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Synthesis and Study of Antibacterial and Antifungal Activities of Novel 2-[[(Benzoxazole/benzimidazole-2-yl)sulfanyl] acetylamino]thiazoles

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Several 2-[[(benzoxazole/benzimidazole-2-yl)sulfanyl]acetylamino]thiazoles derivatives were synthesized by reacting 4-substituted-2-(chloroacetylamino)thiazoles with benzoxazole/benzimidazole-2-thioles in acetone and in the presence of K_2CO_3. The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR, and FAB$^+$-MS spectral data. Their antimicrobial activities against *Micrococcus luteus* (NRLL B-4375), *Bacillus cereus* (NRRL B-3711), *Proteus vulgaris* (NRRL B-123), *Salmonella typhimurium* (NRRL B-4420), *Staphylococcus aureus* (NRRL B-767), *Escherichia coli* (NRRL B-3704), *Candida albicans and Candida globrata* (isolates obtained from Osmangazi Uni. Fac.of Medicine) were investigated and in this investigation, a significant level of activity was illustrated.

Key words: Thiazole, Benzoxazole, Benzimidazole, Antimicrobial activity

INTRODUCTION

The major classes of almost all antibiotics have encountered resistance in clinical applications (Cunha, 1998; Levy, 1998; Rybak and Akins, 2001; Lipsitch, 2001; Doern, 2001). Resistance against β-lactam antibiotics, macrolides, quinolones, and vancomycin is especially among the most important worldwide health problems (Chu *et al.*, 1996; Amyes and Gemmell, 1997; Cunha, 1998; Levy *et al.*, 1998; Cassell and Mekalanos, 2001). In particular, the increasing antibiotic resistance of Gram-positive bacteria is becoming a serious problem for human beings (Rapp, 1999; Cetinkaya, Falk and Mayhall, 2000; Healy *et al.*, 2000; Marchese, Schito and Debbia, 2000).

Apart from this, because of the increased number of immunocompromised patients (AIDS, cancer and transplants), primary and opportunistic fungal infections continue to increase rapidly, and as a consequence, invasive fungal infections constitute a major cause of mortality for these patients. *Candida albicans* is one of the most common opportunistic fungi responsible for these kinds of infections. Although there are new classes of compounds that are now frequently used to treat fungal infections the frequency of deeply invasive candidiasis has increased 10-fold during the past decade. Moreover, many infections caused by the *Candida* spp are actually refractory to antifungal therapy (Hood and Denning, 1996; Alexander and Perfect, 1997).

In order to overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. In drug designing programs an essential component of the search for new leads is the synthesis of molecules, which is novel yet resembles known biologically active molecules by virtue of the presence of critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules (Silverman, 1992; Thompson and Ellman, 1996).

In the last few years, benzoxazole and the related heterocycle benzimidazole have been studied extensively

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for their antitumor, antiviral and antibiotic activities as the new non-nucleoside topoisomerase I poisons, HIV-1 reverse transcriptase inhibitors, and/or potent DNA gyrase inhibitors. A 2-substituted benzoxazole derivative (L-697,661) was observed as a specific non-nucleoside reverse transcriptase inhibitor for the human immunodeficiency virus type 1 (HIV-1) (Perrin *et al.*, 1996).

The other series of 2-substituted benzoxazoles and benzimidazoles were synthesized and studied as topoisomerase I inhibitors (Kim *et al.*, 1996). In evaluating their cytotoxicity, these new topoisomerase I poisons also did not exhibit any significant cross-resistance against cell lines that expressed camptothecin-resistant topoisomerase I. Moreover, substituted pyrimido[1,6'-a]benzimidazoles were found to be a new class of potent DNA gyrase inhibitors. However, their antibacterial activity proved to be inferior relative to quinolone DNA gyrase inhibitors and antibacterial agents such as norfloxacine or fleroxacine (Hubschwerlen *et al.*, 1992).

On the other hand, benzimidazole compounds have been proven to be the most important group of fungicides with systemic activity and are well known for their pronounced ability to control a large number of fungal diseases. Thiabendazole (2-(4-thiazolyl)-1*H*-benzimidazole) which includes benzimidazole and thiazole moiety, is one main example of this fungicide class (Goodman-Gilman, 2001; López-García *et al.*, 2003).

Sulfur and/or nitrogen heterocycles that posses pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. Thiazole moiety is well known for its antimicrobial activity (Onoe and Takahashi, 1994; Pandeya, Sriram and Nath, 1999; Ates, Altintas and Ötük, 2000; Lakhan, Sharma and Shukla, 2000).

Benzimidazole, benzoxazole, and thiazole analogues have been found to have applications in medicine and agriculture. Therefore, development of a simple, fast, and flexible method to generate libraries of such compounds was desirable (Joule and Mills, 2000).

In the interest of the above suggestion, we planned to synthesize a system that combines these two biolabile components which are benzoxazoles/benzimidazoles and thiazoles, together to give a compact structure like title compounds. Especially, thiazole moiety which includes ester residue, i.e. easily hydrolyzes to acid function, was preferred because of the effect of acidic functions on nonspecific antifungal agents (Gringauz, 1997).

MATERIALS AND METHODS

All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus and were uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck). Spectroscopic data were recorded using the following instruments. IR: Shimadzu IR-435 spectrophotometer, ^{1}H-NMR: Bruker 250 MHz spectrometer in DMSO-d_6 using TMS as the internal standard, MS-FAB: VG Quattro Mass spectrometer.

In the present study, 4-substituted-2-(chloroacetylamino) thiazole (**1**) was prepared by reacting 2-amino-4-substituted-thiazole with chloroacetyl chloride in accordance with the method described in the literature (Turan-Zitouni and Kaplancıklı, 1998; Turan-Zitouni *et al.*, 2004).

The reaction of 4-substituted-2-(chloroacetylamino) thiazole (**1**), benzimidazole/ benzoxazole-2-thiole (**2**), and anhydrous potassium carbonate in acetone gave the 4-substituted-2-[[(benzoxazole/benzimidazole-2-yl)sulfanyl] acetylamino]thiazole derivatives (**3**) as shown in Scheme 1. Some characteristics of the synthesized compounds are shown in Table I.

4-Substituted-2-[[(benzoxazole/benzimidazole-2-yl) sulfanyl]acetylamino]thiazoles (3a-l)

A mixture of 4-substituted-2-(chloroacetylamino)thiazole (**1**) (0.01 mol), benzoxazole/benzimidazole-2-thiole (**2**) (0.01 mol), and K_2CO_3 (0.01 mol) in acetone (50 mL) was refluxed for 6-10 hrs. After cooling, the solution was evaporated until dry. The residue was washed with water and recrystallized from ethanol.

Ethyl [2-[[(benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3a)

Yield 75.0%; mp 166 °C, IR (KBr) 3224, 1745, 1655, 1580 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.30 (t, *J*=7.08 Hz, 3H,), 4.25 (q, *J*=7.10 Hz, 2H), 4.40 (s, 2H), 7.20-7.40 (m, 2H), 7.50-7.70 (m, 2H), 7.95 (s, 1H), 12.80 (br, 1H); MS (FAB) (M+1) *m/z* 364.

Table I. Various characteristics of the compounds

Comp.	R	R′	X	M.p. (°C)	Mol. Formula	Mol. weight
3a	$COOC_2H_5$	H	O	166	$C_{15}H_{13}N_3O_4S_2$	363
3b	$COOC_2H_5$	Cl	O	222	$C_{15}H_{12}ClN_3O_4S_2$	397.5
3c	$COOC_2H_5$	NO_2	O	226	$C_{15}H_{12}N_4O_6S_2$	408
3d	$COOC_2H_5$	CH_3	O	159	$C_{16}H_{15}N_3O_4S_2$	377
3e	$COOC_2H_5$	H	NH	180	$C_{15}H_{14}N_4O_3S_2$	362
3f	$COOC_2H_5$	Cl	NH	214	$C_{15}H_{13}ClN_4O_3S_2$	396.5
3g	$CH_2COOC_2H_5$	H	O	83	$C_{16}H_{15}N_3O_4S_2$	377
3h	$CH_2COOC_2H_5$	Cl	O	188	$C_{16}H_{14}ClN_3O_4S_2$	411.5
3i	$CH_2COOC_2H_5$	NO_2	O	170	$C_{16}H_{14}N_4O_6S_2$	422
3j	$CH_2COOC_2H_5$	CH_3	O	96	$C_{17}H_{17}N_3O_4S_2$	391
3k	$CH_2COOC_2H_5$	H	NH	94	$C_{16}H_{16}N_4O_3S_2$	376
3l	$CH_2COOC_2H_5$	Cl	NH	100	$C_{16}H_{15}ClN_4O_3S_2$	410.5

Ethyl [2-[[(5-chloro-benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3b)
Yield 83.0%; mp 222°C, IR (KBr) 3213, 1740, 1635, 1570 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.25 (t, *J*=7.06, Hz, 3H), 4.15-4.30 (m, 4H), 7.30 (dd, *J*=2.10 Hz and *J*=2.13 Hz, 1H), 7.55 (s, 1H), 7.60-7.80 (m, 2H), 12.85 (br., 1H); MS (FAB) (M+1) *m/z* 398.

Ethyl [2-[[(5-nitro-benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3c)
Yield 80.0%; mp 226°C, IR (KBr) 3247, 1742 , 1657, 1572 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.30 (t, *J*=7.10 Hz, 3H), 4.30 (q, *J*=7.11 Hz, 2H), 4.45 (s, 2H), 7.85-8.45 (m, 4H), 12.75 (s, 1H); MS (FAB) (M+1) *m/z* 409.

Ethyl [2-[[(5-methyl-benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3d)
Yield 88.0%; mp 159°C, IR (KBr) 3222, 1743, 1638, 1578 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.25 (t, *J*=7.13 Hz, 3H), 2.35 (s, 3H), 4.05-4.35 (m, 4H), 7.05-7.50 (m, 3H), 7.65 (s, 1H), 12.80 (s, 1H); MS (FAB) (M+1) *m/z* 378.

Ethyl [2-[[(1*H*-benzimidazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3e)
Yield 73.0%; mp 180°C, IR (KBr) 3221, 1752, 1645, 1562 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.25 (t, *J*=7.13 Hz, 3H), 4.25 (q, *J*=7.12 Hz, 2H), 4.35 (s, 2H), 7.05-7.50 (m, 4H), 8.05 (s, 1H), 12.65 (br., 1H), 12.90 (s, 1H); MS (FAB) (M+1) *m/z* 363.

Ethyl [2-[[(5-chloro-1*H*-benzimidazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] carboxylate (3f)
Yield 75.0%; mp 214°C, IR (KBr) 3200, 1745, 1630, 1571, cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.30 (t, *J*=7.15 Hz, 3H), 4.30 (q, *J*=7.10 Hz, 2H), 4.30 (s, 2H), 7.15 (m, 1H), 7.40-7.55 (m, 2H), 8.10 (s, 1H), 12.65 (br., 1H), 12.85 (br., 1H); MS (FAB) (M+1) *m/z* 397.

Ethyl [2-[[(benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] acetate (3g)
Yield 80.0%; mp 83°C, IR (KBr) 3210, 1762, 1649, 1543 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.20 (t, *J*=7.12 Hz, 3H), 3.60 (s, 2H), 4.00-4.40 (m, 4H), 6.60-7.70 (m, 5H), 12.80 (s, 1H); MS (FAB) (M+1) *m/z* 378.

Ethyl [2-[[(5-chloro-benzoxazol-2-yl)sulfanyl]acetylamino] thiazol-4-yl] acetate (3h)
Yield 76.0%; mp 188°C, IR (KBr) 3219, 1765, 1645, 1535 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.15 (t, *J*=7.09 Hz, 3H), 3.55 (s, 2H), 4.05 (q, *J*=7.14 Hz, 2H), 4.30 (s, 2H), 6.70 (s, 1H), 7.25 (dd, *J*=2.08 Hz and *J*=2.16 Hz, 1H), 7.65-7.75 (m, 2H), 12.75 (s, 1H); MS (FAB) (M+1) *m/z* 412.

Ethyl [2-[[(5-nitro-benzoxazol-2-yl)sulfanyl]acetylamino] thiazol-4-yl] acetate (3i)
Yield 81.0%; mp 170°C IR (KBr) 3245, 1760, 1658, 1565 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.15 (t, *J*=7.17 Hz, 3H), 3.70 (s, 2H), 4.05 (q, *J*=7.07 Hz, 2H), 4.40 (s, 2H), 7.00 (s, 1H), 7.25-7.65 (m, 3H), 12.65 (br., 1H); MS (FAB) (M+1) *m/z* 423.

Ethyl [2-[[(5-methyl-benzoxazol-2-yl)sulfanyl]acetylamino]thiazol-4-yl] acetate (3j)
Yield 69.0%; mp 96°C, IR (KBr) 3220, 1746, 1640, 1581 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.20 (t, *J*=7.11 Hz, 3H), 2.40 (s, 3H), 3.70 (s, 2H), 4.10 (q, *J*=7.10 Hz, 2H), 4.35 (s, 2H), 6.85-7.55 (m, 4H), 12.60 (s, 1H); MS (FAB) (M+1) *m/z* 392.

Ethyl [2-[[(1*H*-benzimidazol-2-yl)sulfanyl]acetylamino] thiazol-4-yl] acetate (3k)
Yield 69.0%; mp 94°C, IR (KBr) 3215, 1750, 1635, 1542 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz)δ 1.15 (t, *J*=7.07 Hz, 3H), 3.65 (s, 2H), 4.05 (q, *J*=7.11 Hz, 2H), 4.35 (s, 2H), 6.95 (s, 1H), 7.10-7.50 (m, 4H), 12.55 (br., 1H), 12.80 (br, 1H); MS (FAB) (M+1) *m/z* 377.

Ethyl [2-[[(5-chloro-1*H*-benzimidazol-2-yl)sulfanyl] acetylamino]thiazol-4-yl] acetate (3l)
Yield 65.0%; mp 100°C, IR (KBr) 3230, 1758, 1639, 1583 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 250 MHz) δ 1.15 (t, *J*=7.12 Hz, 3H), 3.70 (s, 2H), 4.10 (q, *J*=7.11 Hz, 2H), 4.35 (s, 2H), 7.00 (s, 1H), 7.10-7.60 (m, 3H), 12.45 (br., 1H), 12.65 (br., 1H); MS (FAB) (M+1) *m/z* 411.

Biological assay

Antimicrobial activities of compounds were tested using the microbroth dilution method (Koneman *et al.*, 1997). Tested microorganism strains were *Micrococcus luteus* (NRLL B-4375), *Bacillus cereus* (NRRL B-3711), *Proteus vulgaris* (NRRL B-123), *Salmonella typhimurium* (NRRL B-4420), *Staphylococcus aureus* (NRRL B-767), *Escherichia coli* (NRRL B-3704), *Candida albicans and Candida globrata* (isolates obtained from Osmangazi Uni.Fac.of Medicine). Microbroth dilution susceptibility assay was used for the antimicrobial evaluation of the compounds. Stock solutions of the samples were prepared in dimethylsulfoxide. Dilution series using sterile distilled water were prepared from 4 mg/mL to 0.007 mg/mL in micro-test tubes and were transferred to 96-well microtiter plates. Bacterial and *C. albicans* suspensions that were grown overnight in double-strength Mueller-Hinton broth were standardized to 10^8 CFU/mL using McFarland No: 0.5 standard solution. 100 µL of each microorganism suspension was then added into the wells. The last well-chain without any microorganisms was used as the negative

Table II. Antimicrobial activities of the compounds (μg/mL)

	A	B	C	D	E	F	G	H
3a	31.25	62.5	7.8	125	250	125	125	125
3b	31.25	62.5	15.6	125	125	125	125	62.5
3c	31.25	62.5	31.25	125	62.5	125	125	125
3d	62.5	62.5	3.9	62.5	125	62.5	62.5	62.5
3e	62.5	125	125	125	125	125	125	125
3f	62.5	125	7.8	125	62.5	125	62.5	62.5
3g	62.5	125	62.5	125	125	125	125	125
3h	31.25	250	31.25	125	125	125	125	125
3i	15.6	125	31.25	62.5	62.5	125	125	62.5
3j	31.25	125	62.5	125	125	125	125	62.5
3k	15.6	125	7.8	125	250	125	125	125
3l	31.25	62.5	31.25	62.5	125	125	62.5	62.5
Reference-1	1.95	125	0.97	0.97	62.5	62.5	-	-
Reference-2	-	-	-	-	-	-	62.5	62.5

Reference-1: Chloramphenicol, Reference -2: Ketoconazole
A: *Micrococcus luteus* (NRLL B-4375), **B:** *Bacillus cereus* (NRRL B-3711), **C:** *Proteus vulgaris* (NRRL B-123), **D:** *Salmonella typhimurium* (NRRL B-4420), **E:** *Staphylococcus aureus* (NRRL B-767), **F:** *Escherichia coli* (NRRL B-3704), **G:** *Candida albicans* (isolates obtained from Osmangazi Uni. Fac.of Medicine), **H:** *Candida globrata* (isolates obtained from Osmangazi Uni. Fac.of Medicine).

control. Sterile distilled water and the medium served as a positive growth control. After incubation at 37°C for 18-24 h, the first well without turbidity, was determined as the minimal inhibitory concentration (MIC). Chloramphenicol was used as the standard antibacterial agent whereas ketoconazole was used as antifungal agent. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table II.

RESULT AND DISCUSSION

Chemistry

In this study, 12 new compounds were synthesized. The structures of the obtained compounds were elucidated by spectral data. In the IR spectra, some significant stretching bands due to N-H, ester C=O, amide C=O, C=N and C=C were at 3247-3200 cm^{-1}, 1765-1740 cm^{-1}, 1658-1630 cm^{-1}, 1583-1535 cm^{-1}, respectively. In the ^{1}H-NMR spectra, the signal due to S-CH_2 methylene protons, present in all compounds, appeared at 4.30-4.45 ppm, as singlets. The NHCO proton was observed at 12.60-12.90 ppm as a singlet or broad. All other aromatic and aliphatic protons were observed at expected regions.

Mass spectra (MS (FAB)) of compounds showed M+1 peaks, which were in agreement with their molecular formula.

Antimicrobial activity

MICs were recorded as the minimum concentration of a compound that inhibits the growth of tested micro-organisms. All of the compounds tested were illustrated significant antibacterial and antifungal activity when compared with reference drugs.

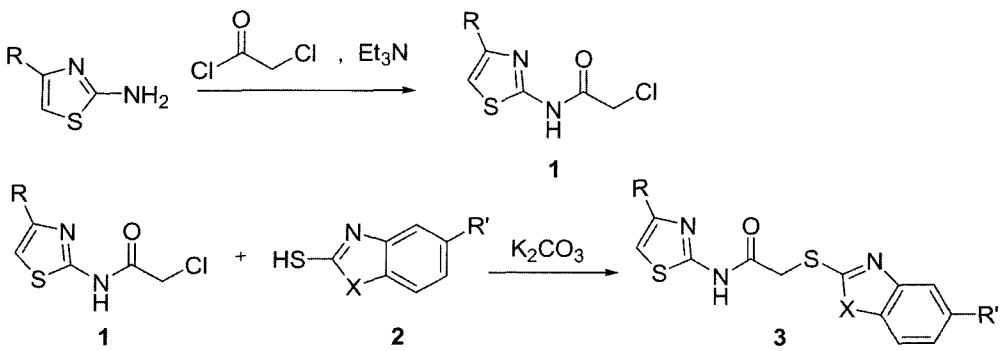
The antibacterial assessment revealed that the compounds posseses significant activity. The MIC values are generally within the range of 3.9-250 μg/mL against all evaluated strains.

In comparing their MIC values with chloramphenicol, all of the compounds were effective against *Bacillus cereus*; **3a**, **3b**, **3c**, **3d**, and **3l** especially showed strong activity. **3e**, **3f**, **3g**, **3i**, **3j**, and **3k** showed a similiar level of activity, and **3h** showed moderate activity when compared with the reference agent.

On the other hand the compounds exhibited comparable activities against *Staphylococcus aureus*. The compounds **3c**, **3f**, and **3i** showed a similar level of activity, and the other compounds showed moderate activity to the reference agent.

When compared with chloramphenicole, only compound **3l** showed similar activity against *Escherichia coli*, whereas all other compounds showed a moderate level of activities.

Considerable results were obtained from the activity screening test against *Micrococcus luteus*. Although MIC values of all compounds against *Micrococcus luteus* were higher than the value of the reference agent, their effective



Scheme 1. Synthesis of compound **3**

concentration values were usually lower than other MIC values obtained from excluding microorganisms.

The compounds were less active against *Salmonella typhimurium*.

Most of the compounds were effective against *Candida globrata* when compared with ketoconazole; in particular **3b**, **3d**, **3f**, **3i**, **3j**, and **3l** showed a similiar level of activity and **3a**, **3c**, **3e**, **3g**, **3h**, and **3k** showed modarate activity.

From the similar results obtained from *Candida albicans*, compounds **3d**, **3f**, and **3l** show similar and compounds **3a**, **3b**, **3c**, **3e**, **3g**, **3h**, **3i**, **3j**, and **3k** show modarate activity when compared with ketoconazole.

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