ИЗВЕСТИЯ ВЫСШИХ УЧЕБНЫХ ЗАВЕДЕНИЙ.
Т 68 (10) Серия «**ХИМИЯ И ХИМИЧЕСКАЯ ТЕХНОЛОГИЯ**» 2025

V 68 (10) **ChemChemTech** 2025

DOI: 10.6060/ivkkt.20256810.7227

# СИНТЕЗ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ НЕКОТОРЫХ ПРОИЗВОДНЫХ БЕНЗО[*d*]ТИАЗОЛА, СОДЕРЖАЩИХ АМИДНУЮ СВЯЗЬ

**Нгуен Дык Зу, Фам Хыу Зьен, Нгуен Тхи Тхак Тхао, Нгуен Тхи Нгок Май, Нгуен Ван Дат, Зыонг Куок Хоан**

Нгуен Дык Зу (ORCID 0009-0003-8221-057X), Фам Хыу Зьен (ORCID 0009-0004-2799-4401), Нгуен Тхи Тхак Тхао (ORCID 0009-0002-7510-1722), Нгуен Ван Дат (ORCID 0009-0007-4623-6819), Зыонг Куок Хоан (ORCID 0000-0001-7540-6142)

Факультет химии, Ханойский национальный педагогический университет, 136 Суан Тху, Каузяй, Ханой, Вьетнам
E-mail: hoandq@hnue.edu.vn

Нгуен Тхи Нгок Май (ORCID 0000-0002-9639-1696)

Кафедра науки, Университет Хонг Дык, Тханьхоа, Вьетнам

***Девять новых производных бензо[d]тиазола (E1–E9), содержащих амидную связь, были успешно синтезированы с использованием эффективной реакции конденсации между карбоновыми кислотами и аминами. В качестве конденсирующего реагента применяли гексафторфосфат азабензотриазолтетраметил урония (HATU), что позволило провести реакцию в мягких условиях. Данный метод обеспечил получение целевых соединений с высоким выходом (75–90%), что свидетельствует о его высокой эффективности и практической применимости. Для подтверждения структуры синтезированных соединений использовали современные спектроскопические методы анализа, включая инфракрасную (IR) спектроскопию, ядерный магнитный резонанс (NMR) и масс-спектрометрию (MS). Полученные спектральные данные убедительно подтвердили образование целевых бензо[d]тиазольных структур, а также позволили провести детальный анализ их строения. Помимо разработки метода синтеза, в рамках исследования была проведена оценка биологической активности полученных соединений. В частности, цитотоксические свойства оценивали в отношении карциномы клеточной линии (KB). Полученные результаты показали, что соединения E1, E3, E4, E6 и E7 обладают умеренной ингибирующей активностью, демонстрируя значения $IC_{50}$, равные 48,29, 115,46, 89,36, 84,09 и 121,89 мкг/мл, соответственно. Однако соединения E6 и E7 не проявили значительной цитотоксической активности против других раковых клеточных линий, таких как Hep-G2, A549 и MCF7. Более того, исследование их антиоксидантных свойств также не выявило заметной активности. Дополнительно был проведен анализ антимикробных свойств соединений E1, E2, E3, E4, E5 и E8. Экспериментальные данные показали, что данные соединения не обладают выраженной активностью против как грамположительных (Gr(+)), так и грамотрицательных (Gr(-)) бактерий, а также неэффективны в отношении грибковых штаммов. Таким образом, проведенное исследование позволило получить новые производные бензо[d]тиазола, изучить их спектральные характеристики и оценить их биологическую активность. Полученные результаты вносят вклад в понимание взаимосвязи между структурой и биологической активностью этих соединений, а также подтверждают их перспективность в качестве возможных кандидатов для разработки новых противоопухолевых агентов.***

**Ключевые слова:** бензо[*d*]тиазол, амид, HATU, цитотоксическая активность, клеточная линия KB, антибактериальная активность, противогрибковая активность

# SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME BENZO[*d*]THIAZOLE DERIVATIVES CONTAINING AN AMIDE BOND

**Nguyen Duc Du, Pham Huu Dien, Nguyen Thi Thach Thao, Nguyen Thi Ngoc Mai, Nguyen Van Dat, Duong Quoc Hoan**

Nguyen Duc Du (ORCID 0009-0003-8221-057X), Pham Huu Dien (ORCID 0009-0004-2799-4401), Nguyen Thi Thach Thao (ORCID 0009-0002-7510-1722), Nguyen Van Dat (ORCID 0009-0007-4623-6819), Duong Quoc Hoan (ORCID 0000-0001-7540-6142)*

Department of Chemistry, Hanoi National University of Education, Hanoi, Vietnam
E-mail: hoandq@hnue.edu.vn*

Nguyen Thi Ngoc Mai (ORCID 0000-0002-9639-1696)

Department of Science, Hong Duc University, Thanh Hoa, Vietnam

***Nine novel benzo[d]thiazole derivatives (E1 – E9) featuring an amide bond were synthesized via an efficient coupling reaction between carboxylic acids and amines using hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) as the coupling reagent. The reaction was carried out under mild conditions, affording the desired products in high yields (75 – 90%). Structural characterization of the synthesized compounds was achieved using modern spectroscopic techniques, including infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS), which confirmed the formation of the targeted benzo[d]thiazole scaffolds. In addition to the synthetic work, the biological activities of selected compounds were evaluated. Cytotoxic activity was assessed against the carcinoma cell line (KB), revealing that compounds E1, E3, E4, E6, and E7 exhibited moderate inhibitory effects, with $IC_{50}$ values of 48.29, 115.46, 89.36, 84.09, and 121.89 μg/mL, respectively. However, compounds E6 and E7 did not show significant cytotoxicity against other cancer cell lines such as Hep-G2, A549, and MCF7, nor did they demonstrate noteworthy antioxidant activity. Furthermore, compounds E1, E2, E3, E4, E5, and E8 were inactive against both Gr(+) and Gr(-) bacteria as well as fungal strains. These findings provide valuable insight into the structure – activity relationships of benzo[d]thiazole derivatives and support their potential development as anticancer agents.***

**Keywords:** benzo[*d*]thiazole, amide, HATU, cytotoxic activities, KB cell line, antibacterial, antifungal

**Для цитирования:**
Нгуен Дык Зу, Фам Хыу Зьен, Нгуен Тхи Тхак Тхао, Нгуен Тхи Нгок Май, Нгуен Ван Дат, Зыонг Куок Хоан Синтез и биологическая активность некоторых производных бензо[*d*]тиазола, содержащих амидную связь. *Изв. вузов. Химия и хим. технология*. 2025. Т. 68. Вып. 10. С. 19–25. DOI: 10.6060/ivkkt.20256810.7227.

**For citation:**
Nguyen Duc Du, Pham Huu Dien, Nguyen Thi Thach Thao, Nguyen Thi Ngoc Mai, Nguyen Van Dat, Duong Quoc Hoan Synthesis and biological activities of some benzo[*d*]thiazole derivatives containing an amide bond. *ChemChemTech* [*Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*]. 2025. V. 68. N 10. P. 19–25. DOI: 10.6060/ivkkt.20256810.7227.

## INTRODUCTION

Benzo[*d*]thiazole is one of the most important derivatives within the group of compounds containing the thiazole ring. They are a rare heterocyclic compound found in alkaloids and play a highly significant role in pharmaceutical chemistry for the development of new drugs [1]. The presence of sulfur atoms in the structure of benzo[*d*]thiazole derivatives imparts distinctive properties that are not found in other heterocyclic compounds. Benzo[*d*]thiazole derivatives containing amide bonds often exhibit intriguing structural characteristics and demonstrate excellent biological activities, such as anticancer [2]; anti-inflammatory [3]; antifungal [4]; and chronic pain suppression properties [5]. Because the molecular framework exhibits a broad spectrum of biological activity in pharmaceuticals, there is an increasing amount of research focused on synthesizing derivatives containing benzo[*d*]thiazole heterocycle. Besides, the amide bond is one of the most common bonds in organic molecules and biological compounds [6-10]. The amide bond is highly prevalent in natural biological molecules due to its stability under various reaction conditions (acidic and basic conditions), elevated temperatures, and the presence of other chemicals [11]. In this report, benzo[*d*]thiazole

derivatives containing amide bond were synthesized by carrying out the benzo[*d*]thiazole ring-closing reaction under irradiation of a domestic microwave oven and subsequently formation of the amide bond using HATU as a coupling reagent.

## MATERIALS AND METHODS

*Materials*

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck Corp, Aladdin, Vietnam, or other Chinese companies were used as received, unless indicated in. NMR spectra were recorded on a Bruker AVANCE 600 MHz spectrometer in DMSO-$d_6$ at 298-300 K. Chemical-shift data for each signal was reported in ppm units. IR spectra were recorded on the Mattson 4020 GALAXY Series FT-IR. Mass spectra were recorded on the Agilent LC-MSD-Trap-SL series 1100 spectrometer. Melting points were measured using a Gallenkamp melting point apparatus. A domestic oven Sharp R-205VN-S, made in China 2022, was used to carry out the reactions.

All cell culture media, sera, and reagents were from GIBCO Co. Ltd. (Grand Island, New York, USA). The Human epithelial carcinoma cell (KB), hepatocellular carcinoma cells (Hep-G2), lung cancer cells (A549) and breast cancer cells (MCF7) were supplied by the Institute of Biotechnology, Vietnam Academy of Science and Technology.

*Methods*

*Synthesis of ethyl 2-(4-(benzo[d]thiazol-2-yl)phenol)acetate (**C**)*

A mixture of anhydrous potassium carbonate (200 mg, 1.5 mmol), ethyl chloroacetate (0.85 mL, 1.0 mmol), and NaI (150 mg, 1.0 mmol) was added into a round-bottom flask containing **B** (113.5 mg, 0.5 mmol) in DMF (3 mL). The mixture was then refluxed for 2 h at room temperature until TLC (ethyl acetate/*n*-hexane, 1:1) showed the total consumption of the starting material. After removal of DMF, the crude mixture was re-crystallized in 96° ethanol to give **C** in about 82% yield, respectively.

*Synthesis of 2-(4-(benzo[d]thiazol-2-yl)phenoxy)acetic acid (**D**)*

A mixture of 2-(4-(benzo[*d*]thiazol-2-)phenoxy) acetate (**C**) (313 mg, 1.0 mmol) and NaOH 1M (5 mL, 200 mg NaOH, 5 mL $H_2O$) was refluxed at 100 °C for 2 h. The solution was cooled to room temperature, then 5% hydrochloric acid was added until pH = 5, and a white precipitate appeared. The precipitate was filtered and recrystallized in 96° ethanol to obtain **D**, yield 85%.

*Synthesis of benzo[d]thiazole derivatives containing an amide bond **E1** – **E9***

*General procedure*

A mixture of 2-(4-(benzo[*d*]thiazol-2-yl)phenoxy)acetic acid (**D**) (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol), *N*-methylmorpholine (NMM, 1.1 mL, 1 mmol) were added into a round-bottom flask containing the amine (0.5 mmol) in DMF (5 mL). The mixture was stirred at room temperature for about 3 h until TLC (ethyl acetate/*n*-hexane, 1:1) showed the total consumption of the starting material. The precipitate was filtered and recrystallized in 96$^o$ ethanol to obtain **E1 – E9**, yield 75-90%.

*Synthesis of 2-(4-(benzo[d]thiazol-2-yl)phenoxyl)-N-ethylacetamide (**E1**)*

Compound **E1** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 90% as a white solid, mp. = 178-179 °C. IR ν ($cm^{-1}$): 3440 ; 1763, 1650; 1210, 1252, 1293, 1482; 1006, 1026, 1050; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 8.09 (d, *J* = 8.4, 1H, H5); 8.01 (t, *J* = 8.4; 6.6, 3H, H2, H9/H13); 7.51 (t, *J* = 7.8, 1H, H3); 7.41 (t, *J* = 7.8, 1H, H4); 7.11 (d, *J* = 7.8, 2H, H10/H12); 4.89 (s, 2H, H14); 4.19 (q, *J* = 7.2, 2H, H16); 1.22 (t, *J* = 7.2, 3H, H17); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 168.3 (C7); 166.8 (C15); 160.0 (C11); 153.6 (C1); 134.2 (C8); 128.7 (C6); 126.4 (C9/C13); 126.1 (C3); 125.1 (C4); 122.4 (C2); 122.1 (C5); 115.2 (C10/C12); 64.7 (C14); 60.7 (C16); 13.9 (C17). ESI-MS $[C_{17}H_{17}N_2O_2S]^+$ *m/z*: 313.1 $[M+H]^+$. *Anal*. Calcd for $C_{17}H_{16}N_2O_2S$ (M 312.39): C, 65.36; H, 5.16; N, 8.97. Found: C, 65.38; H, 5.13; N, 8.98.

*Synthesis of 2-(4-(benzothiazol-2-yl)phenoxyl)-N-phenyl acetamide (**E2**)*

Compound **E2** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 90% as a white solid, mp. = 196-197 °C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 10.15 (s, 1H, NH); 8.10 (d, *J* = 7.8 Hz, 1H, H5); 8.05 (m, *J* = 9.6; 2.0 Hz, 2H, H9/H13); 8.01 (d, *J* = 3.0 Hz, 1H, H2); 7.65 (d, *J* = 7.8 Hz, 2H, H17/H21); 7.52 (t, *J* = 1.2; 7.8 Hz, 1H, H3); 7.42 (td, *J* = 1.2; 8.4 Hz, 1H, H4); 7.33 (t, *J* = 8.4; 7.2 Hz, 2H, H18/H20); 7.19 (d, *J* = 9.0 Hz, 2H, H10/H12); 7.08 (t, *J* = 7.8 Hz, 1H, H19); 4.83 (s, 2H, H14); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 166.9 (C7); 166.0 (C15); 160.3 (C11); 153.6 (C1); 138.3 (C16); 134.2 (C8); 128.8 (C6); 128.7 (C18/20); 126.5 (C9/C13); 126.1 (C19); 125.1 (C3); 123.7 (C4); 122.5 (C2); 122.1 (C5); 119.7 (C17/C21); 115.4 (C10/C12); 67.13 (C14). ESI-MS $[C_{21}H_{17}N_2O_2S]^+$ *m/z*:

361.0, $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{16}N_2O_2S$ (M 360.43): C, 69.98; H, 4.47; N, 7.77. Found: C, 70.00; H, 4.44; N, 7.78.

*Synthesis of 2-(4-(benzothiazole-2-yl)phenoxyl)-N-(2-hydroxyethyl)acetamide (**E3**)*

Compound **E3** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 75% as a white solid, mp. = 187-189 °C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 8.08 (d, $J$ = 7.8, 1H, H5); 7.98 (d, $J$ = 8.4, 1H, H2); 7.97 (d, $J$ = 9.0, 2H, H9/H13); 7.50 (td, $J$ = 8.4; 1.2, 1H, H3); 7.40 (td, $J$ = 0.6; 7.8, 1H, H4); 6.99 (d, $J$ = 9, 2H, H10/H12); 4.32 (s, 2H, H14); 3.56 (t, $J$ = 4.8, 2H, H16); 2.81 (t, $J$ = 5.4, 2H, H17); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 170.7 (C7); 167.2 (C15); 161.6 (C11); 153.7 (C1); 134.1 (C8); 128.5 (C6); 126.4 (C9/C13); 124.9 (C3); 124.7 (C4); 122.3 (C2); 122.1 (C5); 115.2 (C10/C12); 67.3 (C14); 57.9 (C16). HR-MS (ESI +): *m/z* $[C_{17}H_{17}N_2O_3S]^+$, cald. 329.0954, found 329.0960. *Anal*. Calcd for $C_{17}H_{16}N_2O_3S$ (M 328.39): C, 62.18; H, 4.91; N, 8.53. Found: C, 62.20; H, 4.88; N, 8.54.

*Synthesis of 2-(4-(benzothiazol-2-yl)phenoxyl)-N-(4-bromophenyl)acetamide (**E4**)*

Compound **E4** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 90% as a white solid, mp. = 221-223 °C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 10.31 (s, 1H, NH); 8.12 (d, $J$ = 8.4 Hz, 1H, H5); 8.07 (d, $J$ = 3.6; 8.4 Hz, 2H, H9/H13); 8.02 (d, $J$ = 7.8 Hz, 1H, H2); 7.64 (m, 2H, H17/H21); 7.52 (m, 3H, H3, H18/H20); 7.43 (td, $J$ = 1.2; 8.4 Hz, 1H, H4); 7.19 (m, 2H, H10/H12); 4.83 (s, 2H, H14); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 166.8 (C7); 166.2 (C15); 160.2 (C11); 153.6 (C1); 137.7 (C16); 134.2 (C8); 131.5 (C6); 128.8 (C18/C20); 126.4 (C9/C13); 126.1 (C3); 125.1 (C4); 122.4 (C19); 122.1 (C2); 121.6 (C5); 115.4 (C17/C21); 115.3 (C10/C12); 67.1 (C14). ESI-MS *m/z*: $[C_{21}H_{16}{}^{81}BrN_2O_2S]$ 439.84, $[M+H]^+$; $[C_{21}H_{14}{}^{79}BrN_2O_2S]$ 437.28, $[M-H]^-$. *Anal*. Calcd for $C_{21}H_{15}BrN_2O_2S$ (M 439.33): C, 57.41; H, 3.44; N, 6.38. Found: C, 57.40; H, 3.42; N, 6.37.

*Synthesis of 2-(4-(Benzothiazole-2-yl)phenoxyl)-N-(4-nitrophenyl)acetamide (**E5**)*

Compound **E5** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 90% as a white solid (0.182 g, 90%), mp. = 215-217 °C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 10.63 (s, 1H, NH); 8.67 (t, $J$ = 2.4 Hz, 1H, H17); 8.11 (d, $J$ = 7.8 Hz, 1H, H5); 8.08 (m, 2H, H9/H13); 8.03 (td, $J$ = 1.2; 9.0 Hz, 2H); 7.96 (m, 1H, H2); 7.64 (t, $J$ = 8.4 Hz, 1H, H3); 7.52 (td, $J$ = 1.2; 8.4 Hz, 1H, H20); 7.44 (td, $J$ = 1.2; 8.4 Hz, 1H, H4); 7.21 (m, 2H, H10/H12); 4.89 (m, 2H, H14); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 166.9 (C7); 160.1 (C15); 153.6 (C1); 147.9 (C18); 139.4 (C16); 134.2 (C8); 130.1 (C6); 128.8 (C20); 126.4 (C9/C13); 126.2 (C21); 125.6 (C3); 125.1 (C4); 122.4 (C2); 122.1 (C5); 118.2 (C19); 115.5 (C10/C12); 113.8 (C17); 67.0 (C14). ESI-MS $[C_{21}H_{16}N_3O_4S]^+$ *m/z*: 405.8, $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}N_3O_4S$ (M 405.43): C, 62.21; H, 3.73; N, 10.36. Found: C, 62.22; H, 3.70; N, 10.37.

*Synthesis of N-(5-(benzothiazole-2-yl)-2-hydroxyphenyl)-2-(4-(benzothiazole-2-yl)-2-yl)phenoxyl)acetamide (**E6**)*

Compound **E6** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 85% as a white solid, mp. = 280 °C (decomposed). IR ν ($cm^{-1}$): 3417; 1651; 1026; 1003; 1049; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 9.44 (s, 1H, NH); 8.86 (s, 1H, OH); 8.11 (m; 4H, H2/H2', H9/H13); 8.01 (d, $J$ = 8.4 H; 2H, H5/H5'); 7.73 (dd; $J$ = 2.4; 8.4 Hz. 2H, H9', H13'); 7.52 (m; 2H, H3/H3'); 7.43 (m, 2H, H4/H4'); 7.23 (d; $J$ = 9.0 Hz; 2H, H10/H12); 7.07 (d; $J$ = 8.4 Hz. 1H, H10'); 4.96 (m, 2H, H14); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 167.3 (C7); 166.8 (C15); 166.3 (C7'); 160.0 (C11); 153.7 (C1/C1'); 153.6 (C11'); 150.3 (C8); 134.2 (C6/C6'); 134.1 (C12'); 128.9 (C13'); 126.5 (C6/C6'); 126.4 (C12'); 126.3 (C9/C13); 125.1 (C8'); 124.9 (C3/C3'); 124.1 (C4'); 124.0 (C4); 122.5 (C9'); 122.3 (C5/C5'); 122.2 (C2'); 122.1 (C2); 119.6 (C10'); 115.5 (C10/C12); 67.1 (C14). ESI-MS m/z: $[C_{28}H_{18}N_3O_3S_2]^-$ 508.0, $[M-H]^-$; $[C_{28}H_{20}N_3O_3S_2]^+$ 510.0 $[M+H]^+$. *Anal*. Calcd for $C_{28}H_{19}N_3O_3S_2$ (M 509.59): C, 65.99; H, 3.76; N, 8.25. Found: C, 66.01; H, 3.73; N, 8.24.

*Synthesis of N-(6-(benzothiazol-2-yl)-3-hydroxy-3-methoxyphenyl)-2-(4-(benzothiazol-2-yl)-2-yl)phenoxyl)actamide (**E7**)*

Compound **E7** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 85% as a white solid, mp. = 289 °C (decomposed). IR ν ($cm^{-1}$): 3417; 1651; 1026; 1003; 1049; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 9,4 (s, 1H, NH); 8.48 (s, 1H, OH); 8.10 (m, 4H, H2/H2', H9/H13); 8.02 (m, 2H, H5/H5'); 7.54 (m, 2H, H9', H13'); 7.42 (m, 4H, H3/H3', H4/H4'); 7.21 (m, 2H, H10/H12) 4.99 (s, 2H, H14); 3.96 (s, 3H, $OCH_3$); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 167.4 (C7); 166.8 (C15); 166.3 (C7'); 160.2 (C11); 153.6 (C1/C1'); 151.7 (C11'); 147.9 (C8); 134.6 (C6/C6'); 134.2 (C12'); 128.9 (C13'); 126.7 (C6/C6'); 126.5 (C12'); 126.3 (C9/C13);

125.1 (C8'); 123.5 (C3/C3'); 122.9 (C4'); 122.5 (C4); 122.4 (C9'); 122.1 (C5/C5'); 115.5 (C2'); 115.3 (C2); 113.8 (C10'); 106.5 (C12/C12); 67.1 (C14); 56.5 ($OCH_3$). ESI-MS *m/z*: $[C_{29}H_{22}N_3O_4S_2]^+$ 540.0, $[M+H]^+$; $[C_{29}H_{20}N_3O_4S_2]^-$ 538.0, $[M-H]^-$. *Anal*. Calcd for $C_{29}H_{21}N_3O_4S_2$ (M 539.62): C, 64.55; H, 3.92; N, 7.79. Found: C, 64.56; H, 3.90; N, 7.80.

*Synthesis of 2-(4-(benzothiazol-2-yl)phenoxyl)-N-(p-tolyl)acetamide (**E8**)*

Compound **E8** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 85% as a white solid, mp. = 225-227 °C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 10.04 (s, 1H, NH); 8.12 (d, *J* = 7.8 Hz, 1H, H5); 8,06 (dd; *J* = 1.8; 7.2 Hz; 2H, H9/H13); 8.02 (d, *J* = 7.8 Hz; 1H, H2); 7.52 (m, 3H, H3, H17/H21); 7.44 (td; *J* = 1.2; 8.4 Hz; 1H, H4); 7.19 (d; *J* = 9.0 Hz; 2H, H18/H20); 7.14 (d; *J* = 8.4 Hz; 2H, H10/H12); 4.80 (s, 2H, H17); 2.25 (s, 3H, H22); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 166.88 (C15); 165.7 (C7); 160.3 (C11); 153.6 (C1); 135.7 (C19); 134.2 (C16); 132.6 (C8); 129.0 (C6); 128.8 (C18/C20); 126.4 (C9/C13); 126.0 (C3); 125.1 (C4); 122.4 (C5); 122.1 (C2); 119.7 (C17/C21); 115.4 (C10/C12); 67.1 (C14); 20.3 (C22). ESI-MS $[C_{22}H_{19}N_2O_2S]^+$ *m/z:* 374.9, $[M+H]^+$. *Anal*. Calcd for $C_{22}H_{18}N_2O_2S$ (M 374.45): C, 70.57; H, 4.85; N, 7.48. Found: C, 70.59; H, 4.81; N, 7.49.

*Synthesis of 2-(4-(benzothiazole-2-yl)phenoxyl)-N-(4-chlorophenyl)acetamide (**E9**)*

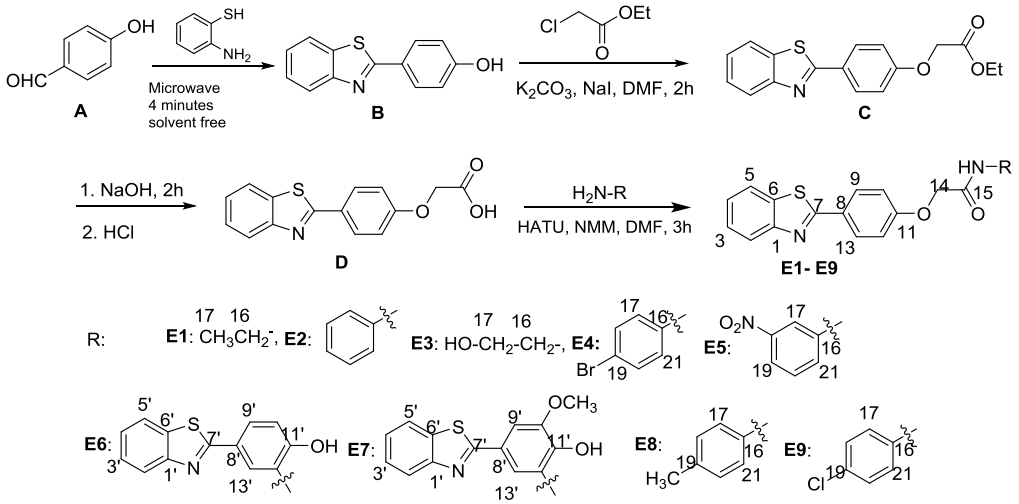
Compound **E9** was synthesized from **D** (129 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and NMM (1.1 mL, 1 mmol) by following the general procedure with a yield of 90% as a white solid, mp. = 205-206 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ (ppm): 10,28 (s, 1H, NH); 8.12 (d, *J* = 7.8 Hz; 1H, H5); 8.07 (dd; *J* = 2.4; 10.8 Hz; 2H, H9/H13); 8.02 ( d, *J* = 8.4 Hz; 1H, H2); 7.68 (dd, *J* = 3.0; 8.4 Hz; 2H, H17/H21); 7.52 (td; *J* = 1.8; 7.8 Hz; 1H, H3); 7.43; (td; *J* = 1.2; 8.4 Hz, 1H, H4); 7.39 (m, 2H, H18/H20); 7.19 (m, 2H, H10/H12); 4.83 (s, 2H, H14); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ (ppm): 166.8 (C16); 166.2 (C7); 160.2 (C11); 153.6 (C6); 137.2 (C16); 134.2 (C8); 128.8 (C1); 128.6 (C19); 127.3 (C18/C20); 126.4 (C9/C13); 126.1 (C4); 125.1 (C3); 122.4 (C2); 122.1 (C5); 121.2 (C17/C21); 115.4 (C10/C12); 67.0 (C14). ESI-MS $[C_{21}H_{16}ClN_2O_2S]^+$ *m/z*: 395.09, $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}ClN_2O_2S$ (M 394.87): C, 63.88; H, 3.83; N, 7.09. Found: C, 63.87; H, 3.80; N, 7.10.

*Bioassay*

The cytotoxicity assessment of the synthesized compounds followed the protocol outlined by the American National Cancer Institute (NCI) [12-13]. First, the cancer cell lines were cultivated as monolayers in a culture medium comprising 2 mM *L*-glutamine, 10 mM HEPES, 1.0 mM sodium pyruvate, and supplemented with 10% fetal bovine serum (FBS) from GIBCO. Next, the cells were cultured for 3-5 days at 37 °C in a humidified atmosphere with 5% $CO_2$. In each well, the cell lines were exposed to 20 µL of samples at concentrations of 20 µg/mL, 0.8 µg/mL, and 0.16 µg/mL. Then the plates were further incubated for 48 h. Following removal of the medium, the cells were fixed using a 10% trifluoroacetic acid solution. $IC_{50}$ values were calculated using the Probit method. Ellipticine (Sigma) served as a positive control, and the reported values for the compounds represent the average of three determinations.

## RESULTS AND DISCUSSIONS

The synthetic process of benzo[*d*]thiazole derivatives containing amide bond was shown in Scheme.




Scheme. Synthesis of benzothiazole derivatives containing an amide bond **E1** – **E9**
Схема. Синтез производных бензотиазола, содержащих амидную связь **E1** – **E9**

The benzo[*d*]thiazole cyclization was carried out according to our protocol using a domestic microwave oven to give **B** in high yield [14-15]. Ester **C** was synthesized from **B** by the method of D. Q. Hoan with yield of 82% [16]. Ester **C** was hydrolyzed in a NaOH solution, followed by acidification of the resulting mixture with an HCl solution. Acid **D** can be easily obtained with a yield of 85%. Finally, the compounds **E1 – E9** were synthesized through a cross-coupling reaction between acid **D** and various amines. Numerous cross-coupling agents have been reported for this reaction. Specifically, the DCC (dicyclohexyl carbodiimide) reagent was introduced by Sheehan and Hess in 1955 [17-18]; the EEDQ (2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) reagent was developed by Belleau and Malek in 1968 [19-20]; and a recent report by Siutkina *et al.* in 2022 also described an amide formation reaction *via* a lactone and amine under high-temperature heating conditions [21]. However, in this report, our group employed the cross-coupling agent HATU (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium) [22]. Under the influence of this reagent, the cross-coupling reaction was carried out very efficiently under room temperature conditions, and the resulting product was easily purified. The final products obtained exhibited very good yields (75-90%). Characteristics of **E2**, **E8** and **E9** were compared with results reported by Diab *et al.* [23].

Compounds **E6** and **E7** were selected for antioxidant activity testing due to the presence of phenolic hydroxy groups within their molecular structures [24]. However, both of these compounds exhibited negligible antioxidant activity, as indicated by $SC_{50}$ > 200 μg/mL. The antioxidant activity data are shown in Table 1.

***Table 1***

**Antioxidant activity of compounds E6 and E7**

***Таблица 1.* Антиоксидантная активность соединений E6 и E7**

| N⁰ | Sample | SC (%) | $SC_{50}$ (μg/ml) |
|---|---|---|---|
| Control | Ascorbic acid | 91.32 ± 0.21 | 18.82 |
| | DPPH | 0.0 ± 0.0 | - |
| 1 | **E6** | 15.24 ± 0.10 | > 200 |
| 2 | **E7** | 16.38 ± 0.11 | > 200 |

Compounds **E1**, **E2**, **E4**, **E6** and **E7** were selected for the investigation of antibacterial activity. However, all of these compounds exhibited no activity against both Gram (+), Gram (-) bacterial, as well as fungi, with MIC > 128 μg/mL. Compounds **E1** – **E9** were selected for cytotoxic activity testing against Epithelial carcinoma cells (KB). The results revealed that compounds **E1**, **E3, E4, E6** and **E7** exhibited inhibitory activity against KB cell lines with $IC_{50}$ values ranging from 48.29 to 121.89 μg/mL, in comparison to the control substance Ellipticine with an $IC_{50}$ of 0.4 μg/mL. The remaining compounds showed no significant activity with $IC_{50}$ > 128 μg/mL. The cytotoxic activity against KB cell lines data are shown in Table 2.

***Table 2***

**Cytotoxic activity of compounds E1 – E9 against KB cell lines**

***Таблица 2.* Цитотоксическая активность соединений E1–E9 по отношению клеточной линии KB**

| N⁰ | Sample | $IC_{50}$ (μg/mL) | | | |
|---|---|---|---|---|---|
| | | KB | Hep-G2 | A549 | MCF7 |
| Control substance | Ellipticine | 0.40 | 0.57 | 0.51 | 0.61 |
| 1 | **E1** | 48.29 | nd | nd | nd |
| 2 | **E2** | >128 | nd | nd | nd |
| 3 | **E3** | 115.46 | nd | nd | nd |
| 4 | **E4** | 89.36 | nd | nd | nd |
| 5 | **E5** | >128 | nd | nd | nd |
| 6 | **E6** | 84.09 | >128 | >128 | >128 |
| 7 | **E7** | 121.89 | >128 | >128 | >128 |
| 8 | **E8** | >128 | nd | nd | nd |
| 9 | **E9** | >128 | nd | nd | Nd |

Notes: nd - no data

Примечание: nd – данные отсутствуют

Compounds **E6** and **E7** were selected for cytotoxic activity testing against Hepatocellular carcinoma cells (Hep-G2), Lung cancer cells (A549) and Breast cancer cells (MCF7). The obtained results indicate that both compounds exhibited no activity against Hep-G2, A549 and MCF7 cell lines. The cytotoxic activity against Hep-G2, A549 and MCF7 cell lines data are shown in Table 2.

## CONCLUSIONS

Nine benzo[*d*]thiazole derivatives containing amide bond **E1 – E9** were synthesized from 4-hydroxy benzaldehyde in high yields. Compounds **E1, E3, E4, E5, E6, E7** are new. Structures of **E1 – E9** were determined with spectral analysis. Compounds **E6** and **E7** didn't exhibit antioxidant activity. Compounds **E1**, **E2**, **E4**, **E6** and **E7** didn't exhibit antibacterial activities against Gram (+), Gram (-) bacterial and fungi. Compounds **E1, E3, E4, E6** and **E7** exhibited activity against KB cell line with $IC_{50}$ values of 48.29; 115.46; 89.36; 84.09 and 121.89 μg/mL.

*Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.*

*The authors declare the absence of a conflict of interest warranting disclosure in this article.*

R E F E R E N C E S
Л И Т Е Р А Т У Р А


1. **Patel N.B., Shaikh F.M.** // *Sci. Pharm.* 2010. V. 78. N 4. P. 753 – 765. DOI: 10.3797/scipharm.1009-15.
2. **Gardner C.R, Cheung B.B, Koach J, Black D.S, Marshall G.M, Kumar N.** // *Bioorg. Med. Chem.* 2013. V. 20. N 23. P. 6877 – 6884. DOI: 10.1016/j.bmc.2012.09.035.
3. **Deb P.K, Kaur R, Chandrasekaran B, Bala M, Gill D, Kaki V.R, Akkinepalli R.R, Mailavaram R.** // *Med. Chem. Res.* 2014. V. 23. P. 2780–279. DOI: 10.1007/s00044-013-0861-4.
4. **Yamazaki K, Kaneko Y, Suwa K, Ebara S, Nakazawa K, Yasuno K.** // *Bioorg. Med. Chem.* 2005. V. 13. N 7. P. 2509 – 2522. DOI: 10.1016/j.bmc.2005.01.033.
5. **Thiel O.R, Bernard C, King T, Dilmeghaniseran M, Bostick T, Larsen R.D, Faul M.M.** // *Org. Chem.* 2008. V. 73. N 9. P. 3508 – 3515. DOI: 10.1021/jo8002216.
6. **Pattabiraman V.R, Bode J.W.** // *Nature*. 2011. V. 480. P. 471 – 479. DOI: 10.1038/nature10702.
7. **Hughes A.B.** Amino Acids, Peptides and Proteins in Organic Chemistry. Weinheim, Germany: Wiley-VCH. 2010. 510 p. DOI: 10.1002/9783527631803.
8. **Kaspar A.A, Reichert J.M.** // *Drug Discovery Today*. 2013. V. 18. N 17 – 18. P. 807–817. DOI: 10.1016/j.drudis.2013.05.011.
9. **Брель А.К., Лисина С.В., Будаева Ю.Н.** // *Изв. вузов. Химия и хим. технология.* 2024. Т. 67. Вып. 3. С. 103-110. **Brel A.K., Lisina S.V., Budaeva Yu.N.** // *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2024. V. 67. N 3. P. 103 - 110. DOI: 10.6060/ivkkt.20246703.6915.
10. **Мухторов Л.Г., Блохин И.В., Иванова Е.В., Шумский А.Н., Шахкельдян И.В., Атрощенко Ю.М.** // *Изв. вузов. Химия и хим. технология.* 2018. Т. 61. Вып. 12. С. 49-55. **Mukhtorov L.G., Blokhin I.V., Ivanova E.V., Shumsky A.N., Shakhkeldian I.V., Atroshchenko Yu.M.** // *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2018. V. 61. N 12. P. 49 – 55 (in Russian). DOI: 10.6060/ivkkt.20186112.5754.
11. **Thorner J, Emr S.D, Abelson J.N.** // *Methods Enzymol.* 2020. V. 326. P. 601 – 617.
12. **Likhitwitayawuid K, Angerhofer C.K, Cordell G.A, Pezzuto J.M, Ruangrungsi N.** // *J. Nat. Prod.* 1993. V. 56. N 1. P. 30 – 38. DOI: 10.1021/np50091a005.
13. **Skehan P., Storeng R., Scudiero D., Monks A., MxMahon J., Vistica D., Warren J.T., Bokesch H., Kenney S., Boyd M.R.** // *J. Natl. Cancer Inst.* 1990. V. 82. N 13. P. 1107 – 1112. DOI: 10.1093/jnci/82.13.1107.
14. **Duong Q.H, Vu T.A.T, Le T.D, Nguyen H.** // *Vietnam J. Chem., Int. Ed.* 2017. V. 55. P. 433 - 437. DOI: 10.15625/2525-2321.2017-00487.
15. **Duong Q.H, Nguyen M.L, Phan T.H, Hoang T.N.Q, Vu T.A.T.** // *J. Sci. HNUE Nat. Sci.* 2018. V. 63. N 6. P. 127 - 135. DOI: 10.18173/2354-1059.2018-0037.
16. **Nguyen T.N.M., Tran T.P.A., Pham T.T.M., Pham P.T., Nguyen V.T., Duong Q.H.** // *J. Sci. HNUE*. 2019. V. 64. N 6. P. 121 - 129. DOI: 10.18173/2354-1059.2019-0039.
17. **Sheehan J.C., Hess G.P.** // *J. Am. Chem. Soc.* 1955. V. 77. N 4. P. 1067 - 1068. DOI: 10.1021/ja01609a099.
18. **Sheehan J.C., Goodman M., Hess G.P.** // *J. Am. Chem. Soc.* 1956. V. 78. N 7. P. 1367 - 1369. DOI: 10.1021/ja01588a029.
19. **Bernard B, Martel R, Lacasse G, Menard M, Weinberg N.L, Perron Y.G.** // *J. Am. Chem. Soc.* 1968. V. 90. N 3. P. 823 - 824. DOI: 10.1021/ja01005a067.
20. **Belleau B., Malek G.** // *J. Am. Chem. Soc.* 1968. V. 90. N 6. P. 1651 - 1652. DOI: 10.1021/ja01008a045.
21. **Сюткина А.И., Чащина С.В., Махмудов Р.Р., Новикова В.В., Чернов И.Н., Игидов Н.М.** // *Изв. вузов. Химия и хим. технология.* 2022. Т. 65. Вып. 3. С. 74-82. **Siutkina A.I., Chashchina S.V., Makhmudov R.R., Novikova V.V., Chernov I.N., Igidov N.M.** // *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2022. V. 65. N 3. P. 74 – 82 (in Russian). DOI: 10.6060/ivkkt.20226503.6522.
22. **Han S.Y, Kim Y.A.** // *Tetrahedron*. 2004. V. 60. N 11. P. 2447–2467. DOI: 10.1016/j.tet.2004.01.020.
23. **Diab H.M, Mohamed D.M, Darweesh A.F, Abdelhamid I.A, Elwahy A.H.M.** // *J. Heterocyclic Chem.* 2023. V. 60. N 5. P. 754 – 767. DOI: 10.1002/jhet.4624.
24. **Shahidi F, Janitha P.K, Wanasundara P.D.** // *Crit. Rev. Food Sci. Nutr.* 1992. V. 32. N 1. P. 67 – 103. DOI: 10.1080/10408399209527581.


*Поступила в редакцию 24.02.2025*
*Принята к опубликованию 28.02.2025*

*Received 24.02.2025*
*Accepted 28.02.2025*