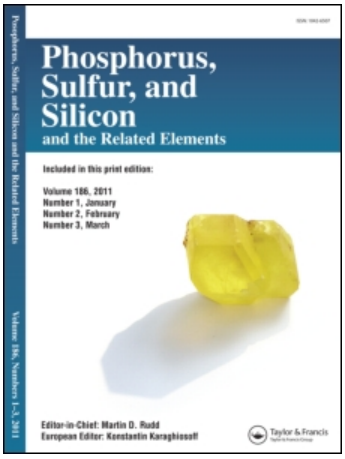

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Synthesis and Antimicrobial Activities of Some 1-[(N, N-Disubstitutedthiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines

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Synthesis and Antimicrobial Activities of Some 1-[(N,N-Disubstitutedthiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines

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The increasing clinical importance of drug-resistant fungal and bacterial pathogens has lent additional urgency to microbiological research and new antimicrobial compound development. For this purpose, new pyrazoline derivatives were synthesized and evaluated for antimicrobial activity.
Some 1-[(N,N-disubstitutedthiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines derivatives were synthesized by reacting 1-(chloroacetyl)-3,5-diaryl-2-pyrazolines with appropriate potassium salts of secondary amine dithiocarbamic acids. The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR, and FAB$^+$-MS spectral data. Their antimicrobial activities against Staphylococcus aureus *(B-767),* Escherichia coli *(B-3704),* Pseudomonas aeruginosa *(ATCC 27853),* Proteus vulgaris *(NRLL B-123), and* Candida albicans *(NRRL-27077) were investigated. The results showed that some of the compounds have notable activity against* S. aureus *and* C. albicans.

Keywords Antimicrobial activity; dithiocarbamic acid; pyrazoline

INTRODUCTION

Pyrazoline derivatives constitute an interesting class of organic compounds with diverse chemical[1] and pharmacological applications.

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The potential activity of 2-pyrazolines as antibacterial,[2–3] antifungal,[4,5] anti-inflammatory, analgesic,[6,7] antidepressant,[8,9] and anticonvulsant[10] agents are well known.

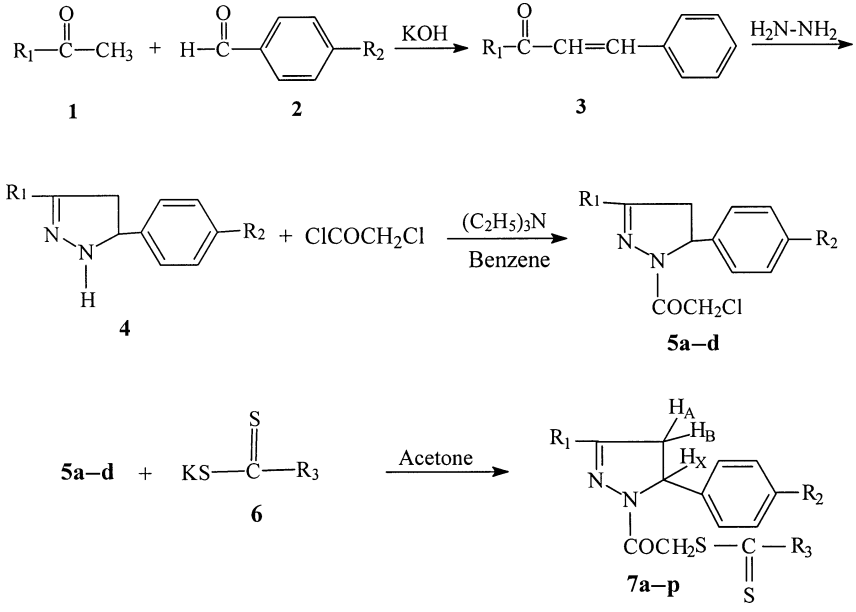
It is also well known that N-mono and N,N-disubstituted dithiocarbamate derivatives show antibacterial and antifungal activities.[11,12] The structure–activity relationship study revealed that the antibacterial activity of thiocarbonyl aromatic compounds was significantly affected by the lipophilicity which is obtained by the thiocarbonyl moiety.[13,14]

Keeping these observations in mind, we decided to undertake the synthesis of 1-[(N,N-disubstituted thiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines carrying an N,N-disubstituted dithiocarbamate moiety and to study their antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

In the present work, 16 new compounds were synthesized. The reaction of 1-(chloroacetyl)-3,5-diaryl-2-pyrazolines (**5**) with appropriate potassium salts of secondary amine dithiocarbamic acids (**6**) gave 1-[(N,N-disubstitutedthiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines (**7**) (Scheme 1, Table I).



SCHEME 1

TABLE I Some Characteristics of the Compounds

Compound	R_1	R_2	R_3	M.P. (°C)	Yield (%)	Molecular formula
5a	Phenyl	H	—	133	70	$C_{17}H_{15}ClN_2O$
5b	Phenyl	OCH_3	—	129	73	$C_{18}H_{17}ClN_2O_2$
5c	3,4-CH_3-phenyl	H	—	112	79	$C_{19}H_{19}ClN_2O$
5d	Tetrahydronaphtalene	H	—	109	77	$C_{21}H_{21}ClN_2O$
7a	Phenyl	H	Piperidine	122	85	$C_{23}H_{25}N_3OS_2$
7b	Phenyl	H	Pyrrolidine	156	84	$C_{22}H_{23}N_3OS_2$
7c	Phenyl	H	Morpholine	158	83	$C_{22}H_{23}N_3O_2S_2$
7d	Phenyl	H	Thiomorpholine	188	81	$C_{22}H_{23}N_3OS_3$
7e	Phenyl	OCH_3	Piperidine	148	85	$C_{24}H_{27}N_3O_2S_2$
7f	Phenyl	OCH_3	Pyrrolidine	159	85	$C_{23}H_{25}N_3O_2S_2$
7g	Phenyl	OCH_3	Morpholine	163	82	$C_{23}H_{25}N_3O_3S_2$
7h	Phenyl	OCH_3	Thiomorpholine	142	80	$C_{23}H_{25}N_3O_2S_3$
7i	3,4-CH_3-phenyl	H	Piperidine	134	85	$C_{25}H_{29}N_3OS_2$
7j	3,4-CH_3-phenyl	H	Pyrrolidine	177	84	$C_{24}H_{27}N_3OS_2$
7k	3,4-CH_3-phenyl	H	Morpholine	167	85	$C_{24}H_{27}N_3O_2S_2$
7l	3,4-CH_3-phenyl	H	Thiomorpholine	150	82	$C_{24}H_{27}N_3OS_3$
7m	Tetrahydronaphtalene	H	Piperidine	118	76	$C_{27}H_{31}N_3OS_2$
7n	Tetrahydronaphtalene	H	Pyrrolidine	142	73	$C_{26}H_{29}N_3OS_2$
7o	Tetrahydronaphtalene	H	Morpholine	148	78	$C_{26}H_{29}N_3O_2S_2$
7p	Tetrahydronaphtalene	H	Thiomorpholine	174	81	$C_{26}H_{29}N_3OS_3$

IR (KBr, cm^{-1}): These Compounds Showed Characteristic IR Bands at 1670–1675 cm^{-1} (C=O), 1225–1255 cm^{-1} (C=S), 1575–1590 (C=N), and 1530–1550 (C=C).

IR data were very informative. In the IR spectra, some significant stretching bands due to C=O, C=N, C=C and C=S were at 1670–1675 cm^{-1}, 1575–1590 cm^{-1}, 1530–1550 cm^{-1}, and 1225–1255 cm^{-1}, respectively.

In the ^{1}H-NMR spectra H_A, H_B, and H_X protons of the pyrazoline ring were seen as a doublet of doublets at about 3.10–3.20 ppm, 3.80–3.90 ppm, and 5.50–5.60 ppm, respectively. $COCH_2$ methylene protons, present in all compounds, appeared at 4.60–4.80 ppm as two doublets. All the other aromatic and aliphatic protons were observed at the expected regions.

Mass spectra (MS (FAB)) of the compounds showed a M+1 peaks, in agreement with their molecular formula (Table II).

Microbiology

All compounds were evaluated for their antimicrobial properties. Considerable activity was observed against *S. aureus*. In comparison with

TABLE II Selected ^{1}H-NMR (δ ppm) (DMSO d_6) and MS (FAB$^+$) m/z of the Compounds

Compound	^{1}H-NMR	MS
5a	4.65 (1H, d (J = 13.84 Hz), CH_2-Cl), 4.80 (1H, d (J = 13.83 Hz), CH_2-Cl)	299 [M+1]
5c	4.60 (1H, d (J = 13.84 Hz), CH_2-Cl), 4.75 (1H, d (J = 13.84 Hz), CH_2-Cl)	327 [M+1]
5d	4.65 (1H, d (J = 13.84 Hz), CH_2-Cl), 4.70 (1H, d (J = 13.84 Hz), CH_2-Cl)	353 [M+1]
7a	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.60 (1H, d (J = 16.03 Hz), CH_2-S), 4.80 (1H, d (J = 16.04 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.25 Hz, J_{AX} = 4.76 Hz, J_{BX} = 11.70 Hz)	424 [M+1]
7b	3.10–3.20 (1H, dd, H_A), 3.85–4.00 (1H, dd, H_B), 4.60 (1H, d (J = 17.78 Hz), CH_2-S), 4.80 (1H, d (J = 17.74 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.25 Hz, J_{AX} = 4.76 Hz, J_{BX} = 11.70 Hz)	
7c	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.60 (1H, d (J = 16.05 Hz), CH_2-S), 4.80 (1H, d (J = 16.06 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.07 Hz, J_{AX} = 4.70 Hz, J_{BX} = 11.63 Hz)	
7d	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.60 (1H, d (J = 16.11 Hz), CH_2-S), 4.80 (1H, d (J = 16.10 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.00 Hz, J_{AX} = 4.65 Hz, J_{BX} = 11.78 Hz)	442 [M+1]
7f	3.10–3.20 (1H, dd, H_A), 3.90–4.00 (1H, dd, H_B), 4.60 (1H, d (J = 15.99 Hz), CH_2-S), 4.80 (1H, d (J = 15.97 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.12 Hz, J_{AX} = 4.55 Hz, J_{BX} = 11.77 Hz)	440 [M+1]
7h	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.60 (1H, d (J = 16.03 Hz), CH_2-S), 4.80 (1H, d (J = 16.03 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 17.60 Hz, J_{AX} = 4.60 Hz, J_{BX} = 11.70 Hz)	472 [M+1]
7i	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.70 (1H, d (J = 17.80 Hz), CH_2-S), 4.80 (1H, d (J = 17.80 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 17.88 Hz, J_{AX} = 4.66 Hz, J_{BX} = 11.70 Hz)	
7k	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.70 (1H, d (J = 17.85 Hz), CH_2-S), 4.80 (1H, d (J = 17.83 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 17.89 Hz, J_{AX} = 4.70 Hz, J_{BX} = 11.65 Hz)	
7l	3.10–3.20 (1H, dd, H_A), 3.80–4.00 (1H, dd, H_B), 4.60 (1H, d (J = 16.11 Hz), CH_2-S), 4.80 (1H, d (J = 16.15 Hz), CH_2-S), 5.50-5.60 (1H, dd, H_X),. (J_{AB} = 18.09 Hz, J_{AX} = 4.62 Hz, J_{BX} = 11.60 Hz)	470 [M+1]
7m	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.70 (1H, d (J = 16.07 Hz), CH_2-S), 4.80 (1H, d (J = 16.04 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 18.02 Hz, J_{AX} = 4.47 Hz, J_{BX} = 11.55 Hz)	478 [M+1]

TABLE II Selected ^{1}H-NMR (δ ppm) (DMSO d_6) and MS (FAB^+) m/z of the Compounds *(Continued)*

Compound	^{1}H-NMR	MS
7o	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.70 (1H, (d J = 16.11 Hz), CH_2-S), 4.80 (1H, d (J = 16.11 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 17.89 Hz, J_{AX} = 4.43 Hz, J_{BX} = 11.52 Hz)	480 [M+1]
7p	3.10–3.20 (1H, dd, H_A), 3.80–3.90 (1H, dd, H_B), 4.70 (1H, d (J = 16.09 Hz), CH_2-S), 4.80 (1H, d (J = 16.08 Hz), CH_2-S), 5.50–5.60 (1H, dd, H_X), (J_{AB} = 17.80 Hz, J_{AX} = 4.56 Hz, J_{BX} = 11.73 Hz)	496 [M+1]

the control antibacterial agent chloramphenicole, an important antibacterial activity was observed for compound **5d** (1.56 μg/mL) against *S. aureus.* Moreover, **7a**, **7e**, and **7g** (6.25 μg/mL) also showed significant activity against *S. aureus*. The other compounds showed approximately similar MIC values against *S. aureus* when compared with the control compound.

On the other hand, the compounds **7b**, **7e**, **7f**, and **7n** exhibited significant antifungal activity against *C. albicans*, whereas the other compounds showed similar activity when compared with the control value. In comparison with the reference, agent all of the compounds showed similar activity against *P. aeuroginosa*. Only the compounds **7d** and **7k** showed the same activity against *P. vulgaris*, whereas all other compounds showed moderate activities when compared with chloramphenicole (Table III).

EXPERIMENTAL

Chemistry

Melting points were determined by using a Gallenkamp apparatus and were uncorrected. Spectroscopic data were recorded by the following instruments: IR, Shimadzu 435 spectrophotometer; ^{1}H-NMR. Bruker 250 MHz spectrometer; and MS, VG Quattro mass spectrometer.

General Synthetic Procedure 1,3-Diaryl-2-propen-1-ones (3)

1,3-diaryl-2-propen-1-one derivatives were synthesized by condensing the appropriate acetophenones (**1**) with substituted benzaldehydes (**2**) according to the Claisen-Schmidt condensation.[15]

TABLE III Antimicrobial Activities of the Compounds as MIC Values (μg/mL). Control Compounds: A; Ketoconazole; B; Chloramphenicole

Compound	*S. aureus*	*P. aeruginosa*	*P. vulgaris*	*E. coli*	*C. albicans*
5a	12.5	25	50	25	50
5b	12.5	25	50	25	50
5c	12.5	25	50	25	50
5d	1.56	25	50	25	50
7a	6.25	25	50	25	50
7b	12.5	25	50	25	25
7c	12.5	25	50	25	50
7d	12.5	25	25	25	50
7e	6.25	25	50	25	25
7f	12.5	25	50	25	25
7g	6.25	25	50	50	50
7h	12.5	25	50	25	50
7i	12.5	25	50	25	50
7j	12.5	25	50	25	50
7k	12.5	25	25	25	50
7l	12.5	25	50	25	50
7m	12.5	25	50	25	50
7n	12.5	25	50	25	25
7o	12.5	25	50	25	50
7p	25	25	50	25	50
A	—	—	—	—	50
B	12.5	25	25	12.5	—

3,5-Diaryl-2-pyrazolines (4)

To the solution of 0.02 mol of the appropriate 1,3-diaryl-2-propen-1-ones (**3**) derivative in 20 mL of ethanol, 0.04 mol of hydrazine hydrate was added and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled at 0°C overnight and the precipitate was then filtered and washed with ethanol.[1]

1-(Chloroacetyl)-3,5-diaryl-2-pyrazolines (5)

The 3,5-diaryl-2-pyrazolines (**4**) (0.015 mol) and triethylamine (0.015 mol) were dissolved in dry benzene (30 mL) with constant stirring. Then the mixture was cooled in an ice bath, and chloroacetylchloride (0.015 mol) was added dropwise with stirring. The reaction mixture was agitated for 1 h at r.t. The precipitate was filtered. The filtrate was evaporated to dryness under reduced pressure and the products were recrystallized from ethanol.[16]

Potassium Salts of N,N-Disubstitued Dithiocarbamic Acids (6)

Potassium hydroxide (0.02 mol) was dissolved in ethanol (80 mL) with constant stirring. After the addition of the secondary amine (0.02 mol), the mixture was cooled in an ice bath and carbon disulphide (0.02 mol) was added dropwise with stirring. The reaction mixture was agitated for 1 h at r.t. and the solvent was evaporated under reduced pressure. The product was obtained from washing of the precipitate with ether.[17]

1-[(N,N-Disubstituted Thiocarbamoylthio)acetyl]-3,5-diaryl-2-pyrazolines (7)

A mixture of 1-(chloroacetyl)-3,5-diaryl-2-pyrazolines (**5**) (0.01 mol) and the appropriate potassium salts of secondary amine dithiocarbamic acids (**6**) (0.01 mol) was stirred in acetone at room temperature for 4 h. The solvent was evaporated and the residue was washed with water and recrystallized from ethanol.[14]

Some characteristics and spectral data of the synthesized compounds are shown in Table I and Table II, respectively.

Microbiology

Microdilution broth susceptibility assay was used for the antimicrobial evaluation of the compounds.[18] Stock solutions of the samples were prepared in dimethylsulfoxide. Dilution series using sterile distilled water were prepared 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. 100 μl of each microorganism suspension then was added into the wells. The last well chain without a 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.

The following were used as a test microorganisms: *Staphylococcus aureus* (B-767), *Escherichia coli* (B-3704), *Pseudomonas aeruginosa* (ATCC 27853), *Proteus vulgaris* (NRLL B-123), and *Candida albicans* (NRRL-27077).

The observed data on the antimicrobial activity of the compounds and control drugs are given in Table III.

REFERENCES

[1] A. Levai, *J. Heterocyclic Chem.*, **39,** 1 (2002).
[2] O. H. Hishmat, A. H. Abd-El-Rahman, E. M. Kandeel, and E. M. Ismail, *Arzneim-Forsch.*, **27,** 2035 (1977).
[3] A. E. Hamed, H. M. Hassaneen, and M. A. Abdullah, *Archiv Der Pharmazie,* **324,** 35 (1991).
[4] C. Şafak, A. Tayhan, and S. Saraç, *J. Indian Chem. Soc.*, **67,** 571 (1990).
[5] M. G. Mamolo, D. Zampieri, V. Falagiani, L. Vio, and E. Banfi, *Farmaco,* **58,** 315 (2003).
[6] R. A Nugent, M. Murphy, S. T. Schlachter, C. J. Dunn, R. J. Smith, N. D. Staite, L. A. Galinet, S. K. Shields, D. G. Aspar, K. A. Richard, and N. A. Rohloff, *J. Med. Chem.,* **36,** 134 (1993).
[7] F. Manna, F. Chimenti, A. Bolasco, M. L. Cenicola, M. D'Amico, C. Parrillo, F. Rossi, and E. Marmo, *Eur. J. Med. Chem.,* **27,** 633 (1992).
[8] A. A. Bilgin, E. Palaska, R. Sunal, and B. Gümüşel, *Pharmazie,* **49,** 67 (1994).
[9] A. A. Bilgin, E. Palaska, and R. Sunal, *Arzneim.-Forsch./Drug Res.,* **43,** 1041 (1993).
[10] S. S. Parmar, B. R. Pandey, C. Dwivedi, and R. D. Harbison, *J. Pharm. Sci.,* **63,** 1152 (1974).
[11] Ö. Ateş, A. Gürsoy, H. Altındaş, G. Ötük, and S. Birteksöz, *Arch. Pharm. Pharm. Med. Chem.,* **336,** 39 (2003).
[12] A. Gürsoy, Ö. Ateş, N. Karali, N. Cesur, and M. Kiraz, *Eur. J. Med. Chem.,* **31,** 643 (1996).
[13] R. Tokuyama, Y. Takahashi, M. Tsubouchi, N. Iwasaki, N. Kado, E. Okezaki and O. Nagata, *Chem. Pharm. Bull.,* **49,** 353 (2001).
[14] Z. A. Kaplancıklı, G. Turan-Zitouni, G. Revial, and G. Iscan, *Phosphorus, Sulfur, and Silicon,* **179,** 1449 (2004)
[15] W. Dawey and D. J. Tivey, *J. Chem. Soc.,* **80,** 1230 (1958).
[16] A. A. Khalaf, R. A. Kabli, M. T. Zimaity, A. M. Khalil, A. M. Kaddah, and H. A. Al-Rifaie, *Indian J. Chem. Sec. B*, **32,** 1125 (1993).
[17] N. Karalı, I. Apak, S. Özkırımlı, A. Gürsoy, S. D. Doğan, A. Eraslan, and O. Özdemir, *Arch. Pharm. Pharm. Med. Chem.,* **332,** 422 (1999).
[18] E. W. Koneman, S. D. Allen, and W. C. Winn, Color Atlas and Textbook of Diagnostic Microbiology, (Lippincott Raven, Philadelphia, 1997), p. 785.