Synthesis, Molecular Docking and Antimicrobial Evaluation of Some Benzothiazoles

Smita J. Pawar (✉ smitapawar4477@yahoo.co.in)

PDEA's Seth Govind Raghunath Sable College of Pharmacy <https://orcid.org/0000-0002-1103-5781>

Amol Kale

PDEA's Seth Govind Raghunath Sable College of Pharmacy Saswad

Priya Zori

PDEA's Seth Govind Raghunath Sable College of pharmacy Saswad

Rahul Dorugade

PDEA's Seth Govind Raghunath Sable College of pharmacy saswad

Research Article

Keywords: Benzothiazole, acetamide, DNA gyrase, antimicrobial

Posted Date: February 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-225494/v1>

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Abstract

Abstract The new series of 2-(substituted amino)-N-(6- substituted-1,3-benzothiazol-2-yl) acetamide BTC(a-t) has been synthesized by appropriate synthetic route from substituted 2-amino benzothiazole. The synthesized compounds were screened experimentally for its antimicrobial property against gram positive, gram negative bacteria and fungi. Zone of inhibition and minimum inhibitory concentration of compounds was determined against selected bacterial and fungal strains. Compound BTC-j N-(6-methoxy-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide and compound BTC-r N-(6-nitro-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide found to have good antimicrobial potential. The compound BTC-j has shown good antibacterial activity against *S. aureus* at MIC of 12.5 µg/ml, *B. subtilis* at MIC of 6.25µg/ml, *E. coli* at MIC of 3.125µg/ml and *P. aeruginosa* at MIC of 6.25µg/ml. No statistical difference in antimicrobial activity of standard and test compounds was found indicating test compounds have comparable activity. Further docking study was carried out to check the probable interactions with the selected protein using V-life MDS 3.5 software. (DNA gyrase, PDB: 3G75). The dock score of compounds and antimicrobial activity found to be consistent.

Introduction

The emergence and spread of resistance are one of the important problems which is needed to be consider as early as possible. This resistance development has limited the selection of antimicrobials to treat the disease. As the incidences of multidrug resistance increases and number of newer drugs that reaches to market are very less. This situation shows the urgent necessity of newer drugs in market.

Benzothiazoles are important class of heterocyclic compounds possessing significant biological activities and interesting chemical features. Various benzothiazole derivatives are reported to possess broad spectrum of biological activities such as antimicrobial [1-6], antitubercular [7-8], anticancer [9-10], anticonvulsant [11-12], antidiabetic [13-14], antiviral [15] and anti-inflammatory [16]. Benzothiazole also showed antimicrobial activity through inhibition of DNA gyrase [17-18]. Various amino derivatives of pyrimidine [19], pyridine [20], benzamide [21] also possessing an antimicrobial activity.

DNA gyrase is classified as topoisomerase II, enzyme that play crucial role in the transcription and replication process of DNA molecule. It plays a vital role in all type of bacteria except higher eukaryotes and which makes DNA gyrase as attractive targets for designing new antimicrobial drugs [22].

Material And Methods

2.1. Chemistry

All the chemicals and reagents used for synthesis were of laboratory grade. The completion of the reaction and purity of all the synthesized compounds was supervised by using chromatography technique. Shimadzu FTIR 8400S was used to record IR spectra by using KBr and the NMR spectra were recorded in NMR Varian-Mercury 300 MHz spectrometer in CDCl₃ and values are expressed in ppm.

2.2. General synthetic procedures

The general reaction sequence for different title compounds is outlined in Scheme 1.

2.2.1. General synthetic procedure for 6-substituted-2-aminobenzothiazoles (BT 1-5)

Method A: BT 1

To 25 ml (0.02mol) Aniline, 25 ml conc. hydrochloric acid was added in a 250 ml beaker and the solution was heated till it becomes warmed. A saturated solution of ammonium thiocyanate in water was prepared and added slowly to the above and boiled until the solution become turbid. The turbid solution was poured into cold water with continuous stirring. Phenylthiourea, separated as precipitate was filtered and recrystallized from aqueous ethanol (80%). To 250 ml round bottom flask containing 75 ml of chloroform, phenylthiourea (0.098mol) was added and stirred it. Bromine in chloroform (5%) was added dropwise to above suspension till an orange-yellow colour appeared, the temperature was maintained at 0-5°C. The reaction mixture was stirred overnight (20 h). The precipitate obtained was filtered and washed with chloroform until the colour disappeared. This precipitate, the hydrobromide salt, was dissolved in acidified water (5% HCl) and basified with concentrated ammonia solution. The precipitate obtained was filtered, dried and recrystallized using ethanol and water mixture [23].

Method B: BT 2-5

To a 250 ml round bottom flask, ammonium thiocyanate (11.93 gm, 0.156mol) and 100 ml acetic acid was added and it was stirred until ammonium thiocyanate dissolved completely. Aniline (10 gm, 0.078mol) was added to above solution. To this, Bromine solution (0.02mol) in acetic acid was added to the reaction mixture maintained at temperature 0-5°C till an orange-yellow colour appeared. The slurry was kept overnight (20 h). Filtered the reaction mixture, precipitate obtained was dissolved in water (200 ml) and filtered to remove any undissolved matter and this filtrate was basified with concentrated ammonia solution. The precipitate obtained was filtered, dried and recrystallized using ethanol: water (80:20) mixture [24].

2-aminobenzothiazole/ 1,3-benzothiazol-2-amine **BT-1**: yield 62%; White coloured solid; mp 124-126°C; ¹H NMR (CDCl₃, 500 MHz) δ: 6.92-7.79 (m, 4H, Ar-H), 4.22 (s, 2H, NH₂); IR (KBr): 3396.7, 3132.5, 1683, 1640.2, 1278, 811 cm⁻¹.

6-methyl-1,3-benzothiazol-2-amine **BT-2**: yield 70%; Buff coloured solid; mp 140-144°C; ¹H NMR (CDCl₃, 500 MHz) δ: 7.21-7.83 (m, 3H, Ar-H) 3.89 (s, 2H, NH₂), 2.32 (s, 3H, CH₃); IR (KBr): 3390, 3005, 2938, 1625, 1531, 1275, 814 cm⁻¹.

6-methoxy-1,3-benzothiazol-2-amine **BT-3**: yield 72%; Shiny brown coloured solid; mp 158-160°C; ¹H NMR (CDCl₃, 500 MHz) δ: 7.17-8.04 (m, 3H, Ar-H), 3.97 (s, 2H, NH₂), 3.75 (s, 3H, OCH₃); IR(KBr): 3340, 3010, 2890, 1629, 1545, 1224, 1150, 813 cm⁻¹

6-chloro-1,3-benzothiazol-2-amine **BT-4**: yield 73%; White coloured solid; mp 198-200°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 7.11-7.69 (m, 3H, Ar-H), 4.09 (s, 2H, NH_2); IR (KBr): 3420, 3020, 1645, 1541, 1220, 809, 715 cm^{-1} .

6-nitro-1,3-benzothiazol-2-amine **BT-5**: yield 75%; Bright yellow coloured solid; mp 245-247°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 7.04-7.75 (m, 3H, Ar-H), 4.16 (s, 2H, NH_2); IR (KBr): 3470, 3012, 1616, 1555, 1535, 1265 cm^{-1} .

2.2.2. General synthetic procedure for 2-Chloro-N-(6-substituted-1,3-benzothiazol-2-yl) acetamide **BTC (1-5)**

To 250 ml round bottom flask, a suspension of the substituted 2-amino benzothiazole BT (1-5) (0.005mol), anhydrous Potassium carbonate (2.5 gm) and 1ml of TEA in dry chloroform (65 ml) was taken. To above suspension, chloroacetylchloride (0.006mol) was added and the mixture was refluxed for 4-5 hrs. The solvent was then evaporated and the resulting solid was washed with cold water and recrystallized using ethanol: water (80:20) mixture affording N-chloroacetyl derivatives **BTC (1-5)** [25].

N-(1,3-benzothiazol-2-yl)-2-chloroacetamide **BTC-1**: yield 72%; Cream coloured solid; mp 165-167°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 11.19 (s, 1H, CONH), 7.38-8.11 (m, 4H, Ar-H), 4.32 (s, 2H, CH_2); IR (KBr): 3012.5, 1670.4, 1612.8, 1555.2, 1460.3, 1354.7, 1275.8, 725.3 cm^{-1} .

2-chloro-N-(6-methyl-1,3-benzothiazol-2-yl) acetamide **BTC-2**: yield 77%; Light cream coloured solid; mp 184-186°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 11.34 (s, 1H, NH), 7.26-7.82 (m, 3H, Ar-H), 4.35 (s, 2H, CH_2), 2.17 (s, 3H, CH_3); IR (KBr): 3042.6, 1681.9, 1550.8, 1465.9, 1334.78, 1273, 709.8 cm^{-1} .

2-chloro-N-(6-methoxy-1,3-benzothiazol-2-yl) acetamide **BTC-3**: yield 75%; Light brown coloured solid; mp 172-174°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 12.84 (s, 1H, NH), 7.28-7.81 (m, 3H, Ar-H), 4.2 (s, 2H, CH_2), 3.7 (s, 3H, OCH_3); IR (KBr): 3078.4, 1666.5, 1604.8, 1550.8, 1465.9, 1348.3, 1265.3, 721.2 cm^{-1} .

2-chloro-N-(6-chloro-1,3-benzothiazol-2-yl) acetamide **BTC-4**: yield 70%; Cream coloured solid; mp 208-210°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 10.83 (s, 1H, CONH), 7.63-8.11 (m, 3H, Ar-H), 4.69 (s, 2H, CH_2); IR (KBr): 3033.20, 1664.2, 1640.2, 1582.2, 1567.1, 1371.1, 1278.5, 730.1 cm^{-1} .

2-chloro-N-(6-nitro-1,3-benzothiazol-2-yl) acetamide **BTC-5**: yield 64%; Light brown coloured solid; mp 180-182°C; ^1H NMR (CDCl_3 , 500 MHz) δ : 11.24 (s, 1H, CONH), 7.20-7.66 (m, 3H, Ar-H), 4.14 (s, 2H, CH_2); IR (KBr): 3041.2, 1675.2, 1638.1, 1534, 1525, 1521, 1350, 1268.3, 722.3 cm^{-1} .

2.2.3. General synthetic procedure for 2-(substituted amino)-N-(6-substituted-1,3-benzothiazole-2-yl) acetamide **BTC (a-t)**

To a solution of 2-chloro-N-(6-substituted-1,3-benzothiazol-2-yl) acetamide BTC (1-5) (0.005mol) and amino derivatives (0.005mol) in dry chloroform was taken in 250 ml round bottom flask and refluxed for 1-2 hrs. The solvent was evaporated and resulting solid was washed with cold water. The solid thus obtained was purified by recrystallization using appropriate solvent gave corresponding BTC (a-t) with 50-70% yield [25].

N-(1,3-benzothiazol-2-yl)-2-(pyrimidin-2-yl amino) acetamide **BTC a**: yield 60% ; cream coloured solid ; mp 208-210 °C ; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 11.5 (s, 1H, NH), 6.9-8.6(m, 7H, Ar-H), 6.5(s, 1H, NH), 4.02(s, 2H, CH_2); IR(KBr): 3371.6, 3140.2, 1767.1, 1735.9, 1651.1, 1566.2, 1315.8 cm^{-1} .

N-(1,3-benzothiazol-2-yl)-2-(pyridin-2-yl amino) acetamide **BTC b**: yield 53%; Brown coloured solid; mp 186-188 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 11.31(s, 1H, NH), 6.5-8.6(m, 8H, Ar-H), 4.5(s, 1H, NH), 3.8(s, 2H, CH_2); IR (KBr): 3201.9, 3001.3, 2970.4, 1666.5, 1627.9, 1589.4, 1538.3, 1290.7 cm^{-1} .

N-[2-(1,3-benzothiazol-2-ylamino)-2-oxoethyl] pyridine-3-carboxamide **BTC c**: yield 67%; light cream coloured solid; mp 190-192 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 12.28(s, 1H, NH), 8.59(s, 1H, NH), 7.39-8.0(m, 8H, Ar-H), 3.81(s, H, CH_2); IR(KBr): 3321.1, 3110, 1778, 1614.1, 1568.1, 1554.5, 1321.2 cm^{-1} .

N-[2-(1,3-benzothiazol-2-ylamino)-2-oxoethyl] benzamide (BTC d): yield 55%; light cream coloured solid; mp 122-124 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ :12.5(s, 1H, NH), 8.1(s, 1H, NH), 7.39-7.87(m, 9H, Ar-H), 4.1 (s, 2H, CH_2) ; IR (KBr): 3301.1, 3082.4, 2905.1, 1687.5, 1628.2, 1528.2, 1527.5, 1285.1 cm^{-1} .

N-(6-methyl-1,3-benzothiazol-2-yl)-2-(pyrimidin-2-ylamino) acetamide **BTC e**: yield 52%; Brown coloured solid; mp 236-238 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ :12.3 (s, 1H, NH), 7.39-8.3 (m, 6H, Ar-H), 6.5 (s, 1H, NH), 3.86 (s, 2H, CH_2), 2.33 (s, 3H, CH_3); IR (KBr): 3011.1, 2949, 1625.3, 1625, 1519.2, 1515.2, 1280.9 cm^{-1} .

N-(6-methyl-1,3-benzothiazol-2-yl)-2-(pyridin-3-ylamino) acetamide **BTC f**: yield 64%; Cream coloured solid; mp 125-127 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 12.35 (s, 1H, NH), 7.13-7.87 (m, 7H, Ar-H), 4.44 (s, 1H, NH), 4.0 (s, 2H, CH_2), 2.6 (s, 3H, CH_3) ; IR (KBr): 3011.2, 2958.4, 1649.8, 1547.3, 1525, 1520.2, 1270 cm^{-1} .

N-[2-[(6-methyl-1,3-benzothiazol-2-yl) amino]-2-oxoethyl] pyridine-3-carboxamide **BTC g**: yield 50 %; Pale yellow coloured solid; mp 220-222 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ : 12.4 (s, 1H, NH), 8.6 (s, 1H, NH), 7.12-7.87 (m, 7H, Ar-H), 4.0 (s, 2H, CH_2), 2.66 (s, 3H, CH_3) ; IR (KBr): 3117, 2978.1, 1645.5, 1535.2, 1515.2, 1465, 1288.4 cm^{-1} .

N-[2-[(6-methyl-1,3-benzothiazol-2-yl) amino]-2-oxoethyl] benzamide **BTC h**: yield 65%; Pale yellow coloured solid; mp 203-205 °C; ^1H NMR (DMSO- d_6 , 500 MHz) δ :12.45 (s, 1H, NH), 8.6 (s, 1H, NH), 7.13-8.6 (m, 8H, Ar-H) 4.0 (s, 2H, CH_2), 2.8 (s, 3H, CH_3) ; IR (KBr): 3110.1, 3058.1, 1757.1, 1732.9, 1651.1, 1599.2, 1318.3 cm^{-1} .

N-(6-methoxy-1,3-benzothiazol-2-yl)-2-(pyrimidin-2-ylamino) acetamide **BTC i**: yield 60%; Brown coloured solid; mp 260-264 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.49 (s, 1H, NH), 7.0-8.9 (m, 6H, Ar-H), 6.7 (s, 1H, NH), 4.5 (s, 3H, OCH₃), 3.7 (s, 2H, CH₂); IR (KBr): 3183.2, 3029.1, 2990.2, 1798.6, 1665.1, 1628.1, 1515.6, 1260.3, 1027 cm⁻¹.

N-(6-methoxy-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide **BTC j**: yield 50%; Light cream coloured solid; mp 189-192 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.72 (s, 1H, NH), 7.12-8.32 (m, 7H, Ar-H), 6.5 (s, 1H, NH), 4.5 (s, 3H, OCH₃), 4.0 (s, 2H, CH₂); IR (KBr): 3294.5, 3000, 2910.4, 1666.5, 1620.2, 1535.3, 1498.2, 1288.4, 1049.3 cm⁻¹.

N{2-[(6-methoxy-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} pyridine-3-carboxamide **BTC k**: yield 52%; Light cream coloured solid; mp 169-198 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.87 (s, 1H, NH), 9.5 (s, 1H, NH), 7.12-8.32 (m, 7H, Ar-H), 4.44 (s, 3H, OCH₃), 4.06 (s, 3H, CH₂); IR (KBr): 3274, 3069, 2989.2, 1655.7, 1620, 1598.6, 1515.6, 1267, 1019.5 cm⁻¹.

N{2-[(6-methoxy-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} benzamide **BTC l**: yield 70%; Light yellow coloured solid; mp 142-144 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.0 (s, 1H, NH), 8.32 (s, 1H, NH), 7.12-8.0 (m, 8H, Ar-H), 4.06 (s, 2H, CH₂), 3.80 (s, 3H, OCH₃); IR (KBr): 3317.3, 3066.2, 2975.2, 1645.9, 1620.2, 1519.3, 1448.2, 1270.4, 1039.1 cm⁻¹.

N-(6-chloro-1,3-benzothiazol-2-yl)-2-(pyrimidin-2-ylamino) acetamide **BTC m**: yield 55%; Brown coloured solid; mp 17.-172 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 13.01, (s, 1H, NH), 6.7-8.9 (m, 6H, Ar-H), 5.5 (s, 1H, NH), 3.83 (s, 3H, CH₂); IR (KBr): 3099.8, 2897.6, 1660.5, 1638.2, 1567.4, 1524.3, 1268.1 cm⁻¹.

N-(6-chloro-1,3-benzothiazol-2-yl)-2-(pyridin-3-ylamino) acetamide **BTC n**: yield 65%; Light cream coloured solid; mp 123-126 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.5 (s, 1H, NH), 6.7-8.9 (m, 7H, Ar-H), 6.00 (s, 1H, NH), 4.0 (s, 2H, CH₂); IR (KBr): 3090.5, 2925.1, 1660.1, 1659.2, 1548, 1525.24, 1269.28 cm⁻¹; MS m/z: 320 [M-Cl]⁺.

N{2-[(6-chloro-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} pyridine-3-carboxamide **BTC o**: yield 60%; Light cream coloured solid; mp 238-240 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.59 (s, 1H, NH), 8.6 (s, 1H, NH), 7.39-7.99 (m, 7H, Ar-H), 3.85 (s, 2H, CH₂); IR (KBr): 3026.1, 2918.1, 1666.5, 1620.2, 1538.3, 1512.2, 1268.1 cm⁻¹.

N{2-[(6-chloro-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} benzamide **BTC p**: yield 70%; Light yellow coloured solid; mp 226-229 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.28 (s, 1H, NH), 8.4 (s, 1H, NH), 7.39-8.2 (m, 8H, Ar-H), 3.85 (s, 2H, CH₂); IR (KBr): 3009, 2877.8, 1797.1, 1712.8, 1651.1, 1558.5, 1303.9 cm⁻¹.

N-(6-nitro-1,3-benzothiazol-2-yl)-2-(pyrimidin-2-yl amino) acetamide **BTC q**: yield 62%; Yellow coloured solid; mp 198-201 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.3 (s, 1H, NH), 8.59 (s, 1H, NH), 7.12-8.0 (m, 6H,

Ar-H), 4.06 (s, 2H, CH₂); IR (KBr): 3294.5, 3000, 2911.8, 1791.1, 1712.8, 1651.1, 1558.5, 1465.9, 1309.8 cm⁻¹.

N-(6-nitro-1,3-benzothiazol-2-yl)-2-(pyridin-2-yl amino) acetamide **BTC r**: yield 60%; Cream coloured solid; mp 123-125 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.53 (s, 1H, NH), 7.12-7.87 (m, 7H, Ar-H), 4.44 (s, 1H, NH), 3.84 (s, 2H, CH₂); IR (KBr): 3394.8, 3015.2, 2918.1, 1666.5, 1620.2, 1553.3, 1512.2, 1435, 1268.1 cm⁻¹.

N-(2-[(6-nitro-1,3-benzothiazol-2-yl) amino]-2-oxoethyl) pyridine-3-carboxamide **BTC s**: yield 65%; Yellow coloured solid; mp 248-250 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.45 (s, 1H, NH), 8.32 (s, 1H, NH), 7.39-8.6 (m, 7H, Ar-H), 4.06 (s, 2H, CH₂); IR (KBr): 3314.3, 3080.2, 2900.1, 1660.5, 1637.2, 1555.3, 1522.1, 1428.2, 1254.2 cm⁻¹.

N-(2-[(6-nitro-1,3-benzothiazol-2-yl) amino]-2-oxoethyl) benzamide **BTC t**: yield 65%; Yellow coloured solid; mp 240-242 °C; ¹H NMR (DMSO-d₆, 500 MHz) δ: 12.6 (s, 1H, NH), 8.06 (s, 1H, NH), 7.39-8.59 (m, 8H, Ar-H), 4.5 (s, 1H, CH₂); IR (KBr): 3300.1, 3074.1, 2968.2, 1630.6, 1621, 1598, 1564.1, 1445.3, 1227.9 cm⁻¹.

2.3. Biological Activity Evaluation

All target compounds, **BTC(a-t)** were screened for their antibacterial, antifungal activity. The synthesized compounds were evaluated for their antimicrobial activity against gram positive, gram negative bacteria and fungi by determining-

1. Zone of inhibition
2. Minimum Inhibitory Concentration (MIC)

The synthesized compounds were evaluated for their antibacterial activity against two-gram positive (*Staphylococcus aureus*, *Bacillus subtilis*) and two-gram negative bacteria (*E. coli*, *Pseudomonas aeruginosa*) by using ciprofloxacin as reference antibacterial agent. Antifungal activity was evaluated against *Candida albicans* and *Aspergillus niger*. fluconazole was used as reference drug. The microbial strains were collected from microbiology laboratory of Waghire college, saswad.

2.3.1. Zone of inhibition using cup plate method

The compounds were evaluated for the antibacterial activity by cup plate method. The results were recorded for each tested compound as average diameter of inhibition zone of bacterial and fungal growth around the cup in mm. The nutrient agar medium containing peptone (1%), beef extract (0.5%), sodium chloride (0.8%) and agar (2.5%) in distilled water. The solution was sterilized for 20 min in an autoclave at 15 psi pressure at 121°C. The basal medium 15-20 ml was poured in the sterile petri-dishes. After solidification of medium, the microorganisms were sub-cultured and then holes of 6mm diameter were bored. To these cups, concentration of 50, 100, 150 µg/ml of the test compounds were added by micropipette. Petri dishes were kept in refrigerator to facilitate the diffusion for about 2 h. These plates were then incubated at 37°C for 48 h. The extent of inhibition was determined by measuring the diameter

of the inhibition zone in mm. For antibacterial and antifungal study, the ciprofloxacin 150 µg/ml and 150 µg/ml of fluconazole were used as reference drugs respectively.

2.3.2. Minimal inhibitory concentration using two folds dilution method (MIC)

The broth dilution was performed by using microtiter plates. The nutrient broth was prepared using peptone (1%), beef extract (0.5%), sodium chloride (0.8%). It was added in microtiter plates except first well. First well of microtiter plate was used to check the sterility of the medium as negative control in which inoculum was not added. Stock solution of test compounds was prepared in DMSO (200µg/ml) followed by twofold dilution at concentrations of (100, 50, 25....3.125 µg/ml). The inoculums were added to the other all wells containing test compounds ranging from 100, 50, 25....3.125 µg/ml. The micro titer plates were then incubated at 37°C for 24 h for bacteria and 48 h for fungi and minimal inhibitory concentration were measured for the growth in the form of turbidity. The ciprofloxacin (150µg/ml) was used as reference drug for antibacterial study while fluconazole (150µg/ml) was used for antifungal study [26].

2.4. Molecular Docking

To check the type of interactions exists between the enzyme and the ligand the docking study is a promising tool. The prediction of predominant binding modes of a ligand with a protein of known three-dimensional structure is one of the important goals of ligand-protein docking. In present study, V Life MDS 3.5 software was used for docking purpose [27-31]. The structure of DNA gyrase protein (PDB: 3G75) was obtained from Protein Data Bank (<http://www.rcsb.org>).

Results And Discussion

The compounds BT (1-5) were prepared as per reported scheme 1. 4-substituted anilines (BT 1-5) were reacted with ammonium thiocyanate and bromine in acetic acid by stirring. The reaction mainly involves formation of intermediate phenylthiourea and cyclisation of phenylthiourea gives 6-substituted 2-amino benzothiazole. The target compounds BTC(a-t) were synthesized by the scheme indicated in scheme 1. The compounds were prepared by refluxing solution of BTC (1-5) and amino derivatives. The synthesized compounds structures were confirmed by spectral analysis using ¹H NMR, IR and Mass were found consistent with the spectral data. IR spectra of BTC(a-t) showed characteristic aromatic CH stretch between 3140-3000 cm⁻¹. The C=N is seen at 3394-3201 cm⁻¹. The carbonyl (C=O) peak is observed between at 1778-1625 cm⁻¹. The absence of C-Cl stretch in the IR spectrum also confirms the formation of 2-(substituted amino)-N-(6-substituted-1,3-benzothiazol-2-yl) acetamide BTC (a-t)

¹H NMR of synthesized compounds are taken in DMSO. Which shows sharp solvent peak at 2.5 and 3.38 ppm. The compounds display aromatic protons between 6.6-8.5 ppm. The compound revealed a characteristic N-H proton of amide around 10.28-12.59 ppm and presence of singlet for N-H proton of substituted amines between 4.5-8.6ppm confirmed the formation of target compounds.

3.1. Antimicrobial activity

The minimum inhibitory concentration of BTC (a-t) compounds was determined using a double dilution method. Cup plate method was used to determine the zone of inhibition. Ciprofloxacin and fluconazole were used as standard drugs for antibacterial and antifungal activity respectively.

The synthesized compounds were evaluated for antibacterial activity by using gram positive bacteria: *B. subtilis*, *S. aureus*, gram negative bacteria: *E. coli*, *P. aeruginosa* and antifungal activity by using *A. niger* and *C. albicans*.

The results of antibacterial activity presented in **Table 1** indicated that all the tested compounds exhibited significant activity.

The in vitro antimicrobial screening data of the synthesized compounds indicate that all the compounds showed good to moderate activity except compound BTC-a, BTC-h and BTC-p. The compound **BTC-a** N-(1,3-benzothiazol-2-yl)-2-(pyrimidin-2-yl amino) acetamide show least activity against gram-negative bacteria while compounds **BTC-h** N-{2-[(6-methyl-1,3benzothiazol-2-yl) amino]-2-oxoethyl} benzamide and **BTC-p** N-{2-[(6-chloro-1,3-benzothiazol2-yl) amino]-2-oxoethyl} benzamide are less active against gram-positive bacteria.

Compound **BTC-j** N-(6-methoxy-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide and compound **BTC-r** N-(6-nitro-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide showed the good activity.

The compound **BTC-j** has shown good antibacterial activity against *S. aureus* at MIC of 12.5 µg/ml, *B. subtilis* at MIC of 6.25 µg/ml, *E. coli* at MIC of 3.125µg/ml and *P. aeruginosa* at MIC of 6.25 µg/ml.

The compound **BTC-j** also shown good antifungal activity against *A. niger* and *C. albicans* at MIC of 3.125 and 6.25 µg/ml respectively.

Table 1 Minimum inhibitory concentration (MIC) of 2-(substituted amino)-N-(6-substituted-1,3-benzothiazo-2yl) acetamide BTC (a-t)

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>A. niger</i>	<i>C. albicans</i>
Ciprofloxacin	6.25	12.5	3.125	3.125	6.25	12.5
/Fluconazole						
a	100	50	50	50	100	100
b	50	50	12.5	12.5	50	25
c	50	50	25	25	25	25
d	50	50	12.5	50	50	50
e	100	50	50	50	50	100
f	12.5	12.5	6.25	6.25	6.25	25
g	25	25	50	25	50	25
h	50	50	25	50	25	50
i	50	50	25	50	50	50
j	12.5	6.25	3.125	6.25	3.125	6.25
k	25	50	50	50	50	50
l	50	50	25	25	25	50
m	50	50	50	50	100	50
n	12.5	12.5	12.5	6.25	25	25
o	25	50	50	25	12.5	50
p	50	100	100	50	100	100
q	100	50	50	25	100	25
r	12.5	12.5	6.25	6.25	6.25	6.25
s	25	25	25	12.5	12.5	6.25
t	50	50	50	50	50	25

MIC given in µg/ml

Zone of inhibition of synthesized compounds BTC (a-t)

For BTC (a-t) zone of inhibition against gram positive bacteria was observed using cup plate method. Ciprofloxacin was used as reference drug and the zone of inhibition observed for gram positive (*S. aureus* and *B. subtilis*) and gram-negative (*E. coli* and *P. aeruginosa*) bacteria are shown in Table 2 and 3 respectively.

Table 2 Zone of inhibition of BTC (a-t) for gram positive bacteria

Sr. No.	Compound	Conc. (µg/ml)	Zone of inhibition (mm)	
			<i>S. aureus</i>	<i>S. aureus</i>
1	Ciprofloxacin	150	33.13±0.20	31.06±0.08
2	a	50	6.3±0.17	5.7±0.09
		100	8.3±0.02	8.6±0.13
		150	11.7±0.17	13.1±0.05
3	b	50	7.5±0.09	7.3±0.05
		100	10.5±0.26	11.3±0.06
		150	12.5±0.14	14.5±0.11
4	c	50	10.1±0.08	11.4±0.07
		100	15.1±0.15	16.3±0.08
		150	17.6±0.15	18.2±0.05
5	d	50	10.5±0.26	11.3±0.08
		100	12.4±0.16	14.1±0.12
		150	18.5±0.05	19.26±0.14
6	e	50	10.8±0.09	11.2±0.17
		100	16.2±0.17	15.4±0.06
		150	19.46±0.06	18.2±0.08
7	f	50	15.2±0.06	14.4±0.12
		100	18.5±0.10	17.6±0.14
		150	22.2±0.08	23±0.03
8	g	50	12.5±0.02	10.5±0.17
		100	15.2±0.12	15.4±0.21
		150	21.2±0.05	20.3±0.11
9	h	50	6.3±0.09	5.8±0.05
		100	8.3±0.05	7.6±0.17
		150	12.5±0.05	11.9±0.11
10	i	50	15.2±0.06	14.7±0.11
		100	18.5±0.10	17.6±0.14

		150	22.2±0.11	23.06±0.03
11	j	50	14.8±0.08	12.5±0.06
		100	20±0.11	17.8±0.05
		150	25.4±0.03	26.3±0.08
12	k	50	9.45±0.24	9.4±0.17
		100	14.4±0.06	15.6±0.12
		150	19.5±0.03	20.3±0.05
13	l	50	13.2±0.03	14.2±0.06
		100	16±0.50	18±0.1,2
		150	23.2±0.08	22.6±0.23
14	m	50	11.2±0.06	10.8±0.09
		100	15.1±0.15	16.3±0.17
		150	20.1±0.11	21.06±0.03
15	n	50	13.5±0.2	11.2±0.18
		100	16.2±0.12	16.4±0.21
		150	22.1±0.03	20.6±0.03
16	o	50	15.3±0.17	14.7±0.06
		100	18.2±0.03	17.6±0.09
		150	20.4±0.05	21.13±0.17
17	p	50	5.4±0.09	4.8±0.17
		100	7.8±0.17	7.3±0.05
		150	10.4±0.14	11.3±0.08
18	q	50	9±0.25	9.5±0.17
		100	13.5±0.06	14.2±0.12
		150	19.3±0.06	20±0.03
19	r	50	16.1±0.07	15.5±0.14
		100	19.6±0.02	18.2±0.19
		150	23.3±0.17	24.4±0.06
20	s	50	17±0.06	15.2±0.07

21	t	100	19.2±0.06	18.1±0.06
		150	22.9±0.03	23.8±0.11
		50	15.2±0.08	13.6±0.11
		100	17.5±0.10	18.2±0.08
		150	21.1±0.13	22.3±0.06

Zone of inhibition in mm, Conc.in µg/ml.

The compounds BTC-j and BTC-r have shown significant zone of inhibition amongst all 20 synthesized compounds. Compounds BTC-j was found to have comparable activity with ciprofloxacin at 150µg/ml against both of gram-positive bacteria. The compound BTC-p was found to be minimum acting among synthesized compounds.

Table 3 Zone of inhibition of BTC (a-t) for gram negative bacteria.

Sr. no	Compound	Conc. µg/ml	Zone of inhibition (mm)	
			<i>E. coli</i>	<i>P. aeruginosa</i>
1	Ciprofloxacin	150	30.4±0.31	31.8±0.31
2	a	50	6.6±0.17	5.3±0.28
		100	8.6±0.5	8.2±0.11
		150	10.1±0.2	11.2±0.12
3	b	50	11.6±0.12	13.3±0.17
		100	15.4±0.11	17.3±0.08
		150	20.7±0.08	21.5±0.26
4	c	50	11.2±0.20	13.9±0.18
		100	14.6±0.10	18.2±0.12
		150	19.7±0.12	20.3±0.16
5	d	50	10.6±0.12	12.2±0.10
		100	14.5±0.20	14.4±0.14
		150	20.3±0.08	21.4±0.05
6	e	50	10.6±0.17	14.3±0.18
		100	14.4±0.20	18.2±0.06
		150	19.2±0.03	20.5±0.14
7	f	50	10.8±0.08	12.2±0.08
		100	14.7±0.12	16.2±0.2
		150	20.6±0.17	21.3±0.05
8	g	50	13.1±0.1	13.3±0.17
		100	16.2±0.12	17.3±0.20
		150	20.7±0.14	20.5±0.0
9	h	50	10.2±0.10	11.3±0.20
		100	15.3±0.08	14.1±0.5
		150	17.6±0.17	18.2±0.17
10	i	50	9.5±0.10	13.2±0.06
		100	12.8±0.15	17.5±0.15

		150	18.3±0.05	19.2±0.11
11	j	50	14.9±0.11	16.2±0.01
		100	18.7±0.08	19.3±0.06
		150	26.5±0.11	27.3±0.05
12	k	50	11.9±0.33	13.2±0.15
		100	14.8±0.50	16.5±0.10
		150	20.3±0.10	21±0.05
13	l	50	15±0.5	16.4±0.06
		100	18.8±0.06	20.2±0.5
		150	21±0.23	22.13±0.03
14	m	50	17.4±0.02	18.4±0.20
		100	19.3±0.10	20.2±0.3
		150	22.2±0.11	23.2±0.05
15	n	50	11.2±0.33	12.4±0.2
		100	14.3±0.20	16.5±0.5
		150	18.06±0.03	19.23±0.06
16	o	50	11.4±0.50	13.5±0.3
		100	15.3±0.02	16.1±0.02
		150	19.36±0.03	19.5±0.17
17	p	50	10.3±0.20	10.9±0.10
		100	14±0.50	15.2±0.05
		150	16.4±0.08	18.1±0.0
18	q	50	17.3±0.06	18.6±0.10
		100	19.2±0.10	20.6±0.50
		150	20.1±0.03	22.4±0.11
19	r	50	16.2±0.6	18.1±0.06
		100	19.4±0.5	22.8±0.17
		150	23.1±0.03	24.1±0.05
20	s	50	17.1±0.33	16.3±0.5

21	t	100	19.3±0.12	19.1±0.17
		150	22.1±0.06	23.13±0.03
		50	12.1±0.25	13.6±0.10
		100	14.5±0.27	18.4±0.12
		150	20.3±0.11	22.2±0.03

Zone of inhibition in mm, Conc.in µg/ml.

Zone of inhibition study for gram negative bacteria shows that compounds BTC-j and BTC-r possess better zone of inhibition in comparison with reference drug ciprofloxacin among the twenty synthesized compounds. Compound BTC-j showed significant zone of inhibition and compound BTC-a possess least activity compared to reference drug.

Zone of inhibition of synthesized compounds BTC(a-t) was measured against two species of fungi. Fluconazole was used as reference drug. The observations are reported in **Table 4**

Table 4 Zone of inhibition of compounds BTC(a-t) against fungus species.

Sr. No	Compound	Conc. $\mu\text{g/ml}$	Zone of inhibition (mm)	
			<i>A. niger</i>	<i>C. albicans</i>
1	Fluconazole	150	25.06$\pm$0.08	23.06$\pm$0.08
2	a	50	8.4 $\pm$ 0.10	7.1 $\pm$ 0.10
		100	9.5 $\pm$ 0.06	8.2 $\pm$ 0.06
		150	10.5 $\pm$ 0.23	9.5 $\pm$ 0.11
3	b	50	10.2 $\pm$ 0.06	8.3 $\pm$ 0.05
		100	12.1 $\pm$ 0.02	9.3 $\pm$ 0.13
		150	12.2 $\pm$ 0.14	10.2 $\pm$ 0.17
4	c	50	7.0 $\pm$ 0.03	5.2 $\pm$ 0.06
		100	9.1 $\pm$ 0.08	7.4 $\pm$ 0.08
		150	11.1 $\pm$ 0.05	10.2 $\pm$ 0.08
5	d	50	9.2 $\pm$ 0.11	7.2 $\pm$ 0.06
		100	11.2 $\pm$ 0.05	8.2 $\pm$ 0.08
		150	12.1 $\pm$ 0.20	13.1 $\pm$ 0.05
6	e	50	13.2 $\pm$ 0.13	6.5 $\pm$ 0.05
		100	15.3 $\pm$ 0.10	8.0 $\pm$ 0.12
		150	18.3 $\pm$ 0.05	10.2 $\pm$ 0.03
7	f	50	12.9 $\pm$ 0.3	9.3 $\pm$ 0.08
		100	15.3 $\pm$ 0.05	10.3 $\pm$ 0.05
		150	17.1 $\pm$ 0.08	13.5 $\pm$ 0.20
8	g	50	9.2 $\pm$ 0.20	6.3 $\pm$ 0.02
		100	10.5 $\pm$ 0.12	7.2 $\pm$ 0.08
		150	13.0 $\pm$ 0.31	9.5 $\pm$ 0.12
9	h	50	10.2 $\pm$ 0.06	8.3 $\pm$ 0.10
		100	12.3 $\pm$ 0.05	9.2 $\pm$ 0.20
		150	13.3 $\pm$ 0.31	12.0 $\pm$ 0.03
10	i	50	8.4 $\pm$ 0.11	6.1 $\pm$ 0.50
		100	10.3 $\pm$ 0.06	6.4 $\pm$ 0.20

		150	12.6±0.14	8.4±0.06
11	j	50	13.2±0.50	14.3±0.12
		100	17.1±0.20	16.3±0.17
		150	20.2±0.17	18.3±0.12
12	k	50	10.2±0.20	8.2±0.06
		100	13.1±0.08	10.5±0.10
		150	14.3±0.11	12.2±0.03
13	l	50	9.0±0.10	8.2±0.08
		100	11.2±0.08	8.4±0.08
		150	13.3±0.03	9.1±0.05
14	m	50	7.0±0.33	5.4±0.06
		100	9.1±0.08	7.2±0.02
		150	11.4±0.08	9.4±0.05
15	n	50	12.5±0.06	7.2±0.08
		100	14.2±0.10	9.2±0.10
		150	17.2±0.05	11.3±0.10
16	o	50	9.2±0.50	8.2±0.08
		100	10.2±0.20	10.2±0.20
		150	13.2±0.05	12.2±0.14
17	p	50	9.3±0.12	7.2±0.08
		100	10.2±0.06	8.4±0.10
		150	13.4±0.23	9.5±0.08
18	q	50	10.5±0.05	9.3±0.08
		100	12.9±0.08	10.4±0.10
		150	15.3±0.05	12.1±0.08
19	r	50	13.2±0.20	14.3±0.05
		100	15.3±0.17	15.1±0.10
		150	18.5±0.12	16.2±0.14
20	s	50	12.2±0.10	9.5±0.50

21	t	100	14.3±0.10	11.2±0.06
		150	17.5±0.14	14.3±0.14
		50	8.4±0.11	6.2±0.50
		100	9.3±0.05	8.5±0.10
		150	13.1±0.08	8.53±0.17

Zone of inhibition in mm, Conc.in µg/ml.

Compound BTC-j was found to be more active as antifungal in all synthesized compounds when compared with fluconazole as reference drug. Compound BTC-a was shown least activity as compared to other synthesised compounds.

Among the screened compounds, compound BTC-j showed good antifungal activity as compared to standard. BTC-f and BTC-r showed a moderate antifungal activity.

It was observed that compounds possessing methoxy substitution were found to hold better antibacterial activity against gram-positive and gram-negative bacteria among the synthesized compounds, whereas most of the compounds did not show good antifungal activity against *C. albicans* species compared to fluconazole.

3.2. Molecular docking

The docking study was carried out to check the interactions of target compounds. All the synthesized compounds BTC(a-t) were docked in DNA gyrase (pdb 3G75) protein. The dock score and binding interactions were recorded **Table 5**. The docking study revealed that the compound BTC-j possess -5.54 Kcal/mol as highest dock score. The compound BTC-j forms hydrogen bond between N-H of amide and N-H of amine with amino group of GLU58A and ASP57A. The compound was held in active site with hydrophobic interactions with ASP57A, GLU58A and ALA 61A amino acid residue. The antibacterial activity was found to be in correlation with dock score.

Table 5: Dock score and binding interactions of newly synthesized compounds BTC (a-t)

Compound	Dock score (Kcal/mol)
a	-5.22
b	-5.32
c	-5.32
d	-5.39
e	-5.29
f	-5.49
g	-5.32
h	-5.29
i	-5.45
j	-5.54
k	-5.32
l	-5.33
m	-5.33
n	-5.40
o	-5.33
p	-5.32
q	-5.35
r	-5.51
s	-5.51
t	-5.51
Reference	-5.04

Conclusion

The number of 2-acetamido substituted benzothiazoles were synthesized and screened for antibacterial and antifungal activity. The antimicrobial activities for the synthesized compounds BTC(a-t) have been shown in Table 1-4 and fig.1-3.

The *in vitro* antimicrobial screening data of the synthesized compounds indicate that all the compounds showed good to moderate activity except compound BTC-a, BTC-h and BTC-p. The compound **BTC-a** N-(1,3-benzothiazol-2-yl)-2-(pyrimidin-2-yl amino) acetamide show least activity against gram-negative

bacteria while compounds **BTC-h** N-{2-[(6-methyl-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} benzamide and **BTC-p** N-{2-[(6-chloro-1,3-benzothiazol-2-yl) amino]-2-oxoethyl} benzamide are less active against gram-positive bacteria.

Compound **BTC-j** N-(6-methoxy-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide and compound **BTC-r** N-(6-nitro-1,3-benzothiazol-2-yl)-2-(pyridine-3-yl amino) acetamide showed the good activity.

The compound **BTC-j** has shown good antibacterial activity against *S. aureus* at MIC of 12.5 µg/ml, *B. subtilis* at MIC of 6.25 µg/ml, *E. coli* at MIC of 3.125 µg/ml and *P. aeruginosa* at MIC of 6.25 µg/ml.

The compound **BTC-j** also shown good antifungal activity against *A. niger* and *C. albicans* at MIC of 3.125 and 6.25 µg/ml respectively.

The docking study was carried out to check the interactions of target compounds with selected protein. All the synthesized compounds BTC(a-t) were docked in DNA gyrase (pdb 3G75) protein. The dock score and binding interactions were recorded in **Table 5**. The docking study revealed that the compound BTC-j possess -5.54 Kcal/mol as highest dock score. The compound BTC-j forms hydrogen bond between N-H of amide and N-H of amine with amino group of GLU58A and ASP57A. The compound was held in active site with hydrophobic interactions with ASP57A, GLU58A and ALA61A amino acid residue. The antibacterial activity was found to be in correlation with dock score.

The results of antimicrobial activity and docking study indicates that methoxy substituted benzothiazole with pyridine substitution have shown good antimicrobial activity compared to other synthesized compounds, nitro substituted benzothiazole with pyridine substitution shown moderate activity when compared with other synthesized compounds.

Thus, we conclude that the synthesized compounds have potential for further development as novel antimicrobial agents.

Declarations

Acknowledgment

The authors wish to thank, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune. for providing required facilities to carry out this research work.

References

1. Taher P, Hitesh P, Santilal P, Sangita S. Synthesis and antibacterial activity of novel benzothiazole based 1,3,4-oxadiazole derivatives. *Inventi J.* 2016; 1: 1-26.
2. Nitendra K S, Vivek A, Ankita R, Satish S and Kohli D V. Synthesis, characterization and antimicrobial evaluation of some 1,3-benzothiazole-2-ylhydrazones derivatives. *Arab. J. of Chem.* 2015;8: 495-99.

3. Bhoi M N, Borad M A, Parmar H B, Patel H D. Synthesis and Characterization of novel N-(benzo[d]thiazol-2-yl)-2-(2-(6chloroquinolin-4-yl) hydrazinyl) acetamide derivatives containing Quinoline linkage as potent antibacterial agents. *Int. lett. Of Chem., Phy. Astr.* 2015; 53:114-21.
4. Balaji P N, Ranganayakulu D, Ramya Y K, Jayamma J, Reddy K S, Sivaramaiah C. Anthelmintic and Anti-microbial activities of synthesized heterocyclic pyrazole and its derivatives from fluoro substituted hydrazino benzothiazole. *Int. J. of Pharm Tech Res.* 2014; 6: 1970-75.
5. Armenise D, Carocci A, Catalano A, Muraglia M, Defrenza I, De Laurentis N, Franchini C. Synthesis and Antimicrobial Evaluation of a New Series of N-1,3-Benzothiazol-2-ylbenzamides. *Journal of Chemistry* 2013; 1–7.
6. Bolelli K, Yalcin I, Ertan-Bolelli T. Synthesis of novel 2-[4-(4-substitutedbenzamido/phenylacetamido) phenyl] benzothiazoles as antimicrobial agents *Medicinal Chemistry Research* 2012;21:3818–25.
7. Bhusari K P, Khedekar, P B, Umath S N, Bahekar R H, Raghu Ram Rao A. Synthesis and antitubercular activity of some substituted 2-(4-aminophenyl sulphonamido) benzothiazoles. *Indian J. Heterocycl. Chem.* 2000; 9: 213-16.
8. Pereira GA, Massabni AC, Castellano EE. A broad study of two new promising antimycobacterial drugs: Ag(I) and Au (I) complexes with 2-(2-thienyl) benzothiazole. *Polyhedron* 2012; 38:291–6.
9. Wang Z, Shi X, Wang J. Synthesis, structure activity relationships and preliminary antitumor evaluation of benzothiazole-2-thiol derivatives as novel apoptosis inducers. *Bioorg and Med Chem Lett.* 2011; 21:1097–101.
10. Kok SHL, Gambari R., Chui CH H. Synthesis and anticancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. *Bioorganic and Medicinal Chemistry* 2008; 16:3626–31.
11. Navale A, Pawar S, Deodhar M, Kale A. Synthesis of substituted benzo[d]thiazol-2-ylcarbmates as potential anticonvulsants. *Medicinal Chemistry Research* 2013;22: 4316–21.
12. Amir M, Asif S, Ali I, Hassan MZ. Synthesis and antimicrobial activity of pyrazolinones and pyrazoles having benzothiazole moiety. *Med Chem Res* 2012; 21:9,2661–70.
13. Patil VS, Nandre KP, Ghosh S. Synthesis, crystal structure and antidiabetic activity of substituted (E)-3-(Benzo-[d]thiazol-2-ylamino) phenyl prop-2-en-1-one. *Eur J Med Chem* 2013; 59:304–9.
14. Navarrete-Vazquez G, Ramirez-Martinez M, Estrada-Soto S. Synthesis, *in vitro* and *in silico* screening of ethyl – (6-substituted benzo[d] thiazol-2-ylamino)-2-oxoacetates as protein tyrosine phosphatase 1B inhibitors. *Eur J Med Chem* 2012; 53:346–55.
15. Nagarajan S R, DeCrescenzo G A, Getman D P. Discovery of novel Benzothiazolesulphonamides as Potent inhibitors of HIV-1 Protease. *Bioorg Med Chem Lett* 2003; 11:4769–77.
16. Shafi S, Alam M M, Mulakayala N. Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: their anti-inflammatory and anti-nociceptive activities. *Eur J Med Chem* 2012; 49:324–33.
17. Ozuturk F, Leyla C, Izzet S, Karei F, Kilie E. Antimicrobial properties and DNA interactions studies of 3-hetarylazoquinoline-2,4-diol compounds. *Turk J Chem.*2012; 36:293-302.

18. Saeed S, Jones P, Ali M, Hussain R. Synthesis, characterization and biological evaluation of some thiourea derivatives bearing benzothiazole moiety as potential antimicrobial and anticancer agents. *European Journal of Medicinal Chemistry* 2010; 45:1323-133.
19. Mohd I, Abida A, Als Salman A J. Synthesis and Antimicrobial Activity of Some 2-Amino-4-(7Substituted/Unsubstituted Coumarin-3-yl)-6(Chlorosubstitutedphenyl) Pyrimidines. *Trop J Pharm Res* 2016;14(7): 1265-72
20. Patel N B, Agravat SN, Shaikh FM. Synthesis and antimicrobial activity of new 4-thiazolidinone derivatives containing 2-amino-6-methoxybenzothiazole. *Med Chem Res* 2010;20(7):1033-41.
21. Singh R K, Rai D. Synthesis and antibacterial activity of benzamide and sulfonamide derived from 2-amino-5-bromo/nitropyridine against bacterial strains isolated from clinical patients. *Indian J Chem* 2011;50B:931-6.
22. Khan T, Sankhe K, Suvana V, Sherje A, Patel K, Dravyankar B. DNA gyrase inhibitors: Progress and synthesis of potent compounds as antibacterial agents. *Biomed & Pharmacol* 2018; 103:923-38.
23. Jimonet, P, Audiau, F, Barreau, M, Blanchard J C, Boireau A, Bour Y. Riluzole series. Synthesis and in vivo "antigliutamate" activity of 6-substituted-2-benzothiazolamines and 3-substituted-2-imino-benzothiazolines. *J. Med. Chem.* 1999; 42:2828-43.
24. Salvi V K, Bhambi D, Jat J L, Talesara G L. Synthesis and antimicrobial activity of some 2- [1-(4-oxo-3,4- dihydrophthalazine-1-yl) alkyl]-1H-isoindole-1,3(2H)-dione and their imidoxy derivatives. *Arkivoc* 2006; 16:133-40.
25. Patel H S, Desai H D, Mistry H J. Synthesis and Antimicrobial Activity of Some New Piperazine Derivatives Containing Aryl Sulfonyloxy Group. *E-J. Chem.* 2004;1: 93-98.
26. Chrysanthou E, Estrella M, Denning D, Donnelly J, Dupont B. Method for determination of minimum inhibitory concentration (MIC) by broth dilution of fermentative yeasts. *Clinical Microbiology and Infection*. 2003; 9:1-8.
27. Venkatraman M, Gibbs, A C, Cummings M D, Jaeger E P, Renee L, Des J. Docking: Successes and challenges. *Curr. Pharm. Design*, **2005**; 11:323-33.
28. Shrivastava V, Gupta S P, Siddiqi M I, Mishra B N. Molecular docking studies on quinazoline antifolate derivatives as human thymidylate synthase inhibitors. *Bioinformation* **2010**; 4(8): 357-65.
29. Kuna A K, Ratnam B M, Kumari D N S S A, Babu PA. Structure based drug design studies on heteroaryl propanoic acid derivatives as ppar γ agonists. *Journal of Pharmaceutical Research and Health Care*. 2009; 1:184- 196.
30. Adinarayana K P S, Reddy P A, Babu A. Structural Studies on Docking Selective COX-2 Inhibitors. *J. Bioinform. Res.* **2012**; 1(1): 21-26.
31. Oblak, M.; Simona, G. G.; Roman, M. K.; Filipic, J.; Tomaz, S. O. In silico fragment-based discovery of indolin-2-one analogues as potent DNA gyrase inhibitors. *Bioorg. Med. Chem. Lett.* **2005**; 15: 5207-10.

Figures

Figure 1

Graph of zone of inhibition against gram-positive bacterial stains Data expressed as Mean±SEM. Data analysed by two-way ANOVA. All test compounds were compared with the standard, Ciprofloxacin. NS: Non-significant

Figure 2

Graph of zone of inhibition against gram-negative bacterial stains Data expressed as Mean±SEM. Data analysed by two-way ANOVA. All test compounds were compared with the standard, Ciprofloxacin. NS: Non-significant

Figure 3

Graph of zone of inhibition against fungal strains Data expressed as Mean ± SEM. Data analysed by two-way ANOVA. All test compounds were compared with the standard, Fluconazole. NS: Non-significant.

Figure 4

Compound BTC-j binding interactions with selected protein (DNA gyrase, PDB: 3G75)