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*Original Article*

# Design, Synthesis and Characterization of Benzothiazole Analogues as Promising Pharmacological Agents

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## ABSTRACT

**Objective:** Benzothiazole moiety containing various functional groups are found to have broad spectrum of biological activity and diverse chemical reactivity. The various pharmacological properties shown by the benzothiazole scaffolds were antitumor, anti-inflammatory, analgesic, antimicrobial, antileishmanial, anticonvulsant, and anti HIV properties. Keeping this in mind a series of (2-(benzo[*d*]thiazol-2-ylmethoxy)-5-substitutedphenyl) (substitutedphenyl) methanone scaffolds **4a–f** has been designed, synthesized and characterized for suitable pharmacological properties. **Methods:** A series of (2-(benzo[*d*]thiazol-2-ylmethoxy)-5-substitutedphenyl) (substitutedphenyl) methanone scaffolds **4a–f** has been synthesized by two steps chemical reactions by conventional stirring method at 40°C. Purification of the title compounds was achieved by silica gel flash column chromatography method. The characterization of the newly synthesized compounds was achieved by means of IR, NMR ($^1$H and $^{13}$C) and HRMS methods. **Results:** The yield of the title compounds were found to be satisfactory in the range of 66–79%. Purity of the compounds were found up to 99.36% by HPLC method. Compounds **4a**, **4b**, **4c**, **4d**, and **4e** were studied for single crystal X-ray studies and detailed interactions are reported. **Conclusion:** Reactions performed to achieve benzothiazole scaffolds **4a–f** were environmentally friendly and yielded satisfactory purity and yield. The purified and characterized title compounds are proposed for suitable pharmacological activities in the following communication.

**Key words:** Benzothiazole analogues, Synthesis, Pharmacological properties, Characterization, Antimosquito, Anti-HIV.

## KEY MESSAGE

The title compounds **4a–f** synthesized by chemical reaction at room temperature was environmentally friendly and yielded satisfactory yield. From the point of pharmacological significance they have been aimed to screen for anti-TB and anti-HIV properties.

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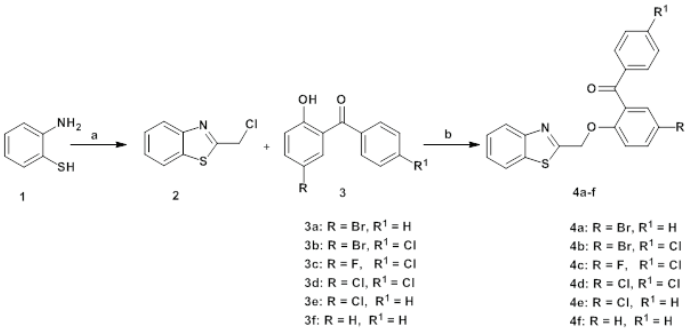
## INTRODUCTION

Benzothiazole analogues have been reported for various pharmacological activities, such as those associated with antitumor,[1] anti-inflammatory,[2] analgesic,[3, 4] antimicrobial,[5, 6] antileishmanial,[7, 8] antimosquito,[9] anticonvulsant,[10, 11] and anti-HIV agents.[12] Keeping all these observations in mind, and in continuation of research on search for cost effective catalysts[13, 14] for the construction of heterocyclic compounds for promising pharmacological properties[15-18] and method developments,[19] in the present investigation, it was envisaged for the design and synthesis of a series of (2-(benzo[d]thiazol-2-ylmethoxy)-substitutedphenyl)(4-substitutedphenyl)methanones 4a–f. The synthesis of the title compounds 4a–f was carried out via reaction between 2-(chloromethyl)-benzo[*d*]-thiazole 2 and 2-hydroxysubstitutedaryl-(substitutedaryl)-methanones 3a–f in dry tetrahydrofuran medium in the presence of potassium carbonate, as depicted in Scheme 1.




**Scheme 1:** Synthetic scheme for the construction of 4a-f. Reagents and conditions: a) chloroacetic acid, polyphosphoric acid, 8h reflux; b) $K_2CO_3$, dry THF, 40°C, overnight.

## METHODS AND MATERIALS

### *General chemistry*

The chemicals were procured from Sigma-Aldrich Co. Reactions were monitored using thin-layer chromatography (TLC) and LC-MS. TLC was performed on Merck 60 F-254 silica gel plates with visualization by ultraviolet (UV) light using ethyl acetate: n-hexane as a solvent system. The melting points were determined on a Büchi Melting Point B-545 apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland). The IR spectra were recorded on a Nicolet 6700 Fourier transform infrared (FT-IR) spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). $^1$H and $^{13}$C NMR spectra were recorded on Bruker AVANCE III 400 MHz instruments (Bruker Corporation, Billerica, MA, USA) with $CDCl_3$ as a solvent. Chemical shifts (δ) were indicated in parts per million downfield from tetramethylsilane, and the coupling constants (*J*) were recorded in Hertz. The splitting pattern is abbreviated as follows: s, singlet; d, doublet; m, multiplet. Mass spectra were recorded using the LC-MS-Agilent 1100 series (Agilent Technologies, Santa Clara, CA, USA) with a mass selective detector (MSD) (ion trap) using 0.1% aqueous trifluoroacetic acid (TFA) in an acetonitrile system on a C18-BDS column for a

duration of 10 minutes. HRMS were acquired using a Bruker MicroToF Q11 time-of-flight mass spectrometer (Bruker Corporation). Clog*P* of the title compounds was determined using ChemBioDraw Ultra v. 13.0 (PerkinElmer, Inc.). The purity of the compounds was assessed using the high-performance liquid chromatography (HPLC) method.

### *Procedure involved in the synthesis of 2-(chloromethyl)-benzo[d]-thiazole (2)*

A mixture of chloroaceticacid (3.72 g, 0.040 mol) and polyphosphoric acid (8 g) was heated to 180°C and 2-aminobenzenethiol (4 g, 0.032 mol) was added and stirred at reflux for 8 h. After cooling, the reaction mixture was basified with 5 N sodium hydroxide and the solution was extracted with chloroform (4 x 20 mL). The organic layer was dried over sodium sulfate and removed under vacuum. The residue obtained was purified by column chromatography on silica gel using ethyl acetate and *n*-hexane as an eluent to yield yellow oil in 61.27% yield. $^1$H NMR (400 MHz $CDCl_3$,): δ = 4.96 (s, 2H, $OCH_2$), 7.41-7.54 (m, 2H, Ar-H), 7.90-7.92 (m, 1H, Ar-H), 8.02-8.05 (m, 1H, Ar-H). LC-MS: m/z 183.6 ($M^+$). Anal. calcd. for $C_8H_6ClNS$: C, 52.32; H, 3.29; N, 7.63 Found C, 52.22; H, 3.31; N, 7.69.

### *General procedure for the synthesis of (2-(benzo[d]thiazol-2-ylmethoxy)-substitutedphenyl)(4-substitutedphenyl)methanone (4a-f)*

To a solution of 2-(chloromethyl)-benzo[*d*]-thiazole (0.5 g, 0.0027 mol) and (2-hydroxysubstitutedphenyl) (substitutedphenyl) methanone (0.0027 mol) in dry THF, dry potassium carbonate (0.380 g, 0.0027 mol) was added and stirred at 40°C overnight. The reaction mixture was concentrated to remove solvent and diluted with ethyl acetate, washed with water, brine solution and dried over anhydrous sodium sulfate. The organic layer was concentrated to yield residue and purified by silica gel flash column chromatography using ethyl acetate and *n*-hexane as eluent.

### *(2-(benzo[d]thiazol-2-ylmethoxy)-5-bromophenyl)(phenyl)methanone (4a)*

A white solid ($R_f$ = 0.71). IR ($cm^{-1}$): 3061 (ArC-H), 1654 (C=O), 1584 (C=N), 1523, 1475 (C=C), 662 (C-Br). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.36 (s, 2H, $OCH_2$), 6.95-6.98 (d, *J* = 8.00Hz, 1H), 7.32-7.36 (m, 1H), 7.42-7.46 (m, 3H), 7.52-7.56 (m, 3H), 7.76-7.84 (m, 3H), 7.93-7.95 (d, *J* = 8.12Hz, 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 68.72, 114.61, 114.84, 121.96, 123.24, 125.51, 126.39, 128.74, 130.10, 131.46, 132.66, 133.70, 134.77, 135.26, 137.40, 152.87, 154.55, 167.34, 194.49. HRMS calculated for $C_{21}H_{15}BrNO_2S$ ($M+H^+$) 424.0001 found 424.0014.

### *(2-(benzo[d]thiazol-2-ylmethoxy)-5-bromophenyl)(4-chlorophenyl) methanone (4b)*

A brown solid ($R_f$ = 0.75). IR ($cm^{-1}$): 3068 (ArC-H), 1653 (C=O), 1584 (C=N), 1520, 1488 (C=C), 756 (C-Cl), 528 (C-Br). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.37 (s, 2H, $OCH_2$), 6.96-6.99 (m, 1H), 7.35-7.56 (m, 6H), 7.75-7.81 (m, 3H), 7.94-7.96 (d, *J* = 8.08Hz, 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 68.70, 114.76, 114.93, 122.06, 123.40, 125.70, 126.55, 129.18, 130.98, 131.48, 132.77, 135.22, 135.91, 140.33, 152.96, 154.57, 166.97, 193.39. HRMS calculated for $C_{21}H_{14}BrClNO_2S$ ($M+H^+$) 457.9612 found 457.9598.

### *(2-(benzo[d]thiazol-2-ylmethoxy)-5-fluorophenyl)(4-chlorophenyl) methanone (4c)*

A yellow solid ($R_f$ = 0.70). IR ($cm^{-1}$): 3068 (ArC-H), 1653 (C=O), 1584 (C=N), 1520, 1488 (C=C), 1087 (C-F), 756 (C-Cl). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.35 (s, 2H, $OCH_2$), 7.02-7.06 (m, 1H), 7.13-7.15 (m, 2H), 7.34-7.47 (m, 4H), 7.64-7.81 (m, 3H), 7.94-7.96 (m. 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 69.18, 114.68, 116.85, 118.71, 122.02, 123.30, 125.62, 126.47, 129.09, 131.44, 135.22, 135.85, 140.17, 151.58, 152.88, 156.46, 158.88, 167.28, 193.51. HRMS calculated for $C_{21}H_{14}ClFNO_2S$($M+H^+$) 398.0412 found 398.0413.

### *(2-(benzo[d]thiazol-2-ylmethoxy)-5-chlorophenyl)(4-chlorophenyl) methanone (4d)*

A brown solid ($R_f$ = 0.73). IR ($cm^{-1}$): 3062 (ArC-H), 1652 (C=O), 1592 (C=N), 1519, 1478 (C=C), 755 (C-Cl). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.37 (s, 2H, $OCH_2$), 7.01-7.04 (d, *J* = 8.64Hz, 1H), 7.37-7.48 (m, 6H), 7.76-7.81 (m, 3H), 7.94-7.96 (d, *J* = 8.12Hz, 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 68.79, 114.50, 122.03, 123.33, 125.68, 126.51, 127.63, 129.11, 129.93, 130.54, 131.43, 132.17, 135.22, 135.87, 140.21, 152.87, 154.01, 166.98, 193.44. HRMS calculated for $C_{21}H_{14}Cl_2NO_2S$ ($M+H^+$) 414.0117 found 414.0118.

### *(2-(benzo[d]thiazol-2-ylmethoxy)-5-chlorophenyl)(phenyl)methanone (4e)*

A white solid ($R_f$ = 0.68). IR ($cm^{-1}$): 3062 (ArC-H), 1653 (C=O), 1593 (C=N), 1523, 1477 (C=C), 758 (C-Cl). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.37 (s, 2H, $OCH_2$), 7.01-7.03 (m, 1H), 7.32-7.46 (m, 6H), 7.53-7.56 (m, 1H), 7.77-7.85 (m, 3H), 7.93-7.95 (d, 8.16Hz, 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 68.82, 114.47, 121.98, 123.25, 125.52, 126.40, 127.47, 128.76, 129.87, 130.12, 131.08, 131.83, 133.72, 135.27, 137.43, 152.89, 154.05, 167.43, 194.64. HRMS calculated for $C_{21}H_{15}ClNO_2S$ ($M+H^+$) 380.0507 found 380.0502.

### *(2-(benzo[d]thiazol-2-ylmethoxy)phenyl)(phenyl)methanone (4f)*

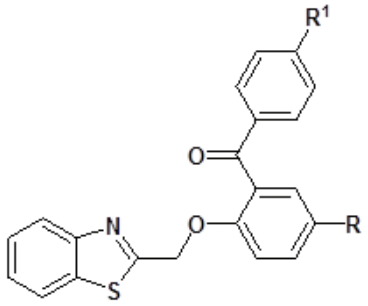
A brown solid ($R_f$ = 0.61). IR ($cm^{-1}$): 3062 (ArC-H), 1653 (C=O), 1593 (C=N),1477 (C=C), 758 (C-Cl). $^1$H NMR (400MHz, $CDCl_3$): δ = 5.41 (s, 2H, $OCH_2$), 7.03-7.06 (m, *J* = 9.51Hz, 1H), 7.26-7.50 (m, 6H), 7.56-7.60 (m, 1H), 7.80-7.88 (m, 3H), 7.97-7.99 (d, 8.07Hz, 1H). $^{13}$C NMR (400MHz, $CDCl_3$): δ = 68.59, 114.31, 121.81, 123.16, 125.43, 126.29, 127.31, 128.67, 129.78, 130.08, 131.01, 131.66, 133.64, 135.18, 137.37, 152.75, 154.00, 167.42, 194.57. HRMS calculated for $C_{21}H_{15}NO_2S$ ($M+H^+$) 346.0721 found 346.0722.

## RESULTS AND DISCUSSION

### *Chemistry*

The 2-hydroxysubstituted aryl-(substitutedaryl)-methanones 3a–f were prepared according to a procedure described in the literature.[20] Conversely, 2-(chloromethyl)-benzo[*d*]-thiazole 2 was synthesized from the equimolar reactions of 2-aminobenzenethiol 1 and 2-chloroacetic acid in the presence of polyphosphoric acid according to the described procedure.[21] The title compounds 4a–f were characterized by infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) ($^1$H and $^{13}$C), and high-resolution mass spectrometry (HRMS). The yield and purity of compounds 4a–f were found to be in the range of 66–79 and >99.36%, respectively. The physicochemical characteristics of the title compounds are reported in Table 1. In the proton NMR spectrum of an intermediate 2-(chloromethyl)-benzo[*d*]-thiazole (2), the methylene protons are observed at δ 4.96 and the molecular mass of the compound is in agreement with the molecular ion peak of 183.6 ($M^+$) on liquid chromatography–mass spectrometry (LC-MS). The IR spectra of the title compounds {2-(benzo[*d*]-thiazol-2-yl-methoxy)-substitutedaryl}-(substitutedaryl)-methanones 4a–f exhibited characteristic carbonyl stretching in the range of 1651–1654 $cm^{-1}$. The proton NMR spectra of compounds 4a–f exhibited singlet methylene protons in the range of δ 5.39–5.41 and carbonyl carbon at δ 193.01–194.33 in the $^{13}$C NMR spectra as well. With respect to HRMS, the molecular ion peaks of title compounds 4a–f were in compliance with the proposed molecular weight. The Clog*P* value of the title compounds 4a–f was calculated using the ChemBioDraw Ultra software (v. 13.0; PerkinElmer, Inc., Waltham, MA, USA) and the values were in the range of 3.9589–6.7397. It was shown that heterocyclic compounds tend to exhibit polymorphic,[22] pseudopolymorphic,[23] and

**Table 1: Physicochemical characteristics of 2-substituted benzothiazole analogues 4a-f**




| Compound | R | $R^1$ | M. F (M. Wt.) | Yield (%)[a] | m.p.(°C) | Clog*P* [b] |
|---|---|---|---|---|---|---|
| 4a | Br | H | $C_{21}H_{14}BrNO_2S$ (422.9929) | 77.62 | 133-134 | 6.0107 |
| 4b | Br | Cl | $C_{21}H_{13}BrClNO_2S$ (456.9539) | 64.00 | 177-178 | 6.7397 |
| 4c | F | Cl | $C_{21}H_{13}ClFNO_2S$ (397.0340) | 78.05 | 146-147 | 6.0541 |
| 4d | Cl | Cl | $C_{21}H_{13}Cl_2NO_2S$ (413.0044) | 83.21 | 175-176 | 6.5897 |
| 4e | Cl | H | $C_{21}H_{14}ClNO_2S$ (379.0434) | 70.80 | 130-131 | 4.7137 |
| 4f | H | H | $C_{21}H_{15}NO_2S$ (345.0823) | 68.21 | 112-113 | 3.9589 |

[a] All the yields are on isolated basis. Purified by silica gel flash column chromatography employing ethyl acetate: n-hexane (7:3) as solvent system.

[b] Clog*P* was calculated using ChemBioDraw Ultra software v13.0.

concomitant polymorphic[24] behavior. Keeping this in mind, an attempt was made to screen the title compounds 4a,[25] 4b,[26] 4c,[27] 4d,[28] and 4e[29] for polymorphic behavior using single crystal X-ray studies; none of the compounds exhibited polymorphic behavior.

## CONCLUSION

Title compounds {2-(benzo[*d*]-thiazol-2-yl-methoxy)-substitutedaryl}-(substitutedaryl)-methanones **4a–f** have been synthesized by two steps chemical reaction. The yield and purity of the compounds were found to be satisfactory. The title compounds are further aimed to screen for suitable pharmacological properties.

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## CONFLICT OF INTEREST

No conflict of interest are declared.

## ABBREVIATION USED

**FT-IR:** Fourier transform infrared; **NMR:** Nuclear magnetic resonance; **HRMS:** High resolution mass spectrometry; **TLC:** Thin layer chromatography; **LC-MS:** Liquid chromatography–mass spectrometry; **HPLC:** High-performance liquid chromatography.

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