September 2007 Volume 3 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 3(3), 2007 [142-149]

Synthesis, Antimicrobial And Analgesic Activity Of 1-(Benzothiazol-2'-Yl)-3-Chloro-Azetidin-2-Ones And 3-(Benzothiazol-2'-Yl)-Thiazolidin-4-Ones

P.Shanmugapandiyan[1], A.Ramesh[2]*

[1]Department of Pharmaceutical Chemistry, Vel's College of Pharmacy, Old Pallavaram, Chennai 600117, (INDIA)

[2]Department of Analytical chemistry, International Institute of Biotechnology and Toxicology (IIBAT), Padappai 601 301, (INDIA)

Phone : +91-44-27174246

E-mail : pspandiyan_68@yahoo.co.in. ; raamesh_a@hotmail.com

Received: 26th December, 2006 ; Accepted: 31st December, 2006

ABSTRACT

In the present study, a new series of 1-(benzothiazol-2'-yl)-3-chloro-azetidin-2-ones and 3-(benzothiazol-2'-yl)-thiazolidin-4-ones were synthesized by the reaction of schiff base(2-aminobenzothiazole and substituted benzaldehyde) with chloroacetyl chloride and mercaptoacetic acid respectively. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, mass spectral and elemental analysis. The synthesized compounds were screened for antibacterial (*Staphylococcus aureus, Bacillus cereus, Escherichia coli* and *Pseudomonas aeruginosa*), antifungal (*Aspergillus niger* and *Candida albicans*) and analgesic activity by writhing reflex method. 1-(Benzothiazol-2'-yl)-3-chloro-azetidin-2-ones(**1**-**13**) did not possess any activity in the screened protocols. 3-(Benzothiazol-2'-yl)-thiazolidin-4-ones (**14**-**26**) exhibited mild antibacterial and significant analgesic activity but were completely devoid of activity against the screened fungi. The analgesic activity of 3-(Benzothiazol-2'-yl)-2-(4"-nitro-phenyl)-thiazolidin-4-one**(19)** and 3-(Benzothiazol-2'-yl)-2-(3",4",5"-trimethoxy-phenyl)-thiazolidin-4-one **(26)** at the dose of 100mg/kg was found to equivalent to diclofenac (25mg/kg).

KEYWORDS

Azetidinone;
Thiazolidinone;
Benzothiazole;
Analgesic;
Antibacterial;
Antifungal.

INTRODUCTION

Azetidinone and thiazolidinone derivatives were reported to possess antibacterial[1-3], antifungal[1-3], antitumor[3] antituberculor activity[4], anti-HIV[5], analgesic[6], anti inflammatory[6], and ulcerogenic activity[7]. Benzothiazole derivatives were reported to possess antimicrobial[8] and analgesic[9] activities. Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities. In this present study 2-aminobenzothiazole were treated

with different substituted aromatic aldehydes to produce schiff's base[10]. The Schiff bases were subjected to addition reactions with chloroacetyl chloride in the presence of triethylamine and thioglycollic acid in the presence of 1,4dioxane-anhydrous zinc chloride to produce 2-azetidinone derivatives and 4-thiazolidinone derivatives respectively[11,12]. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, mass spectral and elemental analysis. The synthesized compounds were screened for antibacterial(*Staphylococcus aureus, Bacillus cereus, Escherichia coli* and *Pseudomonas aeruginosa*), antifungal (*Aspergillus niger* and *Candida albicans*) and analgesic activity by writhing reflex method.

Chemistry

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB104 with KBr pellets. ^{1}H-NMR spectra and ^{13}C-NMR were recorded on 400 MHz-Joel GSX 400 using DMSO-$_{d6}$ as solvent. The chemical shifts are reported as parts per million downfield from tetra methyl silane(Me_4Si). Mass spectra were recorded on Shimadzu GC-MS QP 5050A. Microanalyses for C, H, N were performed in Heraeus CHN Rapid Analyzer and analyses indicated by the symbols of the elements are within ±0.4% of the theoretical values. ^{1}H-NMR and IR spectra were consistent with the assigned structures. The purity of the compounds was checked by TLC on pre-coated aluminum sheets(Silica gel 60 F_{254}) using (4:1) CCl_4: petroleum ether (40-60^{0}C) as mobile phase and visualized by iodine vapors.

General method for the synthesis of schiff base

A mixture of 2-aminobenzothiazole(0.01mol), substituted benzaldehyde(0.01mol) and a drop of acetic acid was dissolved in ethanol(25ml) and heated on a steam bath for 45-60 min. The reaction mixture was allowed to stand at room temperature for 24h, The product separated out was filtered, dried under vacuum and recrystallized by using warm ethanol.

Synthesis of 1-(benzothiazol-2'-yl)-3-chloro-azetidin-2-ones: (1-13)

Chloroacetyl chloride(0.01mol) was added drop wise to a mixture of schiff's base (0.01mol) and triethyl amine(0.02mol) in dioxane(25ml) at room temperature. The mixture was stirred for 8h and allowed to stand at room temperature for 3h. The contents were poured on crushed ice and the precipitate obtained was filtered, washed with 10% w/v sodium bicarbonate solution, vacuum dried and recrystallized using absolute ethanol.

1-(Benzothiazol-2'-yl)-3-chloro-4-phenyl-azetidin-2-one (1)

Yield=48%, m.p. 150-152^{0}C, Rf=0.54. ^{1}H-NMR (DMSO-d_6) δ:7.95(m, 2H; 4',7'-H), 7.73 (m, 2H; 5',6'-H), 7.30-7.46 (m, 5H; 2",3",4",5",6"-H), 4.49(s, 1H; 4-CH), 3.57(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3506, 3384, 3048, 2732, 1694(C=O), 1269, 1176, 865, 808, 731, 562, 541. EI-MS m/z: 314.78 (Calcd for $C_{16}H_{11}ClN_2OS$: 314.80) Anal. Calcd for $C_{16}H_{11}ClN_2OS$: C, 61.05; H, 3.52; N, 8.90. Found: C, 61.12; H, 3.32; N, 8.78.

1-(Benzothiazol-2'-yl)-3-chloro-4-(4''-chloro-phenyl)azetidin-2-one (2)

Yield=44%, m.p. 130-132^{0}C, Rf=0.58. ^{1}H-NMR (DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.29-7.57(m, 4H; 2",3",5",6"-H), 4.49(s, 1H; 4-CH), 3.06(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3379, 3048, 2734, 1694(C=O), 1269, 1177, 865, 809, 775, 731, 562, 506. EI-MS m/z: 349.22 (Calcd for $C_{16}H_{10}Cl_2N_2OS$: 349.24). Anal.Calcd for $C_{16}H_{10}Cl_2N_2OS$: C, 55.03; H, 2.89; N, 8.02. Found: C, 55.16; H, 2.99; N, 8.10.

1-(Benzothiazol-2'-yl)-3-chloro-4-(2''-chloro-phenyl)azetidin-2-one(3)

Yield=38%, m.p. 158-160^{0}C, Rf=0.54. ^{1}H-NMR (DMSO-d_6) δ: 7.95(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.07-7.45(m, 4H; 3",4",5",6"-H), 4.49(s, 1H; 4-CH), 3.57(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3064, 2733, 1696(C=O), 1267, 1116, 876, 758, 749, 724, 575, 507. EI-MS m/z: 349.22 (Calcd for $C_{16}H_{10}Cl_2N_2OS$: 349.24). Anal. Calcd for $C_{16}H_{10}Cl_2N_2OS$: C, 55.03; H, 2.89; N, 8.02. Found: C, 55.16; H, 2.98; N, 8.09.

1-(Benzothiazol-2'-yl)-3-chloro-4-(2''-nitro-phenyl)azetidin-2-one (4)

Yield=54%, m.p. 148-150^{0}C, Rf=0.71. ^{1}H-NMR (DMSO-d_6) δ: 7.92(m, 2H; 4',7'-H), 7.74(m, 2H; 5',6'-

H), 7.30-7.46(m, 4H; 3",4",5",6"-H), 4.48(s, 1H; 4-CH), 3.61(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3380, 3048, 2733, 1694(C=O), 1269, 1176, 865, 808, 776, 562, 541. EI-MS m/z: 359.74 (Calcd for $C_{16}H_{10}ClN_3O_3S$: 359.79). Anal. Calcd for $C_{16}H_{10}ClN_3O_3S$: C, 53.41; H, 2.80; N, 11.70. Found: C, 53.52; H, 3.01; N, 11.92.

1-(Benzothiazol-2'-yl)-3-chloro-4-(3''-nitrophenyl)azetidin-2-one(5)

Yield=16%, m.p. 174-176^{0}C, Rf=0.80. ^{1}H-NMR(DMSO-d_6) δ: 7.95(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.30-7.45(m, 4H; 2",4",5",6"-H), 4.49 (s, 1H; 4-CH), 3.57(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3375, 3047, 2732, 1695(C=O), 1269, 1176, 865, 808, 776, 562, 541. EI-MS m/z: 359.74 (Calcd for $C_{16}H_{10}ClN_3O_3S$: 359.79). Anal. Calcd for $C_{16}H_{10}ClN_3O_3S$: C, 53.41; H, 2.80; N, 11.70. Found: C, 53.56; H, 2.71; N, 11.88.

1-(Benzothiazol-2'-yl)-3-chloro-4-(4''-nitrophenyl)azetidin-2-one (6)

Yield=61%, m.p. 320^{0}C, Rf=0.56. ^{1}H-NMR (DMSO-d_6) δ: 7.97(m, 2H; 4',7'-H), 7.72(m, 2H; 5',6'-H), 7.27-7.45(m, 4H; 2",3",5",6"-H), 4.10(s, 1H; 4-CH), 3.89(s, 1H; 3-CH). IR(KBr) cm^{-1}: 3468, 3067, 2542, 1689(C=O), 833, 754, 702, 614. EI-MS m/z: 359.74(Calcd for $C_{16}H_{10}ClN_3O_3S$: 359.79). Anal. Calcd for $C_{16}H_{10}ClN_3O_3S$: C, 53.41; H, 2.80; N, 11.70. Found: C, 53.54; H, 2.66; N, 11.82.

1-(Benzothiazol-2'-yl)-3-chloro-(4''-methylphenyl)azetidin-2-one (7)

Yield=46%, m.p. 138-140^{0}C, Rf=0.88. ^{1}H-NMR (DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.72(m, 2H; 5',6'-H), 7.30-7.45(m, 4H; 2",3",5",6"-H), 4.49(s, 1H; 4-CH), 3.57(s, 1H; 3-CH), 2.04(s, 3H; 4"-CH_3). IR (KBr)cm^{-1}: 3507, 3382, 1694(C=O), 1269, 1176, 865, 808, 776, 562. EI-MS m/z: 328.79(Calcd for $C_{17}H_{13}ClN_2OS$:328.82). Anal.Calcd for $C_{17}H_{13}ClN_2OS$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.24; H, 3.81; N, 8.39.

1-(Benzothiazol-2'-yl)-3-chloro-4-[4''-(dimethylamino)-phenyl]azetidin-2-one (8)

Yield=10%, m.p. 130-132^{0}C, Rf=0.72. ^{1}H-NMR (DMSO-d_6) δ: 7.95(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.23-7.45(m, 4H; 2",3",5",6"-H), 4.49(s, 1H; 4-CH), 3.90(s, 1H; 3-CH), 2.98(s, 3H; 4''-N-CH_3), 2.79(s, 3H; 4''-N-CH_3). IR(KBr) cm^{-1}: 3507, 3385, 3047, 2735, 1695(C=O), 1269, 1177, 865, 809, 776, 526. EI-MS m/z: 357.85 (Calcd for $C_{18}H_{16}ClN_3OS$: 357.86). Anal. Calcd for $C_{18}H_{16}ClN_3OS$: C, 60.41; H, 4.51; N, 11.74. Found: C, 60.58; H, 4.38; N, 11.62.

1-(Benzothiazol-2'-yl)-3-chloro-4-(2''-hydroxyphenyl)azetidin-2-one (9)

Yield=55%, m.p. 178-180^{0}C, Rf=0.63. ^{1}H-NMR (DMSO-d_6) δ: 7.90(m, 2H; 4',7'-H), 7.68(m, 2H; 5',6'-H), 7.31-7.58(m, 4H; 3",4",5",6"-H), 4.41(s, 1H; 4-CH), 3.73(s, 1H; 2''-OH), 3.04(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3378, 2864, 1696(C=O), 1269, 1176, 865, 808, 776, 525. EI-MS m/z: 330.78 (Calcd for $C_{16}H_{11}ClN_2O_2S$: 330.79). Anal. Calcd for $C_{16}H_{11}ClN_2O_2S$: C, 58.10; H, 3.35; N, 8.47. Found: C, 58.22; H, 3.41; N, 8.59.

1-(Benzothiazol-2'-yl)-3-chloro-4-(3''-hydroxyphenyl)azetidin-2-one (10)

Yield=55%, m.p. 162-164^{0}C, Rf=0.71. ^{1}H-NMR (DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.30-7.45(m, 4H; 2",4",5",6"-H), 4.49 (s, 1H; 4-CH), 3.76(s, 1H; 3"-OH), 3.57(s, 1H; 3-CH). IR (KBr)cm^{-1}: 3507, 3382, 3048, 2863, 2730, 1694 (C=O), 1269, 1176, 865, 808, 776, 526. EI-MS m/z: 330.78 (Calcd for $C_{16}H_{11}ClN_2O_2S$: 330.79). Anal. Calcd for $C_{16}H_{11}ClN_2O_2S$: C, 58.10; H, 3.35; N, 8.47. Found: C, 58.22; H, 3.40; N, 8.60.

1-(Benzothiazol-2'-yl)-3-chloro-4-(4''-hydroxyphenyl)azetidin-2-one (11)

Yield=22%, m.p. 118-120^{0}C, Rf=0.74. ^{1}H-NMR (DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.73(m, 2H; 5',6'-H), 7.30-7.45(m, 4H; 2",3",5",6"-H), 4.49(s, 1H; 4-CH), 3.76(s, 1H; 4"-OH), 3.01(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3382, 3048, 2733, 1694(C=O), 1270, 1177, 865, 809, 774, 526. EI-MS m/z: 330.78 (Calcd for $C_{16}H_{11}ClN_2O_2S$: 330.79). Anal. Calcd for $C_{16}H_{11}ClN_2O_2S$: C, 58.10; H, 3.35; N, 8.47. Found: C, 58.26; H, 3.20; N, 8.33.

1-(Benzothiazol-2'-yl)-3-chloro-4-(3'',4''-dihydroxy-phenyl)azetidin-2-one (12)

Yield=35%, m.p. 110-112 ºC, Rf=0.6. ^{1}H-NMR

(DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.75(m, 2H; 5',6'-H), 7.02-7.61(m, 3H; 2",5",6"-H), 5.18(d,d, J=2.2Hz, 2H; 3",4"-OH), 4.24(s, 1H; 4-CH), 3.43(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3416, 3059, 2852, 1684(C=O), 1270, 1189, 804, 754, 728, 525. EI-MS m/z: 346.78 (Calcd for $C_{16}H_{11}ClN_2O_3S$: 346.79). Anal.Calcd for $C_{16}H_{11}ClN_2O_3S$: C, 55.42; H, 3.20; N, 8.08. Found: C, 55.54; H, 3.31; N, 8.23.

1-(Benzothiazol-2'-yl)-3-chloro-4-(3'',4'',5''-trimethoxy-phenyl)azetidin-2-one (13)

Yield=38%, m.p. 166-168^{0}C, Rf=0.66. ^{1}H-NMR (DMSO-d_6) δ: 7.94(m, 2H; 4',7'-H), 7.72(m, 2H; 5',6'-H), 7.30-7.45(m, 2H; 2",6"-H), 4.49(s, 1H; 4-CH), 3.95, 3.89, 3.82(sss, 9H; 3",4",5"-OCH_3), 3.57(s, 1H; 3-CH). IR (KBr) cm^{-1}: 3507, 3381, 3047, 2862, 1695(C=O), 1269, 1176, 865, 808, 776, 525. EI-MS m/z: 404.86 (Calcd for $C_{19}H_{17}ClN_2O_4S$: 404.87). Anal. Calcd for $C_{19}H_{17}ClN_2O_4S$: C, 56.37; H, 4.23; N, 6.92. Found: C, 56.45; H, 4.11; N, 7.09.

Synthesis of 3-(benzothiazol-2'-yl)-thiazolidin-4-ones: (14-26)

To a mixture of schiff's base(0.01mol) and mercaptoacetic acid(0.01mol) dissolved in dioxane (20ml), anhydrous zinc chloride(0.004mol) was added and refluxed for 8h. The reaction mixture was cooled, filtered, washed with 10% w/v sodium bicarbonate solution, vacuum dried and recrystallised using absolute ethanol.

3-(Benzothiazol-2'-yl)-2-phenyl-thiazolidin-4-one (14)

Yield=64%, m.p. 208-210^{0}C, Rf=0.57. ^{1}H-NMR (DMSO-d_6) δ: 8.02(m, 2H; 4',7'-H), 7.65 (m, 2H; 5',6'-H), 6.90-7.44 (m, 5H; 2",3",4",5",6"-H), 4.15(d, J=2.1Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3183, 2914, 1696(C=O), 1269, 1116, 783, 757, 748, 638. EI-MS m/z: 312.39(Calcd for$C_{16}H_{12}N_2OS_2$: 312.42). Anal. Calcd for $C_{16}H_{12}N_2OS_2$: C, 61.51; H, 3.87; N, 8.97. Found: C, 61.68; H, 3.70; N, 9.09.

3-(Benzothiazol-2'-yl)-2-(4''-chloro-phenyl)-thiazolidin-4-one (15)

Yield=55%, m.p. 198-200^{0}C, Rf=0.62. ^{1}H-NMR (DMSO-d_6) δ: 8.01(m, 2H; 4',7'-H), 7.64(m, 2H; 5',6'-H), 6.90-7.45(m, 4H; 2",3",5",6"-H), 4.15(d, J=2.2Hz, 1H; 2-CH), 2.47(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3182, 2998, 1693(C=O), 1228, 748, 751, 723, 641, 503. EI-MS m/z: 346.84 (Calcd for $C_{16}H_{11}ClN_2OS_2$: 346.86). Anal.Calcd for $C_{16}H_{11}ClN_2OS_2$: C, 55.40; H, 3.20; N, 8.08. Found: C, 55.53; H, 3.31; N, 8.16.

3-(Benzothiazol-2'-yl)-2-(2''-chloro-phenyl)-thiazolidin-4-one (16)

Yield=87%, m.p. 258-260^{0}C, Rf=0.88. ^{1}H-NMR(DMSO-d_6) δ: 8.01(m, 2H; 4',7'-H), 7.62(m, 2H; 5',6'-H), 6.98-7.45 (m, 4H; 3",4",5",6"-H), 4.15(d, J=2.1Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3185, 2914, 1704(C=O), 1228, 784, 747, 721, 640, 504. EI-MS m/z: 346.84 (Calcd for $C_{16}H_{11}ClN_2OS_2$: 346.86). Anal.Calcd for $C_{16}H_{11}ClN_2OS_2$: C, 55.40; H, 3.20; N, 8.08. Found: C, 55.58; H, 3.30; N, 8.22.

3-(Benzothiazol-2'-yl)-2-(2''-nitro-phenyl)-thiazolidin-4-one (17)

Yield=98%, m.p. 178-180^{0}C, Rf=0.57. ^{1}H-NMR(DMSO-d_6) δ: 8.09(m, 2H; 4',7'-H), 7.63(m, 2H; 5',6'-H), 6.97-7.46 (m, 4H; 3",4",5",6"-H), 4.14 (d, J=2Hz, 1H; 2-CH), 2.36(s, J=Hz, 2H; 5-CH_2). IR (KBr)cm^{-1}: 3186, 2912, 1712(C=O), 1229, 1115, 783, 747, 723, 639. EI-MS m/z: 357.39(Calcd for $C_{16}H_{11}N_3O_3S_2$: 357.41). Anal.Calcd for $C_{16}H_{11}N_3O_3S_2$ C, 53.77; H, 3.10; N, 11.76. Found: C, 53.84; H, 3.22; N, 11.84.

3-(Benzothiazol-2'-yl)-2-(3''-nitro-phenyl)-thiazolidin-4-one (18)

Yield=84%, m.p. 208-210^{0}C, Rf=0.55. ^{1}H-NMR (DMSO-d_6) δ: 8.22(m, 2H; 4',7'-H), 7.85(m, 2H; 5',6'-H), 6.96-7.69(m, 4H; 2",4",5",6"-H), 4.19(d, J=2.1Hz, 1H; 2-CH), 2.51(s, 2H; 5-CH_2). IR(KBr) cm^{-1}: 3137, 2910, 1711(C=O), 1229, 1113, 784, 745, 720, 638. EI-MS m/z:357.40(Calcd for $C_{16}H_{11}N_3O_3S_2$: 357.41). Anal.Calcd for $C_{16}H_{11}N_3O_3S_2$: C, 53.77; H, 3.10; N, 11.76. Found: C, 53.62; H, 2.96; N, 11.85.

3-(Benzothiazol-2'-yl)-2-(4''-nitro-phenyl)-thiazolidin-4-one (19)

Yield=84%, m.p. 158-160^{0}C, Rf=0.6. ^{1}H-NMR (DMSO-d_6) δ: 8.01(m, 2H; 4',7'-H), 7.65(m, 2H; 5',6'-

H), 6.90-7.44(m, 4H; 2",3",5",6"-H), 4.15(d, J=2.1Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3183, 2909, 1721(C=O), 1229, 1111, 784, 743, 722, 640. EI-MS m/z: 357.39(Calcd for $C_{16}H_{11}N_3O_3S_2$: 357.41). Anal. Calcd for $C_{16}H_{11}N_3O_3S_2$: C, 53.77; H, 3.10; N, 11.76. Found: C, 53.87; H, 3.21; N, 11.89.

3-(Benzothiazol-2'-yl)-2(4''-methyl-phenyl) thiazolidin-4-one (20)

Yield=82%, m.p. 178-180^{0}C, Rf=0.43. ^{1}H-NMR(DMSO-d_6) δ: 8.01(m, 2H; 4',7'-H), 7.89(m, 2H; 5',6'-H), 6.96-7.65(m, 4H; 2",3",5",6"-H), 4.15(d, J=2Hz, 1H; 2-CH), 2.37(s, 2H; 5-CH_2), 1.80 (s, 3H; 4''-CH_3). IR(KBr)cm^{-1}: 3180, 2978, 1682 (C=O), 1227, 1115, 784, 747, 722, 639. EI-MS m/z: 326.42 (Calcd for $C_{17}H_{14}N_2OS_2$: 326.44). Anal.Calcd for $C_{17}H_{14}N_2OS_2$: C, 62.55; H, 4.32; N, 8.58. Found: C, 62.38; H, 4.45; N, 8.66.

3-(Benzothiazol-2'-yl)-2-[4''-(dimethylamino)-phenyl]thiazolidin-4-one (21)

Yield=80%, m.p. 198-200^{0}C, Rf=0.48. ^{1}H-NMR (DMSO-d_6) δ: 8.02(m, 2H; 4',7'-H), 7.63(m, 2H; 5',6'-H), 6.90-7.44(m, 4H; 2'',3'',5'',6''-H), 4.15(d, J=2.2Hz, 1H; 2-CH), 3.05(s, 3H; 4"-N-CH_3), 2.92(s, 3H; 4"-N-CH_3), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3177, 2914, 1682(C=O), 1229, 1115, 784, 720, 637. EI-MS m/z: 355.47 (Calcd for $C_{18}H_{17}N_3OS_2$: 355.48). Anal. Calcd for $C_{18}H_{17}N_3OS_2$: C, 60.82; H, 4.82; N, 11.82. Found: C, 60.94; H, 4.99; N, 11.71.

3-(Benzothiazol-2'-yl)-2-(2''-hydroxy-phenyl)-thiazolidin-4-one (22)

Yield=79%, m.p. 188-190^{0}C, Rf=0.53. ^{1}H-NMR (DMSO-d_6) δ: 7.99(m, 2H; 4',7'-H), 7.82(m, 2H; 5',6'-H), 6.96-7.63(m, 4H; 3",4",5",6"-H), 5.56(s, 1H; 2"-OH), 3.72(d, J=2.1Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR(KBr) cm^{-1}: 3189, 1695(C=O), 1128, 784, 748, 722, 640. EI-MS m/z: 328.37(Calcd for $C_{16}H_{12}N_2O_2S_2$: 328.42). Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$: C, 58.52; H, 3.68; N, 8.53. Found: C, 58.63; H, 3.59; N, 8.62.

3-(Benzothiazol-2'-yl)-2-(3''-hydroxy-phenyl)-thiazolidin-4-one (23)

Yield=36%, m.p. 198-200^{0}C, Rf=0.58. ^{1}H-NMR (DMSO-d_6) δ: 7.92(m, 2H; 4',7'-H), 7.62(m, 2H; 5',6'-H), 6.96-7.45(m, 4H; 2",4",5",6"-H), 5.82(s, 1H; 3"-OH), 3.91(d, J=2.3Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3180, 2914, 1698(C=O), 1228, 1115, 784, 748, 721, 639. EI-MS m/z: 328.37 (Calcd for $C_{16}H_{12}N_2O_2S_2$: 328.42). Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$: C, 58.52; H, 3.68; N, 8.53. Found: C, 58.59; H, 3.53; N, 8.62.

3-(Benzothiazol-2'-yl)-2-(4''-hydroxy-phenyl)-thiazolidin-4-one (24)

Yield=91%, m.p. 196-198^{0}C, Rf=0.62. ^{1}H-NMR(DMSO-d_6) δ: 8.02(m, 2H; 4',7'-H), 7.65(m, 2H; 5',6'-H), 6.90-7.44(m, 4H; 2",3",5",6"-H), 4.15(d, J=2.1Hz, 1H; 2-CH), 3.77(s, 1H; 4"-OH), 2.49 (s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3170, 2984, 1655(C=O), 1229, 1115, 784, 745, 720, 639. EI-MS m/z: 328.37 (Calcd for $C_{16}H_{12}N_2O_2S_2$: 328.42). Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$: C, 58.52; H, 3.68; N, 8.53. Found: C, 58.46; H, 3.60; N, 8.68.

3-(Benzothiazol-2'-yl)-2-(3'',4''-dihydroxy-phenyl)-thiazolidin-4-one (25)

Yield=68%, mp 208-210^{0}C, Rf=0.51. ^{1}H-NMR (DMSO-d_6) δ: 8.01(m, 2H; 4',7'-H), 7.65(m, 2H; 5',6'-H), 6.90-7.44(m, 3H; 2",5",6"-H), 5.16(d,d, J= 2.2 Hz, 2H; 3",4"-OH), 4.15(d, J= 2 Hz, 1H; 2-CH), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 3181, 2985, 2915, 1682(C=O), 1228, 1115, 746, 722, 640. EI-MS m/z: 344.37 (Calcd for $C_{16}H_{12}N_2O_3S_2$: 344.42). Anal. Calcd for $C_{16}H_{12}N_2O_3S_2$: C, 55.80; H, 3.51; N, 8.13. Found: C, 55.97; H, 3.65; N, 8.26

3-(Benzothiazol-2'-yl)-2-(3'',4'',5''-trimethoxy-phenyl)-thiazolidin-4-one (26)

Yield=75%, m.p. 200-202^{0}C, Rf=0.55. ^{1}H-NMR(DMSO-d_6) δ: 7.99(m, 2H; 4',7'-H), 7.62(m, 2H; 5',6'-H), 6.97-7.48(m, 2H; 2",6"-H), 3.91(d, J=2.1Hz, 1H; 2-CH), 3.55-3.75(m, 9H; 3",4",5"-OCH_3), 2.49(s, 2H; 5-CH_2). IR (KBr) cm^{-1}: 2982, 1683(C=O), 1229, 1116, 746, 720, 638. EI-MS m/z: 402.37 (Calcd for $C_{19}H_{18}N_2O_4S_2$: 402.50). Anal. Calcd for $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.51; N, 6.96. Found: C, 56.88; H, 4.41; N, 7.10.

Antimicrobial activity

The antibacterial activity[13] of the synthesized compounds was tested against gram(+) bacteria (Sta-

TABLE 1 : Antibacterial and analgesic activity of the compounds

Compound no	Antibacterial activity				Analgesic activity	
	Zone of inhibition (MIC)				Mean writhings±SEM	% Protection
	S.aureus	*B.cereus*	*E.coli*	*P.aeruginosa*		
14	8 (175)	7 (200)	7 (200)	9 (125)	21.33±0.88 *	55.19
15	10 (125)	10 (100)	8 (200)	10 (150)	18.5±0.42 *	61.14
16	6 (225)	7 (200)	6 (190)	7 (180)	20.5±0.763 *	56.94
17	10 (100)	8 (160)	6 (190)	9 (150)	9.33±0.42 *	80.4
18	10 (125)	9 (140)	6 (175)	8 (150)	11.16±0.6 *	76.56
19	8 (170)	7 (190)	6 (225)	7 (180)	7.16±0.6 *	84.96
20	6 (210)	7 (200)	6 (210)	7 (190)	21.5±0.763 *	54.84
21	8 (175)	9 (150)	8 (160)	8 (170)	14.16±1.01 *	70.26
22	6 (210)	8 (180)	8 (170)	7 (190)	19.6±0.88 *	58.83
23	8 (180)	10 (130)	8 (170)	9 (140)	23.3±0.88 *	51.06
24	9 (140)	8 (170)	7 (200)	8 (180)	14.5±0.763 *	69.54
25	8 (170)	9 (125)	7 (175)	9 (160)	19.5±0.763 *	59.04
26	6 (220)	10 (120)	8 (160)	8 (175)	6.83±0.596 *	85.66
Cefaclor	19	22	19	20	-	-
Amoxycillin	21	27	24	22	-	-
Control	-	-	-	-	47.16±0.869	-
Diclofenac	-	-	-	-	7.66±0.685 *	83.90

Zone of Inhibition in mm & MIC in μg/ml ; Significance levels: *p<0.001 compared to control

phylococcus aureus NCCS 2079 Bacillus cereus NCCS 2106) and gram(-) bacteria (Escherichia coli NCCS2065 and Pseudomonas aeruginosa NCCS2200) using nutrient agar medium and fungi(Aspergillus niger NCCS 1196 and Candida albicans NCCS 3471) using sabourand dextrose agar medium.

Paper disc diffusion method

The sterilized(autoclaved at 120^0C for 30min), liquefied medium(40-50^0C) was inoculated (1ml/ 100ml of medium) with the suspension of the micro organism(matched to McFarland barium sulphate standard) and poured into the petri dish to give a depth of 3-4mm. The paper discs impregnated with the test compounds(250μg/ml for antibacterial and 100, 250μg/ml for antifungal activity using dimethyl sulphoxide as solvent) were placed on the solidified medium. The plates were refrigerated (pre-incubated) for two hours at 4^0C and then incubated at 37^0C for 24h and 48h for antibacterial and antifungal activity respectively at the end of which the zone of inhibition was observed(TABLE 1). Amoxycillin(10μg/ disc), cefaclor (30μg/disc) and fluconazole(100μg/ disc) were used as standards. The data are presented in TABLE 1.

Minimum inhibitory concentration

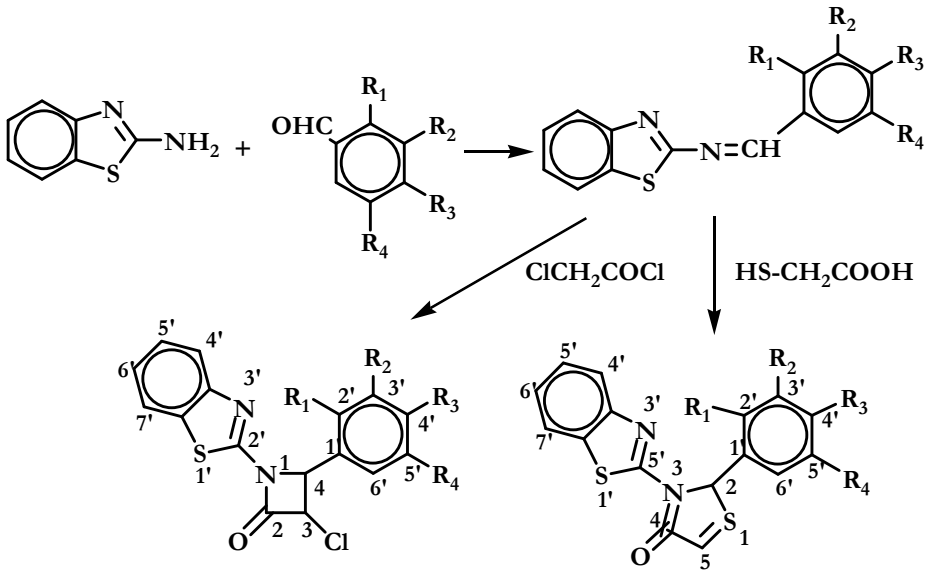
The minimum inhibitory concentration[14] (MIC) against the bacterial strains was determined by the test tube dilution technique using Mueller-Hinton nutrient broth. A series of glass tubes containing different concentrations of the synthesized compounds (In dimethyl sulphoxide) with the medium was inoculated with the required amount of inoculum to obtain a suspension of microorganism which contains 10^5 CFU/ml. One growth control tube was prepared without the addition of microorganism. The tubes were incubated at 37°C for 24h. The minimum inhibitory concentration(MIC-μg/ml) was considered to be the lowest concentration that exhibited the same turbidity as the blank tube. The data are presented in TABLE 1.

Analgesic activity[15]

Inbred wistar albino mice(20-30g) were used. They were kept in colony cages at 25±2^0C, relative humidity 45-55% under 12hr light and dark cycle. The animals were fed with standard animal feed and water ad libitum. All the animals were acclimatized for a week before use.

The analgesic activity was determined by acetic acid induced writhing method-using wistar albino mice(n=6) of either sex selected by random sam-

Full Paper



(1) $R_1=R_2=R_3=R_4=H$
(2) $R_1=R_2=R_4=H$, $R_3=Cl$
(3) $R_1=Cl$, $R_2=R_3=R_4=H$
(4) $R_1=NO_2$, $R_2=R_3=R_4=H$
(5) $R_1=R_3=R_4=H$, $R_2=NO_2$
(6) $R_1=R_2=R_4=H$, $R_3=NO_2$
(7) $R_1=R_2=R_4=H$, $R_3=CH_3$
(8) $R_1=R_2=R_4=H$, $R_3=N(CH_3)_2$
(9) $R_1=OH$, $R_2=R_3=R_4=H$
(10) $R_1=R_3=R_4=H$, $R_2=OH$
(11) $R_1=R_2=R_4=H$, $R_3=OH$
(12) $R_1=R_4=H$, $R_2=R_3=OH$
(13) $R_1=H$, $R_2=R_3=R_4=OCH_3$
(14) $R_1=R_2=R_3=R_4=H$
(15) $R_1=R_2=R_4=H$, $R_3=Cl$
(16) $R_1=Cl$, $R_2=R_3=R_4=H$
(17) $R_1=NO_2$, $R_2=R_3=R_4=H$
(18) $R_1=R_3=R_4=H$, $R_2=NO_2$
(19) $R_1=R_2=R_4=H$, $R_3=NO_2$
(20) $R_1=R_2=R_4=H$, $R_3=CH_3$
(21) $R_1=R_2=R_4=H$, $R_3=N(CH_3)_2$
(22) $R_1=OH$, $R_2=R_3=R_4=H$
(23) $R_1=R_3=R_4=H$, $R_2=OH$
(24) $R_1=R_2=R_4=H$, $R_3=OH$
(25) $R_1=R_4=H$, $R_2=R_3=OH$
(26) $R_1=H$, $R_2=R_3=R_4=OCH_3$

Figure 1 : Synthetic scheme of 1-(benzothiazol-2'-yl)-3-chloro-4-(substituted)-azetidinones and 1-(benzothiazol-2'-yl) -2-(substituted)-thiazolidin-4-ones

pling technique(25-30g) were used for the study. Diclofenac sodium at a dose level of 25mg/kg served as standard drug for comparison. The negative control received solvent only(1% CMC). The test compounds at 100 mg/kg (suspended in 1% CMC) were administered orally by intragastric tube 30min prior to intraperitoneal administration of the writhing agent(0.6% v/v aqueous acetic acid-1 ml/ 100g). The writhings produced in the animal were observed for 20minutes and percentage protection was calculated for analgesic activity. The results are presented in TABLE 1.

% Protection=100-[(experimental/control)×100]

RESULTS AND DISCUSSION

The structure of the synthesized compounds was characterized by IR, ^{1}H-NMR, mass spectral and elemental analysis. 1-(Benzothiazol-2'-yl)-3-chloro-azetidin-2-ones **(1-13)** did not exhibit antimicrobial activity against the screened microorganism and analgesic activity. 3-(Benzothiazol-2'-yl)-thiazolidin-4-ones**(14-26)** exhibited mild antibacterial activity but were completely devoid of activity against the fungal organisms tested (*A.niger and C.albicans*). The MIC of the compounds**(14)** to**(26)** for *S.aureus* (100-125μg/ml), *B.cereus*(100-200 μg/ml), *E.coli*(160-225μg/ml) and *P.aeruginosa*(125-190μg/ml). Compounds **(17**,**15**,**21** and **14)** exhibited highest activity against *S.aureus, B.cereus, E.coli* and *P.aeruginosa* respectively.

3-(Benzothiazol-2'-yl)-thiazolidin-4-ones(**14**-**26**) exhibited highly significant analgesic activity. The analgesic activity of 3-(Benzothiazol-2'-yl)-2-(4''-nitro-phenyl)-thiazolidin-4-one**(19)** and 3-(Benzo thiazol-2'-yl)-2-(3'',4'',5''-trimethoxy-phenyl)-thiazolidin-4-one**(26)** at the dose of 100mg/kg was found to equivalent to diclofenac(25mg/kg).

REFERENCE

[1] G.S.Singh, B.J.Molotsi; Il Farmaco., **60,** 727-730 **(2005)**.
[2] V. P. M.Rahman, S.Mukhtar, W. H.Ansari, G.Lemiere; Eur.J.Med.Chem., **40**, 173-184 **(2005)**.

[3] D.S.Mehta, V.H.Shah; Indian.J.Heterocyc.Chem., **11**, 139–144 **(2001)**.

[4] S.G.Kucukguzel, E.E.Orul, S.Rollas, F.Salin, A.Ozbek; Eur.J.Med.Chem., **37**, 197-206 **(2002)**.

[5] R.K.Rawal, Y.S.Prabhakar, S.B.Katti, E.DeClercq; Bioorg.Med.Chem., **13**, 6771-6776 **(2005)**.

[6] M.G.Vigorita, R.Ottana, F.Monforte, R.Maccari, A. Trovato, M.T.Monforte, M.F.Taviano; Bioorg.Med. Chem.Lett., **11**, 2791-2794 **(2001)**.

[7] B.Goel, T.Ram, R.Tyagi, E.Bansal, A.Kumar, D. Mukherjee, J.N.Sinha; Eur.J.Med.Chem., **34**, 265-269 **(1999)**.

[8] M.A.Mahran, S.M.El-Nassry, S.R.Allam, L.A.El-Zawawy; Pharmazie., **58**, 527-530 **(2003)**.

[9] R.Paramashivappa, P.P.Kumar, S.P.V.Rao, S.A.Rao; Bioorg.Med.Chem.Lett., **13**, 657–660 **(2003)**.

[10] M.Conli, R.Gulielmetli, J.Metzger; Bull.Soc.Chim.Fr, **8,** 2834-2841 **(1967)**.

[11] H.H.Fahmy, W.El-Eraky; Arch.Pharm.Res., **24**, 171-179 **(2001)**.

[12] S.V.More, D.V.Dongarkhadekar, R.N.Chavan, W.N. Jadhav, S.R.Bhusare, R.P.Pawar; J.Indian.Chem.Soc., **79**, 768-769 **(2002)**.

[13] S.H.Gillespie; 'Medical Microbiology-Illustrated', Butterworth Heinemann Ltd., United Kingdom, 234-247 **(1994)**.

[14] P.M.Hawkey, D.A.Lewis; 'Medical Bacteriology–A practical approach', Oxford University Press, United Kingdom, 181-194, **(1994)**.

[15] R.A.Turner, Peter Hebborn (Edt); 'Screening Methods in Pharmacology', Academic Press, New York, 2, **(1971)**.