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Research Article | Araştırma Makalesi

BENZIMIDAZOLE-THIAZOLE HYBRIDS; SYNTHESIS, STRUCTURE ELUCIDATION AND CYTOTOXIC PROPERTIES

BENZİMİDAZOLE-TİYAZOL HİBRİTİ: SENTEZ, YAPI KARAKTERİZASYONU VE SİTOTOKSİK ÖZELLİKLER

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Abstract

Objective: Neuroblastoma is one of the leading tumors among the childhood cancers and the treatment of the disease is currently being investigated. As the metastatic ability of the cells is high, current anticancer therapy needs improvement.

Methods: Therefore, here five novel benzimidazole-thiazole compounds were synthesized. Their structures were elucidated using spectroscopic methods like FTIR, NMR and Mass analysis. The synthesis monitoring and purity of the compounds were performed with chromatographic methods. The compounds biological activity on SH-SY5Y neuroblastoma cell line was investigated using MTT assay.

Results: All of the tested compounds showed moderate cytotoxic activity. The best IC50 was obtained from compound 6b with the IC50 value of 175,02±4,17 µM.

Conclusion: These results indicated that benzimidazole-thiazole core is important for anti neuroblastoma activity, however, the ability of intramolecular hydrogen bonding could block the anticancer activity.

Keywords: Benzimidazole, thiazole, neuroblastoma, cytotoxicity, NMR.

Öz

Amaç: Nöroblastoma, çocukluk çağı kanserleri arasında önde gelen tümörlerden biridir ve hastalığın tedavisi halen araştırılmaktadır. Hücrelerin metastatik yeteneği yüksek olduğundan, mevcut antikanser tedavisinin iyileştirilmesi gerekmektedir.

Yöntem: Bu nedenle, burada beş yeni benzimidazol-tiyazol bileşiği sentezlenmiştir. Yapıları FTIR, NMR ve Kütle analizi gibi spektroskopik yöntemlerle aydınlatılmıştır. Bileşiklerin sentezleri ve saflığı kromatografik yöntemlerle gerçekleştirilmiştir. Bileşiklerin SH-SY5Y nöroblastoma hücre hattı üzerindeki biyolojik aktivitesi, MTT deneyi kullanılarak araştırılmıştır.

Bulgular: Test edilen bileşiklerin tümü, orta derecede sitotoksik aktivite gösterdi. En iyi IC50, 175,02±4,17 uM IC50 değeri ile bileşik 6b'den elde edildi.

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Anahtar Kelimeler: Benzimidazole, thiazole, neuroblastoma, cytotoxicity, NMR.

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Introduction

Neuroblastoma (NB) is defined as a tumor that develops almost anywhere in sympathetic nervous system and occurrence is mainly observed in abdomen. In some NB patients, tumor growth was also recorded in adrenal gland, abdominal regions, neck, thoracia and pelvis.[1] Almost 10% of the childhood malignancies classified as NB tumors.[2] Unfortunately, metastasis is the first clinical profile in NB patients and cortical bone and bone marrow are at high risk.[3] The treatment goal is to target some important cellular pathways in NB. Some promising treatment regiments were introduced to the literature like retinoic acid, angiogenesis inhibition, histone deacetylate inhibition.[4] However, the requirement of a universal treatment is still needed. The tumor heterogeneity, the drug resistance, the drug toxicities lead treatment failure. Therefore, understanding the underlying mechanism and biological profiles of NB is highyl important.

As the drug repurposing is gaining importance in future drug development strategies, newly developed studies on neuroblastoma was investigated. Flubendazole, which has benzimidazole core ring in its structure has shown to have potential activity on neuroblastoma cells.[5] Apart from that, benzimidazole moiety kept the attraction because of their various biological activities.[6-20] The motivation behind this study is the mimic drug-repurposing strategy and keep the active pharmacophore rigid. Therefore, five new benzimidazole derivatives were designed and synthesized. Apart and also originating from the existing literature, SH-SY5Y neuroblastoma cells were used in this study. They were first obtained from metastatic bone tumor.[21]

Methods

Chemistry

All the chemicals were purchased from Merck (Darmstadt, Germany), Sigma-Aldrich (St. Louis, MO). Reactions were monitored by TLC on silica gel plates purchased from Merck (Merck Co., Darmstadt, Germany). Melting points of the synthesized compounds were determined in a Stuart SMP50 Automatic Melting Point apparatus. The purity of the compounds was first checked by TLC and confirmed on LC-MS. NMR spectra were recorded on Bruker 400 MHz (Billerica, MA) for 1H-NMR. Data are reported as follows: chemical shift, multiplicity (b.s.: broad singlet, d: doublet; m: multiples, s: singlet, and t: triplet), coupling constants (Hz), integration. An Agilent 1260 Infinity II HPLC-MS spectra equipped with G7114A 1260DAD detector, G7311B 1260 Quad Pump system, G1328C 1260 manual injection unit and G6125B LC/MSD detector was used for both HPLC and mass analysis. Retention times were recorded with ACE C18 column (particle size: 3 µm, pore size: 100A). The column temperature was adjusted to 25ºC in the column compartment. The mobile phase consisted of acetonitrile- water (90:10, v/v) mixture and delivered at a flow rate of 0.8 mL/min. The injection volume was 20 µL. The high-resolution mass spectra of the compounds were determined on a Shimadzu 8040 LC/MS/MS ITTOF system (Shimadzu, Tokyo, Japan) using a mass spectrometer with the electron spray method (ESI).

Biological Activity

Cytotoxicity Experiment

SH-SY5Y (Neuroblast from neural tissue) cultured and maintained in DMEM/F12 containing 10% FBS and supplemented with penicillin/streptomycin. The cultures were incubated at 37°C in a humidified atmosphere with 5% CO2. Compounds were about 0.1-1000 µM concentration using MTT assay[22] and it is previously reported.[23] IC_{50} values were calculated and cellular analyzes were continued with the compounds 6a, 6b, 6c, 6d, and 6e. Cellular morphological changes were characterized under the microscope. The compounds were dissolved in DMSO, and MTT was performed at a concentration of 0, 0.1, 1,10,100,1000 µM. Cells were incubated for 24 hours, and IC50 values were calculated using Graphpad Prism 7.

Statistical Analysis

All experiments were performed at least in triplicates. Data are presented as mean ± standard deviation. Statistical comparisons were performed through the one-way ANOVA followed by the Tukey test. Statistical significance was set at $p < 0.05$. Statistical analysis and artwork were performed using Graph Pad Prism 7.0d (Graph Pad Software, La Jolla, USA).

Results

Chemistry

Compound 1 was supplied from Sigma-Aldrich. 2-(1-hydroxy) ethylbenzimidazole (1) is oxidized by chromium trioxide to obtain 2-acetylbenzimidazole. 2-acetylbenzimidazole was methylated by dimethyl sulfate to get 1-methyl-2-acetylbenzimidazole (2) and then brominated in acetic acid to obtain 3. Aniline derivatives (4a-e) were reacted with ammonium thiocyanate (NH4SCN) in ethanol and HCl mixture. Resulted thioureas (5a-e) were checked for their melting points and then used for the final step. At the final step, 3 and 5a-e reacted to get thiazole derivatives (6a-e) according to Hantzsch method (Figure 1).

Synthesis of 1-methyl-2-acetylbenzimidazole (2)

1-Methyl-2-(1-hydroxy) ethylbenzimidazole (0,001 mol) is dissolved in acetic acid and stirred at 90 °C until the color of chrom trioxide turns out green by adding chromium trioxide (dissolved in water). After the reaction was complete, equal volume of water was added. Extracted with chloroform. Organic layer was dried with magnesium sulfate and recrystallized from toluene. After

it was dried, dissolved in NaOH solution (including equal mol of NaOH, 1N), dimethyl sulfate was added and shaked for 1 hour. The product is precipitated and collected.

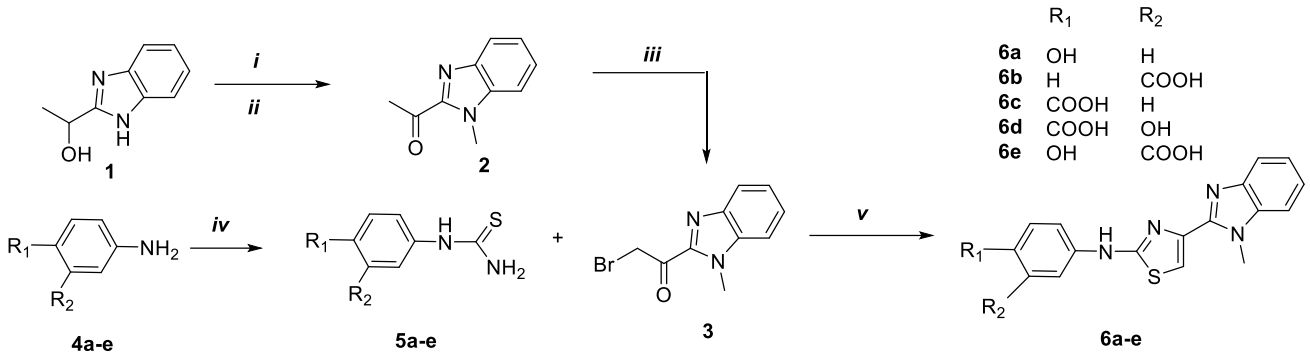

Figure 1: Synthesis scheme of benzimidazole-thiazole compounds; i: chromium trioxide, ii: dimethylsulfate, iii: HBr/acetic acid, iv: ammonium thiocyanate, HCl; v: ethanole

Synthesis of 1-methyl-2-(2-bromoacetyl)benzimidazole (3)

Compound 2 (0.001 mol) is dissolved in acetic acid. Equal mol of bromine is diluted in acetic acid and then added to the reaction dropwise. Catalytic HBr is added and stirred at room temperature for overnight. After the reaction was complete, solids are filtered and the solids dissolved in water and quenched carefully with sodium bicarbonate. Filtered off and dried.

Synthesis of N-(3,4-disubstitutedphenyl)thiourea (5a-e)

Aniline derivatives (4a-e) (300 mmol) is dissolved in ethanol. Equal mole of HCl (330 mmol) and ammonium thiocyanate (330 mmol) is added and refluxed for 4 hours. Resulted precipitation is collected and washed with ethanol for 4-5 times. Solid was recrystallized from ethanol. Melting points was checked and used for the next step.

Synthesis of N-(3,4-disubstitutedphenyl)-4-(1-methyl-1H-benzimidazol-2-yl)-1,3-thiazol-2-amine (6a-e)

Compounds 5a-e (0.001 mol) and compound 3 (0.001 mol) were dissolved in ethanol for 15 min at room temperature and refluxed for 1.5 hours. Quenched with sodium bicarbonate solution to get rid of the salt. Precipitation was collected and recrystallized.

6a: 4-((4-(1-Methyl-1*H*-benzo[d]imidazol-2-yl)thiazol-2-yl)amino)phenol

Mp.: 202 °C. **FT-IR υ_{max}** (cm^{-1}): 3402 (OH sb), 3211 (NH sb), 2982 (CH aliphatic sb), 1602 (C=N sb), 1452 (CH aliphatic bb), 913 (Ar-H bb). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.13 (s, 1H, NH), 9.50 (s, 1H, OH), 7.69 – 7.61 (m, 1H, Ar), 7.59 (d, *J* = 7.7 Hz, 1H, Ar), 7.55 (s, 1H, thiazole H), 7.46 (d, *J* = 8.5 Hz, 2H, Ar), 7.33 – 7.18 (m, 2H, Ar), 6.77 (d, *J* = 8.5 Hz, 2H, Ar), 4.19 (s, 3H, CH3).

HRMS (M+H): For $C_{17}H_{14}N_4OS$ calcd: 323.0961, found: 323.0960.

6b: 3-((4-(1-Methyl-1*H*-benzo[d]imidazol-2-yl)thiazol-2-yl)amino)benzoic acid

Mp.: 247 °C. FT-IR **υ_{max}** (cm^{-1}): 3312 (OH sb), 3152 (NH sb), 2978 (CH aliphatic sb), 1732 (C=O sb), 1589 (C=N sb), 1456 (CH aliphatic bb), 987 (Ar-H bb) **^{1}H NMR (300 MHz) DMSO-d_6 δ (ppm):** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H, COOH), 10.68 (s, 1H, NH), 8.63 (s, 1H, Ar), 7.80 – 7.71 (m, 2H, Ar), 7.68 – 7.55 (m, 3H, Ar), 7.48 (t, *J* = 7.7 Hz, 1H, Ar), 7.27 (m, 2H, Ar), 4.25 (d, *J* = 1.5 Hz, 3H, CH3).

6c: 4-((4-(1-Methyl-1*H*-benzo[d]imidazol-2-yl)thiazol-2-yl)amino)benzoic acid

Mp.: 302 °C. **FT-IR υ_{max}** (cm^{-1}): 3401 (OH sb), 3234 (NH sb), 2976 (CH aliphatic sb), 1745 (C=O sb), 1616 (C=N sb), 1451 (CH aliphatic bb), 899 (Ar-H bb). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 12.60 (s, 1H, COOH), 10.86 (s, 1H, NH), 7.96 (d, 2H, Ar), 7.87 – 7.74 (m, 3H, Ar), 7.71 – 7.56 (m, 2H, Ar), 7.34 – 7.17 (m, 2H, Ar), 4.22 (s, 3H, CH3).

HRMS (M+H): For $C_{17}H_{14}N_4OS$ calcd: 351.0910, found: 351.0909.

6d: 2-Hydroxy-4-((4-(1-methyl-1*H*-benzo[d]imidazol-2-yl)thiazol-2-yl)amino)benzoic acid

Mp.: 211 °C. **FT-IR υ_{max}** (cm^{-1}): 3314 (OH sb), 3298 (NH sb), 2998 (CH aliphatic sb), 1701 (C=O sb), 1579 (C=N sb), 1443 (CH aliphatic bb), 956 (Ar-H bb). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.60 (s, 1H, NH), 9.49 (s, 1H, OH), 8.16 (s, 1H, COOH exchanged), 8.04 (dd, *J* = 6.3, 3.3 Hz, 1H, Ar), 7.85 (dd, *J* = 7.8, 2.7, 2.2 Hz, 1H, Ar), 7.69 – 7.59 (m, 2H, Ar), 7.16 (dd, *J* = 4.9, 2.3 Hz, 3H, Ar), 6.47 (s, 1H, Ar), 4.34 (s, 3H, CH3).

6e: 2-Hydroxy-5-((4-(1-methyl-1*H*-benzo[d]imidazol-2-yl)thiazol-2-yl)amino)benzoic acid

Mp.: 287 °C. **FT-IR υ_{max}** (cm^{-1}): 3398 (OH sb), 3212 (NH sb), 2956 (CH aliphatic sb), 1722 (C=O sb), 1609 (C=N sb), 1467 (CH aliphatic bb), 902 (Ar-H bb). **^{1}H NMR (400 MHz, DMSO-d_6) δ** 15.93 (s, 1H, COOH), 10.03 (s, 1H, NH), 8.13 (d, J = 2.9 Hz, 1H, Ar), 7.63 (d, *J* = 7.7 Hz, 1H, Ar), 7.58 (d, *J* = 8.1 Hz, 1H, Ar), 7.52 (s, 1H, thiazole), 7.43 – 7.32 (m, 1H, Ar), 7.32 – 7.16 (m, 2H, Ar), 6.64 (d, *J* = 8.6, 1.3 Hz, 1H, Ar), 4.23 (s, 3H, CH3), 1.70 (s, 2H, OH exchanged).

Discussion

The purity of the synthesized compounds were proven by chromatographic methods. All the compounds thin layer chromatography results ended with single stain in TLC analysis. The elucidation of the structures were proven by spectroscopic methods. The IR results proved the formation of proposed compounds. The disappearance of C=S stretching bands correlated with the overall structure. The NH stretching bands were recorded between 3298-3152 cm^{-1}. The salicylic acid derivatives among the compounds resulted with additional OH stretching band ranging from 3402-3312 cm^{-1} which also explains the hydrogen bonding. The bending peaks resulting from aromatic rings were also detected in the expected regions. In all our compounds (**6a-6e**), the band belonging to the NH group located between the thiazole and the aromatic ring was observed as a sharp peak around 10 ppm. While the aromatic OH group in **6a** and **6d** compounds is close to 9.5 ppm, in compound 6e this hydrogen has been replaced by water at 1.7 ppm. In the compounds bearing the carboxyl group (6b-e), the COOH peak belonging to the carboxyl group was observed between **12-16** ppm, it was only observed in the aromatic area in the **6d** compound due to intermolecular hydrogen bonds. The methyl group attached to benzimidazole was observed as a singlet around 4.2 ppm in all compounds. The single aromatic hydrogen in the thiazole ring was distinguished in compounds **6a** and **6e** and observed as a singlet at 7.5 ppm, mixed with aromatic hydrogens in other compounds. The total number of hydrogens for all compounds holds the total number in the molecules.

The cytotoxicity assay analysis were performed for all the compounds on SH-SY5Y neuroblastoma cell line. All the compounds were insoluble in water and the test studies were performed in dimethlysulfoxide. Inhibitory concentration, cell viability and CV stain analysis were performed for five compounds. Among them, compound **6b** was found to have the best inhibitory activity. Comparing the IC_{50} values of the compounds, hydroxyl group did not favor for inhibitory activity. The carboxylic acid structure in the meta position of the aniline moiety increased the antitumor activity. The dramatic decrease in the inhibitory activity of hydroxyl group carrying compounds could be explained as a result of addition hydrogen bonding. The ability of intramolecular hydrogen bond could block the interaction with the cancer cell and the µshould be performed in order to understand the underlying mechanism.

The MTT assay studies revealed the IC50 values of the synthesized compounds and results were presented in Table 1.

In SH-SY5Y cells, all compounds were determined the cell viability levels of the cells at a concentration of IC_{50} values in 24 hours. The cell viability results were also performed for the synthesized compounds. After 24 hours in 10µM concentration, compound **6b** inhibited the cell viability 80% (Figure 2).

Table 1. IC_{50} values of the synthesized compounds on SH-SY5Y cell lines

Compound	IC_{50} (µM)
6a	669.18±2.05
6b	175.02±4.17
6c	735.02±6.68
6d	ND
6e	481.59±7.22

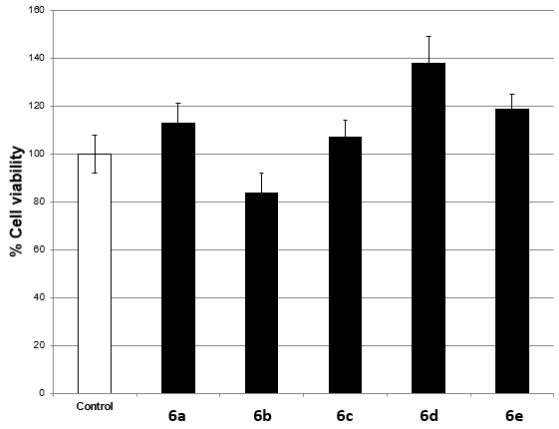

Figure 2. Cell viability results for compounds **6a-6e**.

When the results obtained in the measurement of SH-SY5Y, cell colony forming capacity was evaluated. The CV staining images were made in all tested compounds (Figure **3**). Compound **6b** is the compound that significantly reduced the colony formation levels compared to the control group.

Conclusion

Fully neuroblastoma treatment is still on the research level. The occurrence cell resistance and metastasis is the biggest threat. Within this study, we aimed to develop and synthesize novel benzimidazole-thiazole compounds which may possess anticancer activity. The tested novel five compounds exhibited moderate activity, however, one can considered to have a good potential for future studies. Compound 6b, which have meta carboxylic acid moiety showed the best inhibitory activity on neuroblastoma cells. Even though it is hard to estimate the structure activity relation with cancerous cells, it could maybe lead the idea of intramolecular hydrogen bonding may not be in favor for anticancer activity. Furthermore, benzimidazole and thiazole moiety keeps the importance of strong biological activity profile.

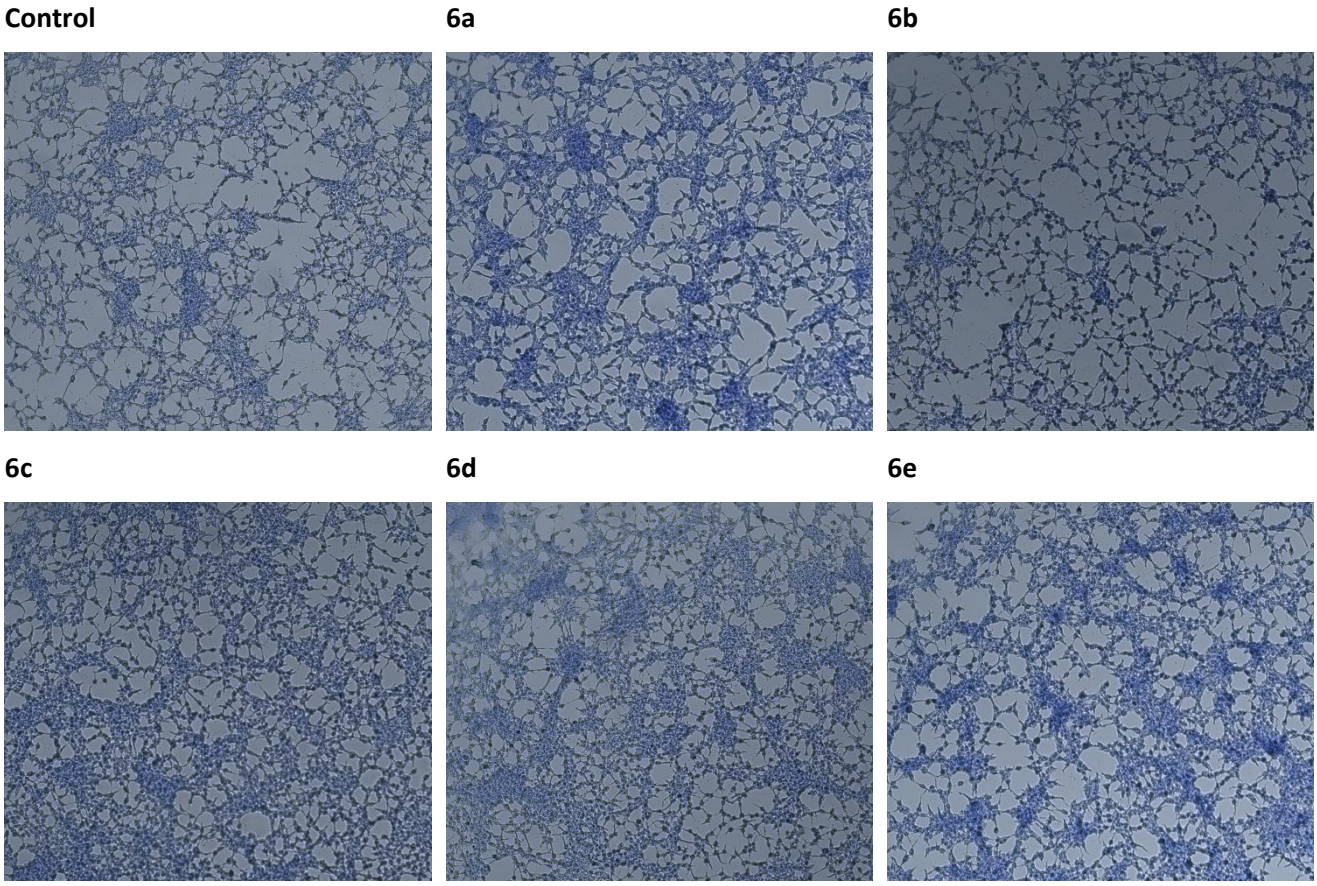

Figure 3. CV stain images of the tested compounds

Ethical Approval
No ethics committee decision is required for the study.

Conflicts of Interests
The authors declare there are no conflict of interest.

Author Contribution
All authors contributed equally to this work.

Financial Disclosure
None.

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