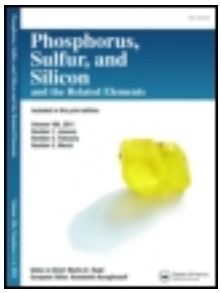

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SYNTHESIS OF SOME DITHIOCARBAMATE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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Some new, 2-[(N-substituted aminothiocarbonylthio)acetyl]aminothiazole, N-substituted aminothiocarbonylthioacetylaminodiphenylmethane and 9-[(N-substituted aminothiocarbonylthio)acetyl]aminofluorene derivatives were synthesized by reacting 2-(chloroacetyl) aminothiazole, chloroacetylaminodiphenylmethane, and 9-(chloroacetyl)aminofluorene with secondary amine dithiocarbamate derivatives in acetone respectively. The structure elucidation of the compounds was performed by IR, ^{1}H-NMR, and FAB$^+$-MS spectral data. The substances were tested for their antimicrobial activity.

Keywords: Antimicrobial activity; diphenylmethane; dithiocarbamate; fluorene; thiazole

It is well known that, N-mono and N,N-di substituted dithiocarbamate derivatives show antibacterial, antiviral and antifungal activities.[1–7]

The structure-activity relationship study revealed that the antibacterial activity on thiocarbonyl aromatic compounds was significantly affected by the lipophilicity, that is obtained by thiocarbonyl moiety, especially the calculated log P value and the balance between hydrophilic substituent and hydrophobic substituent on the aromatic compounds.[2]

Some thiocarbonyl aromatics that were synthesized inspired by the above mentioned rationale were found to possess good in vitro antibacterial activity against gram-positive bacteria.[2]

In view of these observations, some aromatic compounds, i.e., 2-(chloroacetyl)-aminothiazole, chloroacetylaminodiphenylmethane and

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9-(chloroacetyl)aminofluorene were reacted with dithiocarbamates and these compounds were tested for their antibacterial and antifungal activities.

RESULTS AND DISCUSSION

Chemistry

The present report deals with the synthesis of 2-[(N-substituted aminothiocarbonylthio)-acetyl]aminothiazole (**5a–c**), N-substituted aminothiocarbonylthioacetylaminodiphenyl-methane (**6a–c**) and 9-[(N-substituted aminothiocarbonylthio)acetyl]aminofluorene (**7a–d**).

The 2-(chloroacetyl)aminothiazole (**2**), chloroacetylaminodiphenyl-methane (**3**) 9-(chloroacetyl)aminofluorene (**4**) were prepared as starting materials in accordance with the method described in the literature.[1,7]

The reaction of chloroacetylamine (**2**, **3**, **4**) and appropriate secondary amine-dithiocarbamatepotassium (**1**) in acetone, gave the 2-[(N-substituted aminothiocarbonyl-thio)acetyl]aminothiazole (**5a–c**) N-substituted aminothiocarbonylthioacetylaminodiphenyl-methane (**6a–c**) 9-[(N-substituted aminothiocarbonylthio)acetyl]aminofluorene (**7a–d**) (Table I, Scheme 1).

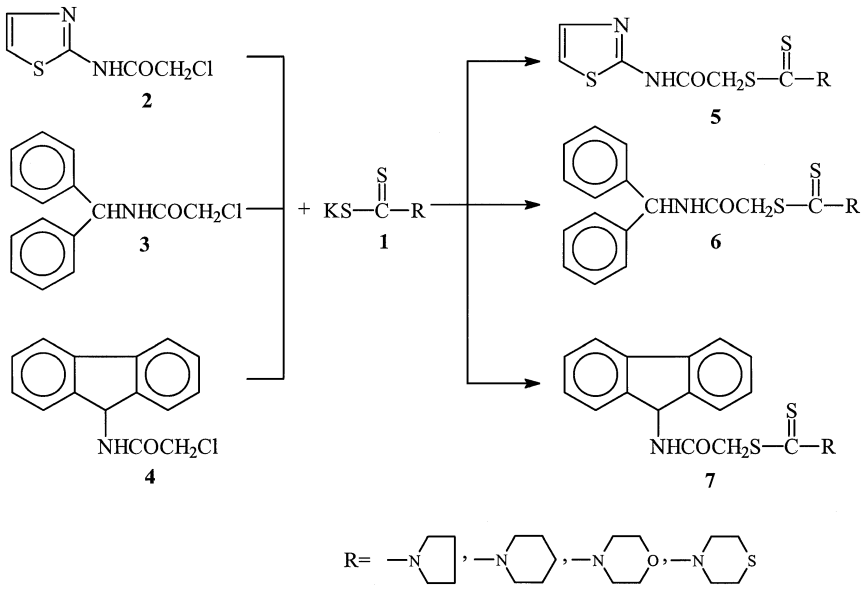
Analytical and spectral data (IR, ^{1}H-NMR, FAB$^+$-MS) confirmed the structure of the compounds (see also Table I).

In the IR spectra, some significant stretching bands due to C=O, C=S, N–H were observed at 1640–1680 cm^{-1}, 1225–1255 cm^{-1}, 3270–3080 cm^{-1} respectively.

In the ^{1}H-NMR spectra, the signal due to $COCH_2$ methylene protons, present in all compounds, appeared at 4.15–4.40 ppm, as singlets.

TABLE I Some Characterizations of the Compounds

Comp.	R	m.p. (°C)	Yield (%)	Molecular formula	Mol. weight
5a	Pyrrolidine	194	80	$C_{10}H_{13}N_3OS_3$	287
5b	Piperidine	190	70	$C_{11}H_{15}N_3OS_3$	301
5c	Morpholine	198	65	$C_{10}H_{13}N_3O_2S_3$	303
6a	Pyrrolidine	110	68	$C_{20}H_{22}N_2OS_2$	370
6b	Piperidine	94	73	$C_{21}H_{24}N_2OS_2$	384
6c	Morpholine	154	85	$C_{20}H_{22}N_2O_2S_2$	386
7a	Pyrrolidine	204	80	$C_{20}H_{20}N_2OS_2$	368
7b	Piperidine	208	60	$C_{21}H_{22}N_2OS_2$	382
7c	Morpholine	228	55	$C_{20}H_{20}N_2O_2S_2$	384
7d	Thiomorpholine	238	65	$C_{20}H_{20}N_2OS_3$	400



SCHEME 1

Aliphatic protons of pyrrolidine, piperidine, morpholine and thiomorpholine were observed at the 1.50–4.50 ppm region. Aromatic protons and NH proton were elucidated at expected regions.

Microbiology

All compounds were evaluated for their antimicrobial properties. The compounds showed moderate inhibitor effects against human pathogenic microorganisms. Especially *E. coli*, *C. albicans* were inhibited by **7c**, with a MIC values of 62.5 μg/ml which is equal to that of the standard antifungal agent. **5c** and **7d** showed significant antibacterial effects against *S. aureus* and *S. typhimurium* (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; MS: fast atom bombardment mass spectra (FAB$^+$-MS) were obtained by VG Quattro mass spectrometer.

TABLE II Antimicrobial Activities of the Compounds

	5a	5b	5c	6a	6b	6c	7a	7b	7c	7d	A	B
E.coli	500	250	125	250	250	125	250	250	62.5	500	31.25	.
S. aureus	250	250	62.5	125	250	125	250	250	125	500	3.9	.
P. aeruginosa	500	250	500	250	500	125	500	500	250	250	62.5	.
E. aerogenes	250	125	250	250	250	250	250	250	250	250	62.5	.
P. vulgaris	250	250	250	250	125	250	125	250	125	125	15.6	.
S. typhimurium	250	250	500	500	250	250	250	125	250	62.5	31.25	.
C. albicans	250	250	500	250	250	500	250	125	62.5	125	—	62.5

*MIC (μg/ml), **A**: Chloramphenicol, **B**: Ketoconazole.

General Procedure for Synthesis of the Compounds

*2-(Chloroacetyl)aminothiazole (**2**), chloroacetylaminodiphenylmethane (**3**), 9-(chloroacetyl)aminofluorene (**4**).* The amine (2-thiazolylamine, diphenylmethylamine, and 9-fluorenylamine) (0.01 mmol) and triethylamine (0.01 mmol) were dissolved in benzene (50 ml) with constant stirring. Later, the mixture was cooled in an ice bath, and chloroacetylchloride (0.01 mmol) 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.[1,7]

*2-[(N-Substituted aminothiocarbonylthio)acetyl]aminothiazole (**5a–c**) N-substituted aminothiocarbonylthioacetylaminodiphenylmethane (**6 a–c**), 9-[(N-substituted aminothiocarbonylthio)acetyl]aminofluorene (**7a–d**).* A mixture of chloroacetylamine (**2**, **3**, **4**) (0.01 mmol) and appropriate secondary amine dithiocarbamate potassium (**1**) (0.01 mmol) was caused to react in acetone at room temperature for 4 h. The solvent was evaporated, washed with water, and the residue recrystallized from ethanol.

IR (KBr, cm^{-1}): These compounds showed characteristic IR bands at 1640–1680 cm^{-1} (C═O), 1225–1255 cm^{-1} (C═S), and 3270–3080 cm^{-1} (N─H).

5a: ^{1}H-NMR (δ ppm) (DMSO-d_6): 1,95–2,15 (4H, two p, C_3 and C_4 protons of pyrrolidine), 3,70 and 3,95 (4H, two t, C_2 and C_5 protons of pyrrolidine), 4,35 (2H, s, $COCH_2$), 6,95 (1H, d, C_5 proton of thiazole), 7,50 (1H, d, C_4 proton of thiazole), 12,45 (1H, br, NH)

MS (FAB^+): m/z: 288 [M + 1]

5b: ^{1}H-NMR (δ ppm)(DMSO-d_6): 1,60–1,80 (6H, br, C_3, C_4 and C_5 protons of piperidine), 3,90 and 4,30 (4H, two br s, C_2 and C_6 protons of piperidine), 4,40 (2H, s, $COCH_2$), 6,95 (1H, d, C_5 proton of thiazole), 7,55 (1H, d, C_4 proton of thiazole), 12,40 (1H, br, NH)

MS (FAB^+): m/z: 302 [M + 1]

6b: ^{1}H-NMR (δ ppm)(DMSO-d_6): 1,50–1,90 (6H, m, C_3, C_4 and C_5 protons of piperidine), 3,85 and 4,25 (4H, two br s, C_2 and C_6 protons of piperidine), 4,20 (2H, s, $COCH_2$), 6,15 (1H, d, CH), 7,10–7,35 (10H, m, aromatic protons), 9,10 (1H, d, NH)

MS (FAB^+): m/z: 385 [M + 1]

6c: ^{1}H-NMR (δ ppm)(DMSO-d_6): 3,60 (4H, br, C_3 and C_5 protons of morpholine), 3,90 (4H, br, C_2 and C_6 protons of morpholine), 4,15 (2H, s, $COCH_2$), 6,10 (1H, d, CH), 7,20–7,35 (10H, m, aromatic protons), 9,10 (1H, d, NH)

MS (FAB^+): m/z: 387 [M + 1]

7a: ^{1}H-NMR (δ ppm)(DMSO-d_6): 1,85–2,15 (4H, two p, C_3 and C_4 protons of pyrrolidine), 3,65 and 3,75 (4H, two t, C_2 and C_5 protons of pyrrolidine), 4,15 (2H, s, $COCH_2$), 6,00 (1H, d, C_9 proton of flourene), 7,20–7,45 (6H, m, aromatic protons), 7,85 (2H, d, C_1 and C_8 protons of fluorene), 7,85 (1H, d, NH)

MS (FAB^+): m/z: 369 [M + 1]

7b: ^{1}H-NMR (δ ppm)(DMSO-d_6): 1,55–1,75 (6H, br, C_3, $C_4$and C_5 protons of piperidine), 3,90 and 4,30 (4H, two br, C_2 and C_6 protons of piperidine), 4,25 (2H, s, $COCH_2$), 6,05 (1H, d, C_9 proton of flourene), 7,25–7,40 (6H, m, aromatic protons), 7,90 (2H, d, C_1 and C_8 protons of fluorene), 8,80 (1H, d, NH)

MS (FAB^+): m/z: 383 [M + 1]

7c: ^{1}H-NMR (δ ppm)(DMSO-d_6): 3,70 (4H, t, C_3 and C_5 protons of morpholine), 4,00 (4H, br, C_2 and C_6 protons of morpholine), 4,25 (2H, s, $COCH_2$), 6,10 (1H, d, C_9 proton of flourene), 7,30–7,60 (6H, m, aromatic protons), 7,90 (2H, d, C_1 and C_8 protons of fluorene), 8,90 (1H, d, NH)

MS (FAB^+): m/z: 385 [M + 1]

7d: ^{1}H-NMR (δ ppm)(DMSO-d_6): 2,70 (4H, t, C_3 and C_5 protons of thiomorpholine), 4,30 and 4,50 (4H, two br, C_2 and C_6 protons of thiomorpholine), 4,20 (2H, s, $COCH_2$), 6,10 (1H, d, C_9 proton of flourene), 7,25–7,45 (6H, m, aromatic protons), 7,95 (2H, d, C_1 and C_8 protons of fluorene), 8,80 (1H, two d, NH)

MS (FAB^+): m/z: 401 [M + 1]

Microbiology

Antibacterial activities of compounds were determined using the tube dilution technique.[8,9] MIC values were calculated as μg/ml. The following were used as a test microorganisms; *Escherichia 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, Eskişehir).

Microdilution broth 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 that were transferred to 96-well microtiter plates. Overnight grown bacterial and *C. albicans* suspensions in double-strength Mueller-Hinton broth were standardised 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 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 minimal inhibitory concentration (MIC). Chloramphenicol was used as standard antibacterial agent whereas ketoconazole was used as antifungal agent.

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