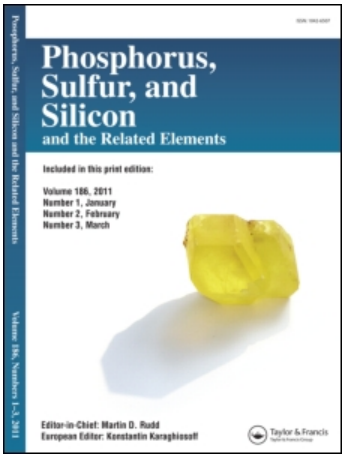

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Some 6-Substituted 3-Aryl-7-oxothiazolo[4,5-*d*]pyrimidin-2(3*H*)-thione Derivatives and Their Antimicrobial Activities

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Some 6-Substituted 3-Aryl-7-oxothiazolo[4,5-*d*]pyrimidin-2(3*H*)-thione Derivatives and Their Antimicrobial Activities

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*In this study, 3-aryl-6-substituted thiazolopyrimidin-2(3H)-thione derivatives **4** and **6** have been synthesized by reacting thiazolopyrimidines **2** with ω-bromoacetophenone **3** and 2-chloro-N-(2-thiazolyl)acetamides **5**. The structure elucidation of the obtained compounds was performed by IR, ^{1}H-NMR, MASS spectroscopy, and elemental analyses. The antibacterial and antifungal activities of the compounds were investigated, and it was reported that the compounds showed remarkable antimicrobial activities.*

Keywords 7-Oxothiazolo[4,5-d]pyrimidin-2(3H)-thione; antimicrobial activity; thiazole

INTRODUCTION

Substituted thiazol-2(3H)-thione derivatives can be regarded as analogues of rhodanines and/or dithiocarbamates, whose their antimicrobial activities are well known. It was reported that the antimicrobial activities of rhodanine and dithiocarbamates might be due to the in situ formation of isothiocyanates.[1,2] Although, it was thought that thiazol-2(3H)-thiones could not be converted into isothiocyanates contrary to rhodanine or dithiocarbamates, they have well known antimicrobial and anticancer activities.[3,4] On the other hand, thiazolopyrimidines

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that have been reported to possess antimicrobial, anticancer, and antiviral activities can be considered as analogues of purine bases in nucleotides.[5–19]

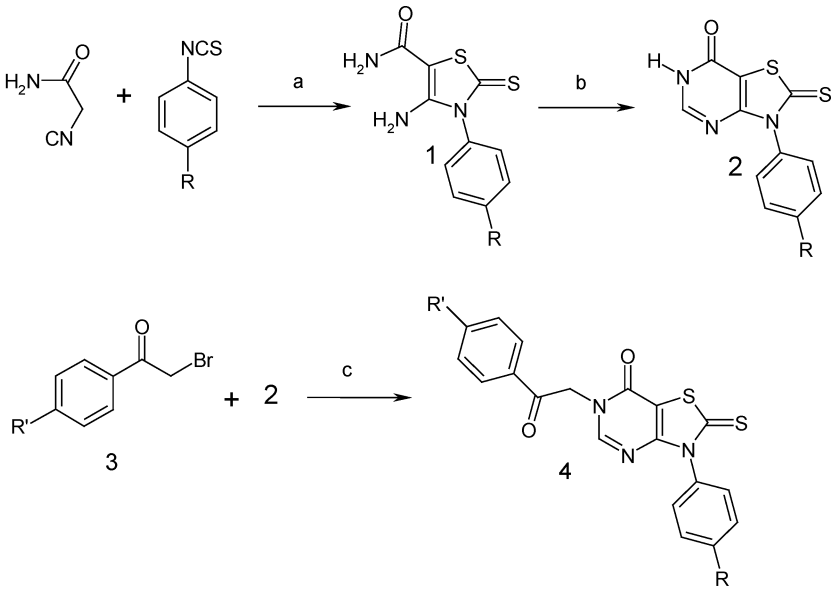
In evaluation of these findings, 3-aryl-6-substituted thiazolopyrimidin-2(3H)-thiones derivatives **4** and **6** were synthesized and their antimicrobial and anifungal activities were tested.

RESULTS AND DISCUSSION

Chemistry

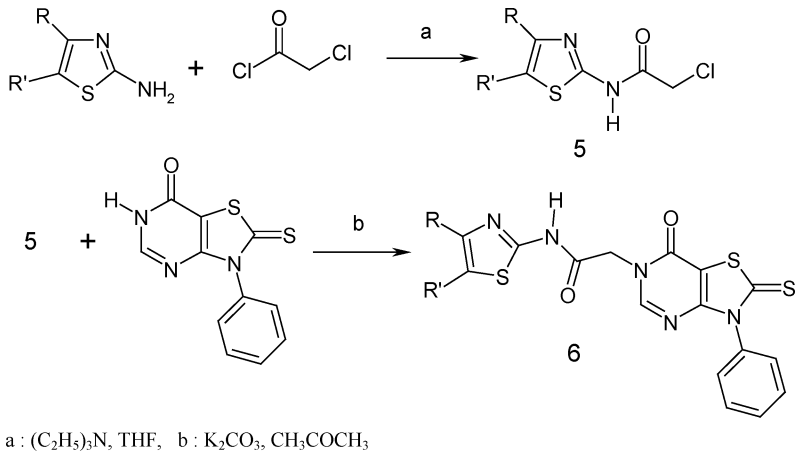
The synthesis of intermediates and target compounds were performed by the reactions illustrated in Scheme 1 and 2.

Compounds **1**, namely, 3-aryl-4-amino-5-carboxamidothiazole-2(3H)-thiones, were synthesized in excellent yields following the methods described by Gewald.[3,5,20] It involved the reaction of cyanoacetamide with sulphur and the appropriate arylisothiocyanates in the presence of triethylamine as a basic catalyst. The aminothiazoles **1** were used for the preparation of the starting compounds **2**, i.e., 3-aryl-7-oxothiazolo[4,5-d]pyrimidin-2(3H)-thione**s**.[20] To achieve this



a : S_8, $(C_2H_5)_3N$, C_2H_5OH, b : $(C_2H_5O)CH$, $(CH_3CO)_2O$, c : K_2CO_3, CH_3COCH_3

SCHEME 1



a : $(C_2H_5)_3N$, THF, b : K_2CO_3, CH_3COCH_3

SCHEME 2

cyclization, the aminothiazoles **1** were heated in a mixture of triethyl orthoformate and acetic anhydride. The target compounds **4** and **6** were prepared by reacting the thiazolopyrimidines **2** and the appropriate 2-bromoacetophenone **3** or 2-chloro-N-(substituted 2-thiazolyl)acetamide derivatives **5** in acetone in the presence of potassium carbonate. The thiazolylacetamide derivatives **5** were obtained by reacting the suitable 2-aminothiazole or 2-aminobenzothiazole derivatives with chloroacetyl chloride in the presence of triethylamine in THF in a common procedure.[21]

Spectroscopic methods confirm the structure of the new compounds. IR spectra of **4** and **6** exhibited characteristic carbonyl bands due to 7-oxothiazolo[4,5-d] pyrimidin-2(3H)-thione **s** and benzoyl or thiazolylacetamide residues, respectively. In the NMR spectra, methylene and thiazolopyrimidine-4-H protons common for all compounds resonated at expected regions.

Antimicrobial Activity

Compounds **4a–l** and **6a–f** were evaluated for antibacterial and antifungal activity against representative bacteria Gram-negative rods *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Salmonella thyphimurium*, *Klebsiella pneumoniae*, and Gram-positive cocci *Staphylococcus aureus* and *Enterococcus faecalis* and fungi *Candida albicans* and *Candida globrata* as shown in Table I. The antibacterial agent, chloramphenicol, and the antifungal agent, ketoconazole, were used as controls.

TABLE I Antibacterial and Antifungal Activities of the Compounds

	MIC (μg/mL) of Bacterial and Fungal Strains								
Comp.	E.C.	P.A.	P.V.	S.T.	K.P.	E.F.	S.A.	C.A.	C.G.
4a	1.25	5	10	1.25	1.25	1.25	5	5	5
4b	1.25	5	5	2.5	2.5	6.25	2.5	10	5
4c	1.25	5	10	1.25	1.25	1.25	2.5	5	5
4d	1.25	5	5	2.5	2.5	2.5	2.5	5	5
4e	2.5	5	10	1.25	1.25	1.25	5	5	5
4f	1.25	5	5	1.25	1.25	1.25	2.5	5	5
4g	1.25	5	10	2.5	1.25	1.25	2.5	5	5
4h	1.25	5	10	1.25	1.25	1.25	5	5	5
4i	1.25	2.5	5	2.5	1.25	2.5	5	5	5
4j	1.25	5	5	2.5	2.5	1.25	2.5	5	5
4k	1.25	5	10	2.5	1.25	1.25	2.5	5	5
4l	2.5	5	10	10	2.5	2.5	5	5	10
6a	1.25	5	10	2.5	2.5	2.5	5	5	5
6b	1.25	5	5	1.25	2.5	1.25	5	5	10
6c	1.25	5	5	1.25	1.25	2.5	2.5	5	5
6d	2.5	5	10	2.5	2.5	1.25	2.5	5	5
6e	2.5	5	10	1.25	2.5	1.25	5	5	10
6f	25	5	10	2.5	2.5	0.62	5	5	5
A	1.25	5	5	1.25	1.25	1.25	1.25	—	—
B	—	—	—	—	—	—	—	2.5	5

E.C. = *Escherichia coli*; P.A. = *Pseudomonas aeruginosa*; P.V. = *Proteus vulgaris*; S.T. = *Salmonella thyphimurium*; K.P. = *Klebsiella pneumoniae*; E.F. = *Enterococcus faecalis*; S.A. = *Staphylococcus aureus*; C.A. = *Candida albicans*; C.G. = *Candida globrata*; A = *Chloramphenicole*; B = *Ketoconazole*.

The results of the tests showed that all of the bacteria were sensitive to the control antibacterial chloramphenicole. With the exception of *Pseudomonas aeruginosa* and *Proteus vulgaris,* quite low MIC values (1.25 μg/mL) were observed for all studied compounds against the bacteria. It was noteworthy that the MIC values obtained for the compounds under investigation against the bacteria mentioned above were either equal or quite close to that of chloramphenicole. However, the MIC values for *P. aeruginosa*, and *P. vulgaris* against chloramphenicole were larger than that of others (i.e., 5 μg/mL). The values obtained for the new compounds were either equal or quite close to these values as well.

Taking into account the antifungal activity, the most sensitive fungi to the control antifungal ketoconazole was *C. albicans* (MIC 2.5 μg/mL). It was found that the MIC values obtained for the compounds were consistent and were 5 μg/mL or 10 μg/mL.

By considering the obtained results, it may be concluded that the new products have noticeable antibacterial and/or antifungal activities.

However, no significant difference in activity was observed for different substituents, on the new compounds.

EXPERIMENTAL

Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments: FTIR: Schimadzu 8400 FTIR spectrophotometer, ^{1}H-NMR: Bruker DPX 400 NMR spectrometer in DMSO-d_6 and AGILENT 1100 MSD MS spectrometer. Analyses for C, H, N were within 0.4% of the theoretical values.

ω-Bromoasetophenone derivatives,[22] 2-bromocyclohexanone,[23] 2-aminothiazole derivatives,[21] 2-aminobenzothiazole,[24] and cyanoacetamide[25] were prepared according to literature methods. 2-Chloro-N-(substituted 2-thiazolyl)acetamide derivatives were obtained by reacting the appropriate 2-aminothiazole or 2-aminobenzothiazole derivatives with chloroacetyl chloride in the presence of triethylamine in THF in a common procedure.[21] 3-Aryl-4-amino-5-carboxamido-thiazole-2(3H)-thione derivatives were obtained by reacting the appropriate aryl isothiocyanate derivatives with cyanoacetamide in the presence of triethylamine in ethanol.[3,5,20] Some characteristics of the synthesized compounds were given in Table II and III.

TABLE II Some Characteristics of the Compounds 4

Comp.	-R	-R′	M.p.(°C)	Yield(%)	Mol. Formula/Anal. C,H,N,S)
4a	—H	—H	204–205	63	$C_{19}H_{13}N_3O_2S_2$
4b	—H	—CH_3	225–226	67	$C_{20}H_{15}N_3O_2S_2$
4c	—H	—OCH_3	268–269	61	$C_{20}H_{15}N_3O_3S_2$
4d	—H	—Cl	241–243	69	$C_{19}H_{12}ClN_3O_2S_2$
4e	—OCH_3	—H	229–230	72	$C_{20}H_{15}N_3O_3S_2$
4f	—OCH_3	—CH_3	198–199	62	$C_{21}H_{17}N_3O_3S_2$
4g	—OCH_3	—OCH_3	211–213	75	$C_{21}H_{17}N_3O_4S_2$
4h	—OCH_3	—Cl	232–233	70	$C_{20}H_{14}ClN_3O_3S_2$
4i	—Cl	—H	225–226	73	$C_{19}H_{12}ClN_3O_2S_2$
4j	—Cl	—CH_3	216–219	64	$C_{20}H_{14}ClN_3O_2S_2$
4k	—Cl	—OCH_3	221–223	78	$C_{20}H_{14}ClN_3O_3S_2$
4l	—Cl	—Cl	202–204	76	$C_{19}H_{11}Cl_2N_3O_2S_2$

TABLE III Some Characteristics of the Compounds 6

Comp.	R	R′	M.p.(°C)	Yield(%)	Mol. Formula/Anal. C,H,N,S)
6a	—H	—H	211–212	54	$C_{16}H_{11}N_5O_2S_3 \cdot 1/2\ H_2O$
6b	—CH_3	—H	200–202	57	$C_{17}H_{13}N_5O_2S_3 \cdot 1/2\ H_2O$
6c	—CH_3	—CH_3	267–268	60	$C_{18}H_{15}N_5O_2S_3 \cdot 1/2\ H_2O$
6d	—CH_2-CH_2	—CH_2-CH_2-	225–226	55	$C_{20}H_{17}N_5O_2S_3 \cdot 1/2\ H_2O$
6e	—C_6H_5	—H	263–264	71	$C_{22}H_{15}N_5O_2S_3 \cdot 1/2\ H_2O$
6f	—CH=CH	—CH=CH-	298–299	68	$C_{20}H_{13}N_5O_2S_3 \cdot 1/2\ H_2O$

General Method for the Preparation of 3-Aryl-7-oxo-thiazolo[4,5-d] pyrimidin-2(3H)-thione Derivatives

A mixture of 3-aryl-4-amino-5-carboksamido-2,3-dihydrothiazol-2-thione (0.01 mol) triethyl orthoformate (15 mL) and acetic anhydride (15 mL) was refluxed for 12 h. The solution obtained was concentrated under vacuum. The residue was triturated with ethanol, filtered, and recrystallized from ethanol. The obtained products were used in the following step. The following two compounds have been prepared for the first time: 3-(4-methoxyphenyl)-7-oxothiazolo[4,5-d]pyrimidin-2(3H)-thione (m.p. 222–223°C) and 3-(4-chlorophenyl)-7-oxothiazolo[4,5-d] pyrimidin-2(3H)-thione (m.p. 242–243°C).

General Method for the Preparation of 3-Substituted 6-(2-aryl-2-oxo-1-ethyl)-7-oxothiazolo[4,5-d]pyrimidin-2(3H)-thione, 4a–t, and 3-Phenyl-6-[N-(substituted thiazole-2-yl)-2-acetamido]-7-oxothiazolo[4,5-d]pyrimidine-2(3H)-thione, 6a–f, Derivatives

A mixture of an appropriate **2** (5 mmol), an appropriate **3** or **5** (5 mmol), and potassium carbonate (0.83 g, 6 mmol) in acetone (100 mL) was refluxed. In the case of compounds **4**, the reflux time was two h and in the case of the compounds **6**, the reflux time was twelve h. The solvent was evaporated at low temperature. The residue was washed with water and then ethanol. The raw product was recrystallized from ethanol.

4a IR (KBr, cm^{-1}) : 1687 (C=O), 1587–1433 (C=N, C=C), 1228 (C=S). ^1H NMR (400 MHz) (DMSO-d_6) δppm : 5.69 (2H, s, $COCH_2$), 7.49–7.52 (2H, m, 3-phenyl $C_{2,6}$-H), 7.57–7.65 (5H, m, Ar-H), 7.74–7.76 (1H, m, benzoyl C_4-H), 8.1 (2H, d, J = 8.5 Hz, 3-phenyl $C_{2,6}$-H), 8.46 (1H, s, thiazolopyrimidine C_5-H). MS(ES) m/z : 381 (M+2, 4%), 379 (M^+, 8%), 378 (M-1, 25%), 364 (100%).

4b IR (KBr, cm^{-1}) : 1689 (C=O), 1606–1427 (C=N, C=C), 1230 (C=S). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 2.09 (3H, s, Ar-CH_3), 5.65 (2H, s, $COCH_2$), 7.43 (2H, d, J = 8.08 Hz, benzoyl $C_{3,5}$-H), 7.49–7.71 (2H, m, 3-phenyl $C_{2,6}$-H), 7.57–7.64 (3H, m, 3-phenyl $C_{3,4,5}$-H), 7.99 (2H, d, J = 8.21Hz, benzoyl $C_{2,6}$-H), 8.45 (1H, s, thiazolopyrimidine C_5-H).

4c IR (KBr, cm^{-1}) : 1676 (C=O), 1596–1417 (C=N, C=C), 1236 (C=S). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 3.88 (3H, s, OCH_3), 5.62 (2H, s, $COCH_2$), 7.07 (2H, d, J = 8.9 Hz, 3-phenyl $C_{3,5}$-H), 7.44–7.64 (5H, m, benzoyl Ar-H), 8.02 (2H, d, J = 8.9 Hz, 3-phenyl $C_{2,6}$-H), 8.44 (1H, s, thiazolopyrimidine C_5-H).

4d IR (KBr, cm^{-1}) : 1676 (C=O), 1589–1429 (C=N ve C=C), 1230 (C=S). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 5.68 (2H, s, -CH_2-CO-), 7.50 (2H, d, J = 7.09 Hz, 3-phenyl $C_{2,6}$-H), 7.57–7.64 (3H, m, 3-phenyl $C_{3,4,5}$-H), 7.70 (2H, d, J = 8.49 Hz, benzoyl $C_{3,5}$-H), 8.11 (2H, d, J = 8.53 Hz, benzoyl $C_{2,6}$-H), 8.44 (1H, s, thiazolopyrimidine C_5-H).

4e IR (KBr, cm^{-1}) : 1685 (C=O), 1600–1409 (C=N, C=C), 1234 (C=S), 1170–1029 (C—O). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 3.86 (3H, s, -OCH_3), 5.69 (2H, s, —$COCH_2$-), 7.13 (2H, d, J = 8.96 Hz, 3-aryl $C_{3,5}$-H), 7.40 (2H, d, J = 8.92 Hz, 3-Aryl $C_{2,6}$-H), 7.61–7.65 (2H, m, benzoyl $C_{3,5}$-H), 7.74–7.78 (1H, m, benzoyl C_4-H), 8.1 (2H, d, J = 8.38 Hz, benzoyl $C_{2,6}$-H), 8.46 (1H, s, thiazolopyrimidine C_5-H).

4f IR (KBr, cm^{-1}) : 1685 (C=O), 1606–1427 (C=N, C=C), 1232 (C=S), 1170–1022 (C—O). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 2.42 (3H, s, Ar-CH_3), 3.85 (3H, s, Ar-OCH_3), 5.64 (2H, s, -$COCH_2$-), 7.14 (2H, d, J = 8.92 Hz, 3-aryl $C_{3,5}$-H), 7.40 (2H, d, J = 9.14 Hz, 3-aryl $C_{2,6}$-H), 7.43 (2H, d, J = 9.09 Hz, benzoyl $C_{3,5}$-H), 8.10 (2H, d, J = 8.13 Hz, benzoyl $C_{2,6}$-H), 8.45 (1H, s, thiazolopyrimidine C_5-H).

4g IR (KBr, cm^{-1}) : 1674 (C=O), 1600–1421 (C=N, C=C), 1224 (C=S), 1182–1020 (C—O). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 3.84 (3H, s, Ar-OCH_3), 3.88 (3H, s, Ar-OCH_3), 5.66 (2H, s, -$COCH_2$-), 7.07 (2H, d, J = 8.86 Hz, 3-phenyl $C_{3,5}$-H), 7.42 (2H, d, J = 8.09 Hz, benzoyl $C_{3,5}$-H), 8.02 (2H, d, J = 8.9 Hz, 3-phenyl $C_{2,6}$-H), 8.11 (2H, d, J = 8.13 Hz, benzoyl $C_{2,6}$-H), 8.45 (1H, s, thiazolopyrimidine C_5-H). MS(ES) m/z : 442 (M+3, 7%), 441 (M+2, 32%), 440 (M+1, 5%), 439 (M^+, 10%), 438 (M-1, 35%), 255 (100%).

4h IR (KBr, cm^{-1}): 1689 (C=O), 1600–1433 (C=N, C=C), 1236 (C=S), 1170–1093 (C—O). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 3.86 (3H, s, Ar-OCH_3), 5.65 (2H, s, -$COCH_2$-), 7.11 (2H, d, J = 8.66 Hz, 3-phenyl $C_{3,5}$-H), 7.72 (2H, d, J = 8.37 Hz, benzoyl $C_{3,5}$-H), 8.08 (2H, d, J = 8.60 Hz, 3-phenyl $C_{2,6}$-H), 8.12 (2H, d, J = 8.43 Hz, Benzoyl $C_{2,6}$-H), 8.42 (1H, s, thiazolopyrimidine C_5-H).

4i IR (KBr, cm^{-1}) : 1693 (C=O), 1595–1429 (C=N, C=C), 1230 (C=S). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 5.69 (2H, s, -$COCH_2$-), 7.58

(2H, d, J = 8.66 Hz, 3-aryl $C_{2,6}$-H), 7.6–7.65 (2H, m, benzoyl $C_{3,5}$-H), 7.69 (2H, d, J = 8.7 Hz, 3-aryl $C_{3,5}$-H), 7.74-7.78 (1H, m, benzoyl C_4-H), 8.10 (2H, d, J = 8.39 Hz, benzoyl $C_{2,6}$-H), 8.47 (1H, s, thiazolopyrimidine C_5-H).

4j IR (KBr, cm^{-1}) : 1689 (C=O), 1606–1429 (C=N, C=C), 1228 (C=S). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 2.44 (3H, s, Ar-CH_3), 5.66 (2H, s, -$COCH_2$-), 7.42 (2H, d, J = 8.92 Hz, benzoyl $C_{3,5}$-H), 7.55 (2H, d, J = 8.71 Hz, 3-aryl $C_{2,6}$-H), 7.71 (2H, d, J = 8.66 Hz, 3-aryl $C_{3,5}$-H), 8.04 (2H, d, J = 8.89 Hz, benzoyl $C_{2,6}$-H), 8.46 (1H, s, thiazolopyrimidine C_5-H). MS(ES) m/z : 432 (M+4, 3%), 430 (M+3, 5%), 429 (M+2, 10%), 428 (M+1, 45%), 427 (M^+, 25%), 426 (M-1, 100%).

4k IR (KBr, cm^{-1}) : 1685 (C=O), 1602–1429 (C=N, C=C), 1228(C=S), 1170–1085 (C-O). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 3.88 (3H, s, Ar-CH_3), 5.63 (2H, s, -$COCH_2$-), 7.13 (2H, d, J = 8.92 Hz, benzoyl $C_{3,5}$-H), 7.57 (2H, d, J = 8.71 Hz, 3-aryl $C_{2,6}$-H), 7.69 (2H, d, J = 8.66 Hz, 3-aryl $C_{3,5}$-H), 8.07 (2H, d, J = 8.89 Hz, benzoyl$C_{2,6}$-H), 8.46 (1H, s, thiazolopyrimidine C_5-H).

4l IR (KBr, cm^{-1}) : 1695 (C=O), 1630–1427 (C=N, C=C), 1230 (C=S). ^{1}H NMR (400 MHz) (DMSO-d_6) δppm : 5.68 (2H, s, -CH_2-CO-), 7.57 (2H, d, J = 8.46 Hz, 3-aryl $C_{2,6}$-H), 7.70 (2H, d, J = 8.72 Hz, 3-aryl $C_{3,5}$-H), 7.71 (2H, d, J = 8.81 Hz, benzoyl $C_{3,5}$-H), 8.04 (2H, d, J = 8.37 Hz, benzoyl $C_{2,6}$-H), 8.46 (1H, s, thiazolopyrimidine C_5-H).

6a IR (KBr, cm^{-1}) : 3178 (N–H), 1685 (C=O), 1558–1429 (C=N, C=C), 1234 (C=S), 1168–1091–1022 (C-O). ^{1}H NMR (90 MHz) (DMSO-d_6) δppm : 5.00 (2H, s, $COCH_2$), 7.06–7.7 (7H, m, Ar-H and thiazole $C_{4,5}$-H), 8.48 (1H, s, thiazolopyrimidine C_5-H), 12.5 (1H, bs, NH).

6b IR (KBr, cm^{-1}) : 3272 (N–H), 1677 (C=O), 1587–1429 (C=N, C=C), 1239 (C=S), 1170–1021 (C–O). ^{1}H-NMR(400 MHz)($CDCl_3$) δ (ppm) : 2.78 (3H, s, thiazole-4-CH_3), 4.99 (2H, s, $COCH_2$), 7.49–7.57 (2H, m, 3-phenyl $C_{2,6}$-H), 7.63–7.73 (3H, m, 3-phenyl $C_{3,4,5}$-H), 7.91 (1H, s, thiazole C_5-H), 8.57 (1H, s, thiazolopyrimidine C_5-H), 10.68 (1H, bs, NH).

6c IR (KBr, cm^{-1}) : 3201 (N–H), 1664 (C=O), 1557–1419 (C=N, C=C), 1238 (C=S), 1089–1024 (C–O). ^{1}H NMR (400 MHz) ($CDCl_3$) δppm : 2.14 (3H, s, 4-CH_3), 2.23 (3H, s, 5-CH_3), 4.95 (2H, s, $COCH_3$), 7.46–7.48 (2H, m, 3-phenyl $C_{2,6}$-H), 7.55–7.64 (3H, m, 3-phenyl $C_{3,4,5}$-H), 8.48 (1H, s, thiazolopyrimidine C_5-H), 12.25 (1H, bs, NH). MS(ES) m/z : 432 (M+3, 5%), 431 (M+2, 10%), 430 (M+1, 15%), 429 (M, 20%), 428 (M-1, 100%).

6d IR (KBr, cm^{-1}) : 3218 (N–H), 1683 (C=O), 1558–1431 (C=N, C=C), 1236 (C=S). ^{1}H NMR (400 MHz) ($CDCl_3$) δppm : 1.7–1.85 (4H, m, tetrahydrobenzothiazole $C_{5,6}$-H), 2.5-2.65 (4H, m, tetrahydrobenzothiazole $C_{4,7}$-H), 4.96 (2H, s, $COCH_2$), 7.45–7.48 ((2H, m, 3-phenyl

$C_{2,6}$-H), 7.56–7.63 (3H, m, 3-phenyl $C_{3,4,5}$-H), 8.48 (1H, s, thiazolopyrimidine C_5-H), 12.4 (1H, bs, NH). MS(ES) m/z : 457 (M+2, 5%), 456 (M+1, 12%), 455 (M, 25%), 454 (M-1, 100%).

6e IR (KBr, cm^{-1}) : 3253 (N—H), 1550–1431 (C=N, C=C), 1238 (C=S), 1072–1027 (C—O). ^{1}H NMR (400 MHz) ($CDCl_3$) δppm : 5.02 (2H, s, $COCH_2$), 7.31–7.35 (2H, m, 3-phenyl $C_{2,6}$-H), 7.39–7.48 (3H, m, 3-phenyl $C_{3,4,5}$-H), 7.53–7.63 (3H, m, thiazole-4-phenyl $C_{3,4,5}$-H), 7.68 (1H, s, thiazole-C_5-H), 7.87–7.91 (2H, m, thiazole-4-phenyl $C_{2,6}$-H), 8.5 (1H, s, thiazolopyrimidine C_5-H), 12.84 (1H, bs, NH). MS(ES) m/z : 479 (M+2, 5%), 478 (M+1, 15%), 477 (M, 20%), 476 (M-1, 100%).

6f IR (KBr, cm^{-1}) : 3182 (N—H), 1681 (C=O), 1602–1429 (C=N, C=C), 1232 (C=S), 1022 (C—O). ^{1}H NMR (400 MHz) ($CDCl_3$) δppm : 5.07 (2H, s, $COCH_2$), 7.34–7.36 (1H, m, benzothiazole C_6-H),), 7.42–7.51 (3H, m, 3-Phenyl $C_{2,6}$-H and benzothiazole C_5-H), 7.55-7.65 (3H, m, 3-phenyl $C_{3,4,5}$-H), 7.78–7.8 (1H, m, benzothiazole C_7-H), 7.98-8.02 (1H, m, benzothiazole C_4-H), 8.52 (1H, s, thiazolopyrimidine C_5-H), 12.43 (1H, bs, NH).

Antimicrobial Activity

The study was designed to compare MICs obtained by the NCCLS reference M27-A2 broth microdilution method.[26,27] Two MIC readings were performed with each chemical agent. For both the antibacterial and antifungal assays, the compounds were dissolved in DMSO. Further dilutions of the compounds and standard drugs in a test medium were prepared at the required quantities of 10, 5, 2.5, 1.25, 0.62, 0.31, 0.15, 0.075, and 0.040 μg/ml concentrations with Mueller-Hinton Broth and Sabouroud Dextrose Broth.

In order to ensure that the solvent per se had no effect on bacteria or yeast growth, a control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in our experiments; the solvent was found inactive in culture medium.

All the compounds were tested for their in vitro growth inhibitory activity against human pothogenic as Gram-negative rods *Escherichia coli* (ATCC 35218), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus vulgaris* (NRLL B-123), *Salmonella thyphimurium* (NRRL B-4420), *Klebsiella pneumoniae* (ATCC 700603) and as Gram-positive cocci *Staphylococcus aureus* (ATCC 25923) and *Enterococcus faecalis* (ATCC 29212) and fungi *Candida albicans* (obtained from Faculty of Medicine Osmangazi University, Eskisehir, Turkiye) and *Candida glabrata* (ATCC 36583). Chloramphenicol and ketokanozole were used as control drugs. The observed data regarding antibacterial and antifungal activity of the compounds and the control drugs are given in Table I.

For the control antibiotic, chloramphenicol, lowest MIC values were obtained against *E. coli,. S. thyphimurium*, *K. pneumoniae*, *E. faecalis,* and *S. aureus,* i.e., 1.25 μg/mL and for the control antifungal, ketoconazole, the lowest MIC value was obtained against *C. albicans*, i.e. 1.25 μg/mL. The lowest MIC value for the compounds under investigation was obtained for **6f** against *E. faecalis*, i.e., 0.62 μg/mL.

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