8 (C-16); 129.8 (C-14); 130.1 (C-13 and C-15); 131.7 (C-20 and C-22); 132.6 (C-3a); 136.4 (C-11); 138.7 (C-18); 136.7 (C-17); 143.2 (C-5″); 145.9 (C-7a); 161.1 (C-2′); 168.7 (C-4″); FAB Mass (*m/z*): 469 [M^+]. Elemental analysis data for $C_{26}H_{23}N_5O_2S$: calculated, %: C, 66.50; H, 4.93; N, 14.91; found, %: C, 66.46; H, 4.89; N, 14.87.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(4-chlorophenyl)-4-oxo-5-(4-chlorobenzylidene)-1,3-thiazolidine carboxamide (5b). Yield: 60%; m.p. 89–91 °C; IR spectrum (cm^{-1}): 732 (C–Cl), 1470 (C=CH), 2868 (C=CH), 1344 (C–

NH), 1485 (C=C), 1546 (N=N), 1680 (CO), 1742 (CO cyclic), 1452, 2846, 2908 (CH_2), 3039 (CH–Ar), 3381 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.41–2.46 (m, 2H, H-9); 3.59–3.63 (m, 2H, H-10); 4.50 (t, 2H, *J* = 7.45 Hz, H-8); 5.79 (s, 1H, H-1′); 5.21 (s, 1H, H-2′′); 6.71 (s, 1H, H-17); 6.86–7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 39.7 (C-9); 42.9 (C-10); 50.4 (C-8); 62.2 (C-2"); 116.2 (C-4); 120.9 (C-7); 123.7 (C-5); 127.7 (C-12 and C-16); 128.0 (C-19 and C-23); 128.6 (C-6); 129.4 (C-13 and C-15); 130.3 (C-20 and C-22); 131.4 (C-16); 131.9 (C-14); 132.8 (C-3a); 136.7 (C-18); 136.7 (C-11); 137.2 (C-17); 143.5 (C-5′′); 146.9 (C-7a); 164.1 (C-2′); 174.5 (C-4′′); Mass FAB (*m/z*): 538 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SCl_2$: calculated, %: C, 57.99; H, 3.93; N, 13.00; found, %: C, 57.94; H, 3.87; N, 12.94.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(3-chlorophenyl)-4-oxo-5-(3-chlorobenzylidene)-1,3-thiazolidine carboxamide (5c). Yield: 62%; m.p. 86–87 °C; IR spectrum (cm^{-1}): 738 (C–Cl), 1335 (N–C), 1474 (C=CH), 2862 (C=CH) 1489 (C=C), 1552 (N=N), 1685 (CO), 1747 (CO cyclic), 1452, 2854, 2914 (CH_2), 3047 (CH–Ar), 3382 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.45–2.49 (m, 2H, H-9); 3.60–3.65 (m, 2H, H-10); 4.47 (t, 2H, *J* = 7.50 Hz, H-8); 5.95 (s, 1H, H-1′); 5.23 (s, 1H, H-2′′); 6.68 (s, 1H, H-17); 6.86–7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 38.6 (C-9); 43.6 (C-10); 47.3 (C-8); 61.9 (C-2′′); 114.2 (C-4); 118.4 (C-7); 124.3 (C-5); 126.7 (C-12); 127.5 (C-19); 128.3 (C-16); 128.9 (C-23); 129.1 (C-6); 129.9 (C-14); 130.5 (C-21); 131.4 (C-13); 132.9 (C-22); 134.4 (C-3a); 135.3 (C-13); 136.6 (C-20); 138.1 (C-11); 139.7 (C-18); 140.1 (C-17); 143.2 (C-5"); 147.9 (C-7a); 164.3 (C-2′); 171.2 (C-4′′); FAB Mass (*m/z*): 538 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SCl_2$: calculated, %: C, 57.99; H, 3.93; N, 13.00; found, %: C, 57.92; H, 3.76; N, 12.91.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(2-chlorophenyl)-4-oxo-5-(2-chlorobenzylidene)-1,3-thiazolidine carboxamide (5d). Yield: 61%; m.p. 82–83 °C; IR spectrum (cm^{-1}): 742 (C–Cl), 1576 (C=CH), 2866 (C=CH) 1338 (C–NH), 1492 (C=C), 1549 (N=N), 1684 (CO), 1752 (CO cyclic), 1454, 2857, 2917 (CH_2), 3046 (CH–Ar), 3388 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.37–2.43 (m, 2H, H-9); 3.53–3.59 (m, 2H, H-10); 4.44 (t, 2H, *J* = 7.55 Hz, H-8); 5.85 (s, 1H, H-1′); 5.29 (s, 1H, H-2′′); 6.72 (s, 1H, H-17); 6.86–7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 36.8 (C-9); 43.8 (C-10); 47.6 (C-8); 63.4 (C-2′′); 114.5 (C-4); 119.9 (C-7); 124.7 (C-5); 127.6 (C-13); 128.2 (C-22); 128.9 (C-6); 129.4 (C-13); 130.1 (C-20); 130.4 (C-14); 131.6 (C-21); 132.2 (C-16); 132.2 (C-23); 133.3 (C-3a); 135.1 (C-12); 135.1 (C-19); 137.9 (C-11); 137.9 (C-8); 138.3 (C-17); 143.1 (C-5"); 147.4 (C-7a); 163.6 (C-2′); 173.7 (C-4′′); FAB Mass (*m/z*): 538 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SCl_2$: calculated, %: C, 57.99; H, 3.93; N, 13.00; found, %: C, 57.90; H; 3.85, N, 12.90.

N-[3-(1H-1,2,3-benzotriazol-1-yl)-propyl]-2-(4-bromophenyl)-4-oxo-5-(4-bromobenzylidene)-1,3-thiazolidine carboxamide (5e). Yield: 62%; m.p. 78–79 °C; IR spectrum (cm^{-1}): 561 (C–Br), 1472 (C=CH), 2856 (C=CH) 1346 (C–N), 1490 (C=C), 1553 (N=N), 1681 (CO), 1750 (CO cyclic), 1455, 2852, 2915 (CH_2), 3042 (CH–Ar), 3385 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.38–2.42 (m, 2H, H-9); 3.52–3.57 (m, 2H, H-10); 4.46 (t, 2H, *J* = 7.45 Hz, H-8); 5.92 (s, 1H, H-1′); 5.11 (s, 1H, H-2′′); 6.77 (s, 1H, H-17); 6.86–

7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 39.4 (C-9); 43.8 (C-10); 47.6 (C-8); 63.4 (C-2″); 112.4 (C-4); 119.4 (C-7); 123.9 (C-14); 123.9 (C-21); 124.5 (C-5); 128.6 (C-6); 130.8 (C-12 and C-16); 131.2 (C-19 and C-23); 131.4 (C-13 and C-15); 131.8 (C-20 and C-22); 132.6 (C-3a); 136.5 (C-11); 137.7 (C-18); 138.8 (C-17); 141.9 (C-5"); 147.9 (C-7a); 164.2 (C-2′); 172.3 (C-4″); FAB Mass (*m/z*): 627 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SBr_2$: calculated, %: C, 49.77; H, 3.37; N, 11.16; found, %: C, 49.73; H, 3.33; N, 11.12.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(3-bromophenyl)-4-oxo-5-(3-bromobenzylidene)-1,3-thiazolidine carboxamide (5f). Yield: 64%; m.p. 81–82 °C; IR spectrum (cm^{-1}): 568 (C–Br), 2852 (C=CH), 1475 (C=CH), 1347 (C–NH), 1484 (C=C), 1550 (N=N), 1679 (CO), 1745 (CO cyclic), 1450, 2848, 2909 (CH_2), 3040 (CH–Ar), 3384 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.40–2.44 (m, 2H, H-9); 3.60–3.67 (m, 2H, H-10); 4.51 (t, 2H, *J* = 7.40 Hz, H-8); 5.89 (s, 1H, H-1′); 5.19 (s, 1H, H-2″); 6.68 (s, 1H, H-17); 6.86–7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 37.5 (C-9); 44.3 (C-10); 49.3 (C-8); 64.6 (C-2″); 109.2 (C-4); 118.9 (C-7); 123.7 (C-13); 124.6 (C-20); 124.7 (C-5); 125.6 (C-16); 125.6 (C-23); 128.4 (C-6); 129.8 (C-12); 130.8 (C-19); 132.5 (C-13); 133.4 (C-22); 133.9 (C-14); 134.3 (C-21); 134.5 (C-3a); 140.3 (C-11); 140.8 (C-17); 142.5 (C-5″); 142.7 (C-18); 145.6 (C-7a); 163.7 (C-2′); 172.6 (C-4″); FAB Mass (*m/z*): 627 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SBr_2$: calculated, %: C, 49.77; H, 3.37; N, 11.16; found, %: C, 49.72; H, 3.34; N, 11.14.

N-[3-(1H-1,2,3-benzotriazol-1-yl)-propyl]-2-(2-bromophenyl)-4-oxo-5-(2-bromobenzylidene)-1,3-thiazolidine carboxamide (5g). Yield: 63%; m.p. 75–76 °C; IR spectrum (cm^{-1}): 564 (C–Br), 1479 (C=CH), 2856 (C=CH), 1352 (C–NH), 1494 (C=C), 1551 (N=N), 1686 (CO), 1749 (CO cyclic), 1456, 2857, 2915 (CH_2), 3045 (CH–Ar), 3386 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.40–2.45 (m, 2H, H-9); 3.55–3.61 (m, 2H, H-10); 4.49 (t, 2H, *J* = 7.50 Hz, H-8); 5.91 (s, 1H, H-1′); 5.17 (s, 1H, H-2″); 6.59 (s, 1H, H-17); 6.86–7.72 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 40.3 (C-9); 45.9 (C-10); 48.4 (C-8); 62.6 (C-2″); 111.1 (C-4); 119.5 (C-7); 120.3 (C-12); 122.6 (C-19); 125.7 (C-5); 126.5 (C-15); 127.2 (C-22); 128.4 (C-6); 129.3 (C-16); 130.1 (C-23); 131.3 (C-14); 132.8 (C-21); 133.2 (C-3a); 134.5 (C-13); 135.7 (C-20); 138.7 (C-17); 142.2 (C-5″); 142.6 (C-11); 144.2 (C-22); 147.9 (C-7a); 163.1 (C-2′); 172.5 (C-4″); FAB Mass (*m/z*): 627 [M^+]. Elemental analysis data for $C_{26}H_{21}N_5O_2SBr_2$: calculated, %: C, 49.77; H, 3.37; N, 11.16; found, %: C, 49.70; H, 3.30; N, 11.10.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(4-nitrophenyl)-4-oxo-5-(4-nitrobenzylidene)-1,3-thiazolidine carboxamide (5h). Yield: 60%; m.p. 73–74 °C; IR spectrum (cm^{-1}): 865 (C–NO), 1495 (N=O), 1578 (C=CH), 2857 (C=CH), 1345 (C–N), 1488 (C=C), 1547 (N=N), 1683 (CO), 1744 (CO cyclic), 1451, 2850, 2912 (CH_2), 3045 (CH–Ar), 3387 (NH); ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.34–2.39 (m, 2H, H-9); 3.52–3.58 (m, 2H, H-10); 4.50 (t, 2H, *J* = 7.55 Hz, H-8); 5.13 (s, 1H, H-2″); 5.87 (s, 1H, H-1′); 6.61 (s, 1H, H-17); 6.81–7.71 (m,12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 37.7 (C-9); 44.8 (C-10); 48.9 (C-8); 64.2 (C-2″); 112.2 (C-4); 118.5 (C-7); 122.6 (C-13 and C-15); 123.2 (C-20 and C-22); 124.8 (C-5); 126.9 (C-12 and C-16); 127.4 (C-19 and C-23); 128.3 (C-6); 132.4 (C-3a); 139.8 (C-11);

138.3 (C-17); 140.3 (C-18); 142.3 (C-5″); 145.9 (C-7a); 147.9 (C-14); 148.5 (C-21); 163.7 (C-2′); 173.6 (C-4″); FAB Mass (*m/z*): 559 [M^+]. Elemental data analysis for $C_{26}H_{21}N_7O_6S$: calculated, %: C, 55.80; H, 3.78; N, 17.52; found, %: C, 55.77; H, 3.72; N, 17.48.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(3-nitrophenyl)-4-oxo-5-(3-nitrobenzylidene)-1,3-thiazolidine carboxamide (5i). Yield: 64%; m.p. 81–82 ^oC; IR spectrum (cm^{-1}): 841 (C–NO), 1480 (C=CH), 1497 (N=O), 2864 (C=CH), 1350 (C–N), 1493 (C=C), 1548 (N=N), 1682 (CO), 1748 (CO cyclic), 1453, 2853, 2910 (CH_2), 3044 (CH–Ar), 3384 (NH); ^1H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.43–2.48 (m, 2H, H-9); 3.50–3.54 (m, 2H, H-10); 4.48 (t, 2H, *J* = 7.50 Hz, H-8); 5.15 (s, 1H, H-2″); 5.90 (s, 1H, H-1′); 6.69 (s, 1H, H-17); 6.79–7.68 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 40.2 (C-9); 45.2 (C-10); 49.7 (C-8); 65.8 (C-2″); 113.3 (C-4); 118.9 (C-7); 121.8 (C-12); 122.7 (C-19); 123.6 (C-14); 124.8 (C-21); 125.9 (C-5); 128.8 (C-6); 129.4 (C-15); 130.4 (C-22); 132.6 (C-3a); 132.9 (C-16); 134.2 (C-23); 139.7 (C-11); 140.3 (C-17); 141.4 (C-18); 143.1 (C-5″); 146.9 (C-7a); 147.9 (C-13); 148.2 (C-20); 163.1 (C-2′); 175.6 (C-4″); FAB Mass (*m/z*): 559 [M^+]. Elemental analysis data for $C_{26}H_{21}N_7O_6S$: calculated, %: C, 55.80; H, 3.78; N, 17.52; found, %: C, 55.75; H, 3.73; N, 17.46.

N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(2-nitrophenyl)-4-oxo-5-(2-nitrobenzylidene)-1,3-thiazolidine carboxamide (5j). Yield: 62%; m.p. 84–85 ^oC; IR spectrum (cm^{-1}): 852 (C–NO), 1478 (N=O), 1489 (C=CH), 2870 (C=CH), 1355 (C–NH), 1497 (C=C), 1553 (N=N), 1689 (CO), 1751 (CO cyclic), 1457, 2858, 2919 (CH_2), 3047 (CH–Ar), 3387 (NH); ^1H NMR spectrum (300 MHz, $CDCl_3$, TMS), δ: 2.34–2.40 (m, 2H, H-9); 3.60–3.65 (m, 2H, H-10); 4.53 (t, 2H, *J* = 7.45 Hz, H-8); 5.14 (s, 1H, H-2″); 5.83 (s, 1H, H-1′); 6.62 (s, 1H, H-17); 6.89–7.75 (m, 12H, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS), δ: 38.6 (C-9); 45.5 (C-10); 50.9 (C-8); 63.8 (C-2″); 112.4 (C-4); 117.4 (C-7); 121.2 (C-13); 122.5 (C-20); 123.8 (C-5); 126.8 (C-16); 127.6 (C-23); 128.6 (C-6); 130.8 (C-14); 131.3 (C-21); 132.9 (C-3a); 133.5 (C-11); 134.8 (C-18); 135.3 (C-15); 136.7 (C-22); 141.2 (C-17); 144.9 (C-5″); 145.7 (C-7a); 146.5 (C-12); 147.9 (C-19); 161.1 (C-2′); 174.5 (C-4″); FAB Mass (*m/z*): 559 [M^+]. Elemental analysis data for $C_{26}H_{21}N_7O_6S$: calculated, %: C, 55.80; H, 3.78; N, 17.52; found, %: C, 55.72; H, 3.74; N, 17.45.

RESULTS AND DISCUSSION

The reaction of 1-bromo-3-chloropropane with 1,2,3-benzotriazole was carried out in methanol as solvent to afford the compound **1.** The spectroscopic analyses of the compound **1** showed the occurrence of absorption peaks for N–CH and C–Cl at 1324 cm^{-1} and 749 cm^{-1} in the IR spectrum. The IR spectrum confirms the formation of compound **1**. This fact is also supported by the disappearance of NH absorption band of 1,2,3-benzotriazole. The compound **1** on the reaction with urea on continuous stirring at room temperature yielded compound **2**. When analyzing compound **2** spectroscopically, we found three absorption peaks in IR spectrum for NH, NH_2 and CO at 3365, 3415 cm^{-1} and 1662 cm^{-1}, respectively, while absorption of C–Cl had disappeared. This clearly

indicated the formation of the compound **2.** This fact was also supported by ^{1}H and ^{13}C NMR spectral data because two signals appeared in the ^{1}H NMR spectrum for NH and NH_2 group absorption at δ 5.69 and δ 5.96 ppm, respectively. The formation of the compound **2** was fully supported by a CO group signal at δ 163.3 ppm in the ^{13}C NMR spectrum. All these facts together gave the strong evidence for the synthesis of compound **2**. Substituted benzaldehydes entered the condensation reaction with the compound **2** giving Schiff bases, that was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data of compounds **3a**. In the IR spectra an absorption band was found at 1550 cm^{-1} while a strong signal appeared at δ 7.94 and δ 145.2 ppm in the ^{1}H NMR and ^{13}C NMR spectra of compounds **3a**, respectively. These facts are also supported by the disappearance of the signal of NH_2 group in the ^{1}H NMR spectrum of the compound **2**. The compounds **3**(**a**–**j**) on reaction with equimolar amount of thioglycolic acid in the presence of $ZnCl_2$ (acted as a catalyst) in trace amounts gave the cycloaddition products – a five-membered thiazolidinone ring containing compounds, compounds **4**(**a**–**j**). The compounds **4a** showed a characteristic absorption band of the cyclic carbonyl group at 1672 cm^{-1} in the IR spectra. The ^{1}H NMR spectra of compounds **4a** aroused our attention and clearly indicated the presence of the active methylene protons of the thiazolidine ring at δ 3.37 ppm. The ^{13}C NMR spectra of compounds **4a** also supported the fact that cyclic carbonyl group presented a signal at δ 168.7 ppm. All these facts were also supported by the two evidences – the disappearance of N=CH proton and appearance of N–CH proton at δ 5.15 ppm in the ^{1}H NMR spectra of compounds **4a**. The compounds **4**(**a**–**j**) underwent the Knoevenagel condensation reaction with substituted benzaldehydes in the presence of alkali metal alkoxide (C_2H_5ONa). We had followed the above-described procedure to afford compounds **5**(**a**–**j**). In the ^{1}H NMR spectra of the compounds **5**(**a**–**j**), we observed the disappearance of two methylene protons of compounds **4(a-j)**, an appearance of a new signal for C=CH in the range of δ 6.52–6.77 ppm in the ^{1}H NMR spectra and that of two new signals for C=CH and C=CH groups in the range of δ 136.7–141.2 and δ 141.9–144.9 ppm, respectively, in the ^{13}C NMR spectra of the compounds **5**(**a**–**j**). All these facts clearly confirmed the synthesis of the final products.

The results of the all described activities (antibacterial, antifungal, antitubercular and antiinflammatory) were summarized in Tables 1 and 2. The results of the antimicrobial screening revealed that the compounds **5**(**a**–**j**) showed considerable and varied activity against the selected microorganisms. A new series of N-[3-(1H-1,2,3-benzotriazol-1-yl)propyl]-2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)-1,3-thiazolidine carboxamide, compounds **5**(**a**–**j**), was synthesized and screened for their antimicrobial, antitubercular and antiinflammatory activity (as shown in Table 1 and 2). The results from the Tables revealed that all the synthesized compounds **5**(**a**–**j**) possessed a structure – activity relationship (SAR) because activities of compounds varied with substitution. Compounds containing nitro group (**5h**, **5i** and **5j**) showed higher activity than compounds containing chloro (**5c**, **5d**), or bromo group (**5e**, **5f).** Chloro and bromo derivatives also had higher activity than other compounds**.** On the basis of SAR, the activity of compounds was found to depend on electron

withdrawing nature of the substituted groups. The investigation of antimicrobial (antibacterial, antifungal and antitubercular) data revealed that the compounds **5c**, **5d**, **5e**, **5f**, **5h**, **5i** and **5j** displayed high activity in the series, the compounds **5b** and **5g** showed the moderate activity and the rest compounds showed less activity against all the strains compared with standard drugs. As concerning the antiinflammatory activity, the compounds **5c**, **5d**, **5e**, **5f**, **5h**, **5i** and **5j** showed the high activity while other compounds displayed moderate to lower activity.

Biological study

Antibacterial, antifungal and antitubercular activities

Series of newly synthesized compounds exhibited activity against selected microorganisms. The minimal inhibition concentrations were determined using the filter paper disc diffusion method and the concentrations had been used in μg/ml. All the finally synthesized compounds **5(a–j)** had been screened *in vitro* for their antibacterial activity against *B. subtilis, E. coli* and *S. aureus* and antifungal activity against *A. niger, A. flavus, C. albicans*. The MIC values of standard Streptomycin and Griseofulvin for all bacteria and fungi were in the range of 1.25–6.25 and 12.5–25 μg/ml, respectively. The antitubercular activity was screened against the *M. tuberculosis*. For the antitubercular activity Isoniazid and Rifampicin (MIC 1.25 and 4 μg/ml) were used as standards. Standards also were screened under the similar conditions for comparison (Table 1).

Table 1. **Antibacterial, antifungal and antitubercular activities of compounds 5(a–j)**

Compound	Antibacterial activity			Antifungal activity			Antitubercular activity
	B. subtilis	*E. coli*	*S. aureus*	*A. niger*	*A. flavus*	*C. albicans*	*M. tuberculosis*
5a	10.25	13.5	7.25	25	22.50	20.25	12.50
5b	15.5	7.25	7.25	13.5	12.50	10.50	2.25
5c	5.25	7.25	4.25	10.25	9.25	13.50	1.75
5d	8.25	13.5	7.25	9.25	10.50	10.25	3.25
5e	8.25	4.25	7.25	13.5	12.25	13.50	3.50
5f	4.25	7.25	6.25	13.5	12.50	10.25	2.25
5g	7.25	13.5	7.25	13.5	15.25	13.50	3.75
5h	4.25	4.25	7.25	8.25	10.50	9.50	1.25
5i	4.25	4.25	4.25	10.50	10.25	9.75	1.50
5j	4.25	6.25	4.25	8.50	8.75	9.50	1.75

Antiinflammatory activities

Carageenan-induced rat paw oedema method was employed for evaluating the antiinflammatory activity of compounds at a dose of 50 mg/kg (b/w) in albino rats (weighing 80–110 g, each group contained 5 animals) using phenylbutazone as a standard drug for comparison at a dose of 30 mg/kg (b/w). The rate paw oedema was produced by the method of Winter et al. The percentage inhibition of inflammation was calculated by applying Newbould formula. *In vivo* studies had been approved by institutional ethical committee, Dr. H.S. Gour University, Sagar. Results for compounds **5(a–j)** were given in Table 2.

Table 2. **Antiinflammatory activity of compounds 5(a–j)**

Compound code	Before carageenan administration (mean ± SEM)	Total increase in paw volume after 5 hours (mean ± SEM)	Percent inhibition
5a	0.60 ± 0.02	0.16 ± 0.02	50.00
5b	0.64 ± 0.02	0.14 ± 0.02	56.25
5c	0.66 ± 0.02	0.13 ± 0.01	59.38
5d	0.68 ± 0.02	0.13 ± 0.02	59.38
5e	0.66 ± 0.03	0.14 ± 0.02	56.25
5f	0.65 ± 0.02	0.12 ± 0.01	62.50
5g	0.67 ± 0.02	0.13 ± 0.01	59.38
5h	0.64 ± 0.03	0.12 ± 0.01	62.50
5i	0.65 ± 0.02	0.10 ± 0.03	68.75
5j	0.67 ± 0.03	0.11 ± 0.02	65.63
Control	0.66 ± 0.02	0.32 ± 0.01	–
Standard (phenylbutazone)	0.68 ± 0.03	0.08 ± 0.02	75.00

CONCLUSIONS

All the compounds have been synthesized giving better yields and reaction time. Antimicrobial, antitubercular and antiinflammatory activity data of compounds (shown in Table 1 and 2) have revealed that the compounds showed moderate to good activities against all the strains compared with standard drugs.

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DAŽU JAUNU TIAZOLIDĪNA ATVASINĀJUMU SINTĒZE UN BIOLOĢISKĀ NOZĪME

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K O P S A V I L K U M S

Izstrādāts efektīvs ceļš jaunas rindas N-[3-(1H-1,2,3-benzotiazol-1-il)propil-2-(aizvietoto fenil)-4-okso-5-(aizvietoto benzilidēn)-1,3-tiazolidīnu karboksamīdu **5**(**a**–**j**) sintēzei. Savienojumi **5**(**a**–**j**) sintezēti un raksturoti ar IS, ^{1}H KMR, ^{13}C KMR, FAB masspektroskopiju un ķīmiskās analīzes datiem. Visiem galaproduktiem pārbaudīta antimikrobiālā aktivitāte pret dažām izvēlētām baktērijām, sēnītēm, kā arī prettuberkulozes (pret *M. tuberculosis*) un pretiekaisuma aktivitāte uz albino žurkām.

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