DOI: 10.21276/sjmps.2017.3.3.19

Saudi Journal of Medical and Pharmaceutical Sciences
Scholars Middle East Publishers
Dubai, United Arab Emirates
Website: http://scholarsmepub.com/

ISSN 2413-4929 (Print)
ISSN 2413-4910 (Online)

Original Research Article

Synthesis of Possible Anti-Cancer and Anti-Mycobacterial Fluoro Substituted Sulphonamide Benzothiazoles Comprising Potent Thiazolidinone

Jagtap VA*[1], Gautam DT[1], Mule VS[1], Gandhi SM[1], Jayachandran E[2]

[1]Dept. of Pharmaceutical Chemistry, Yashwantrao Bhonsale College of Pharmacy, Sawantwadi – 416 510, Dist: Sindhudurg (M. S.), India

[2]PG Dept. of Pharmaceutical Chemistry, S. C. S. College of Pharmacy, Harapanahalli – 583 131, Dist: Davangere (K. S.), India

***Corresponding Author:**
Jagtap VA
Email: drvajagtap@gmail.com

Abstract: In the present study, a series of *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide and *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide derivatives were synthesized in good yields and characterized by FTIR, ^{1}HNMR, mass spectral and elemental analyses. All synthesized compounds were evaluated for their preliminary in vitro anti-mycobacterial activity against Mycobacterium tuberculosis H37 Rv strain by tube dilution assay method. Some selected synthesized compounds were also evaluated for cytostatic activities against malignant human cell lines: cervical (HeLa), bone marrow (K-562) and kidney cell (HEK-293).

Keywords: Fluorobenzothiazole, Sulphonamido, Thiazolidinone, Anti-mycobacterial activity, Anti-cancer activity

INTRODUCTION

Emergences of multi drug resistant–TB synergized with other immune-compressive diseases have increased the life threatening capacities of the disease [1-2]. One third of the world's population is thought to have been infected with M. tuberculosis [3-4]. Therefore, there is an urgent need for novel anti-mycobacterial agents with a different mode of action. Literature study reveals that 2-substituted benzothiazole derivatives have anti-mycobacterial [5-10], anti-cancer [11-17] and other broad spectrum of biological activities. More recently, sulphonamides have been found to be potent cysteine protease inhibitors, which could possibly extent their therapeutic application to include conditions such as alzheimer's disease, arthritis and cancer. As a class the sulfa drugs have a variable history of application for the treatment of bacterial infections [18-19]. Benzothiazole with sulphonyl group were reported to possess anti-mycobacterial [20], cytotoxic activity [21]. Based on the above observations we have synthesized some Fluoro substituted sulphonamide benzothiazoles. In addition to this we have incorporated a potent thiazolidinone heterocycle. Thiazolidinones are well known heterocyclic compounds for their known activities such as anti-mycobacterial [22], anti-cancer [23], anti-HIV [24], and antimicrobial [25]. It was to be found that incorporation of thiazolidinone moiety into sulphonamidobenzothiazole scaffold enhances its activity. Thus in the present investigation, 24 different derivatives of *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide and *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide derivatives were synthesized and evaluated for their anti-mycobacterial and anti-cancer activity.

MATERIAL AND METHODS

General

All commercial reagents and chemicals were used without further purification. Reactions were monitored by TLC. Melting points were determined by open capillary method and are uncorrected. The infrared spectra were recorded by a Fourier transform infrared (FTIR) spectrometer Bruker Vertex 70 equipped with an attenuated total reflection (ATR) accessory with a diamond crystal. 1HNMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethyl silane (TMS) as an internal standard and DMSO-d_6 as a solvent. The 1HNMR chemical shift values (δ) are expressed in ppm referred to tetramethyl silane (TMS) and coupling constants (*J*) in Hz. Precoated Merck Silica Gel 60F-254 plates were used for thin layer chromatography (TLC) and the spots were detected under UV light (254 nm). Elemental analyses were carried out using FLASH EA 1112 CHN analyzer

from Thermo Finnigen, Italy and values were within ± 0.4 % of the calculated.

The synthetic route of targeted compounds *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide derivatives **6 (a-l)** and *N*-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzene sulphonamide derivatives **6 (m-x)** were done from schiff's base illustrated in Figure 1.

Synthesis

It has been found that reaction of commercially available compound (**1)** with *p*-acetamido benzene sulphonyl chloride in presence of pyridine and acetic anhydride in ethanol produced the condensed derivative (**2)** in 80% yield. Compound **2** hydrolyzed by boiling in 80% acetic acid give product (**3)** in 74 % yield. Compound (**3)** with two different aromatic aldehydes viz. 3-nitro benzaldehyde and 4-nitrobenzaldehyde in presence of ethanol and 2-3 drops of hydrochloric acid yields Schiff's bases **4 (a-b).** Schiff's bases on further treatment of 2-thioglycolic acid in presence of 1,4-dioxane and sodium bicarbonate yields compound **5 (a-b)**. Compound **5 (a-b)** on treatment with equimolar quantities of various aromatic amines in presence of dimethyl formamide yields target compounds **6 (a-x)**. Physical and analytical of all target compounds is given in Table I.

Chemistry

Specific examples presented below illustrate general synthetic procedure.

7-Chloro-6-fluoro-1,3-benzothiazol-2-amine (1)

4-fluoro-3-chloro-aniline (0.01 mol) was treated with potassium thiocyanate (0.08 mol) in presence of cool glacial acetic acid (20 ml) bromine (1.6 ml) and ammonia to get yellow solid compound **1.** (51.02%) m.p. 212 ºc (d); Anal. calcd. for $C_7H_4ClFN_2S$: C 41.53 H 2.04 N 13.85 Found C 41.30 H 2.01 N 13.82.

***N*-[4-[(7-Chloro-6-fluoro-1,3-benzothiazol-2-yl)sulfamoyl]phenyl]acetamide (2)**

To a suspension of compound **(1)** (0.013 mol), pyridine (4 ml) and acetic anhydride (20 ml), p-acetamido benzene sulphonyl chloride (0.01 mol) was added and refluxed in water bath for 2 h. After cooling of reaction mixture in ice cold water the precipitated solid obtained was filtered and recrystalised from dil ethanol (80%). (60.15 %,) m.p. 221ºc (d)); Anal. calcd. for $C_{15}H_{11}ClFN_3O_3S_2$, C, 45.10; H, 2.84; N, 10.55 Found C, 45.06; H, 2.80; N, 10.53.

4-Amino-*N*-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)benzenesulphonamide (3)

The compound **(2)** (0.01 mol) hydrolyzed by boiling in 50 ml of 80% acetic acid for 4 to 5 h and the contents were poured onto crushed ice. The obtained hydrolyzed derivatives were filtered at suction and dried. (76.12%) m.p. 189ºc (d)); Anal. calcd. for $C_{13}H_9ClFN_3O_2S_2$, C, 43.64; H, 2.45; N, 11.47; Found C, 43.62; H, 2.41; N, 11.43.

***N*-(7-Chloro-6-fluoro-1,3-benzothiazol-2-yl)-4-[(E)-(3-nitrophenyl)methyleneamino] benzenesulphonamide (4a)**

0.01 mol of compound **(3)** with 0.015 mol solution of 3-nitro benzaldehyde, added 20 ml ethanol and 3-4 drops of HCl and refluxed for 2-3 h. Solution cooled and poured into crushed ice. Recrystalised with benzene and ethanol. (80.15%) m.p.195ºc (d)); Anal. calcd. for $C_{20}H_{12}ClFN_4O_4S_2$, C, 48.95; H, 2.55; N, 11.34; Found C, 48.91; H, 2.51; N, 11.30.

***N*-(7-Chloro-6-fluoro-1,3-benzothiazol-2-yl)-4-[(E)-(4-nitrophenyl)methyleneamino] benzenesulphonamide (4b)**

0.01 mol of compound **(3)** with 0.015 mol solution of 4-nitro benzaldehyde, added 20 ml ethanol and 3-4 drops of HCl and refluxed for 2-3 h. Solution cooled and poured into crushed ice. Recrystalised with benzene and ethanol. (78.15%) m.p.190ºc (d)); Anal. calcd. for $C_{20}H_{12}ClFN_4O_4S_2$, C, 48.95; H, 2.55; N, 11.34; Found C, 48.93; H, 2.53; N, 11.32.

***N*-(7-Chloro-6-fluoro-1,3-benzothiazol-2-yl)-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (5a).**

To a solution of Schiff's base **(4a)** (0.01 mol) added 1,4-dioxane (50ml) and 2-thoglycolic acid (0.025 mol) refluxed for 12 h. After reflux cooled and triturated with 10% sodium bicarbonate solution. The product was recrystalised from benzene and ethanol. (72.21%) m.p. 234ºc (d)); Anal. calcd. for $C_{22}H_{14}ClFN_4O_5S3$; C, 46.86; H, 2.55; N, 9.90; Found C, 46.82; H, 2.52; N, 9.88.

***N*-(7-Chloro-6-fluoro-1,3-benzothiazol-2-yl)-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (5b).**

To a solution of Schiff's base **(4b)** (0.01 mol) added 1,4-dioxane (50ml) and 2-thoglycolic acid (0.025 mol) refluxed for 12 h. After reflux cooled and triturated with 10% sodium bicarbonate solution. The product was recrystalised from benzene and ethanol. (78.00%) m.p. 245ºc (d)); Anal. calcd. for $C_{22}H_{14}ClFN_4O_5S3$; C, 46.86; H, 2.55; N, 9.90; Found C, 46.81; H, 2.53; N, 9.87.

***N*-[6-Fluoro-7-(2-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6a)**

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 2-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (72.00%) m.p. 180ºc (d)); IR (cm^{-1}):υ = 3385,

3080, 1815, 1450, 1397, 1380, 1300, 1193, 1190, 720; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.5-7.9 (m, Ar-H), 5.3 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

_N_-[6-Fluoro-7-(3-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6b)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 3-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (78.00%) m.p. 132ºc (d)); IR (cm^{-1}):υ = 3400, 3100, 1830, 1435, 1385, 1295, 1280, 1200, 725; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.6-7.6 (m, Ar-H), 5.1 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

_N_-[6-Fluoro-7-(4-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6c)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 4-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (83.00%) m.p. 97ºc (d)); IR (cm^{-1}):υ = 3390, 3090, 1830, 1440, 1390, 1285, 1210, 1195, 718; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.7-7.4 (m, Ar-H), 5.2 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

_N_-[6-Fluoro-7-(2-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6d)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 2-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (88.00%) m.p. 170ºc (d)); IR (cm^{-1}):υ = 3128, 3369, 1825, 1607, 1290, 1282, 1607, 1197, 1182; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.5-7.2 (m, Ar-H), 5.2 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.34; H, 2.93; N, 10.71.

_N_-[6-Fluoro-7-(3-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6e)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 3-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (70.00%) m.p. 125ºc (d)); IR (cm^{-1}):υ = 3315, 3228, 1820, 1699, 1555, 1296, 1295, 1385, 1195, 1184; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.2-7.2 (m, Ar-H), 5.5 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.32; H, 2.92; N, 10.74.

_N_-[6-Fluoro-7-(4-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6f)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 4-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (80.00%) m.p. 82ºc (d)); IR (cm^{-1}):υ = 3452, 3201, 1825, 1690, 1512, 1397, 1390, 1300, 1297, 1172; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.4-7.1 (m, Ar-H), 5.6 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.35; H, 2.99; N, 10.76.

4-[[6-Fluoro-2-[[4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]phenyl]sulfonylamino]-1,3-benzothiazol-7-yl]amino]benzoic acid (6g)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of 4-amino benzoic acid refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (89.00%) m.p. 90ºc (d)); IR (cm^{-1}):υ = 3200, 3110, 1820, 1550, 1380, 1397, 1390, 1310, 1195, 1184; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.2-7.4 (m, Ar-H), 5.5 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{29}H_{20}FN_5O_7S_3$ C, 52.34; H, 3.00; N, 10.55; Found C, 52.30; H, 2.99; N, 10.54.

_N_-[6-Fluoro-7-(anilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6h)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of aniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (80.00%) m.p. 72ºc (d)); IR (cm^{-1}):υ = 3370, 3100, 1825, 1600, 1380, 1295, 1249, 1170; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.3-7.4 (m, Ar-H), 5.8 (s, NH), FAB-MS m/z 622 $[M+1]^+$; Anal. calcd. for $C_{28}H_{20}FN_5O_5S_3$ C, 54.10; H, 3.20; N, 11.34; Found C, 54.11; H, 3.16; N, 11.30.

_N_-[6-Fluoro-7-(morpholino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6i)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of morpholine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (67.00%) m.p. 145ºc (d)); IR (cm^{-1}):υ = 3350, 3095, 1835, 1597, 1395, 1300, 1295, 1280; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.5-7.2 (m, Ar-H), 5.4 (s, NH), FAB-MS m/z 616 $[M+1]^+$; Anal. calcd. for $C_{26}H_{22}FN_5O6_6S_3$ C, 50.77; H, 3.61; N, 11.44; Found C, 50.73; H, 3.59; N, 11.41.

_N_-[6-Fluoro-7-(piperazino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6j)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of piperazino refluxed for 2 h in presence of DMF, recrystalised from alcohol and

benzene. (72.00%) m.p. 110ºc (d)); IR (cm^{-1}):υ = 3400, 3080, 1820, 1540, 1385, 1295, 1195, 1170; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.3-7.0 (m, Ar-H), 5.2 (s, NH), FAB-MS m/z 615 $[M+1]^+$; Anal. calcd. for $C_{26}H_{23}FN_6O_5S_3$ C, 50.87; H, 3.81; N, 13.71; Found C, 50.86; H, 3.80; N, 13.68.

N-[6-Fluoro-7-(N,N-diphenylamino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6k)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of N,N-diphenylamine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (68.00%) m.p. 280ºc (d)); IR (cm^{-1}):υ = 3406, 3101, 1823, 1616, 1390, 1290, 1249, 1170; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.1-7.1 (m, Ar-H), 5.1 (s, NH), FAB-MS m/z 698 $[M+1]^+$; Anal. calcd. for $C_{34}H_{24}FN_5O_5S_3$ C, 58.50; H, 3.51; N, 10.08; Found C, 58.49; H, 3.52; N, 10.10.

N-[6-fluoro-7-(N,N-dimethylamino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6l)

Compound **(5a)** (0.01 mol) was treated with equimolar quantity of N,N-dimethylamine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (68.00%) m.p. 280ºc (d)); IR (cm^{-1}):υ = 3406, 3101, 1823, 1616, 1390, 1290, 1249, 1170; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.3-7.4 (m, Ar-H), 5.4 (s, NH), FAB-MS m/z 574 $[M+1]^+$; Anal. calcd. for $C_{24}H_{20}FN_5O_5S_3$ C, 50.35; H, 3.51; N, 12.21; Found C, 50.31; H, 3.52; N, 12.20.

N-[6-fluoro-7-(2-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6m)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 2-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (78.00%) m.p. 110ºc (d)); IR (cm^{-1}):υ = 3300, 3100, 1822, 1456, 1334, 1200, 725; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 7.7-8.7 (m, Ar-H), 9.0 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

N-[6-fluoro-7-(3-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6n)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 3-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (89.00%) m.p. 156ºc (d)); IR (cm^{-1}):υ = 3423, 3200, 1856, 1434, 1390, 1295, 1290, 1297, 778; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.8-7.2 (m, Ar-H), 8.3 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

N-[6-fluoro-7-(4-nitroanilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6o)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 4-nitroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (76.00%) m.p. 125ºc (d)); IR (cm^{-1}):υ = 3345, 3100, 1876, 1456, 1400, 1287, 1231, 1200, 789; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.7-7.3 (m, Ar-H), 5.5 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}FN_6O_7S_3$ C, 50.44; H, 2.96; N, 12.61; Found C, 50.41; H, 2.93; N, 12.64.

N-[6-fluoro-7-(2-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6p)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 2-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (75.00%) m.p. 90ºc (d)); IR (cm^{-1}):υ = 3372, 3200, 1825, 1708, 1359, 1295, 1278, 1200, 1190; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.6-7.2 (m, Ar-H), 5.7 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.34; H, 2.93; N, 10.71.

N-[6-fluoro-7-(3-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6q)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 3-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (82.00%) m.p. 115ºc (d)); IR (cm^{-1}):υ = 3318, 3220, 1823, 1700, 1578, 1398, 1300, 1286, 1187; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.5-7.5 (m, Ar-H), 5.7 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.32; H, 2.92; N, 10.74.

N-[6-fluoro-7-(4-chloroanilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6r)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 4-chloroaniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (89.00%) m.p. 142ºc (d)); IR (cm^{-1}):υ = 3400, 3301, 1825, 1698, 1562, 1399, 1385, 1309, 1289, 1183; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.2-7.2 (m, Ar-H), 5.8 (s, NH), FAB-MS m/z 657 $[M+1]^+$; Anal. calcd. for $C_{28}H_{19}ClFN_5O_5S_3$ C, 51.31; H, 2.96; N, 10.73; Found C, 51.35; H, 2.99; N, 10.76.

4-[[6-fluoro-2-[[4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]phenyl]sulfonylamino]-1,3-benzothiazol-7-yl]amino]benzoic acid (6s)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of 4-amino benzoic acid refluxed for

2 h in presence of DMF, recrystalised from alcohol and benzene. (79.00%) m.p. 92ºc (d)); IR (cm^{-1}):υ = 3208, 3200, 1827, 1600, 1380, 1329, 1200, 1198; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.1-7.4 (m, Ar-H), 5.1 (s, NH), FAB-MS m/z 668 $[M+1]^+$; Anal. calcd. for $C_{29}H_{20}FN_5O_7S_3$ C, 52.34; H, 3.00; N, 10.55; Found C, 52.30; H, 2.99; N, 10.54.

N-[6-fluoro-7-(anilino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6t)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of aniline refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (62.00%) m.p. 120ºc (d)); IR (cm^{-1}):υ = 3380, 3298, 1825, 1640, 1390, 1323, 1289, 1170; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.3-7.3 (m, Ar-H), 5.1 (s, NH), FAB-MS m/z 622 $[M+1]^+$; Anal. calcd. for $C_{28}H_{20}FN_5O_5S_3$ C, 54.10; H, 3.20; N, 11.34; Found C, 54.11; H, 3.16; N, 11.30.

N-[6-fluoro-7-(morpholino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6u)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of morpholine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (87.00%) m.p. 165ºc (d)); IR (cm^{-1}):υ = 3370, 3100, 1840, 1597, 1345, 1309, 1300; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.3-7.2 (m, Ar-H), 5.2 (s, NH), FAB-MS m/z 616 $[M+1]^+$; Anal. calcd. for $C_{26}H_{22}FN_5O6_6S_3$ C, 50.77; H, 3.61; N, 11.44; Found C, 50.73; H, 3.59; N, 11.41.

N-[6-fluoro-7-(piperazino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6v)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of piperazino refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (82.00%) m.p. 188ºc (d)); IR (cm^{-1}):υ = 3390, 3100, 1890, 1560, 1385, 1300, 1209, 1150; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.1-7.0 (m, Ar-H), 5.2 (s, NH), FAB-MS m/z 615 $[M+1]^+$; Anal. calcd. for $C_{26}H_{23}FN_6O_5S_3$ C, 50.87; H, 3.81; N, 13.71; Found C, 50.86; H, 3.80; N, 13.68.

N-[6-fluoro-7-(N,N-diphenylamino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6w)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of N,N-diphenylamine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (56.00%) m.p. 210ºc (d)); IR (cm^{-1}):υ = 3306, 3120, 1867, 1623, 1395, 1289, 1250, 1200; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.0-7.0 (m, Ar-H), 5.6 (s, NH), FAB-MS m/z 698 $[M+1]^+$; Anal. calcd. for $C_{34}H_{24}FN_5O_5S_3$ C, 58.50; H, 3.51; N, 10.08; Found C, 58.49; H, 3.52; N, 10.10.

N-[6-fluoro-7-(N,N-dimethylamino)-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide (6x)

Compound **(5b)** (0.01 mol) was treated with equimolar quantity of N,N-dimethylamine refluxed for 2 h in presence of DMF, recrystalised from alcohol and benzene. (76.00%) m.p. 156ºc (d)); IR (cm^{-1}):υ = 3397, 3100, 1820, 1455, 1395, 1356, 1287, 1240; ^{1}HNMR (400 MHz, DMSO-d_6), δ (ppm) 6.2-7.4 (m, Ar-H), 5.3 (s, NH), FAB-MS m/z 574 $[M+1]^+$; Anal. calcd. for $C_{24}H_{20}FN_5O_5S_3$ C, 50.35; H, 3.51; N, 12.21; Found C, 50.31; H, 3.52; N, 12.20.

Pharmacological activity

Anti-mycobacterial activity

The entire test compounds were assayed in anti-mycobacterial activity was evaluated against H37Rv strain of M. tuberculosis (ATCC 27294). The MIC was determined by the test tube dilution technique using modified Kirchner's culture medium containing 0.5% sterilized horse serum for anti-mycobacterial activity. Rifampcin and isoniazid (INH) were used as reference standard for anti-mycobacterial activity. The stock solution (2–4 lg/mL) of test compounds was prepared in a mixture of sterile water and dimethyl formamide (8:2) solvent. The stock solution was sterilized by passing through a 0.2 mm polycarbonate sterile membrane (Nuclepore) filters. Further, the serial dilution of test compounds was carried out and the following concentration was used: 1000, 500, 250, 125, 62, 32, 16, 8, 4 and 1 lg/mL. Test compounds at various concentrations were added to culture medium in a sterilized borosilicate test tube and different bacterial strains were inoculated at 106 bacilli/mL concentration. The tubes were incubated at 37º for 14 and 21 days for anti-mycobacterial activity and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The MIC values were obtained from the lowest concentration of the test compound where the tubes remained clear, indicated that the bacterial growth was completely inhibited at this concentration.

Anti-cancer activity

1. General

Hela- Human cervix, K-562 – Human chronic myelogenous Leukemia bone marrow and HEK 293 – Human Kidney cells were centrifuged at 1000 rpm for 1 min. After centrifugation 2 ml supernatant of cells mixed with 200 µl of MEM medium in required number of wells using 96 well plates with 50 µl of cell line in each well. Into these wells 10µl, 20µl, and 30µl of testing compounds were added and Kept in CO_2 incubator at 37ºC and 5% CO_2 for 72 h. After 72 h. observed whether lysis occur or not under inverted microscope. All the procedure was carried out under

aseptic conditions. MTT solution (10 mg in 10 ml of Hank's balanced solution) was used.

2. Cell culture

The cell line were maintained in 96 wells micro titer plate containing MEM (Minimum Essential medium) supplemented with 10% heat inactivated fetal calf serum (FCS), containing 5% of mixture of gentamycin, penicillin (100 Units/ ml) and streptomycin (100µg/ml) in presence of 5% CO_2 at 37ºC for 3-4 days. After 3-4 days removed the supernatant and replaced MEM media with Hank's balanced solution supplemented with gentamycin, penicillin and streptomycin and were incubated for overnight.

3. Cytotoxicity Assay

In vitro growth inhibition effect of test compounds were assessed by calorimetric or spectrophotometric determination of conversion of MTT into "Formazan blue" by living cells. Supernatant removed from the plate added with fresh Hank's balanced salt solution and treated with different concentration of extract or compound appropriately diluted with DMSO. Control group contains only DMSO. After 24 h incubation at 37ºC in a humidified atmosphere of 5% CO_2, the medium were replaced with MTT solution (100µl, 1mg per ml in sterile Hank's balanced solution) for further 4 h incubation. The supernatant carefully aspirated, the precipitated crystals of "Formazan blue' were solubalised by adding DMSO (200µl) and optical density was measured at wavelength of 570nm. The result were represents the mean of three readings. Results are calculated by considering concentration at which the optical density of treated cells was reduced by 50% with respect to the untreated control.

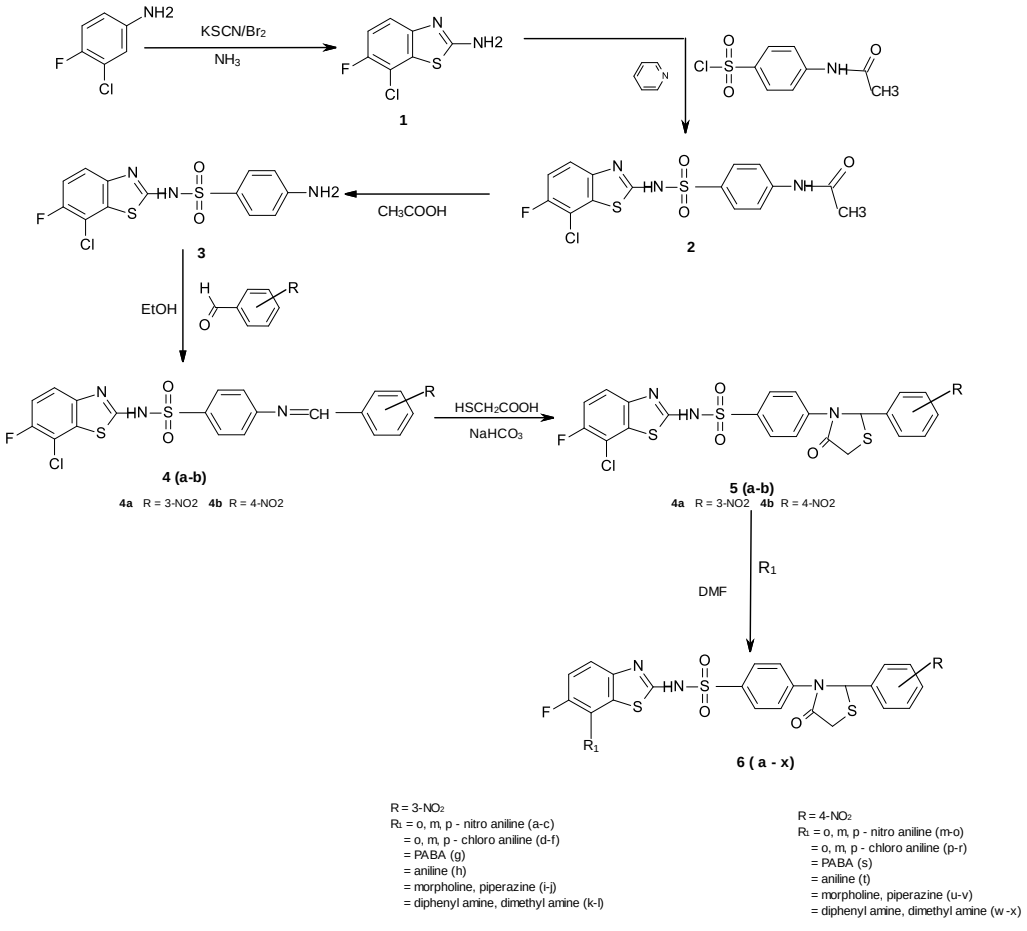

Fig-1: General scheme for synthesis of N-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamides 6 (a-l) and N-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamides 6 (m-x)

RESULTS

Anti-mycobacterial activity

All the test compounds were assayed for in vitro anti-mycobacterial activity evaluated against H37 Rv strain of M. tuberculosis strain using standard protocol [26]. The minimum inhibitory concentration (MIC) was determined by the test tube dilution technique using modified Kirchner's culture medium

containing 0.5% sterilized horse serum for anti-mycobacterial activity. The MIC values were also tested for standard antibiotics rifampin and isoniazide (INH) to compare the anti-mycobacterial activity of test compounds. All experiments were performed in triplicate. The lowest concentration, which showed no visible growth, was taken as the end point i.e. minimum inhibitory concentration (MIC).

Anti-cancer activity [27-29]

In vitro cytotoxicity studies were carried out on human cells using Hela- Human cervix, K-562 – Human chronic myelogenous Leukemia bone marrow and HEK 293 – Human Kidney cells. Cell suspension (100 µl x 10^{-6} cells per ml) was transferred to each cell of a 96 well plates. Cell viability was determined after 24 h at 37º in a humidified 5% CO_2 atmosphere by the Microculture Tetraolium Assay (MTT) method [30]. In vitro growth inhibition effect of test compounds were assessed by calorimetric or spectrophotometric determination of conversion of MTT into "Formazan blue" by living cells. DMSO was used as a control. The optical density were noted at 570 nm and compared with control. The results are expressed as % cell death at different concentrations.

DISCUSSION

In present study, novel N-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide derivatives **6 (a-l)** and N-[6-fluoro-7-substituted-1,3-benzothiazol-2-yl]-4-[2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl]benzenesulphonamide derivatives **6 (m-x)** were synthesized and characterized using various analytical and spectral studies. All new compounds tested for their in vitro anti-mycobacterial activity using standard protocol. The MIC values of the test compounds are summarized in Table II. For comparison, the MICs of standard compounds rifampicin and isoniazide are also tabulated. The results revealed that the test compounds **6 (a-x)** exhibit remarkable anti-mycobacterial activities against H37Rv strain of M. tuberculosis. The MIC values are in the range of 13 – 27. Some selected three new synthesized compounds were screened for their anti-cancer activity using 3-cell line study. Percentage surviving cells were calculated using MTT assay method. Hela- Human cervix, K-562 – Human chronic myelogenous Leukemia bone marrow and HEK 293 – Human Kidney cells were used for 3-cell line study. All three viz. 6k, 6r and 6t showed lyses (cytotoxic) against Hela- Human cervix cell and also showed less surviving cell percentage in all 10µl, 20µl, and 30µl concentration using MTT assay method. Compound 6k and 6r showed 50% lyses (active) and 50% less surviving cell percentage against K-562 and HEK 293 cells in 30µl concentration using MTT assay method. All 6k, 6r and 6t compounds in all concentrations except 30 µl (compound B_6) were found inactive in cytotoxic activity where no lyses found. Cytotoxicity of the compounds were compared with standard anti-cancer drugs viz. cisplatin and vincristine. Anticancer activity of test compounds is tabulated in Table III, IV and V.

Table 1: Physical and analytical data of compounds

Compound	R	R'	Molecular Formula	MP	Yield	Mass [M+1]
6a	3-Nitro	o-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	180	72	667
6b	3-Nitro	m-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	132	78	667
6c	3-Nitro	p-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	97	83	667
6d	3-Nitro	o-chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	170	88	656
6e	3-Nitro	m- chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	125	70	656
6f	3-Nitro	p- chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	82	80	656
6g	3-Nitro	PABA	$C_{29}H_{20}FN_5O_7S_3$	90	89	667
6h	3-Nitro	Aniline	$C_{28}H_{20}FN_5O_5S_3$	80	72	622
6i	3-Nitro	N-morpholine	$C_{26}H_{22}FN_5O_6S_3$	145	67	616
6j	3-Nitro	N-piperazine	$C_{26}H_{23}FN_6O_5S_3$	110	72	615
6k	3-Nitro	N,N-diphenyl amine	$C_{34}H_{24}FN_5O_5S_3$	280	68	698
6l	3-Nitro	N,N-dimethyl amine	$C_{24}H_{20}FN_5O_5S_3$	101	74	574
6m	4-Nitro	o-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	110	78	667
6n	4-Nitro	m-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	156	89	667
6o	4-Nitro	p-nitro aniline	$C_{28}H_{19}FN_6O_7S_3$	125	76	667
6p	4-Nitro	o-chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	90	75	656
6q	4-Nitro	m- chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	115	82	656
6r	4-Nitro	p- chloro aniline	$C_{28}H_{19}ClFN_5O_5S_3$	142	89	656
6s	4-Nitro	PABA	$C_{29}H_{20}FN_5O_7S_3$	92	79	667
6t	4-Nitro	Aniline	$C_{28}H_{20}FN_5O_5S_3$	120	62	622
6u	4-Nitro	N-morpholine	$C_{26}H_{22}FN_5O_6S_3$	165	87	616
6v	4-Nitro	N-piperazine	$C_{26}H_{23}FN_6O_5S_3$	188	82	615
6w	4-Nitro	N,N-diphenyl amine	$C_{34}H_{24}FN_5O_5S_3$	210	56	698
6x	4-Nitro	N,N-dimethyl amine	$C_{24}H_{20}FN_5O_5S_3$	156	76	574

Table 2: Anti-mycobacterial activity of test compounds

Compounds	H37RV strain of *M. tuberculosis* 21 days MIC values
6a	23
6b	25
6c	24
6d	15
6e	13
6f	17
6g	21
6h	18
6i	14
6j	14
6k	14
6l	14
6m	20
6n	22
6o	27
6p	23
6q	22
6r	18
6s	20
6t	21
6u	20
6v	17
6w	16
6x	23
Rifampicin (Std 1)	0.25
Isoniazide (Std 2)	0.007

Table 3: Anti-cancer activity of test compounds

Compounds	Conc.	Human Cell Lines		
		HeLa	K – 562	HEK – 293
6k	10 µl	Lyses	No Lyses	No Lyses
	20 µl	Lyses	No Lyses	No Lyses
	30 µl	Lyses	No Lyses	Lyses
6r	10 µl	Lyses	No Lyses	No Lyses
	20 µl	Lyses	No Lyses	No Lyses
	30 µl	Lyses	50% Lyses	50% Lyses
6t	10 µl	Lyses	No Lyses	No Lyses
	20 µl	Lyses	No Lyses	No Lyses
	30 µl	Lyses	No Lyses	No Lyses

No Lyses: No cytotoxic Activity
Lyses: Cytotoxic Activity

Table 4: Optical density of test compounds

		Observed O. D. (at 570 nm)		
Compounds	Conc.	HeLa	K – 562	HEK – 293
6k	10 µl	1.32 (55.0%)	2.18(83.84%)	1.68(62.22%)
	20 µl	1.45(60.41%)	2.15 (82.69%)	1.64(60.74%)
	30 µl	1.52(63.33%)	2.0(76.92%)	1.53(56.66%)
6r	10 µl	1.38(57.5%)	2.17(83.46%)	2.51(92.96%)
	20 µl	1.35(56.25%)	1.96(75.38%)	2.48(91.85%)
	30 µl	1.36(56.66%)	1.78(68.46%)	1.82(67.40%)
6t	10 µl	1.41(58.75%)	2.54(97.69%)	2.42(89.62%)
	20 µl	1.40(58.33%)	2.51(97.53%)	2.10(77.77%)
	30 µl	1.38(57.50%)	2.46(94.61%)	1.96(72.59%)
DMSO	---	2.4	2.6	2.7

Table 5: MTT assay of test compounds

		MTT assay (In %)		
Compounds	Conc.	HeLa	K – 562	HEK – 293
6k	10 µl	55.00%	83.84%	62.22%
	20 µl	60.41%	82.69%	60.74%
	30 µl	63.33%	76.92%	56.66%
6r	10 µl	57.50%	83.46%	92.96%
	20 µl	56.25%	75.38%	91.85%
	30 µl	56.66%	68.46%	67.40%
6t	10 µl	58.75%	97.69%	89.62%
	20 µl	58.33%	97.53%	77.77%
	30 µl	57.50%	94.61%	72.59%

ACKNOWLEDGEMENTS

We gratefully thankful to Dr. Kishore G. Bhat, Professor and Head, Department of Microbiology, Maratha Mandal's N.G.H. Institute of Dental Sciences and Research centre, Belgaum for his assistance during the anti-cancer testing and also thankful to Dr. A. S. Bobde, Haffkine Institute, Mumbai for providing testing facilities for Anti-mycobacterial activity.

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