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ABSTRACT

A series of new benzothiazole derivatives were synthesized and evaluated for anti-inflammatory and anti-diabetic activity. The structures of the compounds were confirmed by $^1$H-NMR, $^{13}$C-NMR, FT-IR, and LC-MS. Among the all synthesized compounds, 4a showed very good anti-inflammatory activity. The compounds 3a, 3c, 3d, 5b also showed good anti-inflammatory activity. In anti-diabetic studies, the compounds 5a, 5b, and 3d showed moderate alpha-amylase inhibition activity.

Keywords: benzothiazole, anti-inflammatory, alpha-amylase, anti-diabetic

INTRODUCTION

In the 1950’s, a number of 2-aminobenzothiazole derivatives were intensively studied, as the 2-amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [1-2] and reported cytotoxic on cancer cells [3]. It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well-known approach to design new drug-like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. Numerous compounds bearing benzothiazole ring are known to possess important of pharmacological activities such as antimicrobial [4-5] anticancer [6-7], antiviral [8], anti-HIV [9], antidiabetic [10]. They are also useful as anti-allergic [11], antileishmanial [12] and antitubercular [13-14] agents. In addition, the benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Due to their importance in pharmaceutical utilities, the synthesis of different benzothiazole derivatives is of considerable interests.

On the basis of exhaustive literature review, it has been found that benzothiazole derivatives have potential to exhibit anti-inflammatory [15-19] and anti-diabetic activity [20-21]. The present study describes the synthesis of 2,6-disubstituted benzothiazole derivatives and evaluation of in vitro anti-inflammatory and anti-diabetic activity.

EXPERIMENTAL SECTION

2.1. Chemistry

The synthetic starting material, reagents, and solvents were of analytical reagent grade or the highest quality commercially available and were purchased from sigma-Aldrich Chemical Co., Merck Chemical Co. Melting points were recorded by labtronics digital melting point apparatus. The $^1$H-NMR and $^{13}$C-NMR spectra were recorded in DMSO-d$_6$ solvent on Bruker 300 MHz spectrophotometer using tetramethylsilane as an internal reference. The apparent resonance multiplicity is described as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). Infrared measurements were recorded in the range 400–4000 cm$^{-1}$ by Perkin Elmer. Mass spectra were recorded on a Thermo LCQ Deca XP MAX at70eV. Thin layer chromatography (TLC) analysis was carried out on 5x20 cm plate coated with silica gel GF$_{254}$.
2.1.1. Synthesis of N-(6-nitro-1,3-benzothiazol-2-yl)acetamide (1)

To a solution of 2-amino-6-nitrobenzothiazole (10 g, 0.051 mol) in 40 ml acetic anhydride, pyridine (12.4 ml, 0.153 mol) was added. The reaction mixture was heated to 90°C for 4 hr, and then allowed to cool. The reaction mass was poured to 200 ml of 2N HCl. The resulting solid was filtered, washed with water and diethyl ether to afford compound 1. Pale yellow solid; Yield 79%; m.p. 285-286°C; IR (KBr) νmax in cm⁻¹: 3387 (NH), 3091, 2944 (CH), 1701(C=O), 1554 (NH bend), 1514, 1340 (NO₂), 1267 (C=N), 750 (CH); ¹H NMR (DMSO-d₆) δ ppm: 2.19 (s,3H), 6.62 (d,1H), 7.66 (d,1H), 7.45 (t,1H), 7.51 (d,1H), 7.56 (d,1H), 7.74 (d,1H), 7.70 (d,1H), 8.41 (d,1H), 10.36 (s,1H), 12.30 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.7, 55.3, 112.8, 112.9, 117.2, 119.8, 119.9, 120.2, 129.5, 131.6, 134.9, 136.2, 144.8, 157.1, 159.1, 165.1, 169.2. LC-MS (ESI) m/z : 340.60 (M-H)⁻.

2.1.2. Synthesis of N-(6-amino-1,3-benzothiazol-2-yl)acetamide (2)

A solution of compound 1(10g, 0.0421mol) in 80 ml 12N HCl, SnCl₂ (47.4g, 0.210 mol) was added at RT. The reaction solution was cooled to 0°C and stirred for 4 hr. The reaction mass was poured to 200 ml of 2N HCl. The resulting solid was filtered, washed with water and diethyl ether to afford compound 2. Yellow solid; Yield 79%; m.p. 285-286°C; IR (KBr) νmax in cm⁻¹: 3387 (NH), 1669 (C=O), 1469 (CH bend), 1273 (C=N), 1173 (C-O), 748(CH); ¹H NMR (DMSO-d₆) δ ppm: 2.19 (s,3H), 6.62 (d,1H), 6.65 (1H,d), 6.86 (1H,d), 7.40 (d,1H), 7.56 (dd,1H), 7.68 (d,1H), 7.83 (s,1H), 8.42 (d,1H), 10.37 (s,1H), 12.29 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.7, 111.4, 112.5, 114.5, 153.0.

2.1.3. Synthesis of N-(2-acetamido-1,3-benzothiazol-6-yl)-3-methoxy benzamide (3a)

Prepared as reported above for 3a, starting from compound 2 and 3-methoxybenzoic acid. This reaction was carried out at room temperature for 10 hr. The reaction mass was stirred with 300 ml of cold water. The resulting solution was diluted with 300 ml of cold water. The resulting solution was washed with 3N HCl (1x25, Brine (1x250mL) and dried over anhydrous Na₂SO₄. The resulting ethyl acetate layer was concentrated under reduced pressure to afford compound 3a. Yellow solid; Yield 35%; m.p. 170-171°C; IR (KBr) νmax in cm⁻¹: 3323 (NH), 3074, 2984 (CH), 1698 (C=O), 1692 (C=O), 1565 (NH bend), 1514, 1340 (NO₂), 1267 (C=N), 750 (NH bend); ¹H NMR (DMSO-d₆) δ ppm: 2.14 (s,3H), 5.13 (s,2H), 6.69 (dd,1H), 6.99 (d,1H), 7.39 (d,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.6, 104.2, 114.3, 120.7, 132.8, 139.6, 145.6, 153.0, 156.6; LC-MS (ESI) m/z : 206.2 (M-H)⁻.

2.1.4. Synthesis of (2-acetamido-1,3-benzothiazol-6-yl)-3-(2-furyl)acrylamide  (3d)

Prepared as reported above for 3a, starting from compound 2E)-3-(furan-2-yl) acryloyl chloride was added. The resulting reaction mass was concentrated under reduced pressure to afford compound 3d. Yellow solid; Yield 21%; m.p. 170-171°C; IR (KBr) νmax in cm⁻¹: 3387 (NH), 3087, 2984 (CH), 1698 (C=O), 1692 (C=O), 1565 (NH bend), 1514, 1340 (NO₂), 1267 (C=N), 750 (CH); ¹H NMR (DMSO-d₆) δ ppm: 2.19 (s,3H), 7.16 (dd,1H), 7.45 (t,1H), 7.51 (d,1H), 7.56 (d,1H), 7.74 (d,1H), 7.70 (d,1H), 8.41 (d,1H), 10.36 (s,1H), 12.30 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.6, 104.2, 114.3, 120.7, 132.8, 139.6, 145.6, 153.0, 156.6; LC-MS (ESI) m/z : 206.2 (M-H)⁻.

2.1.5. Synthesis of (2-acetamido-1,3-benzothiazol-6-yl)-2-(3-fluorophenyl)acetamide (3c)

Prepared as reported above for 3a, starting from compound 2 and 3-fluorobenzoic acid. This reaction was carried out at room temperature for 6 hr. Pale yellow solid; Yield 20%; m.p.257-258°C; IR (KBr) νmax in cm⁻¹: 3347 (NH), 3074, 2984 (CH), 1698 (C=O), 1621 (C=O), 1575 (NH bend), 1322 (C-N), 1273, 1039 (C-O), 710 (CH); ¹H NMR (DMSO-d₆) δ ppm: 2.19 (s,3H), 3.84 (s,3H), 7.16 (dd,1H), 7.45 (t,1H), 7.51 (d,1H), 7.56 (d,1H), 7.74 (d,1H), 7.70 (d,1H), 8.41 (d,1H), 10.36 (s,1H), 12.30 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.6, 104.2, 114.3, 120.7, 132.8, 139.6, 144.8, 157.1, 159.1, 165.1, 169.2. LC-MS (ESI) m/z : 340.60 (M-H)⁻.

2.1.6. Synthesis of (2E)-N-(2-acetamido-1,3-benzothiazol-6-yl)-3-(2-furyl)acrylamide (3d)

To a solution of compound 2 (0.489g, 0.0025mol) and HOBt (0.260,0.0019 mol) was added. The reaction mixture was cooled to 0°C and stirred for 4 hr. The reaction mixture was allowed to RT and stirred for 4 hr. The reaction solution was concentrated under reduced pressure and separated between ethyl acetate (50mL) and water (40mL). The combined ethyl acetate layer was washed with 2N HCl (1x25), 10% NaHCO₃ (1x250mL) and dried over anhydrous Na₂SO₄. The resulting ethyl acetate layer was concentrated under reduced pressure to afford compound 3d. Yellow solid; Yield 35%; m.p. 170-171°C; IR (KBr) νmax in cm⁻¹: 3358 (NH), 1673 (C=O), 1575 (NH bend), 1273 (C=N), 731 (CH); ¹H NMR (DMSO-d₆) δ ppm: 2.18 (s,1H), 3.76 (s,2H), 6.98 (t,1H ), 7.07 (t,1H), 7.29 (d,1H), 7.36 (d,1H), 7.55 (dd,1H), 7.65 (d,1H), 8.30 (d,1H), 10.28 (s,1H), 10.93 (s,1H), 12.84(s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.6, 33.7, 108.2, 111.2, 111.7, 118.3, 118.4, 120.3, 120.9, 123.3, 127.13, 131.7, 135.2, 136.0, 144.3, 156.7, 169.1,169.5; LC-MS (ESI) m/z : 365.27 (M+H)⁺.
118.4, 119.3, 120.5, 127.2, 131.9, 135.2, 144.5, 145.5, 145.1, 150.9, 156.9, 163.2, 169.2; LC-MS (ESI) m/z : 328.27 (M+H)+.

2.1.7. Synthesis of N-(6-[(4-cyclohexylphenyl)sulfonyl]amino)-1,3-benzothiazol-2-yl) acetamide (4a)

To a solution of compound 2 (0.4g, 0.019 mol) in 10 mL 1,2-dichloroethane, pyridine (0.46mL,0.0057mol) and 4-cyclohexylbenzene-1-sulfonylchloride (0.62g,0.0024 mol) was added. The reaction mixture was heated to 90°C for 7 hr. The reaction mixture was cooled to RT, diluted with 30 mL of ethyl acetate. The combined ethyl acetate layer was washed with 2N HCl (1X30), 10% NaHCO₃ (1X40), Brine (1x50mL) and water (40mL). The ethylacetate layer was washed with Brine (1x250mL) and dried over anhydrous Na₂SO₄. The resulting ethyl acetate layer was concentrated under reduced pressure to afford compound 4a. White solid. Yield 39%; m.p.267-268°C.

IR (KBr) νmax in cm⁻¹: 3312 (NH), 2924, 2852 (CH), 1689 (C=O), 1619 (C=N), 1549 (NH bend), 1470 (CH bend), 1275 (C-N), 1327, 1154 (S=O); ¹H NMR (DMSO-d₆) δ ppm: 1.29-1.32 (m,5H), 1.64-1.73 (m,5H), 2.16 (s,3H), 7.13 (dd,1H), 7.36 (d,2H), 7.57 (d, 1H), 7.64 (s,1H), 7.66 (d,2H), 10.28 (s,1H), 12.28 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 22.6, 25.3, 26.0, 33.3, 43.4, 113.2, 119.8, 120.7, 126.7, 132.1, 133.4, 136.9, 145.3, 152.6, 157.4, 169.3; LC-MS (ESI) m/z : 430.27 (M+H)+.

2.1.8. Synthesis of N-(6-[(2,5-dichloro-3-thiényl)sulfonyl]amino)-1,3-benzothiazol-2-yl) acetamide (4b)

Prepared as reported above for 4a, starting from compound 2 and 2,5-Dichlorothiophene-3-sulfonyl chloride. This reaction was carried out at RT for 3hr. Pale yellow solid; Yield 38%; m.p: 245-246 °C; IR (KBr) νmax in cm⁻¹: 3410 (NH), 3062, 2973 (CH), 1675 (C=O), 1561 (NH bend), 1276(C-N), 1345, 1163 (S=O), 1044(C-Cl), 725(CH bend); ¹H NMR (DMSO-d₆) δ ppm: 2.18 (s,3H), 7.16 (dd,1H), 7.31 (s,1H), 7.64 (d,1H), 7.72 (d,1H), 10.70 (s,1H), 12.35 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 23.1, 110.9, 115.7, 118.4, 120.4, 120.9, 132.6, 136.9, 136.50, 144.18, 153.2, 156.5, 159.3, 169.6; LC-MS (ESI) m/z : 328.27 (M+H)+.

2.1.9. Synthesis of N-(6-[(4-fluorophenyl)carbamoyl]amino)-1,3-benzothiazol-2-yl) acetamide (5a)

Prepared as reported above for 5a, starting from compound 2 and 4-fluorophenyl isothiocyanate. This reaction was carried out at RT for 1 hr. White solid; Yield 30%; m.p.262-263 °C; IR (KBr) νmax in cm⁻¹: 3410 (NH), 3062, 2973(CH), 1675 (C=O), 1561 (NH bend), 1276(C-N), 1345, 1163 (S=O), 1044(C-Cl), 725(CH bend); ¹H NMR (DMSO-d₆) δ ppm: 1.29-1.32 (m,5H), 1.64-1.73 (m,5H), 2.16 (s,3H), 7.13 (dd,1H), 7.36 (d,2H), 7.57 (d, 1H), 7.64 (s,1H), 7.66 (d,2H); LC-MS (ESI) m/z : 329.27 (M+H)+.

2.1.10. Synthesis of N-(6-[(3-methoxyphenyl)carbamoyl]amino)-1,3-benzothiazol-2-yl)acetamide (5b)

Prepared as reported above for 5a, starting from compound 2 and 3-methoxy phenyl isocyanate. This reaction was carried out at RT for 3hr. Pale yellow solid; Yield 25%; m.p.262-263 °C; IR (KBr) νmax in cm⁻¹: 3278 (NH), 3068, 2997 (CH), 1635 (C=O), 1557 (NH bend), 1216 (C-F), 1270 (C-N), 719 (CH bend); ¹H NMR (DMSO-d₆) δ ppm: 2.18 (s,3H), 7.16 (dd,1H), 7.31 (s,1H), 7.64 (d,1H), 7.72 (d,1H), 10.70 (s,1H), 12.35 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 23.1, 110.9, 115.7, 118.4, 120.4, 120.9, 132.6, 136.9, 136.50, 144.18, 153.2, 156.5, 159.3, 169.6; LC-MS (ESI) m/z : 345.27 (M+H)+.

2.1.11. Synthesis of N-(6-[(4-fluorophenyl)carbamothioyl]amino)-1,3-benzothiazol-2-yl) acetamide (5c)

Prepared as reported above for 5a, starting from compound 2 and 4-fluorophenyl isothiocyanate. This reaction was carried out at RT for 1 hr. White solid; Yield 36%; m.p.231-232 °C; IR (KBr) νmax in cm⁻¹: 3330 (NH), 2931 (CH), 1688 (C=O), 1600 (C=N), 1552 (NH bend), 1265 (C-N), 220 (C-F), 723(CH bend); ¹H NMR (DMSO-d₆) δ ppm: 2.21 (s,3H), 7.17 (t,1H), 7.43 (d,1H), 7.48 (d,2H), 7.69 (d,1H), 8.03 (s,1H), 9.75 (s,1H), 9.90 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 27.9, 120.3, 122.5, 125.3, 128.9, 131.6, 136.7, 140.1, 141.0, 151.1, 162.8, 162.9, 174.5, 185.5; LC-MS (ESI) m/z : 361.27 (M+H)+.

2.1.12. Synthesis of N-(6-[(3-methoxyphenyl)carbamothioyl]amino)-1,3-benzothiazol-2-yl) acetamide (5d)

Prepared as reported above for 5a, starting from compound 2 and 3-methoxy phenyl isothiocyanate. This reaction was carried out at RT for 2 hr. White solid; Yield 45%; m.p.241-242 °C; IR (KBr) νmax in cm⁻¹: 3477 (NH), 3022, 2884 (CH), 1693 (C=O), 1600 (C=N), 1552 (NH bend), 1264 (C-N), 723(CH bend); ¹H NMR (DMSO-d₆) δ ppm: 2.18 (s,3H), 3.71 (s,3H), 6.70 (d,1H), 7.03 (s,1H), 7.17 (d,1H), 7.20 (t,1H), 7.43 (d,1H), 7.66 (d,1H), 8.01 (s,1H), 9.79 (s,1H), 9.86 (s,1H); ¹³C NMR (DMSO-d₆) δ ppm: 27.9, 60.2, 114.5, 115.0, 120.9, 122.5, 125.3, 128.9, 139.4, 136.7, 140.2, 145.8, 151.0, 162.9, 164.4, 174.5, 184.9; LC-MS (ESI) m/z : 373.27 (M+H)+.
2.2. Biology

2.2.1. In vitro anti-inflammatory activity (Anti-denaturation assay):
The experiment was carried out with minor modification. The standard drug and synthesized compounds were dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). The final concentration of DMF in all solution was less than 2.5%. Test Solution (4ml) containing different concentrations of the drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 37°C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in water bath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from the control where no drug was added. The diclofenac sodium was used as a standard drug. The percentage inhibition of denaturation was calculated by using following a formula.

\[
\% \text{ of Inhibition} = 100 \times \left( \frac{At - Ac}{At} \right)
\]

where, \( At \) = O.D. of control

2.2.2. In vitro anti-diabetic activity - \( \alpha \)-amylase assay
\( \alpha \)-amylase was dissolved in phosphate buffer saline (PBS, 0.02 mol/L, pH 6.8) at a concentration of 0.1 mg/mL. Various concentrations of sample solutions (0.25 mL) were mixed with \( \alpha \)-amylase solution (0.25 mL) and incubated at 37 °C for 5 min. Then the reaction was initiated by adding 0.5 mL 1.0% (w/v) starch substrate solution to the incubation medium. After incubation at 37 °C for 3 min, the reaction was stopped by adding 0.5 mL DNS reagent (1% Dinitrosalicylic acid, 0.05% Na₂SO₃ and 1% NaOH solution) to the reaction mixture and boiling at 100 °C for 5 min. After cooling to room temperature, the absorbance (Abs) at 540 nm was recorded by a spectrophotometer. The inhibition percentage was calculated by the following equation:

\[
\text{Inhibition (\%)} = \left( \frac{\text{Abs}_1 - \text{Abs}_2}{\text{Abs}_1} \right) \times 100
\]

where, \( \text{Abs}_1 \) = sample and \( \text{Abs}_2 \) = control.

RESULTS AND DISCUSSION

3.1. Chemistry
The route for the synthesis of the intermediates and target compounds are shown in the scheme (1-3). The Intermediate 1 was prepared by using the reagent acetic anhydride and pyridine. The compound 2 was taken as a common scaffold for the synthesis of the new series of 2,6-disubstituted benzothiazole derivatives.

![Scheme 1](image1)

*Scheme 1. Reagents and conditions: (i). (ACO)₂O, Pyridine, 4h, 90°C; (ii). SnCl₂·2H₂O, HCl, 2h, RT*

The amide derivatives 3a, 3b, 3c was prepared by using the reagent 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI). The corresponding acid chloride was used for making of amide derivatives for 3d. The synthetic methods are shown in Scheme.2

![Scheme 2](image2)

*Scheme 2. Reagents and conditions: (i). TEA, THF, O°C; (ii). THF, EDCI, HOBt, TEA*

The sulfonamide derivatives 4a, 4b were prepared by using corresponding sulfonyl chlorides and Compound 2. The reaction was carried out in the presence of pyridine at 90°C. The corresponding isocyanates and isothiocyanates
were respectively used to prepare urea and thiourea derivatives 5a, 5b, 5c, and 5d. The synthetic methods are shown in Scheme 3.

Scheme 3 Reagents and conditions: (i). Pyridine, 90°C; (ii). MDC, 0°C

Table 1: Anti-inflammatory activity of benzothiazole derivatives

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<td>3b</td>
<td>6.32</td>
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<td>3c</td>
<td>7.22</td>
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<td>3d</td>
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<td>4a</td>
<td>59.72</td>
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<tr>
<td>4b</td>
<td>4.31</td>
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<td>5a</td>
<td>3.26</td>
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<tr>
<td>5b</td>
<td>32.58</td>
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<tr>
<td>5c</td>
<td>5.32</td>
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<tr>
<td>5d</td>
<td>7.29</td>
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<tr>
<td>Diclofenac sodium</td>
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Fig.1. Anti-inflammatory activity of benzothiazole derivatives

3.2. Biology
All synthesized compounds have been screened for in vitro anti-inflammatory, and detailed profile of activity has been listed in table no.1. Most of the synthesized compounds exhibited enhanced anti-inflammatory activity. Among them, sulfonamide derivative 4a showed potent anti-inflammatory activity compared with amide, urea, and thiourea.
derivatives. The percentage of inhibition was plotted against concentrations for different samples. The graph is shown below in Fig.1.

Similarly for all the compounds, alpha-amylase assay were carried out by DNS method. The results revealed that only a few compounds showed moderate alpha-amylase inhibition activity. The compound 3d, 5a showed moderate anti-diabetic activity. Anti-diabetic screening data of tested compounds are depicted in table no.2. The percentage of alpha-amylase inhibition was plotted against concentrations for different samples. The graph is shown below in Fig.2.

Table 2: Alpha-amylase activity of benzothiazole derivatives

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<th>compound</th>
<th>% of inhibition</th>
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<td>50µg 100µg 250µg 500µg 1000µg</td>
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<td>3a</td>
<td>11.26 17.11 27.58 35.71 41.67</td>
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<tr>
<td>3b</td>
<td>8.69 13.69 28.41 37.62 49.19</td>
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<tr>
<td>3c</td>
<td>4.54 12.51 14.86 19.23 24.03</td>
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<tr>
<td>3d</td>
<td>5.97 13.69 22.21 46.61 64.41</td>
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<td>4a</td>
<td>11.26 17.11 24.09 25.88 27.58</td>
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<td>4b</td>
<td>14.86 20.25 24.09 27.58 31.52</td>
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<tr>
<td>5d</td>
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</tr>
<tr>
<td>Acarbose</td>
<td>11.26 35.71 60.87 75.58 85.31</td>
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</table>

Fig.2. Alpha-amylase inhibition effect of benzothiazole derivatives

CONCLUSION

A series of new 2,6-disubstitutedbenzothiazol derivatives were synthesized, and their anti-inflammatory and anti-diabetic activities were evaluated in vitro. The sulfonamide derivative 4a showed very good anti-inflammatory activity in contrast with 3a,3c,3d,5b that showed moderate activity. On the other hand, in anti-diabetic studies the compounds 3d, 5a, 5b showed moderate alpha-amylase inhibition activity. These data suggested that the compound 4b may be a powerful anti-inflammatory agent and be worth being further investigated as a potential of an anti-inflammatory agent. Further, the compound 5a may be potent to alpha-amylase inhibition that needs to be further studied.

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