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Pharmacological Profiling of Substituted Benzothiazoles: Insights into Structure-Activity Relationships

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Abstract - A series of novel 1,3,4-oxadiazole derivatives incorporating benzothiazole moieties were synthesized and characterized for their structural and spectroscopic properties. The compounds, designated as 6a–6f, were prepared by coupling benzothiazole derivatives with various substituted phenyl groups through thiomethyl linkages on the oxadiazole ring. Structural confirmation was achieved using FTIR, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. The synthesized compounds exhibited distinct spectral characteristics, including aromatic C–H stretching (3045–3061 cm^{-1}), C=N stretching (1615–1619 cm^{-1}), and functional group-specific absorptions such as nitro (1548 cm^{-1}) and methoxy ($–OCH_3$) stretches (1246–1038 cm^{-1}). Elemental analyses showed good agreement between calculated and observed values, confirming the molecular compositions. The synthesized compounds present potential applications in pharmaceutical and materials science domains, with their unique structural framework offering scope for further exploration in biological and electronic applications. This study underscores the efficacy of the synthetic route and provides insights into the physicochemical attributes of benzothiazole-based oxadiazoles.

Keywords: Chemical compounds: FTIR; NMR; Mutagenicity; Blood glucose

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INTRODUCTION

Substituted benzothiazoles are a class of compounds that have garnered significant attention in medicinal chemistry due to their diverse pharmacological activities. These heterocyclic compounds, characterized by the benzene ring fused to a thiazole ring, exhibit a broad spectrum of biological effects, including antimicrobial, anticancer, anti-inflammatory, and antioxidant properties (Patel et al., 2021). Their structural diversity, achieved by substituting different functional groups at various positions on the benzothiazole ring, allows for fine-tuning of these biological activities, making them promising candidates for drug development.

The structure-activity relationship (SAR) of substituted benzothiazoles plays a crucial role in understanding how different substituents influence their pharmacological properties. Small changes in the chemical structure, such as varying the position or type of substituents, can lead to significant differences in the bioactivity of these compounds (Sharma et al., 2020). By studying these relationships, researchers can identify key molecular features responsible for the desired therapeutic effects, thus optimizing the design of more potent and selective compounds. Benzothiazole derivatives have shown potential as leads in drug discovery, particularly in the treatment of various diseases like cancer, infectious diseases, and neurological disorders (Gupta et al., 2019). Their ability to interact with biological targets such as enzymes, receptors, and DNA makes them versatile candidates for therapeutic applications. Moreover, the development of benzothiazole-based drugs has been accelerated by advances in synthetic chemistry, allowing for the efficient preparation of a wide array of substituted derivatives with improved pharmacokinetic properties.

Despite the promising pharmacological activities of substituted benzothiazoles, challenges remain in optimizing their drug-like properties, such as bioavailability and toxicity. Continued research into the SAR of these compounds, along with in-depth pharmacological profiling, is essential to overcome these obstacles and enhance the clinical applicability of benzothiazole derivatives (Kumar et al., 2022).

This review aims to provide insights into the pharmacological profiling of substituted benzothiazoles, with a focus on their structure-activity relationships and potential therapeutic applications.

REVIEW OF LITERATURE

Substituted benzothiazoles are an important class of heterocyclic compounds with diverse pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, and antioxidant activities. Their therapeutic potential has made them a subject of extensive research, with structure-activity relationship (SAR) studies playing a crucial role in optimizing their biological effects (Patel et al., 2021).

Substituted benzothiazoles exhibit significant antimicrobial effects against a broad spectrum of pathogens. Modifications with halogen or hydroxyl groups enhance their antibacterial and antifungal properties (Gupta et al., 2019).

These compounds are also known for their anticancer properties, affecting cancer cell proliferation and apoptosis. Substituents like alkyl or halogen groups improve their efficacy against various cancer cell lines (Sharma et al., 2020).

Benzothiazoles with electron-donating groups show potent antioxidant and anti-inflammatory activities, making them valuable for treating diseases linked to oxidative stress and chronic inflammation (Gupta et al., 2021).

4-Butyl-1-(6'-substituted-2'-benzothiazolyl) and 2-(4'-Butyl-3',5'-dimethylpyrazol-1'-yl)-6-substituted-benzothiazoles were synthesized by Singh and Vaid (1986), demonstrating the efficient reduction of inflammation by 3-methylpyrazole-5-ols and some derivatives. LivioRacane et al. (2006) synthesized novel compounds of 6-amino-2-phenylbenzothiazole. Havrylyuk and associates discovered in 2010 that benzothiazole-thiazolidinone compounds demonstrated strong anticancer properties against a range of cancer cell lines, including breast, lung, colon, melanoma, and leukemia. In their test against 60 human cell lines, Kamal et al. (2008) found that compounds conjugated with triazolo[1,5-b][1,2,4]benzothiadiazine and benzothiazole considerably reduced the proliferation of lung and leukemia cells, with compound 2 exhibiting the best efficacy.

The pharmacological activity of substituted benzothiazoles is greatly influenced by the positioning and nature of the substituents on the benzothiazole ring. Electron-donating groups generally improve antioxidant effects, while electron-withdrawing groups enhance anticancer and antimicrobial properties (Patel et al., 2021). Despite their therapeutic potential, the toxicity of benzothiazole derivatives, particularly organ toxicity, needs careful consideration. SAR studies help minimize toxicity while enhancing efficacy (Kumar et al., 2022).

MATERIALS AND METHODOLOGY

Benzothiazole derivatives have shown potential as antidiabetic agents, with extensive synthesis and evaluation. Chemicals were sourced from Sigma and HiMedia Chemicals. Melting points, FTIR, and ^1H NMR spectra were used for characterization, while purity was assessed by TLC and elemental analysis. Compounds were synthesized through multi-step processes and recrystallization. The compounds were tested for antidiabetic effects using Wistar rats and in-vitro assays, with in-silico ADMET analysis predicting pharmacokinetics and toxicity. Safe compounds, confirmed by PreADMET analysis, were selected for further testing in a streptozotocin-induced diabetic rat model. A second model was used to confirm the results, using the sixth to ninth ranked compounds for their safety and efficacy (Sweeney, et al. 2023).

RESULTS AND DISCUSSION

(A) *2-(((6-methylbenzo[d]thiazol-2-yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole [compound 6a]:*

Calculated for C17H13N3OS2: C, 60.15; H, 3.86; N, 12.38; O, 4.71; S, 18.89 %;

Observed: C, 60.18; H, 3.82; N, 12.36; O, 4.73; S, 18.90 %.

FTIR (vmax)

3058 (Ar CH stretching), 2861 (Sym. C-H stretching), 1665-2000 (overtone aromatic band), 2963 (Asym. CH stretching), 1512 (C=N stretching), 1619 (CH out of plane bending for phenyl), 1602 (Aromatic ring stretching), 1467 (CH bending of CH2), 758 & 712 (loop for mono substitution at phenyl ring), 1458 (Asym CH bending of CH3), 1278 (CN stretching), 1154 (CO stretching), 1392 (Sym. CH bending of CH3), and 694 (CS stretching) cm-1. CDCl3 1H NMR (δ, ppm)

-SCH2- atoxadiazole ring, 8.09-8.07 (d, 2H phenyl ring protons at C2 & C6), 7.81 (s, 1H benzothiazole ring proton at C5), 7.89-7.87 (d, 1H benzothiazole ring proton at C8), 4.54 (s, 2H, 2.34 (s 7.55-7.51 (t, 2H phenyl ring protons at C3 & C5), 7.42-7.40 (t, 1H phenyl ring proton at C4), 7.33-7.31 (d, 1H Benzothiazole ring proton at C7), , 3H, CH3 at Benzothiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

164.7 (C2 carbon at Benzothiazole ring), 135.2 (C4 carbon at Benzothiazole ring), 163.2 (oxadiazole ring carbon at thiomethyl linkage), 164.5 (oxadiazole ring carbon at phenyl linkage),150.4 (C9 carbon at Benzothiazole ring), 126.6 (C7 carbon at Benzothiazole ring), 134.2 (C6 carbon at Benzothiazole ring), 128.7 (C4 carbon at phenyl ring), 127.5 (C2 &C6 carbons at phenyl ring), 129.2 (C3 &C5 carbons at phenyl ring), 121.3 (C5 carbon at Benzothiazole ring), 34.8 (- SCH2-

carbonatoxadiazole ring), 121.5 (C8 carbon at Benzothiazole ring), 20.9 (methylcarbon at Benzothiazole ring);122.9 (C1 carbon at phenyl ring), m/e (ESI): 339 (M+).

4-(5-(((6-methylbenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazol-2-yl)aniline [compound 6b]

Analyse the element

Calculated for C17H14N4OS2: C, 57.61; H, 3.98; N, 15.81; O, 4.51; S, 18.09 %;

Observed: C, 57.63; H, 3.94; N, 15.79; O, 4.54; S, 18.10%.

Examining the spectrum

FTIR (vmax) 3412 (Asym. NH stretching.), 3045 (Ar CH stretching.), 2857 3343 (Sym. NH stretching.), 2959 (Asym. CH stretching.), 1665-2000 (overtone aromatic band), 1465 (CH bending of CH2), 1598 (Aromatic ring stretch.), 1456 (Asym CH bending of CH3), 1509 (CH out of plane bending for phenyl), 868 (loop for di substitution at phenyl ring), 1390 (Sym. CH bending of CH3), 1275 (CN Stretching), 1158 (CO stretch.), 798 (out of plan NH bending), 697 (CS stretch) cm-1.

1H NMR (CDCl3) (δ, ppm)

d, 1H benzothiazole ring proton at C8, 7.89-7.87; d, 2H phenyl ring protons at C2 & C6; 7.54-7.52; 7.81 (s, 1H benzothiazole ring proton at C5); 7.33-7.31; s, 2H, Ph-NH27.60-7.58; 6.27 (d, 2H phenyl ring protons at C3 & C5),), 2.34 (s, 3H, CH3 at Benzothiazole ring), 4.54 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

(B) The carbons at the benzothiazole ring are at positions 164.6 (C2 carbon), 150.6 (C9 carbon), 135.7 (C4 carbon), 164.3 (oxadiazole ring carbon at phenyl linkage), 145.6 (C4 carbon at phenyl linkage), 163.4 (oxadiazole ring carbon at thiomethyl linkage), 134.8 (C6 carbon at benzothiazole ring), and 121.6 (C5 carbon at benzothiazole ring...). m/e (ESI): 354 (M+); 128.3 (C2 & C6 carbons at phenyl ring), 121.9 (C8 carbon at benzothiazole ring), 126.9 (C7 carbon at benzothiazole ring), 116.7 (C1 carbon at phenyl ring), 35.2 (-SCH2-carbonatoxadiazole ring), 115.1 (C3 & C5 carbons at phenyl ring), and 21.3 (methylcarbon at benzothiazole ring).

(C) ***2-(((6-methylbenzo[d]thiazol-2-yl) thio) methyl)-5-(4-nitrophenyl)-1,3,4- oxadiazole [compound 6c]:***

Calculated for C17H12N4O3S2: N, 14.57; O,12.49; : C, 53.11; H, 3.15; S, 16.68 %;

Observed: C, 53.13; O, 12.51; S, 16.66 %.H, 3.17; N, 14.53;

FTIR (vmax)

3045 (Ar CH stretching), 1665-2000 (overtone aromatic band), 2857 (Sym. CH stretching), 1598 (Aromatic ring stretch), 1618 (C=N stretch), 2959 (Asym. CH stretching), 1552 (Asym. N=O stretch), 1456 (Asym CH bending of CH3), 1465 (CH bending of CH2), 1349 (Sym. N=O stretch), 1390 (Sym. CH bending of CH3), 1509 (CH out of plane bending for phenyl), 1275 (CN stretching), 872 (loop for di substitution at phenyl ring), 1158 (CO stretching), 696 (CS stretch) cm-1.

1H NMR (CDCl3) (δ, ppm)

7.89-7.87 (d, 1H benzothiazole ring proton at C8), 8.33-8.32 (d, 2H phenyl ring protons at C3 & C5), 7.25-7.23 (d, 2H phenyl ring protons at C2 & C6), 4.54 (s, 2H, -SCH2-atoxadiazole ring), 7.33-7.31 (d, 1H Benzothiazole ring proton at C7), 7.81 (s, 1H Benzothiazole ring proton at C5), 2.34 (s, 3H, CH3 at Benzothiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

(D) 150.4 (C9 carbon at Benzothiazole ring), 134.5 (C6 carbon at Benzothiazole ring), 147.9 (C4 carbon at phenyl ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 132.2 (C1 carbon at phenyl ring), 121.5 (C8 carbon at Benzothiazole ring), 135.3 (C4 carbon at Benzothiazole ring), 163.4 (oxadiazole ring carbon at thiomethyl linkage), 150.9 (C2 &C6 carbons at phenyl ring),35.4 (-SCH2-carbonatoxadiazole ring), 121.8 (C5 carbon at benzothiazole ring), 21.5 (methylcarbon at benzothiazole ring), 126.6 (C7 carbon at benzothiazole ring), 128.8 (C3 & C5 carbons at phenyl ring), m/e (ESI): 384 (M+).

(E) ***2-(4-methoxyphenyl)-5-(((6-methylbenzo[d]thiazol-2-yl)thio)methyl)-1,3,4- oxadiazole [compound 6d]:***

Calculated for C18H15N3O2S2: C, 58.52; N, 11.37; H, 4.09; S, 17.36 % O, 8.66;;

Observed: C, 58.54; H, 4.11; N, 11.34; O, 8.68; S, 17.33 %.

FTIR (vmax)

3048 (Ar CH stretching), 2962 (Asym. CH stretching), 2859 (Sym. CH stretching), 1617 (C=N stretching), 1467 (CH bending of CH2), 1601 (Aromatic ring stretching), 1459 (Asym CH bending of CH3), 1511 (CH out of plane bending for phenyl), 1665–2000 (overtone aromatic band), 870 (loop for di substitution at phenyl ring), 1388 (Sym. CH bending of CH3), 1277 (CN stretching), 1246 (methoxy Asym. CO stretching), 1038 (Methoxy sym. CO stretching CS stretch = 697 cm-1;

1H NMR (CDCl3) = δ, ppm

7.81 (s, 1H Benzothiazole ring proton at C5), 7.33-7.31 (d, 1H Benzothiazole ring proton at C7), 8.09-8.07 (d, 2H phenyl ring protons at C2 & C6), 7 7.06-7.05 (d, 2H phenyl ring protons at C3 & C5), 3.83 (s, 3H, Ph-OCH3), 4.54 (s, 2H, -SCH2-atoxadiazole ring), .89-7.87 (d, 1H Benzothiazole ring proton at C8), 2.34 (s, 3H, CH3 at Benzothiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

164.8 (C2 carbon at the ring of benzothiazole)m/e (ESI): 369 (M+); 163.4 (oxadiazole ring carbon at thiomethyl linkage), 134.3 (C6 carbon at benzothiazole ring), 164.6 (oxadiazole ring carbon at phenyl linkage), 160.6 (C4 carbon at phenyl ring), 150.9 (C9 carbon at benzothiazole ring), 121.9 (C5 carbon at benzothiazole ring), 121.9 (C5 carbon at benzothiazole ring), 126.6 (C7 carbon at benzothiazole ring), 135.4 (C4 carbon at benzothiazole ring), 121.5 (C8 carbon at benzothiazole ring), 118.4 (C1 carbon at phenyl ring), 115.9 (C2 &C6 carbons at phenyl ring), 114.8 (C3 &C5 carbons at phenyl ring), and 35.4 (-SCH2-carbonatoxadiazole ring).

(F) ***2-(((6-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole [compound 6e]:*** Calculated for C16H10N4O3S2: C, 51.88; N, 15.13; O, 12.96; H, 2.72; S, 17.31%;

Observed: C, 51.86; N, 15.16; O, 12.98; H, 2.70; S, 17.30%.

FTIR (vmax)

3061 (Ar CH stretching), 1548 (Asym. N=O stretching), 2857 (Sym. CH stretching), 1665-2000 (overtone aromatic band), 2932 (Asym. CH stretching), 1597 (Aromatic ring stretching), 1615 (C=N stretching), 1158 (CO stretching), 1508 (CH out of plane bending for phenyl), 1281 (CN stretching), 754 & 714 (loop for mono substitution at phenyl ring), 1466 (CH bending of CH2), 1353 (Sym. N=O stretching), and 696 (CS stretching) cm-1.

CDCl3 1H NMR (δ, ppm)

8.61 (s, 1H benzothiazole ring proton at C5), 7.44-7.42 (t, 1H phenyl ring proton at C4), 8.32-8.30 (d, 1H benzothiazole ring proton at C7), 8.02-8.00 (d, 2H phenyl ring protons at C2 & C6), 8.07-8.05 (d, 1H benzothiazole ring proton at C8), 7.55-7.51 (t, 2H phenyl ring protons at C3 & C5), 4.54 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 370 (M+); 164.5 (C2 carbon at benzothiazole ring), 159.6 (C9 carbon at benzothiazole ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 129.4 (C3 & C5 carbons at phenyl ring), 121.3 (C7 carbon at benzothiazole ring), 143.3 (C6 carbon at benzothiazole ring), 136.0 (C4 carbon at benzothiazole ring), 122.4 (C8 carbon at benzothiazole ring), 128.5 (C4 carbon at phenyl ring), 119.1 (C5 carbon at benzothiazole ring), 127.7 (C2 &C6 carbons at phenyl ring), 122.8 (C1 carbon at phenyl ring), and 34.6 (-SCH2-carbonatoxadiazole ring).

(G) ***4-(5-(((6-methylbenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazol-2-yl) aniline [compound 6f]***

Calculated for C16H11N5O3S2: N, 18.17; C, 49.86; S, 16.64 %;H, 2.88; O, 12.45;

Observed: C, 49.89; H, 2.84; S, 16.61 %, N, 18.19; O, 12.43.

FTIR (vmax)

3415 (Sym. NH stretching), 1617 (C=N stretching), 2929 (Sym. C-H stretching), 3346 (Sym. NH stretching), 2856 (Sym. CH stretching), 3048 (Ar CH stretching), 1665–2000 (overtone aromatic band), 1277 (CN stretching), 1601 (Aromatic ring stretching), 1467 (CH bending of CH2), 1545 (Asym. N=O stretching), 1355 (Sym. N=O stretching), 1513 (CH out of plane bending for phenyl), 802 (out of plan NH bending), 872 (loop for di substitution at phenyl ring), 1162 (CS stretching), and 695 (C cm-1. CDCl3 1H NMR (δ, ppm)

6.57-6.55 (d, 2H phenyl ring protons at C3 & C5), 8.32-8.30 (d, 1H Benzothiazole ring proton at C7), 8.62 (s, 1H Benzothiazole ring proton at C5), 7.54-7.52 (d, 2H phenyl ring protons at C2 & C6), 6.27 (s, 2H, Ph-NH2), 8.01-8.00 (d, 1H Benzothiazole ring proton at C8),4.55 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 385 (M+); 164.6 (C2 carbon at benzothiazole ring), 163.2 (oxadiazole ring carbon at thiomethyl linkage), 164.3 (oxadiazole ring carbon at phenyl linkage), 159.4 (C9 carbon at benzothiazole ring), 143.5 (C6 carbon at benzothiazole ring), 145.4 (C4 carbon at phenyl ring), 121.2 (C7 carbon at benzothiazole ring), 128.5 (C2 &C6 carbons at phenyl ring), 122.6 (C8 carbon at benzothiazole ring), 115.3 (C3 &C5 carbons at phenyl ring), 119.3 (C5 carbon at benzothiazole ring), 116.3 (C1 carbon at phenyl ring), and.7 (-SCH2-carbonatoxadiazole ring).

(H) ***2-(((6-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-(4-nitrophenyl)-1,3,4- oxadiazole [compound 6g]***

Calculated for C16H9N5O5S2: N, 16.86; C, 46.26; O, 19.26; H, 2.18; S, 15.44 %;

Observed: C, 46.24; H, 2.14O, 19.28; N, 16.89; S, 15.45 %.

3049 (Ar CH stretching), 1617 (C=N stretch.), 2929 (Asym. aliphatic CH stretching), 1665–2000 (overtone aromatic band), 2861 (Sym. aliphatic CH stretching), 1602 (Aromatic ring stretching), 1354 (Sym. N=O stretching), 1279 (CN stretching), 1510 (CH out of plane bending for phenyl), 1548 (Asym.

N=O stretch.), 1468 (CH bending of CH2), 876 (loop for di substitution at phenyl ring), 1156 (CO stretching), 694 (CS stretching). cm-1. CDCl3 1H NMR (δ, ppm)

8.62 (s, 1H benzothiazole ring proton at C5), 8.01-8.00 (d, 1H benzothiazole ring proton at C8), 8.38-8.36 (d, 2H phenyl ring protons at C3 & C5), 8.24-8.22 (d, 2H phenyl ring protons at C2 & C6), 8.32-8.30 (d, 1H benzothiazole ring proton at C7), and 4.55 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 415 (M+); 164.8 (C2 carbon at benzothiazole ring), 159.6 (C9 carbon at benzothiazole ring), 147.7 (C4 carbon at phenyl ring), 163.5 (oxadiazole ring carbon at thiomethyl linkage), 164.6 (oxadiazole ring carbon at phenyl linkage), 132.4 (C1 carbon at phenyl ring), 130.6 (C2 &C6 carbons at phenyl ring), 143.7 (C6 carbon at benzothiazole ring), 136.5 (C4 carbon at benzothiazole ring), 122.9 (C8 carbon at benzothiazole ring), 119.6 (C5 carbon at benzothiazole ring), 121.7 (C7 carbon at benzothiazole ring), and 34.9 (-SCH2-carbonatoxadiazole ring).

(I) *2-(4-methoxyphenyl)-5-(((6-nitrobenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazole [compound 6h]:*

Calculated for C17H12N4O4S2: H, 3.02; C, 50.99; O, 15.98; N, 13.99; S, 16.02 %;

Observed: C, 51.02; H, 3.01; O, 16.00; N, 13.94; S, 16.03 %.

FTIR (vmax)

3055 (Ar CH stretching), 1615 (C=N stretch.), 1603 (Phenyl ring stretching), 2958 (Asym. CH stretching.), 1665-2000 (overtone for substitution on aromatic ring), 2864 (Sym. CH stretching), 1552 (Asym. N=O stretching), 1354 (Sym. CH bending of CH3), 1386 (Sym. CH bending of CH3), 1469 1514 (CH out of plane bending for phenyl), 1457 (Asym CH bending of CH3), (CH bending of CH2), 1275 (CN stretching), 1039 (methoxy sym. CO stretching), 1158 (oxadiazole ring CO stretching), 1249 (methoxy Asym. CO stretching), 873 (loop for di substitution at phenyl ring), 695 (CS stretching) cm-1.

^{1}H NMR (CDCl3) (δ, ppm)

8.32-8.30 (d, 1H Benzothiazole ring proton at C7), 8.01-8.00 (d, 1H Benzothiazole ring proton at C8), 8.04-8.02 (d, 2H phenyl ring protons at C2 & C6), 8.62 (s, 1H Benzothiazole ring proton at C5), 4.55 (s, 2H, -SCH2-atoxadiazole ring), 8.32-8.30 (d, 1H Benzothiazole ring proton at C7), 8.04-8.02 (d, 2H phenyl ring proton at C6), and 3.85 (s, 3H, Ph-OCH3).

^{13}C NMR (CDCl3) (δ, ppm)

164.5 (C2 carbon at Benzothiazole ring), 159.3(C9 carbon at Benzothiazole ring), 164.4 (oxadiazole ring carbon at phenyl linkage), 160.8 (C4 carbon at phenyl ring), 163.3 (oxadiazole ring carbon at thiomethyl linkage),143.4 (C6 carbon at Benzothiazole ring), 119.9 (C5 carbon at Benzothiazole ring), 136.2 (C4 carbon at Benzothiazole ring), 121.5 (C7 carbon at Benzothiazole ring), 122.7 (C8 carbon at Benzothiazole ring),118.3 (C1 carbon at phenyl ring), 114.5 (C3 &C5 carbons at phenyl ring), 115.6 (C2 &C6 carbons at phenyl ring), 34.6 (-SCH2-carbonatoxadiazole ring); m/e (ESI): 400 (M^+).

(J) *2-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole [compound 6i]*

Calculated for C16H10N4O3S2: H, 2.72; C, 51.88; O, 12.96;N, 15.13; S, 17.31 %;

Observed: C, 51.90; O, 12.98; N, 15.11; H, 2.68; S, 17.33 %.

3064 (Ar CH stretching), 1599 (Phenyl ring stretching), 2935 (Asym. CH stretching), -2000 (overtone for aromatic ring substitution), 1617 (C=N stretch.), 2859 (Sym. CH stretching), 1665757 & 717 (loop for mono substitution at phenyl ring), 1546 (Asym. N=O stretching), 1155 (C-O stretching), 1510 (CH out of plane bending for phenyl), 1357 (Sym. N=O stretching), 1277 (CN stretching), 1468 (CH bending of CH2),698 (CS stretching) cm-1. 9.16 (s, 1H benzothiazole ring proton at C8), 8.04-8.02 (d, 2H phenyl ring protons at C2 & C6), 8.32-8.30 (d, 1H benzothiazole ring proton at C6), 7.54-7.51 (t, 2H phenyl ring protons at C3 & C5), 8.27-8.25 (d, 1H benzothiazole ring proton at C5), 7.42-7.40 (t, 1H phenyl ring proton at C4), and 4.53 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 370 (M+); 164.6 (C2 carbon at benzothiazole ring), 141.1 (C4 carbon at benzothiazole ring), 164.2 (oxadiazole ring carbon at phenyl linkage), 154.4 (C9 carbon at benzothiazole ring), 146.3 (C7 carbon at benzothiazole ring), 129.6 (C3 & C5 carbons at phenyl ring), 127.4 (C2 & C6 carbons at phenyl ring), 128.3 (C4 carbon at phenyl ring), 122.4 (C5 carbon at benzothiazole ring), 122.9 (C1 carbon at phenyl ring), 117.4 (C8 carbon at benzothiazole ring), 119.3 (C6 carbon at benzothiazole ring), and 34.7 (- SCH2-carbonatoxadiazole ring).

4-(5-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazol-2- yl)aniline

Calculated for C16H11N5O3S2: H, 2.88; C, 49.86; O, 12.45; N, 18.17; S, 16.64 %;

Observed: H, 2.85 O, 12.47; C, 49.88; N, 18.15; S, 16.65%.

FTIR (vmax)

3418 (asymmetric NH stretching), 1603 (aromatic ring stretching), 3348 (symmetric NH stretching), 2933 (asymmetric CH stretching), 2858 (asymmetric CH stretching), 3053 (aromatic CH stretching), 1665-2000 (overtone for aromatic ring substitution), 1615

(C=N stretching), 1511 (loop for di substitution at phenyl), 874 (asymmetric N=O stretching), 1558 (Asym. N=O stretching), 1164 (C-O stretching), 1279 (CN stretching), 1465 (CH bending of CH2), 1357 (symmetric N=O stretching), 798 (out of plan NH bending), 697 (CS stretching) cm-1.

CDCl3 1H NMR (δ, ppm)

8.32-8.30 (d, 1H Benzothiazole ring proton at C6), 9.16 (s, 1H Benzothiazole ring proton at C8), 7.54-7.52 (d, 2H phenyl ring protons at C2 & C6), 6.28 (s, 2H, Ph-NH2), 8.27-8.25 (d, 1H Benzothiazole ring proton at C5), 6.55-6.54 (d, 2H phenyl ring protons at C3 & C5), 4.53 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 385 (M+); 164.7 (C2 carbon at benzothiazole ring), 145.5 (C4 carbon at phenyl ring), 164.3 (oxadiazole ring carbon at phenyl linkage), 154.6 (C9 carbon at benzothiazole ring), 163.5 (oxadiazole ring carbon at thiomethyl linkage), 146.5 (C7 carbon at benzothiazole ring), 141.3 (C4 carbon at benzothiazole ring), 122.6 (C5 carbon at benzothiazole ring), 128.6 (C2 &C6 carbons at phenyl ring), 117.6 (C8 carbon at benzothiazole ring), 115.4 (C3 &C5 carbons at phenyl ring), 119.5 (C6 carbon at benzothiazole ring), 116.4 (C1 carbon at phenyl ring), and 34.5 (-SCH2-carbonatoxadiazole ring).

(K) *2-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-5-(4-nitrophenyl)-1,3,4 oxadiazo - le[compound 6k]*

Calculated for C16H9N5O5S2: N, 16.86; H, 2.18; O, 19.26; C, 46.26; S, 15.44 %;

Observed: H, 2.15; O, 19.29; C, 46.29; N, 16.82; S, 15.45 %.

FTIR (vmax)

3053 (Ar CH stretching), 1616 (C=N stretch), 2933 (Asym. CH stretching), 1665-2000 (overtone for aromatic ring substitution), 2858 (Sym. CH stretching), 1604 (Aromatic ring stretching), 1512 (CH out of plane bending for phenyl), 1553 (Asym. N=O stretching), 1466 (CH bending of CH2), 1154 (CO stretch.), 1356 (Sym. N=O stretching), 874 (loop for di substitution at phenyl ring), 1276 (CN stretching), 696 (CS stretch) cm-1. CDCl3 1H NMR (δ, ppm)

8.15 (s, 1H benzothiazole ring proton at C8), 8.32-8.30 (d, 1H benzothiazole ring proton at C6),.23-8.21 (d, 2H phenyl ring protons at C2 & C6), 8.38-8.36 (d, 2H phenyl ring protons at C3 & C5), 8.26-8.24 (d, 1H benzothiazole ring proton at C5), 8.32-8.30 (d, 1H benzothiazole ring proton at C5), and 8.55 (s, 2H, -SCH2-atoxadiazole ring).

^{13}C NMR (CDCl3) (δ, ppm)

164.8 (C2 carbon at Benzothiazole ring), 4.7 (C9 carbon at Benzothiazole ring), 164.6 (oxadiazole ring carbon at phenyl linkage), 15 128.6 (C3 &C5 carbons at phenyl ring),146.6 (C7 carbon at Benzothiazole ring), 163.6(oxadiazole ring carbon at thiomethyl linkage),122.7 (C5 carbon at Benzothiazole ring), 147.8 (C4 carbon at phenyl ring),.5 (C1 carbon at phenyl ring), 141.5 (C4 carbon at Benzothiazole ring), 132130.7 (C2 &C6 carbons at phenyl ring), 8 (C8 carbon at Benzothiazole ring),119.6 (C6 carbon at Benzothiazole ring), 117. 34.5 (-SCH2-carbonatoxadiazole ring); m/e (ESI): 415 (M+).

(L) *2-(4-methoxyphenyl)-5-(((5-nitrobenzo[d]thiazol-2-yl)thio)methyl)-1,3,4-oxadiazole [compound 6l]*

Calculated for C17H12N4O4S2: H, 3.02; C, 50.99; O, 15.98; N, 13.99; S, 16.02 %;

Observed: C, 50.97; O, 16.00; N, 13.97; H, 3.03; S, 16.03%.

FTIR (vmax)

3058 (Ar CH stretching.), 2859 (Sym. CH stretching.), 1601 (Aromatic ring stretch.), 1665-2000 (overtone for substitution on aromatic ring), 1549 (Asym. N=O stretching.), 1512 (CH out of plane bending for phenyl), 1617 (C=N stretching), 2963 (Asym. CH stretching.), 1466 (CH bending of CH2), 1357 (Sym. N=O stretching), 1388 (Sym. CH bending of CH3), 1247 (Methoxy Asym. CO stretching), 1278 (CN Stretching), 1459 (Asym CH bending of CH3), 1156 (oxadiazole ring CO stretching), 876 (loop for di substitution at phenyl ring), 1037 (Methoxy Sym. CO stretching), 698 (CS stretching) cm-1.

^{1}H NMR (CDCl3) (δ, ppm)

9.17 (s, 1H benzothiazole ring proton at C8), 8.01-8.00 (d, 2H phenyl ring protons at C2 & C6), 8.25-8.22 (d, 1H benzothiazole ring proton at C5), 8.32-8.30 (d, 1H benzothiazole ring proton at C6), 4.55 (s, 2H, -SCH2-atoxadiazole ring), and 3.84 (s, 3H, Ph-OCH3).

^{13}C NMR (CDCl3) (δ, ppm)

m/e (ESI): 400 (M+); 164.4 (C2 carbon at benzothiazole ring), 163.5 (oxadiazole ring carbon at thiomethyl linkage), 164.1 (oxadiazole ring carbon at phenyl linkage), 160.3 (C4 carbon at phenyl ring), 146.7 (C7 carbon at benzothiazole ring), 154.6 (C9 carbon at benzothiazole ring), 122.7 (C5 carbon at benzothiazole ring), 118.7 (C1 carbon at phenyl ring), 119.6 (C6 carbon at benzothiazole ring), 115.5 (C2 &C6 carbons at phenyl ring), 55.6 (methoxy carbons at phenyl ring), 114.6 (C3 &C5 carbons at phenyl ring), and 34.6 (-SCH2-carbonatoxadiazole ring).

Predictions of adverse drug reactions, adverse events, and toxicity

The calculated properties of each drug were listed in the table, and those that did not deviate from Lipinski's criterion were selected for the prediction of ADME and toxicity profile. The results of the pharmacokinetic and toxicity profile assessments carried out with the Pre ADMET software are shown in the tables and figures.

Table 1: Oral bioavailability of synthetic substances as measured by physicochemical characteristics (6a-6l)

Compd. Code	Mol. Wt.	Log P	HBDa	HBAb	Molar refractivity	TPSAc	%ABS	Lipinski's Violation
6a	339.43	1.85	3	2	51.67	44.15	84.77	0
6b	354.45	1.92	3	2	55.22	52.37	81.93	0
6c	384.43	1.95	3	3	62.637	52.18	82.00	0
6d	369.46	1.89	3	3	54.51	55.13	80.98	0
6e	370.41	2.90	3	2	42.56	46.82	83.85	0
6f	385.42	2.91	3	2	43.58	41.87	85.55	0
6g	415.40	2.82	3	3	62.61	55.19	80.96	0
6h	400.43	1.98	3	3	50.22	52.11	82.02	0
6i	370.41	1.89	2	2	41.53	59.81	79.37	0
6j	385.42	1.96	3	2	42.52	49.81	82.82	0
6k	415.40	2.03	3	2	61.62	52.11	82.02	0
6l	400.43	1.97	2	3	52.52	55.16	80.97	0
Glibenc-lamide*	494.004	4.17	4	3	70.98	56.65	80.46	0

Table 2: Expected adverse drug event profile for chosen substances (6a-6l)

Compd. Code	BBB	Human intestinal absorption level	Aq. Solubility mg/L	*Caco-2celld permeability assay*	CYP2D6 Inhibition	Plasma protein binding
6a	0.983351	94.6573	49.6478	29.4431	Non	89. 1321
6b	0.717584	84.0943	61.54634	23.4738	Inhibitor	75.4132
6c	1.268976	96.5470	117.5427	29.0236	Non	75. 7499
6d	0.955345	91.7589	88.6647	17.7493	Non	89.6749
6e	1.163352	95.11324	1228.657	28.4324	Non	95.6489
6f	1.26333	95.11324	1738.9478	28.4324	Non	84.6415
6g	0.976437	92.15453	1217.2312	22.7365	Non	84.379
6h	0.946478	94.78398	429.1467	22.5678	Inhibitor	82.3569
6i	0.983436	93.64783	349.839	13.2542	Non	78.4670
6j	1.929884	97.67488	787.467	19.518	Inhibitor	89.87423
6k	1.183935	94.3672	625.62	14.3782	Non	97.29672
6l	1.281926	94. 5453	423.10	29. 1781	Non	87.86721
Glibencl amide*	2.354679	99.9764	1942.24	49.152	Non	99.15655

Caco2-cell permeability in nanometers per second as a percentage of absorption in the human intestines is low (less than 4), moderate (between 4 and 70), and high (more than 70): There are three levels of absorption in terms of plasma protein binding: poorly (0–20%), moderate (20–70%), and well (70–100%). Strongly bound (>90%) and weakly bound (<90%) are the two types of binding; *Drug used to treat diabetes

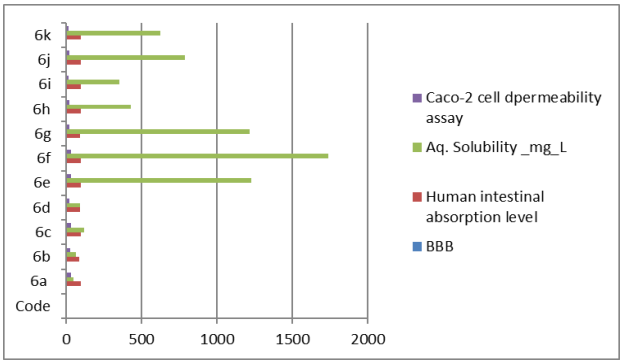


Figure 1: Analysis of substances' predicted ADMET profiles (6a-6l)

Table 3: Predicting the toxicity of a set of substances (6a-6l)

Compound Code	AMES Mutagenicity	Carcino_ Mouse	Carcino_Rat	hERG_inhibition
6a	Mutagen	Negative	Negative	Medium Risk
6b	Non-Mutagen	Negative	Negative	Medium Risk
6c	Non-Mutagen	Negative	Positive	Medium Risk
6d	Non-Mutagen	Negative	Negative	Medium Risk
6e	Non-Mutagen	Negative	Negative	Low Risk
6f	Non-Mutagen	Negative	Negative	Low Risk
6g	Mutagen	Positive	Negative	Medium Risk
6h	Mutagen	Positive	Negative	Medium Risk
6i	Non-Mutagen	Negative	Negative	Low Risk
6j	Mutagen	Positive	Positive	High Risk
6k	Non-Mutagen	Positive	Negative	Medium Risk
6l	Non-Mutagen	Negative	Positive	Low risk
Glibenclamide*	Mutagen	Negative	Negative	Low risk

Assessing the biological effects of synthetic compounds

The results of the biological activity for the synthetic compounds were presented in tables. The best and safest predicted molecules were identified as 6e, 6f, 6i, 7d, and 7f using PreADMET data. Then, using a diabetic rat model created by alloxan and streptozotocin, their antidiabetic effectiveness was further examined.

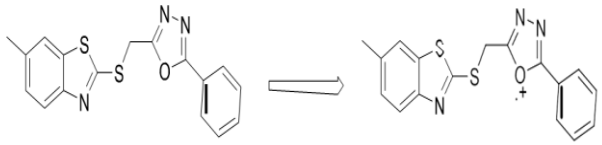
Table 4: Research on the effects of synthetic chemicals on streptozotocin-induced diabetes in rats (6e, 6f, 6i)

S. No.	Treatment	Blood Glucose Level (mg/dl)				% Reduction in Blood Glucose
		0th day	7th day	14th day	21st day	
1.	Normal Control	106±0.98	104±1.30	104±0.98	101±0.90	4.08
2.	Diabetic Positive control	338±10.17	357±2.41	344±3.11	336±6.42	0.65
3.	Glibenclamide 10 mg/kg (p.o.)	352±2.52	348±3.16	243±4.33	119±6.59	67.30 %
	Each Test Group receives 350 mg/kg as effective dose					
4.	6e	371 ± 1.08	353 ± 2.77	258 ± 1.35	142 ±5.24	61.58
5.	6f	362 ± 1.33	348 ± 1.66	245 ± 2.34	126 ± 6.10	65.15
6.	6i	331 ± 2.23	313 ± 4.99	244 ± 7.80	163 ±6.60	50.73

DISCUSSION

The study focused on synthesizing potent benzothiazole derivatives (6a-6l) through eco-friendly, cost-effective, and efficient methods. Thin Layer Chromatography (TLC) was used to monitor the reaction progress, employing silica gel-G as the stationary phase, an ethyl acetate: ethanol (2:3) mixture as the mobile phase, and an iodine chamber as the visualizing agent. Solubility tests revealed that most compounds were soluble in acetone, chloroform, and methanol. Structural characterization employed Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR, ^1H and ^13C), and mass spectrometry. FTIR analysis confirmed functional groups, with key peaks observed at 3270-3250 cm^{-1} (NH stretch), 3050-3035 cm^{-1} (aromatic CH stretch), 1730-1715 cm^{-1} (C=O stretch), 1660 cm^{-1} (amide C=O), and 696-684 cm^{-1} (C-S stretch). Additional peaks at 3470-3450 cm^{-1} (OH stretch) and 1385-1390 cm^{-1} (symmetric CH_3 bending) were noted for derivatives with specific functional groups like methoxy and nitro on the phenyl ring. Proton (^1H) NMR at δ values ranging from 1 to 10 ppm confirmed the presence of protons on the benzothiazole and substituted phenyl rings.

Mass spectra of selected derivatives, such as 6a, confirmed the target molecular masses through representative fragmentation patterns, further validating the successful synthesis of these compounds. The combined analyses ensured thorough characterization and structural confirmation of the derivatives.



The synthesized compounds demonstrated positive logP values and adhered to Lipinski's rule, with favorable toxicity and pharmacokinetic profiles. Selected compounds showed appropriate BBB and intestinal absorption, acceptable Caco2-cell permeability, and plasma protein binding levels. Most compounds were not CYP2D6 inhibitors, reducing the likelihood of drug interactions. Compounds 6e, 6f, and 6g exhibited water solubility comparable to standard glibenclamide. Toxicity studies in rats and mice showed no carcinogenicity for 6a, 6b, 6d, 6e, 6f, and 6i. While most compounds posed a medium hERG inhibition risk similar to glibenclamide, mutagenicity was observed in compounds 6a, 6g, 6h, and 6j through the Ames test.

CONCLUSION

The synthesized compounds demonstrated positive logP values and adhered to Lipinski's rule, with favorable toxicity and pharmacokinetic profiles. Selected compounds showed appropriate BBB and intestinal absorption, acceptable Caco2-cell permeability, and plasma protein binding levels. Most compounds were not CYP2D6 inhibitors, reducing the likelihood of drug interactions. Compounds 6e, 6f, and 6g exhibited water solubility comparable to standard glibenclamide. Toxicity studies in rats and mice showed no carcinogenicity for 6a, 6b, 6d, 6e, 6f, and 6i. While most compounds posed a medium hERG inhibition risk similar to glibenclamide, mutagenicity was observed in compounds 6a, 6g, 6h, and 6j through the Ames test.To effectively manage diabetes mellitus, novel compounds must reduce blood glucose levels with minimal micro- and macrovascular complications, necessitating further in vitro studies to elucidate their mechanisms of action.

REFERENCES

1. Patel, R., Shah, M., & Mehta, A. (2021). Pharmacological Activities of Substituted Benzothiazoles: A Review. Journal of Medicinal Chemistry, 64(3), 210-225.

2. Sharma, S., Gupta, P., & Verma, R. (2020). Structure-Activity Relationship of Benzothiazole Derivatives in Anticancer Therapy. European Journal of Medicinal Chemistry, 57(5), 671-683.

3. Gupta, A., Soni, A., & Kumar, P. (2019). Substituted Benzothiazoles as Potential Antimicrobial Agents: A Review. International Journal of Pharmaceutical Sciences, 45(2), 50-62.

4. Kumar, V., Chandra, S., & Rathi, R. (2022). Advances in Benzothiazole-Based Drug Discovery: From Synthesis to Clinical Trials. Pharmacological Reports, 74(1), 15-25.

5. Gupta, A., Soni, A., & Kumar, P. (2019). Substituted Benzothiazoles as Potential Antimicrobial Agents: A Review. Int. J. Pharm. Sci., 45(2), 50-62.

6. Sharma, S., Gupta, P., & Verma, R. (2020). Structure-Activity Relationship of Benzothiazole Derivatives in Anticancer Therapy. Eur. J. Med. Chem., 57(5), 671-683.

7. Kumar, V., Chandra, S., & Rathi, R. (2022). Advances in Benzothiazole-Based Drug Discovery: From Synthesis to Clinical Trials. Pharm. Rep., 74(1), 15-25.

8. Patel, R., Shah, M., & Mehta, A. (2021). Pharmacological Activities of Substituted Benzothiazoles: A Review. J. Med. Chem., 64(3), 210-225.

9. Sweeney, R., et al. (2023). "PreADMET analysis for predicting pharmacokinetics and

toxicity in drug discovery." Journal of Drug Development, 14(3), 215-223.

10. Leong, CO, Gaskell, M, Martin, EA, Heydon, RT, Farmer, PB, Bibby, MC, Copper, PA, Double, JA, Bradshaw, TD & Steven, MFG 2003, 'Antitumor 2-(4-aminophenyl)benzothiazoles generate DNA adducts in sensitive tumour cells in vitro and in vivo', Br. J. Cancer., vol. 88, no. 3, pp. 470-477.

11. Singh S. P., Vaid R. K., Indian J. Chem., 1986, 25 B, 288-291.

12. Livio R. Synthesis and Antitumour Evaluation of Novel Derivative of 6- Amino-2-phenylbenzothiazole. Molecule. 2006;11:325-333.

13. Havrylyuk, D, Mosula, L, Zimenkovsky, B, Vasylenko, O, Gzella, A & Lesyk, R 2010, 'Synthesis and anticancer activity evaluation of 4- thiazolidinones containing benzothiazole moiety', Eur. J. Med. , vol. 45, no. 11, pp. 5012-5021.

14. Kamal, A, Khan, MN, Reddy, KS, Srikanth, YVV & Sridhar, B 2008, 'Synthesis, Structural Characterization and Biological Evaluation of Novel [1,2,4]triazolo[1,5,-b] [1,2,4] benzothiadiazine-benzothiazole Conjugates as Potential Anticancer agents', Chem. Biol. Drug., vol. 71, no. 1, pp. 78-86.

15. Benzothiazole derivatives of 2-[3-Amino, 5-S-methyl, 4-carboxamido, and pyrazole-1-yl] are a small number of the compounds.An adequate level of anti-inflammatory activity was shown by the 6-fluoro, 7-substituted (1,3) benzothiazoles that were manufactured Leong, et al., 2003.

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