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SYNTHESIS OF SOME 2-SUBSTITUTED BENZOTHIAZOLE DERIVATIVES AND EVALUATION OF THEIR ANTICANCER AND ANTI-MICROBIAL ACTIVITIES

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ABSTRACT

Benzothiazole and cyclic imide derivatives with anticancer and anti-microbial effects have attracted considerable attention in medicinal chemistry. This study aims to design derivatives of two biologically active moieties to improve biological effects. A three step procedure was used for the synthesis of target compounds, including: S-alkylation of benzothiazole-2-thiol, synthesis of acid hydrazide throught hydrazinolysise and, in the final step, the imide-linked compounds were obtained by conjugating acid hydrazide with cyclic anhydrides and the pyrazol-linked compound was obtained by reacting acid hydrazide with ethyl acetoacetate. The cytotoxicity was evaluated by MTT assay against two cell lines. Screening for antimicrobial activity against bacteria and fungi were performed. Final compounds did not show significant antitumor activity against cell lines. Compound **5** (benzothiazole- succinic) indicated mild effect against both types of bacteria.

Keywords: Antimicrobial, Benzothiazole-2-thiol, Cytotoxic, Phthalimide, Synthesis

INTRODUCTION

Benzothiazoles, the bicyclic scaffold, occupy a special position among fused heterocyclic framework because of their diverse biological activities including, antimicrobial **(Gupta and Rawat, 2010; Bari *et al*., 2015)**, antioxidant **(Abdelgawad *et al*., 2016; Cressier *et al*., 2009)**, anticancer **(Gupta and Rawat, 2010; Bari *et al*., 2015; Abdelgawad *et al*., 2016; Sadhasivam *et al.*, 2015; Jena, 2014)**, anticonvulsant **(Siddiqui *et al*., 2009; Rana *et al*., 2007),** and anti-inflammatory **(Rana *et al*., 2007)** properties. Moreover, benzothiazole pharmacophore are present in some of the marketed drugs **(Fig1)** and many of natural compounds **(Gill *et al*., 2015)**. 2-Substituted benzothiazole compounds are the privileged structures in medicinal chemistry. The studies of structure–activity relationship revealed that change of substituent at C-2 position can be used to modify activity. Designed amide derivatives at this position showed potent anticancer properties **(Gupta and Rawat, 2010; Sadhasivam *et al*., 2015; Ma *et al*., 2014; Caputo *et al*., 2012; Gurdal *et al*., 2015; Singh *et al*., 2016; Akhtar *et al*., 2008; Trapani *et al*., 2001; .Devmurari *et al*., 2010; Firoozpour *et al*., 2018)**. The latter intuitation have been shown that the benzothiazole-2-thiol as a pharmacophore can be employed to design new anticancer compounds, but these compounds have been less studied. Inhibition of HepG2 cell growth were reported for benzothiazole-2-thiol derivative including amide linkages and phenyl or pyridinyl rings **(Shi *et al*., 2012; Wang *et al*., 2011) (Fig2, compounds 1 and 6)**. Derivatives of benzothiazole-2-thiol with cytotoxic or antimicrobial activities have been synthesized **(Fig 2, compounds 4 and 5) (Devmurari *et al*., 2010; Bari *et al*., 2015**). On the other hand, cyclic imide pharmacophore is important building block for the synthesis and design of chemotherapy compounds, especially, antimicrobial and cytotoxic agents. Lipophilic structure followed by easy crossing through the biologic membranes can be a reason for the biological effects of these compounds **(Hassanzadeh *et al*., 2018; Jafari *et al*., 2017)**. Cyclic imides, in particular, phthalimides (isoindoline-1, 3- dione) have been shown enough attraction for researchers to design and synthesis of phthalimide pharmacophore - based anti tumour **(Kushwaha and Kaushik, 2016; SilvaJunior *et al*., 2019; Ferreira *et al*., 2015; Kok *et al*., 2008)**, antimicrobial **(Kushwaha and Kaushik, 2016; SilvaJunior *et al*., 2019; Lamie *et al*., 2015; Othman *et al*., 2019)** and anti-inflammatory agents **(Kushwaha and Kaushik, 2016; SilvaJunior *et al*., 2019; Lamie *et al*., 2015)**. Hybrid molecules containing, benzothiazole -phthalimide moieties with cytotoxic, antimicrobial **(Kok *et al*., 2008; Barbarossa *et al*.,2023)(Fig2. Compound 2)** and anti angiogenic **(Mercurio *et al*., 2019) (Fig2, compound 3)** properties were reported. According to promising anticancer and antimicrobial profiles of benzothiazole and cyclic imides, molecular hybridization strategy has been employed to design derivatives of two biologically active moieties (benzothiazole and cyclic imide) to improve biological effects. All the newly prepared derivatives were subjected for evaluation of biological activities.

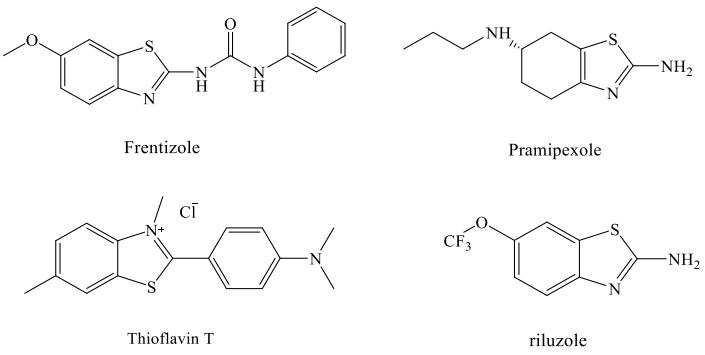


Figure1 Some of the marketed drugs with benzothiazole structure.

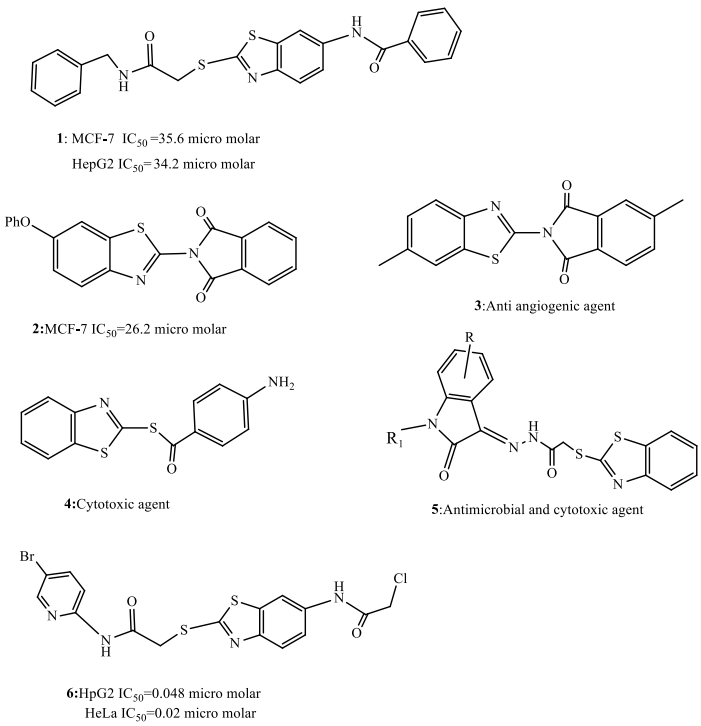


Figure 2 Some of the benzothiazole derivatives with cytotoxic or antimicrobial activities.

MATERIAL AND METHODS

Material

Materials were obtained from Merck (Germany) and Aldrich (USA) companies. Silica gel 60 F_{254} plates (Germany) were used for thin layer chromatography (TLC) to monitor reactions. Bruker spectrometer (Germany, 400 MHz), was used for registering proton nuclear magnetic resonance (^{1}H-NMR) spectra. PerkinElmer infrared spectrophotometer (Germany) was used for recording infrared (IR) Spectra. Electro thermal 9200 melting point device (United Kingdom) was used to record melting points and is uncorrected. The proposal of this research has been approved by Isfahan University (IR.MUI.REC.1396.3.811).

Chemistry

Ethyl2-(benzo[d]thiazol-2-ylthio) acetate (1)

Ethyl 2-chloroacetate (0.02mol) was added to a mixture of anhydrous potassium carbonate (0.02 mol) and benzothiazole-2-thiol (0.02mol) in dry acetone (10mL). The refluxe was continued for 3 h. Upon completion, mixture filtered off and the solvent was removed under vacuum, residue was recrystalized from ethanol to obtain compound **1 (Wang *et al*., 2011)** (Scheme1).

2-(Benzo[d]thiazol-2-ylthio)acetohydrazide (2)

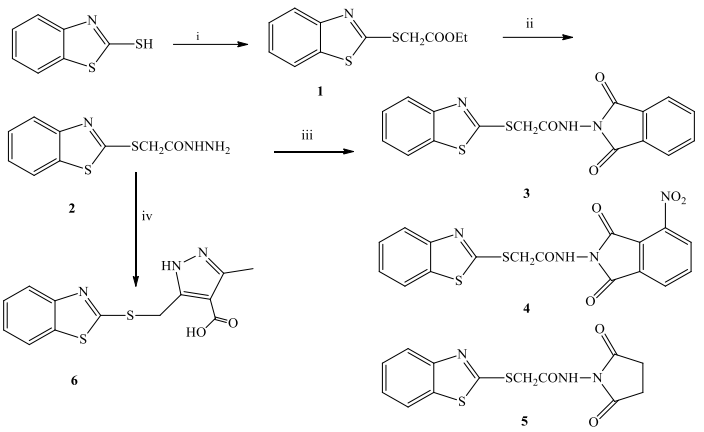
Compound **1** (0.01mol) was dissolved in absolute ethanol then hydrazinolysise was performed with hydrazine hydrate (0.02mol) in reflux situation for 2 h. After evaporation of solvent, precipitated product was recrystallized from ethanol to give compound **2** **(Kumar *et al*; 2012)** (Scheme1).

Synthesis of final compounds (3-5)

Compound **2** (0.01mol) and anhydride derivatives (phthalic anhydride, 3-nitrophthalic anhydride or succinic anhydride) (0.01mol) was heated in glacial acetic acid (15 mL) for 4 h. The acquired suspension was cooled and filtered off to give final products **3-5** (Scheme1).

Synthesis of final compound (6)

Compound **2** (0.01mol) and ethyl acetoacetate (0.01mol) in the presence of catalytic amount of triethylamine was refluxed in ethanol (20 mL) for 18 h, After completion reaction, the solvent was removed under vacuum. The remaining product was recrystallzed from ethanol (Scheme1).



Scheme 1 Synthetic route to final compounds **(3-6). (i)** K_2CO_3, $ClCH_2COOEt$, dry Aceton, 3h reflux; **(ii)** NH_2NH_2, EtOH, 2h reflux; **(iii)** Glacial CH_3COOH, phthalic, 3-nitrophthalic and succinic anhydrides), 4 h reflux ; **(iv)** $C_2H_5OCOCH_2COCH_3$,TEA, EtOH,18h reflux.

In vitro cytotoxic activitiy

Cancer cells : MCF-7 (breast), and HeLa (cervical) were taken from pasture research center (Tehran, I.R. Iran). Both cell lines were preserved in 5% CO_2, 95% humidified atmosphere at 37° C in (RPMI-1640) medium containing 5% (v/v) of FBS, and 1% of 100 units/mL penicillin/100 µg/mL streptomycin. After subcultures, cells with a density of 5×10^4 cells/mL were cultured in plates and incubated for 24 h. Then concentrations of the compounds (0.1, 1, 10 and 100 µM) were added to cells. Paclitaxel as the positive and dimethyl sulfoxide (DMSO) (1%) as negative control were employed. Incubation was executed at 37 °C for 48 h. After this time, each well was exposed to 20μL of MTT, and plates were placed for 3 h at the incubation condition. The formazan crystals produced by enzymatic activity of vital cells were dissolved by adding 150 μL of DMSO per well and absorbance was entered using an ELISA plate reader at 570 nm **(Hassanzadeh *et al*., 2019[a]; Hassanzadeh *et al*., 2019 [b] ; Hassanzadeh *et al*., 2020)**. The trials were completed in triplicate and the results were reported as mean ± SD.
Cell viability was calculated:

$$Cell\ Survival(\%) = \frac{\text{Mean absorbance of drug treated wells} - \text{Mean absorbance of blank}}{\text{Mean absorbance of negative control well} - \text{Mean absorbance of blank}} \times 100$$

The results are reported in **Fig 3** and **Table 1**.

Antimicrobial properties

Antimicrobial properties of final synthesized compounds **(3-6)** against *Escherichia coli* (PTCC1338), *Staphylococcus aureus* (PTCC1337) and *Candida albicans* (PTCC5027) were evaluated using agar plate count assay. Briefly, compounds were dissolved using DMSO to prepare stock solutions (20 mg/mL) and then diluted with 0.9% NaCl to make working solutions (2 mg/mL). Working solution (100µL) was added to microbial suspension 900 µL (10^3 CFU/mL) and incubated at 37 °C overnight.Then, the samples were added to a sterile petri dish (plate) consisting molten Mueiller-Hinton agar (MHB) or Sabouraud Dextrose Agar (SDA) for bacteria (*S. Aureus* and *E. coli*) and fungus (*C. albicans*) respectively. Incubation of plates were performed at 37 °C and 25 °C for bacteria and fungi, respectively. Then, emerging colonies were carefully counted and results were reported as antimicrobial effectiveness values **(Rezazadeh *et al*.,2018)**. The logarithmic reduction of microorganism number was calculated as fallow:
Antimicrobial effectiveness = Log So – Log Sy
Where So and Sy are the number of counted colonies for solvent (blank) and synthesized compounds (sample), respectively. Antimicrobial activity are reported in Table 2.

RESULTS AND DISCUSSION

Chemistry

Benzothiazole scaffold has been exhibitied a broad spectrum of activities and is widely used by the medicinal chemists for drug design **(Devmurari *et al*., 2010; Firoozpour *et al*., 2018).** Literature surveys in the field of benzothiazole hetrocycle and cyclic imides have been shown positive background of antimicrobial and cytotoxic effects for these two pharmacophores **(Hassanzadeh *et al*., 2017; Hassanzadeh *et al*., 2018; Ferreira *et al*., 2015; Kok *et al*., 2008).** In a cell-based screening assay of benzothiazole derivatives for anticancer effects, a hit compound of benzothiazol bearing S-CH_2CONH-R linker exhibited moderate

inhibition on MCF-7 cell line **(Wang *et al*., 2011)**. Most of the benzothiazole derivatives which showe anticancer activity have the second aromatic group directly linked to C-2 or through an amide or an urea moiety **(Caputo, *et al*., 2012).** In the present work, some conjugated derivatives of benzothiazole were synthesized through change of substitutions at 2 position of benzothiazole-2-thiol.

2-(Benzo[d]thiazol-2-ylthio) acetohydrazide (2)

White, Yield 70%, m.p.166-168°C (lit: 168-170°C **(Kumar *et al*., 2012),** IR 3417, 3295 (NH), 1647 (C=O) (cm^{-1}).

2-(Benzo[d]thiazol-2-ylthio)-N-(1,3-dioxoisoindolin-2-yl)acetamide (3)

White solid, Yield 65%, m.p.166-169°C (decomposed), IR 3460 (NH), 3117 (C-H, Ar) 1736, 1674 (C=O) (cm^{-1}). ^{1}H-NMR: (400 MHz; $CDCl_3$): δ 10.19(1H, s, NH), 7.83-7.81 (3H, m, H-Phthalic , benzothiazole), 7.73 (1H, d, *J*=8Hz, H-benzothiazole), 7.71-7.69 (2H, m, H-Phthalic), 7.38 (1H, t, *J*=8Hz, H-benzothiazole), 7.30 (1H, t, *J*=8Hz, H-benzothiazole), 4.07(2H, s, CH_2).

2-(Benzo[d]thiazol-2-ylthio)-N-(4-nitro-1, 3-dioxoisoindolin-2-yl)acetamide (4)

White solid, Yield 60%, m.p.156.7-159 °C, IR, 3292 (NH), 1749, 1711(C=O), 1548, 1352 (NO_2) (cm^{-1}).^{1}H-NMR: ($CDCl_3$): δ 10.60 (1H, s, NH), 8.18-8.22 (2H, m, H-nitroPhthalic), 7.99 (1H, t, *J*=8Hz ,H-nitrophthalic), 7.90 (1H, d, *J*=8Hz, H-benzothiazole), 7.83 (1H, d, *J*=8Hz,H-benzothiazole), 7.48(1H, t ,*J*=8Hz, H-benzothiazole), 7.39 (1H, t, *J*=8Hz, H-benzothiazole), 4.15 (2H, s, CH_2).

2-(Benzo[d]thiazol-2-ylthio)-N-(2,5-dioxopyrrolidin-1-yl)acetamide (5)

White solid, Yield 50%, m.p.99.5-100 °C, IR 3356 (NH), 3161 (C-H, Ar), 2910 (C-H, aliphatic),1736, 1709 (C=O) (cm^{-1}). ^{1}H-NMR: ($CDCl_3$): δ 10.29 (1H, s, NH), 7.88 (1H, d, *J*=8Hz, H-benzothiazole), 7.80 (1H, d, *J*=8Hz,H-benzothiazole),7.47(1H, t, *J*=8Hz, H-benzothiazole), 7.38(1H, t, *J*=8Hz, H-benzothiazole),4.1(2H, s, CH_2), 2.83(4H, s, CH_2-Succinic).

5-(Benzo[d]thiazol-2-ylthio) methyl)-3-methyl-1H-pyrazole-4-carboxylic acid (6)

White solid, Yield 65%, m.p.197.5-198 °C, IR 3438 (br, OH,) 3182 (NH), 1638 (C=O) (cm^{-1}). ^{1}H-NMR: ($CDCl_3$): δ 11.42 (1H,s, OH) 8.05 (1H, d, *J*=8Hz, H-benzothiazole), 7.68 (1H, d, *J*=8Hz ,H-benzothiazole), 7.42(1H, t, *J*=8Hz, H-benzothiazole), 7.28 (1H, t, *J*=8Hz, H-benzothiazole),3.91 (2H, s, CH_2),1.48 (3H, s, CH_3).

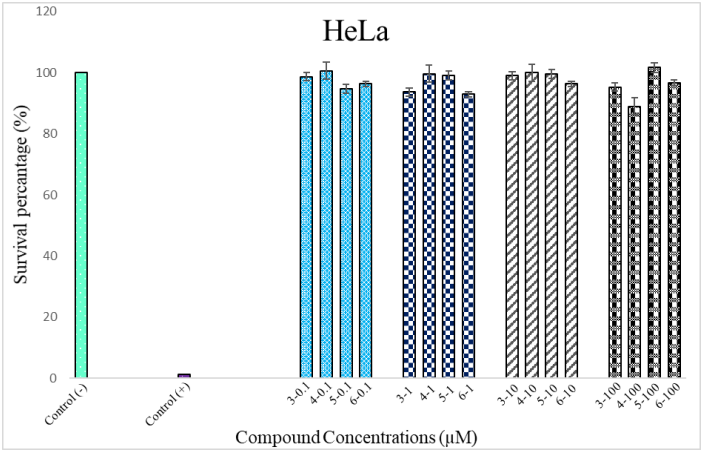
Cytotoxic

These derivatives have been evaluated for possible cytotoxic activities. Cytotoxic results were presened in Table 1 and **Fig 3** respectively. As a result of this study, none of the tested derivatives had significant cytotoxic activity.

Table 1 The IC_{50} value of final compounds (**3-6**).

Tested Compounds	(µM) MCF-7	(µM) HeLa
3	>100	>100
4	>100	>100
5	>100	>100
6	>100	>100
Paclitaxel	6.1	9.08

A



B

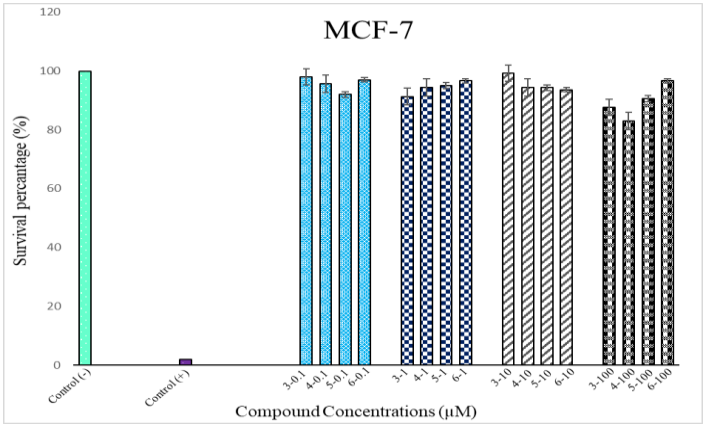


Figure 3 Cytotoxicity of compounds **3-6** against HeLa cells (A) and MCF-7(B) after 48h incubation. Data are proffered as mean ± SD, n = 3.

Antimicrobial

Among benzothiazole-cyclic imide derivatives with constant S-CH_2CONH linker, compound **5** (benzothiazole- succinic hybrid) has been found to be relatively effective against gram positive and negative bacteria. This compound didn't show remarkable effect on *Candida albicans*. (Table 2).

Table 2 Evaluation of antimicrobial properties of final compounds (**3-6**) (mean±SD, n=3)

	Final compounds			
	3	**4**	**5**	**6**
E. coli	-1.852±0.043	-1.138±0.042	1.173±0.027	-1.397±0.089
S. aureus	-1.519±0.055	-1.586±0.048	0.984±0.026	-0.385±0.022
C. albicans	-0.1527±0.062	-0.031±0.015	-0.033±0.014	0.009±0.029

Nystatine (3.5±0.3) , Ciprofloxacin (3.9±0.5)

CONCLUSION

Benzothiazole attached with cyclic imides or pyrazole to increase biological activity resulted in hybrid molecules. Unfortunately cytotoxic properties were not observed for final compounds. Our antimicrobial results were also similar to the cytotoxic activities except for **5** which had mild effect against gram positive and negative bacteria. Considering that the compound **5** (benzothiazole- succinic) is not cytotoxic but has shown a mild antimicrobial effect against gram positive and negative bacteria, it can be used to design new and effective antimicrobial compounds.

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