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Synthesis and Biological Evaluation of 2-Phenyl Benzothiazole Derivatives as Cytotoxic Agents

L. Firoozpour[1], A. Mokhtari[1], S. Moghimi[1], M. Safavi[2], A. Foroumadi[*3,4]

[1] *Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*
[2] *Department of Biotechnology, Iranian Research Organization for Science and Technology, Tehran 33535-111, Islamic Republic of Iran*
[3] *Department of Medicinal Chemistry, Faculty of Pharmacy and Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Islamic Republic of Iran*
[4] *Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*

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Abstract

Cancer is a leading cause of death worldwide. Many heterocyclic cores are present in the structures of clinically approved anticancer drugs. Meanwhile, benzothiazoles have been reported as one of the most important heterocyclic scaffolds in previously reported anticancer agents in the literature. Therefore, in this report, a novel series of 2-phenyl benzothiazole derivatives was synthesized, biologically evaluated against breast cancer cell line (T47D) and compared with etoposide as a reference drug. The anticancer activities were evaluated by MTT colorimetric assay. Among all tested compounds, N-(4-(6-methoxybenzo[d]thiazol-2-yl)phenyl)acetamide illustrated the most potent cytotoxic activity.

Keywords: Phenyl benzothiazole; Thiobenzanilides; Jacobson synthesis; Cancer.

Introduction

Benzothiazole core frequently occurs in synthetic and natural products of pharmacological importance [1,2]. A quick literature survey shows that substituted benzothiazoles evince diverse range of properties including anticonvulsant [3-5], anti alzheimer [6] antileishmanial [7], anti tubercular [8,9], antimalarial [10], antifungal [11], anti-inflammatory [12] and anti tumor activities [13,14]. Regarding the biological importance of this scaffold, plethora of strategies [15] have been reported for the preparation of these compounds and continuously attracting much attention in academia and industry.

A number of named cyclization methods have been introduced to date including Hofmann and Jacobson cyclization, known as the main synthetic routes toward this unit. Jacobson method emerged as a powerful method for the generation of 2-substituted benzothiazoles. This method is based on the annulation of thiobenzanilides by employing alkaline potassium ferricyanide, producing cyclized compound in moderate yield. With the widespread use of organocatalyst in organic synthesis, a number of catalytic systems were also utilized for the mild and efficient generation of diverse ranges of benzothiazole derivatives. A great deal of effort has also been devoted to the generation of this ring through transition metal-catalyzed cyclization. It is

* Corresponding author: Tel: +982166954708; Fax: +982166461178; Email: aforoumadi@yahoo.com

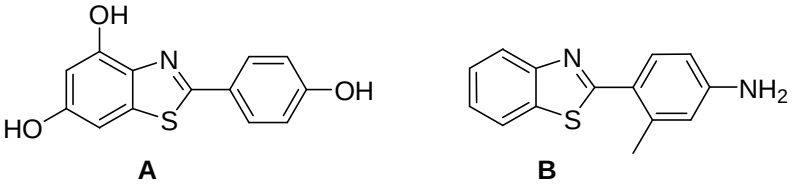


Figure 1. Structures of benzothiazole containing anti-tumor agents.

not surprising that this method gives us the opportunity to prepare this scaffold from totally different starting materials, compared with traditional approaches.

Heterocyclic compounds are featured in different compounds with anticancer activities [16,17]. 2-Phenyl benzothiazoles have been well discussed as anticancer agents in the literature [18]. This core is present in the structures of 4,6-dihydroxy-2-(4-hydroxyphenyl) benzothiazole **A** [19] and 4-(benzo[*d*]thiazol-2-yl)-3-methylbenzenamine **B**, which are active against several human tumor cell lines [Figure 1]. Inspired by these stuctures, and following our interests in synthesizing bioactive heterocycles [20-23] with promising anticancer activities [24-26], herein, we report the synthesis and cytotoxic activity of some novel 2-phenyl benzothiazoles.

Materials and Methods

Experimental

Melting points were taken on a Kofler hot stage apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-500, using TMS as an internal standard. The IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (in KBr). All reagents and solvents were obtained from Merck and Aldrich and used without any purification. Silica gel 60 (0.040-0.063 mm) were used for column chromatography Thin layer chromatography (TLC) was performed using silica gel 60/Kieselguhr F254 precoated on aluminum sheets (thickness 0.2 mm), commercially available from Merck. Visualization of spots on TLC plate was accomplished with UV light.

N-(4-Methoxyphenyl)-4-nitrobenzamide **(2):**[14] Yellow solid; yield: 75%, mp = 195-197 °C. IR (KBr): 3297 (NH), 2958, 1715 (C=O), 1348, 1514 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.95 (s, 3H, O-CH_3), 6.93 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.79 (s, 1H, NH), 8.01 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H) ppm.

N-(4-Methoxyphenyl)-4-nitrobenzothioamide **(3):**[27] Yellow solid; yield: 64%, mp = 174-176 °C. IR (KBr): 3348 (NH), 3062 (C-H), 1603 (C=S), 1352, 1518 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.95 (s, 3H, O-CH_3), 6.98 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 2H), 9.81 (s, 1H, NH) ppm.

6-Methoxy-2-(4-nitrophenyl)benzo[d]thiazole **(4):**[14] Yellow solid; yield: 60%, mp = 215-217 °C. IR (KBr): 3062, 1615 (C=N), 1355, 1558 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.88 (s, 3H, O-CH_3), 7.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 2H) ppm.

Synthesis of 4-(6-methoxybenzo[d]thiazol-2-yl)benzenamine **(5):** A mixture of 6-methoxy-2-(4-nitrophenyl)benzothiazoles **4** (1 mmol) and tin(II) chloride dihydrate (3 mmol) were stirred in boiling ethanol under nitrogen for 4 h. The solvent was evaporated and the precipitate was extracted with ethyl acetate (3× 50 mL) and aqueous sodium hydroxide solution (2M, 3 × 50 mL). The organic layer was dried and removed to obtain the desired product.

4-(6Methoxybenzo[d]thiazol-2-yl)benzenamine **(5):** White solid; yield: 81%, mp = 190-192 °C. IR (KBr): 3418, 3425 (NH_2), 3062, 1610 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.90 (s, 3H, O-CH_3), 6.72 (d, *J* = 8.0 Hz, 2H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.83-7.89 (m, 4H) 7.96 (d, *J* = 8.8 Hz, 1H) ppm.

Synthesis of 2-bromo-4-(6-methoxybenzo[d]thiazol-2-yl)benzenamine **(6):** Compound **5** (1 mmol) was treated with a solution of bromine (0.5 mmol) in dichloromethane (50 mL) at -5 ºC for 10 min. Upon completion, the mixture was poured into ice-water (100 mL) and stirred for 1 h. The organic layer was separated, dried over Na_2SO_4, and evaporated to give the title product.

2-Bromo-4-(6-methoxybenzo[d]thiazol-2-yl)benzenamine **(6):** White solid; yield: 79%, mp = 195-197 °C. IR (KBr): 3325, 3338 (NH_2), 3062, 1610 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.78 (s, 3H, O-CH_3), 6.41 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.31 (brs, 2H, NH_2), 7.43 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.91 (s, 1H), 8.09 (d, *J* = 7.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 56.0, 108.3, 111.5, 111.7, 116.3, 122.8, 127.5, 127.7, 133.8, 136.5, 149.9, 154.2, 157.3, 162.4.

Synthesis of N-(4-(6-methoxybenzo[d]thiazol-2-yl)phenyl)acetamide **(7):** Compound **6** (1 mmol) was

refluxed in a solution of acetic acid and acetic anhydride for 4 h. The solvent was evaporated under reduced pressure and the residue was recrystallized from petroleum ether/ethyl acetate.

***N-(4-(6-Methoxybenzo[d] thiazol-2-yl)phenyl) acetamide* (7):** Pale yellow solid; yield: 63%, mp = 227-229 °C. IR (KBr): 3333 (NH), 3055, 1640 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.23 (s, Me), 3.84 (s, 3H, O-CH_3), 6.55 (s, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 1H) ppm.

***Synthesis of N-(2-bromo-4-(6-methoxybenzo[d]thiazol-2-yl)phenyl)acetamide* (8):** The reaction was carried out according to the mentioned method for the preparation of compound **6**.

***N-(2-Bromo-4-(6-methoxybenzo[d]thiazol-2-yl)phenyl)acetamide* (8):**

White solid; yield: 58%, mp = 132-135 °C. IR (KBr): 3312 (NH), 3062, 1623 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.24 (s, Me), 3.83 (s, 3H, O-CH_3), 6.95 (s, 1H), 7.01 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.64-7.66 (m, 2H), 7.75 (d, *J* = 2.0 Hz, 1H), 8.00 (d, *J* = 6.5 Hz, 1H), 8.09 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.6, 56.2, 111.5, 114.7, 115.0, 116.3, 122.8, 127.0, 133.6, 134.4, 136.7, 146.6, 150.0, 157.3, 162.4, 170.2.

***Synthesis of 2-(4-nitrophenyl)benzo[d]thiazol-6-ol* (9):** 6-Methoxy-2-(4-nitrophenyl)benzo[*d*]thiazole **4** (1 mmol**)** was heated in hydrobromic acid (10 mL) under reflux condition for 3 h. The residual yellow solid was filtered off, washed and used without further purification.

***2-(4-Nitrophenyl)benzo[d]thiazole-6-ol* (9):** Yellow solid; yield: 75%, mp = 253-255 °C. IR (KBr): 3520 (O-H), 2976, 1605 (C=N), 1362, 1524 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.01 (s, O-H), 7.07 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 8.38 (d, *J* = 8.0 Hz, 2H) ppm.

***Synthesis of 5-bromo-2-(4-nitrophenyl) benzo[d] thiazol-6-ol* (10):** To a solution of compound **9** (1 mmol) in acetic acid (10 mL) was added a mixture of bromine (2.5 mmol) in acetic acid (5 mL) at 25 °C and the reaction was continued at this temperature for 20 h. The acetic acid was removed under reduced pressure and the residue was extracted with dichloromethane (2 × 50 mL) and water (2 × 50 mL). The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent afforded compound **10**.

***5-Bromo-2-(4-nitrophenyl)benzo[d]thiazol-6-ol* (10):** Yellow solid; yield: 59%, mp =170-176 °C. IR (KBr): 3250 (O-H), 3062, 1615 (C=N), 1355, 1535 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.05 (s, OH), 7.69 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 2H) ppm.

***Synthesis of 5-bromo-6-methoxy-2-(4-nitrophenyl) benzo[d]thiazole* (11):** To the solution of compound **10** (1 mmol) in DMF (5 mL), K_2CO_3 (0.1 mmol) and methyl iodide (2 mmol) were added. The reaction was heated at 60 °C for 4 h. Then, the reaction mixture poured into ice-water and the precipitate was collected and recrystallized from ethanol.

***5-Bromo-6-methoxy-2-(4-nitrophenyl) benzo [d] thiazole* 11:** Yellow solid; yield: 75 %, mp = 160-165 °C. IR (KBr): 3418, 3425 (NH_2), 3062, 1615 (C=N), 1345, 1541 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.76 (s, 3H, O-CH_3), 7.25 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.31 (d, *J* = 8.8 Hz, 2H), 8.39 (s, 1H) ppm.

Biological study

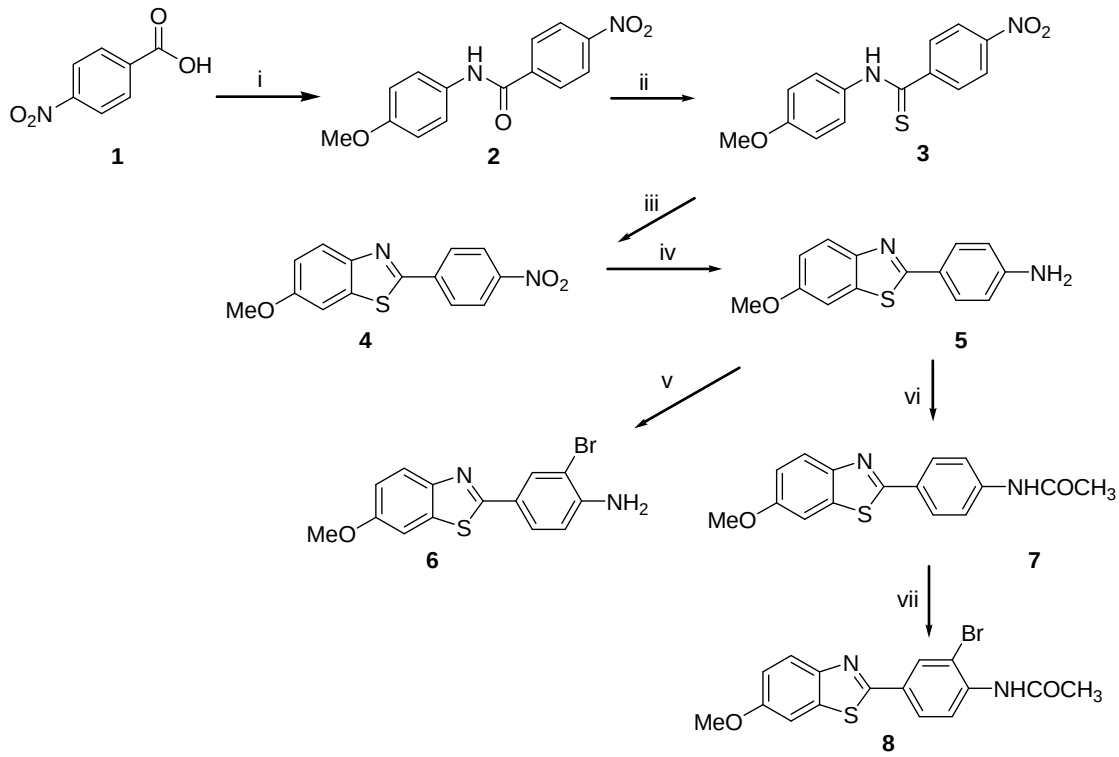
Briefly, cell viability was evaluated by MTT colorimetric assay in which the viable cell number is directly proportional to the production of purple formazan by mitochondrial dehydrogenases. After trypsinization, 195 µl of the cell suspension was seeded into the wells of 96-well plates (Nunc, Denmark). Then, the cells were treated with 5 µl of the media containing various concentrations (final concentration 1, 5, 10 and 20 µg/ml) of the compounds for 48 h. Etoposide and DMSO (solvent) were used as positive and negative controls, respectively. The final concentration of DMSO was less than 1%. After 48 h, the culture medium was removed, and cells were incubated with 200 µL of MTT solution (final concentration 0.5 mg/mL) for further 4 h.

The absorbance of the product determined spectrophotometrically at 570 nm using an ELISA plate reader.The percent inhibition of viability for each concentration of compound was calculated compared to the control wells and IC_{50} values (concentration of the compound that induces 50% inhibition of cell viability) were calculated by linear regression and expressed in Mean ± SD using a Microsoft Excel-based analytic method.

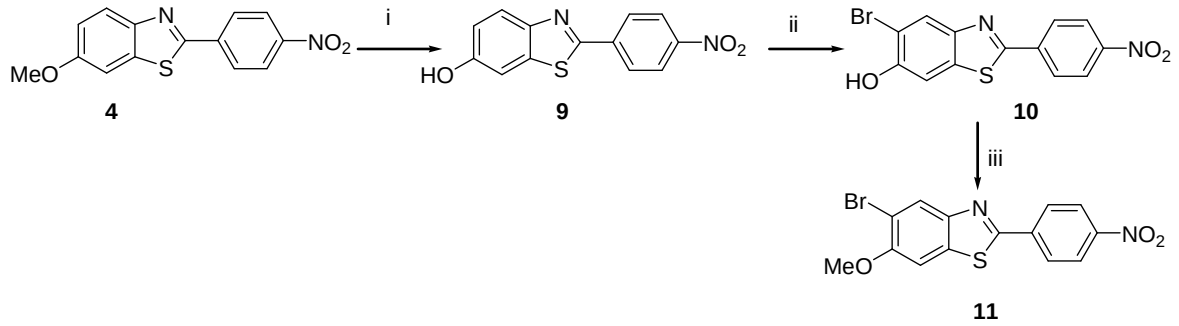
Results and Discussion

Chemistry

Target compounds were synthesized as shown in [Scheme 1-2]. Compound **2** was prepared according to previously reported method by Stevens, started from 4-nitrobenzoic acid **1** [14]. *N*-(4-Methoxyphenyl)-4-nitrobenzamide **2** was treated with Lawesson's reagent [27] to yield nitrobenzothioamide with a total yield of 64%. In the ring closure reaction, compound **3** was cyclized under Jacobson condition [28], gave the desired product **4**. Then, the nitro group was reduced by the action of tin (II) chloride dihydrate in ethanol [29] to



Scheme 1. (i) (a) *p*-Methoxy aniline, benzen, reflux, 3 h; (b) pyridine, reflux, 2 h; (ii) Lawesson's reagent, chlorobenzene, 3 h; (iii) $K_3Fe(CN)_6$, aqueos NaOH; (iv) $SnCl_2.H_2O$, EtOH, 4 h; (v) Br_2, CH_2Cl_2; (vi) $(CH_3CO)_2O$, acetic acid, reflux, 4 h; (vii) Br_2, CH_2Cl_2.



Scheme 2. (i) HBr, reflux, 3 h; (ii) Br_2 , acetic acid, 20 h; (iii) K_2CO_3, DMF, MeI, 60 ^oC, 4 h.

afford 4-(6-methoxybenzo[*d*]thiazol-2-yl) benzenamine **5** [30,31]. Afterwards, compound **5** was reacted with bromine to give brominated product **6** in good yield. The *N*-acetylated product **7** was obtained by employing acetic anhydride/acetic acid which further underwent bromination to generate compound **8**.

The demethylation reaction from intermediate **4** takes place by the action of hydrobromic acid. Then, compound 2-(4-nitrophenyl)benzo[*d*]thiazol-6-ol **9** was reacted with bromine to furnish **10** followed by methylation with methyl iodide, yielding compound **11**, 5-bromo-6-methoxy-2-(4-nitrophenyl)benzo[*d*]thiazole. The structures of all the synthesized compounds were confirmed on the basis of their spectra (^{1}H-NMR, and FT-IR).

Cytotoxicity assay

The synthesized compounds were evaluated for their cytotoxic activity against T47D (breast cancer cell line) using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay [32]. The obtained IC_{50} values of synthesized compounds as well as etoposide (reference drug) were listed in Table 1. According to the obtained results, most of the synthesized compounds (except **2**, **6**) exhibited better anti-tumor activity compared with etoposide (IC_{50} =

Table 1. *In vitro* cytotoxic activities of synthetic compounds against T47D cancer cell line

Compound	IC_{50} (µM)
2	50.6±2.3
3	32.1±4.5
4	22.5±1.8
5	26.8±4.0
6	41.0±0.3
7	19.7±3.1
8	34.9±5.2
9	25.0±3.8
10	26.2±5.6
11	24.4±2.3
Etoposide	36.6 ±7.1

36.6 µM). Compound **2** was determined as the least active compound, while conversion of amide to thioamide functionality enhanced the cytotoxic activity. The acetylation of amino group markedly increased the activity. The presence of methoxy group led to the slightly better inhibitory activity in comparison to hydroxyl containing counterparts. By inserting bromine group in the 2-aryl residue, the potency of target compounds decreased.

Conclusion

In summary, a series of functionalized 2-phenyl benzothiazole derivatives was synthesized and evaluated *in vitro* against breast cancer cell line. Compound **7** exhibited the most potent cytotoxic activity and should be considered for further optimization.

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