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Synthesis of novel Sultams containing azetidinone heterocycles

P. Ramesh Babu[*], L. K. Ravindranath[**] and D. Rajesh[**]

[*]*Department of Chemistry, Rayalaseema University, Kurnool, India*
[**]*Department of Chemistry, S. K. University, Anantapur, India*

ABSTRACT

*Novel Azetidinones Synthesis of 3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-substituted phenylazetidin-2-one**7(a-f)** were synthesized by condensation reaction between synthesis of 2-(2-(4-substituted benzylideneamino)ethyl)-1,2-thiazetidine 1,1-dioxide **6(a-f)** and a mixture of mono chloro acetyl chloride and ethyl amine**.** Synthesis of 2-(2-(4-substituted benzylideneamino)ethyl)-1,2-thiazetidine 1,1-dioxide **6(a-f)** was condensed with 4-substituted benzaldehyde in absolute alcohol. The synthesis of 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide**(4)** was synthesized by condensation of synthesis of 1,2-thiazetidine 1,1-dioxide (β-Sultam)**(3)** a mixture of K2CO3, TEBA , Acetonitile and 2-chloro ethanamide**.** Synthesis of 1,2-thiazetidine-1,1-dioxide**(β-Sultam) (3)** was synthesized with Taurinesulfonylchloride **(2)** with Na2CO3, Ethyl acetate**.** Taurinesulfonylchloride **(2)** was synthesized by S-S bond cleavage Cystaminedihydroxychloride **(1)** with mixture of Chlorine gas, Chloroform and Ethanol solvent mixture**.***

Key words: Sultam, Azetidinone, Cylization, Antibacterial and antifungal activity.

INTRODUCTION

Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial[37-53], pesticidal[53], antitumor[54], antitubercular[55], anticancer[56], cytotoxic[57-59], enzyme inhibitors[62], elastase inhibitors[61] & cholesterol absorption inhibitors[62]. Many β-lactam drugs had been reported in the literature. 13 Heterocycles possessing azetidin-2-one ring were found to show various types of biological activities[63-77].

Cyclic sulfonamides (sultams) although not found in nature [1] have also found applications in drug development. Examples of biologically active sultams include the antiepileptic agent Sulthiame, [2] the antiinflamatory agent Ampiroxicam, [3] Brinzolamide [4, 5] for the treatment of glaucoma, S-2474, [6] a new anthiarthritic drug candidate that is now under clinical trials, HIV-1 inhibitors [7, 8] selective inhibitors of Calpain I, [9] and most recently PBTD's [10] which are a new class of candidates for the treatment of chronic myelogenous leukemia (CML).

In addition to their medicinal value, sultams have been successfully used as chiral auxiliaries,[11, 12] reagents, [13-15] artificial sweeteners (i.e. saccharin), [16] and agricultural agents.[17] For example, the well known Oppolzer sultam has been utilized in numerous asymmetric reactions,[11,12] sultams has been used as a stereoselective oxidizing agent [15] and sultam has also found application as an electrophilic fluorinating agent to provide monofluorinated ketones. [13, 14] In agriculture, sultams have been used as herbicides.[17]

MATERIALS AND METHODS

Experimental

All the chemicals were used as received without further purification. Melting points were measured on a gallenkamp electro thermal melting point apparatus and are uncorrected. Reactions were carried out using household micro oven (power consumption 1200w, microwave frequency 2450MHz) and monitored by thin layer chromatography (TLC) on silica gel plates (60F254) visualizing with ultraviolet light or iodine spray. 1H NMR spectra were determined in DMSO- d6 solution on JOEL AL300 spectrometers. Proton chemical shifts are relative to tetramethylsilane as internal standard and expressed in ppm.

taurine sulfonyl chloride (2)

A suspension of cystamine dihydrochloride (1) (10.0 g, 44.4 mmol) was mixed in drychloroform (250 mL) and dry ethanol (125 mL). Chlorine was passed into the solution at -10°C under an atmosphere of nitrogen until complete saturation, noted by a permanent pale green colouration (1 hour). The system was purged with nitrogen, and dry diethyl ether (60 mL) was added to the mixture, which was stirred for a further 1 hour at room temperature. The reaction mixture was stored at 4°C overnight. The white precipitate was filtered off under vacuum and washed with dry diethyl ether to give taurine sulfonyl chloride (2) the product as a white solid (13.82 g, 94%). The yield of taurinesulfonylchloride (2) was found to be (94%, 13.82g) with M.P.141-143^{0}C. The structure of taurinesulfonylchloride (2) was established by IR. The IR spectrum of taurinesulfonylchloride (2) was recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bonds around. The IR spectra of taurinesulfonylchloride (2) recorded in the 4000-450 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bands around 2995 (w), 2912 (w), 2910 (bs, NH3), 1599 (w), 1558 (w), 1515 (w), 1399 (w)1371 (s, SO2), 1279 (w), 1173 (m), 1159 (s, SO2) groups respectively; The elemental analysis C2H7NO2S Cl2 (180); found % C, 13.33; H, 3.88; N, 7.77 agreed well with the calculated % C, 13.38; H, 3.93; N, 7.82.

1,2-thiazetidin-1,1-dioxide (*β*-sultam) (3)

Taurine sulfonyl chloride (2) 13.54 g, 81.5 mmol) was added to finely ground anhydrous Sodium carbonate (17.28 g, 163.0 mmol, 2 eq.) in dry ethyl acetate (370 mL) and stirred at RT for 46 hours. The reaction mixtutre was filtered through Celite®. The solvent was removed *in vacuo* to give the product as a white solid (2.62-5.29 g, 14-60 %, m.p.= 50-52°C, lit: m.p.=53°C29). The structure of 1,2-thiazetidin-1,1-dioxide (3) was established by IR, ^{1}H-NMR and ^{13}C NMR. The IR spectrum of 1,2-thiazetidin-1,1-dioxide (3) was recorded in the 4000-400 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bonds around 3581 (br), 3297 (br, NH), 3048 (w), 2987 (w), 2919 (w), 1629 (w), 1485 (w),1415 (w), 1300 (s, SO2), 1252 (s), 1150 (s, SO2), 1114 (m), 992 (w), 963 (m), 917 (w), 763 (m), 654 (m) respectively; The ^{1}H NMR structure of the compound 1,2-thiazetidin-1,1-dioxide (3) in CDCl3 showed the following signals at δppm (400 MHz, CDCl3) 5.32 (1H, bs, NH), 4.25 (2H, dt, *J*=7.0 CH2SO2), 3.33 (2H, dt, *J*=7.0 and 3.9 Hz, CH2NH). ^{13}C NMR δppm (400 MHz, CDCl3); The ^{13}C NMR δppm (400 MHz) data of the compound 1,2-thiazetidin-1,1-dioxide (3) was recorded in CDCl3 showed the following signals at 60.93 (CH2SO2), 28.14 (CH2NH); The elemental analysis C2H5NO2S (107); found % C, 22.42; H, 4.67; N, 13.08 agreed well with the calculated % C, 22.47; H, 4.72; N, 13.13.

Synthesis of 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4)

To a solution of sultam (0.25 mmol) and TEBA (5,7 mg, 0.025 mmol) in dryacetyonitrile (1 mL) at 25^{0}C, anhydrous potassium carbonate (51.8 mg, 0.375 mmol) was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX (0.375 mmol) was added and the reaction was monitored by TLC until completion. The mixture zwas filtered through a celite pad and, after evaporation of the solvent (RV), the crude was purified by Flash Column Chromatography. The structure of 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4) was characterized by IR, (KBr), ^{1}H NMR spectra and Elemental analysis. The IR spectra of 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4) recorded in the 4000-450 cm^{-1} range in KBr pellets reflect the molecular structure and showed the characteristic bands around 3581 (br), 3297 (br, NH), 3048 (w), 2987 (w), 2919 (w), 1629 (w), 1485 (w),1415 (w), 1300 (s, SO2), 1252 (s), 1150 (s, SO2), 1114 (m), 992 (w), 963 (m), 917 (w), 763 (m),654 (m); The ^{1}H NMR structure of the compound 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4) in DMSO d6 showed the following signals at δppm^{1}H NMR δ (400 MHz, DMSO d6): 5.11 (1H, bs, NH2), 4.25 (2H, dt, *J*=7.0 and 1.7 Hz, CH2SO2),3.33 (2H, dt, *J*=7.0 and 3.9 Hz, CH2NH2), 3.11 (2H, dt, *J*=7.0 and 3.9 Hz, CH2N), 2.81 (2H, dt, *J*=7.0 and 3.9 Hz, CH2); The elemental analysis C4H10N2O2S (150); found % C, 32.00; H, 6.66; N, 32.00 agreed well with the calculated % C, 32.05; H, 6.71; N, 32.05.

Synthesis of 2-(2-(4-substituted benzylideneamino)ethyl)-1,2-thiazetidine 1,1-dioxide 6(a-f)
Equimolar quantities of 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4) and Benaldehyde (5a-f) were dissolved in absolute alcohol and heated at 100^0C for 5-6 hours. The progress of the reaction was monitored by TLC using hexane : ethylacetate(7:3) as mobile phase, the reaction mixture was kept overnight and evaporation of the solvent under reduced pressure with rotaevaporator afforded residue which was recrystallized from DCM(Dichloro methane) affored 2-(2-(4-substituted benzylideneamino)ethyl)-1,2-thiazetidine 1,1-dioxide (6a). The yield was 70% and m.p.166-168^0C. The similar procedure was adopted with 2-(2-aminoethyl)-1,2-thiazetidine 1,1-dioxide (4) and 4-methylbenzaldehyde, 4-flourobenzaldehyde, 4-chlorobenzaldehyde, 4-triflourobenzaldehyde and 4-ntrobenzaldehyde. The structure of (6a-f) was established by IR and ^{1}HNMR and elemental analysis.

IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919 (Aliphatic C-H), 1620 (>C=N), 1300 & 1252 (SO2); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),7.10-7.20(m, 5H of C6H5); The elemental analysis C11H14N2O2S (238); found % C,55.46; H,5.88; N,11.76 agreed well with the calculated % C,55.51; H,5.93; N,11.81.

2-(2-((4-methylbenzylidene)amino)ethyl)-1,2-thiazetidine 1,1-dioxide6(b): yield 60%, m.p.172^0C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919 (Aliphatic C-H), 1615 (>C=N), 1300 & 1252 (SO2). ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),6.90-7.10(m, 4H of C6H4), 2.34(s,3H,-CH3); The elemental analysis C12H16N2O2S (252); found % C,57.14; H,6.34; N,11,11 agreed well with the calculated % C,57.19; H,6.39; N,11.16.

2-(2-((4-fluorobenzylidene)amino)ethyl)-1,2-thiazetidine 1,1-dioxide6(c): yield 70%, m.p.159^0C; IR(KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919 (Aliphatic C-H), 1620 (>C=N), 1300 & 1252 (SO2); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),7.30-7.40(m, 4H of C6H4); The elemental analysis C11H13N2O2FS (255); found% C,51.76; H,5.09; N,10.98 agreed well with the calculated % C,51.81; H,5.14; N,11.03.

2-(2-((4-chlorobenzylidene)amino)ethyl)-1,2-thiazetidine 1,1-dioxide6(d): yield 68%, m.p.151^0C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919 (Aliphatic C-H), 1617 (>C=N), 1300 & 1252 (SO2); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),7.25-7.36(m, 4H of C6H4); The elemental analysis C11H13N2O2ClS (272.5); found % C,48.44; H,4.77; N,10.27 agreed well with the calculated % C,48.49; H,4.82; N,10.32.

2-(2-((4-(trifluoromethyl)benzylidene)amino)ethyl)-1,2-thiazetidine 1,1-dioxide 6(e): yield 72%, m.p.184^0C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919***)*** (Aliphatic C-H), 1622 (>C=N), 1300 & 1252 (SO2); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),7.40-7.50(m, 4H of C6H5); The elemental analysis C12H13N2O2F3S (303); found % C, 47.52; H,4.29; N,9.24 agreed well with the calculated % C,47.57; H,4.34; N,9.29.

2-(2-((4-nitrobenzylidene)amino)ethyl)-1,2-thiazetidine 1,1-dioxide6(f) : yield 68%, m.p.193^0C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 2987 & 2919 (Aliphatic C-H), 1625 (>C=N), 1622 (>C=N), 1300 & 1252 (SO2). ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H, J=7.0, -CH2SO2 of sultam ring), 3.33 (t, 2H, J=7.0, -CH2 attached to nitrogen sultam ring), 8.70(s,1H, -CH=N-, attached to phenyl ring),7.5-7.8(m, 4H of C6H4); The elemental analysis C11H13N3O4S (283); found % C,46.64; H,4.59; N,14.84 agreed well with the calculated % C,46.69; H,4.64; N,14.89.

Synthesis of 3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-phenylazetidin-2-one (7 a-f) .
Monochloroacetyl chloride (0.01 mol) was added drop wise to schiff's base (0.01 mol) and triethyl amine (0.02 mol) in dioxane (25ml) at room temparature. The mixture was stirred for 8h and left at room temparature for 3 days. Pour the contents on crushed ice. The product thus formed was filtered and washed with sodium bicarbonate solution. The dired product was recrystlised with absolute alcohol. The similar procedure was adopted to synthesize 7(b-f) from

6 (b-f) and monochloroacetylchloride. The structure of the compounds 7(a-f) was established by IR, ^{1}HNMR,^{13}CNMR, Mass Spectral analysis and elemental analysis.

3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-phenylazetidin-2-one7(a): yield 60%, m.p.142^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3040 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.10-7.20(m, 5H of C6H5); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 127.0 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11; The elemental analysis C13H15N2O3ClS (314.05); found % C,49.67; H,4.77; N,8.91 agreed well with the calculated % C,49.72; H,4.82; N,8.96.

3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(p-tolyl)azetidin-2-one7(b) : yield 50%, m.p.157^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3035 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.0-7.10(m, 5H of C6H5), 2.34(s, 3H, -CH3); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 127.0, 21.3 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11, C14; The elemental analysis C14H17N2O3ClS (331.05); found% C,51.21; H,5.18; N,8.53 agreed well with the calculated % C,51.26; H,5.23; N,8.58.

3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-fluorophenyl)azetidin-2-one7(c):yield 65%, m.p.133^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3042 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.25-7.35(m, 5H of C6H4); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 129.5 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11; The elemental analysis C13H14N2O3FClS (331.05); found % C,47.40; H,4.25; N,8.50 agreed well with the calculated % C,47.45; H,4.30; N,8.55.

3-chloro-4-(4-chlorophenyl)-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)azetidin-2-one7(d):yield 70%, m.p.134^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3043 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.20-7.30(m, 5H of C6H4); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 128.2 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11; The elemental analysis C13H14N2O3Cl2S (348.10); found % C,45.01; H,4.03; N,8.07 agreed well with the calculated % C,45.06; H,4.08; N,8.12.

3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)azetidin-2-one7(e) : yield 55%, m.p.167^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3045 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond);^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.35-7.45(m, 5H of C6H4); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 126.7,124.1 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11, C14; The elemental analysis C14H14N2O3F3ClS (379.05); found % C,44.55; H,3.71; N,7.42 agreed well with the calculated % C,44.60; H,3.76; N,7.47.

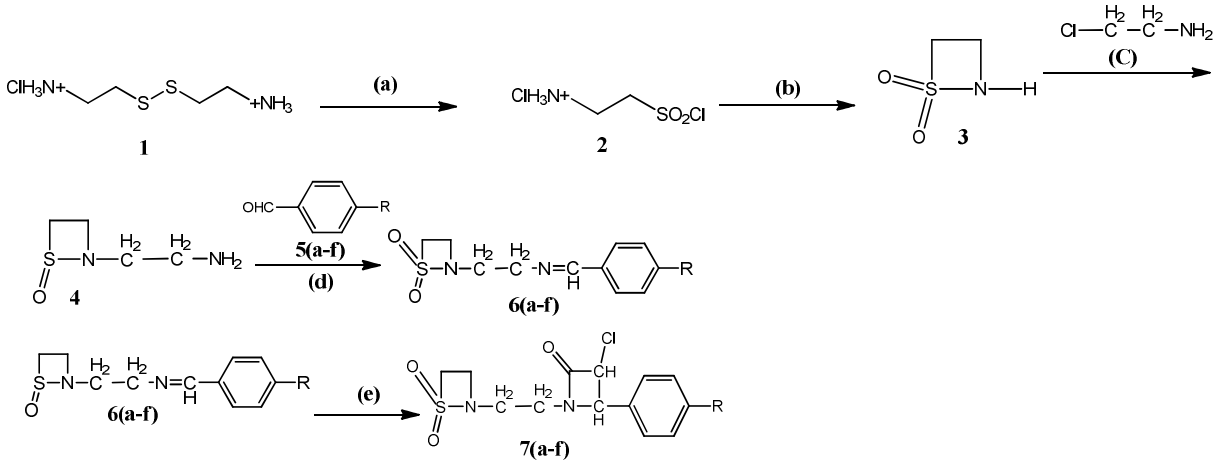
3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-nitrophenyl)azetidin-2-one7(f): yield 45%, m.p.176^{0}C; IR (KBr) pellets reflect the molecular structure and showed the characteristic bonds around 3050 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO

d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.40-7.50(m, 5H of C6H4); ^{13}CNMR(CDCl3) (δ ppm): 53.3, 43.0, 54.1, 46.1, 166.5, 62.4, 65.7, 138.3, 127.9, 128.5, 146.2 and the signals are ascribed to C1, C2,C3, C4, C5, C6, C7, C8, C9 & C13, C10 & C12, C11; The elemental analysis C13H14N3O5ClS (359.05); found % C,43.44; H,3.89; N,11.69 agreed well with the calculated % C,43.49; H, 3.94; N,11.74.

RESULTS AND DISCUSSION

The development of sultam-azetidinone heterocycles was described in the scheme-1 of synthetic sequence. The different steps involve simple reaction conditions and good yield procedure. Compounds 6(a-f) were allowed to react with 4-substituted benzaldehyde 5(a-f) to afford 7(a-f) in good yield. The IR spectrum of 7a revealed the appearance of bands characteristics of 3040 (Ar-H stretching), 2987 & 2960 (Aliphatic C-H), 1690 (>C=O group); 1300 & 1150 (SO2 group); 667 (C-Cl bond); ^{1}HNMR(DMSO d6) (δ ppm) : 4.25(t, 2H,- CH2, of 1,2-thiazetidin, J=7 Hz), 3.33 (t, 2H, - CH2- SO2 of thiazetidin, J=7 Hz), 2.80(t, 2H,- CH2 attached to thiazetidin, J=8Hz) 3.11 (t,2H,-CH2, attached to azetidin ring), 4.79(d,1H,-CH of azetidin attached to phenyl ring, J=7.8Hz), 7.10-7.20(m, 5H of C6H5); ^{13}CNMR(CDCl3) (δ ppm): C1-53.3, C2-43.0, C3-54.1, C4-46.1, C5-166.5, C6-62.4, C7-65.7, C8-138.3, C9 & C13-127.9, C10 & C12-128.5, C11-127.0 conformed the formation of sultam-azetidinone (7a).

Scheme-1



	6a	6b	6c	6d	6e	6f
Compound	7a	7b	7c	7d	7e	7f
R	-H	-CH3	-F	-Cl	CF3	NO2

Anti- Microbial Activity

The anti-microbial activity of 7a-f was determined by the disc diffusion method with Amoxicillin and Griseofulvin as the reference antibiotics [18]. The newly synthesized compounds were examined, respectively, against *Staphylococcus aureus, Bacillus Cereus, Escherichia Coli* and *Pseudomonas aeruginosa* bacteria. The test results were presented in the table-1, suggest that –Nitro, -Chloro and –Flouro exhibit high activity against the tested bacteria, the rest of the compounds were found to be either slightly active or inactive against the tested microorganisms. The order of anti-bacterial activity was found to be 7f>7d>7e>7b>7a>7c.

Table 1. Antibacterial Activity by the disc diffusion method

S.No.	Compound	Zone of Inhibition			
		***Staphylococcus aureus* NCCS2079**	***Bacillus Cereus* NCCS2106**	***Escherichia Coli* NCCS2065**	***Pseudomonas aeruginosa* NCCS2200**
1	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-phenylazetidin-2-one7(a)*	07	08	06	06
2	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(p-tolyl)azetidin-2-one7(b)*	05	07	05	06
3	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-fluorophenyl)azetidin-2-one7(c)*	06	07	06	07
4	*3-chloro-4-(4-chlorophenyl)-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)azetidin-2-one7(d)*	06	07	06	05
5	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)azetidin-2-one7(e)*	09	09	07	09
6	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-nitrophenyl)azetidin-2-one7(f)*	08	08	06	07
7	*Amoxycillin*	21	22	24	27

Antifungal activity

Antifugal activity of final compounds 3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-phenylazetidin-2-one7(a-f) were screened against *Aspergillus niger*, *Helminthosporium Oryzae*. The compounds 7(a-f) showed more fungal activity while 7(a-c) exhibited low activity. The fungal activity dioxido-1,2-thiazetidin 7(a-f) was shown in the (Table-2). Here Griseofulvin [19-20] is tested as reference compound to compare the activity.

Table 2. Antifungal Activity by the disc diffusion method

S.No.	Compound	Zone of Inhibition	
		***Aspergillus niger* NCCS 1196 250(µg/disc)**	***Helminthosporium Oryzae* 250(µg/disc)**
1	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-phenylazetidin-2-one7(a)*	9	8
2	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(p-tolyl)azetidin-2-one7(b)*	10	9
3	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-fluorophenyl)azetidin-2-one7(c)*	8	6
4	*3-chloro-4-(4-chlorophenyl)-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)azetidin-2-one7(d)*	18	19
5	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)azetidin-2-one7(e)*	16	17
6	*3-chloro-1-(2-(1,1-dioxido-1,2-thiazetidin-2-yl)ethyl)-4-(4-nitrophenyl)azetidin-2-one7(f)*	17	18
7	*Griseofulvin*	28	26

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