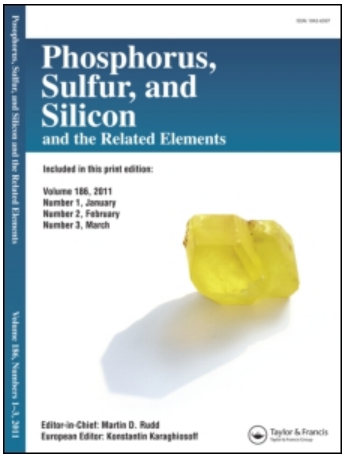

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SYNTHESIS OF SOME 2-[(BENZAZOLE-2-YL)THIO]-DIPHENYLMETHYLACETAMIDE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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G. Turan-Zitouni,[a] *Z. A. Kaplancıklı,*[a] *Ü. Uçucu,*[a] *A. Özdemir,*[a] *P. Chevallet,*[b] *and Y. Tunalı*[c]
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Some 2-[(benzazole-2-yl)thio]diphenylmethylacetamide derivatives were synthesized by reacting 2-chloroacethylaminodiphenylmethane with benzazole-2-thions. The structure elucidation of the compounds was performed by IR, ^{1}H NMR, and MS-FAB spectral data.

Antimicrobial activity of the compounds was examined. Some of the compounds have shown similar antifungal activities against C. albicans *when compared with ketoconazole. It was also observed that some of these compounds have moderate antimicrobial activity when compared with chloramphenicole.*

Keywords: Antimicrobial activity; benzimidazole; benzothiazole; benzoxazole

INTRODUCTION

The number of cases of multidrug-resistant bacterial infections are increasing at a significant rate. Clinicians have become reliant on antibiotics for serious infections that are resistant to traditional agents,[1] so there is a need for new classes of antibacterial agents.

The benzothiazole ring is present in various marine or terrestrial natural compounds that have useful biological activities.[2–5] Benzothiazole and its bioisosteres, benzoxazole and benzimidazole, were studied

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for their antitumor, antiviral, and antimicrobial activities.[6–10] In the last few years, it was reported that the 2- and 5-substituted benzothiazole, benzoxazole, and benzimidazole derivatives have antimicrobial activities against some Gram-positive and Gram-negative bacteria and yeast, and these compounds provided a wide variety of in vitro antimicrobial effects, especially against the enterobacter *Pseudomonas aeruginosa* and the yeast *Candida albicans*.[11–17]

In view of these observations, we synthesized new 2-[(benzazole-2-yl)thio]-diphenylmethylacetamide derivatives and tested them for antibacterial and antifungal activities.

RESULTS AND DISCUSSION

Chemistry

In the present work, 2-(chloroacetylamino)diphenylmethane (**1**) was prepared by reacting diphenylmethylamine with chloroacetyl chloride in accordance with the method described in the literature.[18–20]

2-[(Benzazole-2-yl)thio]diphenylmethylacetamide derivatives (**3a–h**) were synthesized by reacting **1** and benzazol-2-thiol derivatives (**2**) (Scheme 1 and Table I).

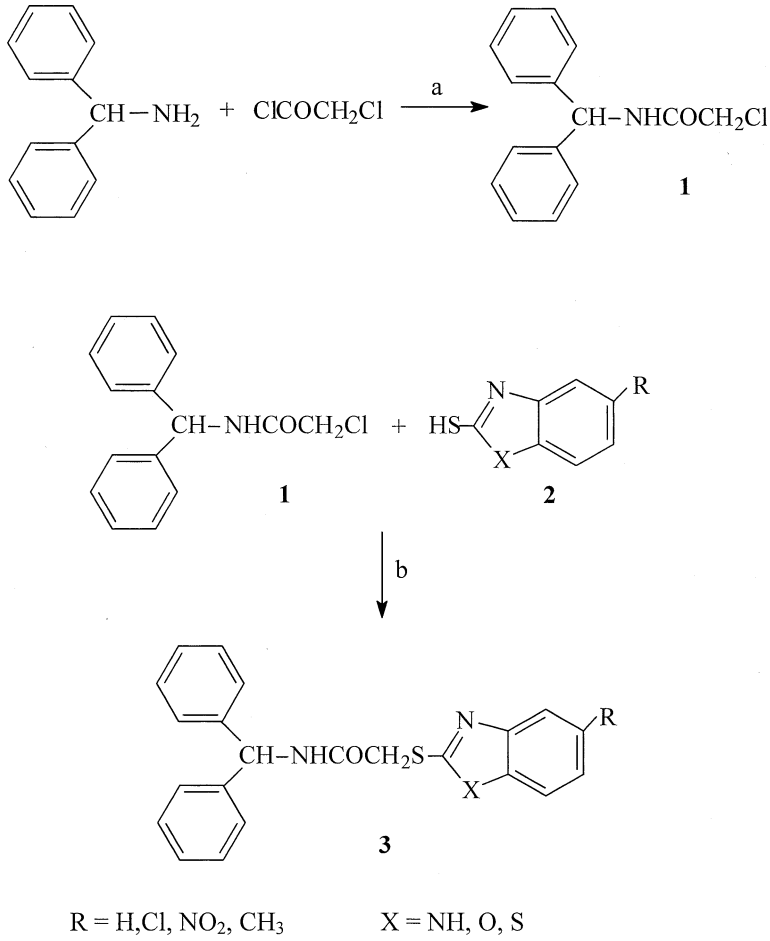
Analytical and spectral data (IR, ^{1}H NMR, MS (FAB$^+$)) confirmed the structures of **3a–h**.

The structures of the obtained compounds were elucidated by spectral data. In the IR spectra some significant stretching bands due N—H and C=O were at 3270–3080 and 1670–1640 cm^{-1}, respectively.

In the ^{1}H NMR spectra, the signal due to $COCH_2$ methylene protons, present in all compounds, appeared at 4.2–4.3 ppm as singlets. The signals due to CH proton appeared at 6.1 ppm as doublets. The aromatic protons were observed at 6.8–7.6 ppm as multiplets. The NH proton was observed at 9.3–9.4 ppm as a doublet.

TABLE I Some Characterizations of the Compounds

Compound	R	X	m.p.(°C)	Yield (%)	Molecular formula	M.W.
3a	H	NH	207	72	$C_{22}H_{19}N_3OS$	373
3b	Cl	NH	227	75	$C_{22}H_{18}ClN_3OS$	407.5
3c	CH_3	NH	202	78	$C_{23}H_{21}N_3OS$	387
3d	NO_2	NH	231	72	$C_{22}H_{18}N_4O_3S$	418
3e	H	O	172	69	$C_{22}H_{18}N_2O_2S$	374
3f	Cl	O	130	71	$C_{22}H_{17}ClN_2O_2S$	408.5
3g	CH_3	O	156	70	$C_{23}H_{20}N_2O_2S$	388
3h	H	S	201	70	$C_{22}H_{18}N_2OS_2$	390



SCHEME 1

Microbiology

All compounds were evaluated for their antimicrobial properties. Minimal inhibitory concentrations (MICs) were recorded as the minimum concentration of compound, which inhibits the growth of tested microorganisms. Compounds **3b** and **3e** showed similar antifungal activities against *C. albicans,* when compared with ketoconazole. It was also observed that all of the compounds have changing antimicrobial activity

TABLE II Antimicrobial Activities of the Compounds

Microorganism	**3b**	**3c**	**3e**	**3f**	**3g**	**A**	**B**
E. coli	>250	>250	125	125	>250	31.25	—
S. aureus	62.5	125	125	>250	125	3.9	—
P. aeruginosa	>250	>250	>250	>250	>250	62.5	—
E. aerogenes	125	500	>250	>250	>250	62.5	—
P. vulgaris	125	62.5	125	125	125	15.6	—
S. typhimurium	31.25	250	250	250	62.5	31.25	—
C. albicans	62.5	125	62.5	>250	125	—	62.5

MIC (as μg /ml), Control compounds; **A**, Chloramphenicole; **B**, Ketoconazole.

ranges against all tested bacteria when compared with chloramphenicole (Table II).

EXPERIMENTAL

Chemistry

Melting points were determined by using a Gallenkamp apparatus. Spectroscopic data were recorded by the following instruments: IR, Shimadzu IR-435 spectrophotometer; ^{1}H NMR, Bruker 250 MHz spektrometer; and MS, fast atom bombardment mass spectra (FAB$^+$-MS) were obtained by VG Quattro mass spectrometer.

General Procedure for Synthesis of the Compounds

2-Chloroacetylaminodiphenylmethane (1)

Chloroacetyl chloride (0.02 mol) and triethylamine (0.03 mol) were dissolved in anhydrous benzene (30 ml) with constant stirring. The mixture was cooled in an ice bath, and chloroacetyl chloride (0.02 mol) was added dropwise with stirring. The reaction mixture thus obtained was further agitated for 1 h at room temperature. The precipitate was filtrated, the solvent was evaporated to dryness under reduced pressure, and the products were recrystallized from ethanol.

2-[(Benzazole-2-yl)thio]diphenylmethylacetamide Derivatives (3a–h)

A mixture of 2-chloroacetylaminodiphenylmethane (**1**) (0.01 mol), benzazol-2-thiol (**2**) (0.01 mol), and K_2CO_3 (0.01 mol) were treated in acetone (50 ml) at room temperature for 8 h. The solvent was evaporated until dryness. The residue was washed with water and recrystallized from ethanol.

3a–h: IR (KBr) $\nu_{max}(cm^{-1})$: 3220 (NH), 1645 (C=O), 1570 (C=N), 1530 (C=C), 1210 (C—O—C).
3b: ^{1}H NMR (250 MHz) (DMSO-d_6) δ (ppm): 4.2 (2H, s, $COCH_2$), 6.1 (1H, d, —CH—), 7.1–7.5 (13H, m, aromatic protons), 9.4 (1H, d, NHCO). MS (FAB^+): m/z: 408 (M + 1).
3c: ^{1}H NMR (250 MHz) (DMSO-d_6) δ (ppm): 2.4 (3H, s, CH_3), 4.1 (2H, s, $COCH_2$), 6.1 (1H, d, —CH—), 6.9–7.4 (13H, m, aromatic protons), 9.4 (1H, d, NHCO). MS (FAB^+): m/z: 388 (M + 1).
3e: ^{1}H NMR (250 MHz) (DMSO-d_6) δ (ppm): 4.3 (2H, s, $COCH_2$), 6.1 (1H, d, —CH—), 7.2–7.6 (14H, m, aromatic protons), 9.3 (1H, d, NHCO). MS (FAB^+): m/z: 375 (M + 1).
3f: ^{1}H NMR (250 MHz) (DMSO-d_6) δ (ppm): 4.3 (2H, s, $COCH_2$), 6.2 (1H, d, —CH—), 7.1–7.5 (13H, m, aromatic protons), 9.4 (1H, d, NHCO). MS (FAB^+): m/z: 409 (M + 1).
3g: ^{1}H NMR (250 MHz) (DMSO-d_6) δ (ppm): 2.4 (3H, s, CH_3), 4.3 (2H, s, $COCH_2$), 6.2 (1H, d, —CH—), 7.1–7.4 (13H, m, aromatic protons), 9.3 (1H, d, NHCO). MS (FAB^+): m/z: 389 (M + 1).

Microbiology

Antimicrobial activities of the compounds were determined using the tube dilution technique.[21] MIC values were calculated as μg/ml. Standard bacteria strain used were *Esherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus vulgaris* (NRRL B-123), *Enterobacter aerogenes* (NRRL 3567), *Salmonella typhimurium* (NRRL B-4420), and *Candida albicans* (University of Osmangazi, Faculty of Medicine, Eskisehir).

Microdilution broth susceptibility assay was used for the antimicrobial evaluation of the compounds. Stock solutions of the samples were prepared in dimethylsulfoxide (DMSO). Dilution series using sterile distilled water were prepared from 4 mg/ml to 0.007 mg/ml in micro-test tubes that were transferred to 96-well microtiter plates. Overnight-grown bacterial and *C. albicans* suspensions in double-strength Mueller-Hinton broth were standardized to 10^8 CFU/ml using McFarland No: 0.5 standard solution. One hundred microliters of each microorganism suspension was then added into the wells. The last well-chain without microorganism was used as a negative 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 MIC. Chloramphenicol was used as standard antibacterial agent, whereas ketoconazole was used as antifungal agent.

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