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# Synthesis and antimicrobial activity of some 5-aryl-2-[(*N*,*N*-disubstituted thiocarbamoylthio)acylamino]-1,3,4-oxadiazoles

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**Abstract**

In this study, a number of novel 5-aryl-2-[(*N*,*N*-disubstituted thiocarbamoylthio)acylamino]-1,3,4-oxadiazole derivatives were synthesized by the reaction of potassium salts of *N*,*N*-disubstituted dithiocarbamoic acids with 2-[(α-chloro-α-phenylacetyl/α-bromopropionyl)-amino]-5-aryl-1,3,4-oxadiazoles. Structures of the compounds were confirmed by the spectral data (IR, $^1$H NMR, EIMS) and elemental analyses. Most of the compounds were tested against various microorganisms and four of them were found to be weakly active against *Staphylococcus aureus* and *Staphylococcus epidermidis*. © 1998 Elsevier Science S.A. All rights reserved.

*Keywords:* Antibacterial drugs; 5-Aryl-2-[(*N*,*N*-disubstituted thiocarbamoylthio)acylamino]-1,3,4-oxadiazole; Microbiology; Synthesis

## 1. Introduction

Both dithiocarbamates and 2-amino-1,3,4-oxadiazoles are known to possess antimicrobial activity [1–10], along with other activities. In this study, potassium salts of *N*,*N*-disubstituted dithiocarbamoic acids were reacted with 2-[(α-chloro-α-phenylacetyl/α-bromopropionyl)amino]-5-aryl-1,3,4-oxadiazoles to obtain a series of new compounds which were expected to be antimicrobial agents. As a result of microbiological research, four of the compounds were found to be weakly active against *Staphylococcus aureus* and *Staphylococcus epidermidis*.

## 2. Chemistry

Aromatic aldehyde semicarbazones (**1a,b**) [11] suspended in glacial acetic acid were stirred with bromine and anhydrous sodium acetate to give 5-aryl-2-amino-1,3,4-oxadiazoles (**2a,b**) [12]. Reaction of these with α-chloro-α-phenylacetyl chloride or α-bromopropionyl bromide yielded 5-aryl-2-[(α-chloro-α-phenylacetyl/α-bromopropionyl)amino]-1,3,4-oxadiazoles (**3a–d**) [6]. Compounds **3a–d** were reacted with potassium salts of *N*,*N*-disubstituted dithiocarbamoic acids (**4a–e**) [7–10] and 5-aryl-2-[(*N*,*N*-disubstituted thiocarbamoylthio)acylamino]-1,3,4-oxadiazoles (**5a–n**) were obtained (Scheme 1, Table 1).

The structure of the compounds was elucidated by elemental analyses and IR, $^1$H NMR and EI mass spectral data. The IR spectra of the compounds showed bands at 3466–3158, 1741–1697 and 1248–1150 cm$^{-1}$ indicating N–H, C=O and C=S stretchings, respectively. $^1$H NMR spectral data of compounds were also consistent with the assigned structures. The EI mass spectra of compounds **5a** and **5k** showed molecular ions which confirmed their molecular weights. The major fragmentation pathway involved the cleavage of the C–S bonds or bonds adjacent to the carbonyl group, which was in accordance with the literature [10,13]. The proposed fragmentation route of compounds **5a** and **5k** is shown in Scheme 2.

## 3. Experimental

Melting points were measured on a Büchi 530 melting point apparatus (Flawil, Switzerland) in open capillaries and are uncorrected. The compounds were checked for purity by TLC on Silicagel $HF_{254}$. IR Spectra (KBr) were recorded on a Perkin Elmer Model 1600 FT-IR spectrophotometer. $^1$H NMR spectra were obtained in DMSO-$d_6$ on Bruker AC 200 (200 MHz) and Bruker DPX 400 (400 MHz) NMR spectrophotometers using TMS as the internal standard. EIMS was recorded on a VG Zab Spec (70 eV) mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Starting materials were purchased from E. Merck (Darmstadt, Germany).

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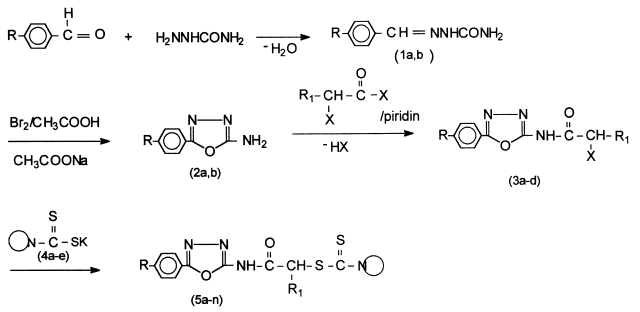


Scheme 1.

Aromatic aldehyde semicarbazones [11], 5-aryl-2-amino-1,3,4-oxadiazoles [12], 5-aryl-2-acylamino-1,3,4-oxadiazoles [6] and potassium salts of *N,N*-disubstituted dithiocarbamoic acids [7–10] were prepared as previously described.

### *3.1. 5-Aryl-2-[(N,N-disubstituted thiocarbamoylthio)-acylamino]-1,3,4-oxadiazoles (**5a–n**)*

2-[(α-Chloro-α-phenylacetyl/α-bromopropionyl)amino]-5-phenyl/*p*-chlorophenyl-1,3,4-oxadiazole (0.005 mol) and 0.005 mol of potassium salt of *N,N*-disubstituted dithiocarbamoic acid in 30 ml of ethanol were refluxed on a water bath for 1 h. Crystals were filtered off and recrystallized from ethanol. Physical data of compounds **5a–n** are reported in Table 1.

Table 1
Physical constants of compounds **5a–n**

| Compd. | R | R′ | N◯ | Formula (MW) | Yield (%) | M.P. (°C) | Analysis |
|---|---|---|---|---|---|---|---|
| **5a** | H | $C_6H_5$ | $-N(CH_3)_2$ | $C_{19}H_{18}N_4O_2S_2$ (398.48) | 82 | 195-7 | C, H, N |
| **5b** | H | $C_6H_5$ | $-N(C_2H_5)_2$ | $C_{21}H_{22}N_4O_2S_2$ (426.54) | 92 | 151-5 | C, H, N |
| **5c** | H | $C_6H_5$ |  | $C_{21}H_{20}N_4O_3S_2$ (440.52) | 86 | 204-6 | C, H, N |
| **5d** | H | $C_6H_5$ |  | $C_{22}H_{22}N_4O_2S_2$ (438.55) | 80 | 220-2 | C, H, N |
| **5e** | H | $C_6H_5$ |  | $C_{21}H_{20}N_4O_2S_2$ (424.52) | 90 | 223-5 | C, H, N |
| **5f** | H | $CH_3$ | $-N(CH_3)_2$ | $C_{14}H_{16}N_4O_2S_2$ (336.42) | 79 | 179-81 | C, H, N |
| **5g** | H | $CH_3$ |  | $C_{16}H_{18}N_4O_3S_2$ (378.45) | 68 | 188-90 | C, H, N |
| **5h** | Cl | $C_6H_5$ | $-N(C_2H_5)_2$ | $C_{21}H_{21}ClN_4O_2S_2$. 1,5$H_2O$ (460.983) | 62 | 183-6 | C, H, N |
| **5i** | Cl | $C_6H_5$ |  | $C_{21}H_{19}ClN_4O_3S_2$ (474.963) | 69 | 235-6 | C, H, N |
| **5j** | Cl | $C_6H_5$ |  | $C_{22}H_{21}ClN_4O_2S_2$ (472.993) | 88 | 189-92 | C, H, N |
| **5k** | Cl | $CH_3$ | $-N(CH_3)_2$ | $C_{14}H_{15}ClN_4O_2S_2$ (370.863) | 57 | 185-7 | C, H, N |
| **5l** | Cl | $CH_3$ |  | $C_{16}H_{17}ClN_4O_3S_2$ (412.903) | 73 | 211-3 | C, H, N |
| **5m** | Cl | $CH_3$ |  | $C_{17}H_{19}ClN_4O_2S_2$ (410.923) | 63 | 206-7 | C, H, N |
| **5n** | Cl | $CH_3$ |  | $C_{16}H_{17}ClN_4O_2S_2$ (396.903) | 50 | 217-9 | C, H, N |

IR, $^1$H NMR and EI mass spectral data of some novel compounds chosen as prototypes are as follows.

### *3.2. 5-Phenyl-2-[(N,N-dimethylthiocarbamoylthio)-phenylacetylamino]-1,3,4-oxadiazole (**5a**)*

IR [$\nu$, cm$^{-1}$, KBr]: 3447 (N–H), 3034 (arom. C–H), 2927 (aliph. C–H), 1704 (C=O), 1580, 1547, 1489 (arom. C=C), 1448 (CO–CH), 1381 (C–N, ter. amine), 1252 (N–H and C–N), 1150 (C=S), 1021, 986 (oxadiazole C–O–C).

$^1$H NMR [400 MHz, $\delta$ ppm, DMSO-$d_6$]: 3.40 (s, 3H, $CH_3$), 3.49 (s, 3H, $CH_3$), 5.91 (s, 1H, CH–S), 7.33–7.97 (m, 10H, $H_{arom.}$), 12.19 (s, 1H, NH).

MS: *m/z* (%): 398 (2), 310 (40), 279 (22), 237 (95), 210 (4), 209 (22), 188 (39), 161 (45), 145 (35), 122 (17), 120 (47), 118 (75), 117 (3), 105 (50), 103 (21), 90 (45), 88 (100), 78 (11), 77 (57), 57 (1), 56 (6).

### *3.3. 5-Phenyl-2-[2-(N,N-dimethylthiocarbamoylthio)-propionylamino]-1,3,4-oxadiazole (**5f**)*

IR [$\nu$, cm$^{-1}$, KBr]: 3158 (N–H), 3070 (arom. C–H), 2978 (aliph. C–H), 1697 (C=O), 1614, 1584, 1508, 1488 (arom. C=C), 1450 (CO–CH), 1379 (C–N, ter. amine), 1248 (C=S), 1213 (N–H and C–N), 1038, 968 (oxadiazole C–O–C).

$^1$H NMR [400 MHz, $\delta$ ppm, DMSO-$d_6$]: 1.52 (d, $J$ = 7.29 Hz, 3H, CH–$CH_3$), 3.31 (s, 3H, N–$CH_3$), 3.37 (s, 3H, N–$CH_3$), 4.68 (q, 1H, CH–S) 7.13–7.87 (m, 5H, $H_{arom.}$), 12.06 (s, 1H, NH).

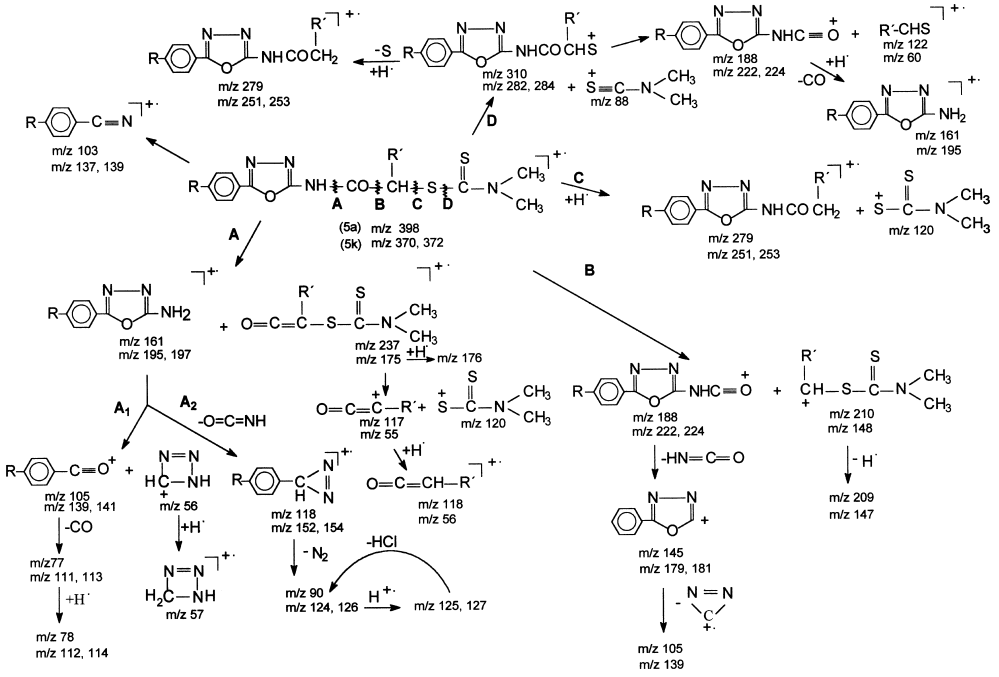
### *3.4. 5-(p-Chlorophenyl)-2-[(N,N-diethylthiocarbamoyl-thio)phenylacetylamino]-1,3,4-oxadiazole (**5h**)*

IR [$\nu$, cm$^{-1}$, KBr]: 3436 (N–H), 3056 (arom. C–H), 2973, 2932 (aliph. CH), 1727 (C=O), 1607, 1576, 1546, 1485 (arom. C=C), 1452 (CO–CH), 1355 (C–N, ter. amine), 1273 (N–H and C–N), 1206 (C=S), 1047, 983 (oxadiazole C–O–C).

$^1$H NMR [200 MHz, $\delta$ ppm, DMSO-$d_6$]: 1.17 (t, 3H, $CH_3$), 1.23 (t, 3H, $CH_3$), 3.74 (q, 2H, $CH_2$), 3.93 (q, 2H, $CH_2$), 5.91 (s, 1H, CH–S), 7.38–7.51 (m, 5H, $H_{arom.}$), 7.65 (d, $J$ = 8.40 Hz, 2H, $C_{3,5}$–H of phenyl bonded to oxadiazole), 7.90 (d, $J$ = 8.48 Hz, 2H, $C_{2,6}$–H of phenyl bonded to oxadiazole), 12.41 (s, 1H, NH).

### *3.5. 5-(p-Chlorophenyl)-2-[2-(N,N-dimethylthiocarbamoyl-thio)propionylamino]-1,3,4-oxadiazole (**5k**)*

IR [$\nu$, cm$^{-1}$, KBr]: 3463 (N–H), 3139 (arom. C–H), 2870 (aliph. C–H), 1741 (C=O), 1606, 1576, 1499, 1482 (arom.



Scheme 2.

C=C), 1450 (CO–CH), 1383 (C–N, ter. amine), 1260 (N–H and C–N), 1157 (C=S), 1048, 992 (oxadiazole C–O–C).

$^1$H NMR [200 MHz, $\delta$ ppm, DMSO-$d_6$]: 1.58 (d, $J$ = 7.27 Hz, 3H, CH–$CH_3$), 3.37 (s, 3H, N–$CH_3$), 3.43 (s, 3H, N–$CH_3$), 4.74 (q, $J$ = 7.21 Hz, 1H, CH–S), 7.66 (d, $J$ = 8.52 Hz, 2H, $C_{3,5}$–H of phenyl bonded to oxadiazole), 7.92 (d, $J$ = 8.62 Hz, 2H, $C_{2,6}$–H of phenyl bonded to oxadiazole), 12.15 (s, 1H, NH).

MS (*m*/z): 372 (3), 370 (6), 284 (32), 282 (62), 253 (2), 251 (4), 224 (3), 222 (9), 197 (11), 195 (26), 181 (5), 179 (16), 176 (70), 175 (60), 154 (8), 152 (14), 148 (3), 147 (22), 141 (12), 139 (32), 137 (13), 127 (1.5), 126 (1), 125 (5), 124 (2), 120 (34), 114 (1.5), 113 (11), 112 (3), 111 (26), 90 (21), 88 (100), 60 (8.5), 57 (3), 56 (13).

## 4. Microbiology

Derivatives **5a–n** except **5g**, **5h** and **5k** were tested in vitro for antibacterial activity against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi, Shigella flexneri, Proteus mirabilis* and for antifungal activity against *Candida albicans* ATCC 10231.

### *4.1. Microbiological experimental*

The disc diffusion method was used for antimicrobial activity where each disc contained 160 μg of the tested compound. For this method, Mueller–Hinton agar (DIFCO) was melted at 100°C and after cooling to 56°C, was poured into petri plates of 9 cm diameter in quantities of 20 ml, and left on a flat surface to solidify and the surface of the medium was dried at 37°C. Then, cultures of each bacteria and yeast strain, after being kept in Mueller-Hinton broth (DIFCO) at 37°C for 18–24 h and diluted with Mueller–Hinton broth to $10^5$ cfu/ml, were pipetted into the Mueller–Hinton agar plate prepared as described above. The surface of the medium was allowed to dry. The 8000 μg/ml (in DMSO) compound impregnated discs were applied to the surface of inoculated plates. The petri plates were placed in an incubator at 37°C. After 18–24 h of incubation, the petri plates were examined and it was found that compounds **5f**, **5l**, **5m** and **5n** were active against *S. aureus* and *S. epidermidis*.

The minimum inhibitory concentrations (MIC) of the compounds were determined by the microbroth dilution technique using Mueller–Hinton broth (Difco Laboratories, Detroit, MI). Serial two-fold dilutions ranged from 2500 to 2.4 mg/l for compounds. The inoculum was prepared in broth which had been kept overnight at 37°C and which had been diluted with Mueller–Hinton broth to give a final concentration of $10^5$ cfu/ml in the test tray. The trays were covered and placed in plastic bags to prevent drying. After

Table 2
MIC values of compounds **5f**, **5l**, **5m** and **5n**

| Compound | MIC (μg/ml) | |
|---|---|---|
| | *S. aureus ATCC 6538* | S. *epidermidis ATCC 12228* |
| **5f** | 78 | 78 |
| **5l** | 1250 | 625 |
| **5m** | 1250 | 1250 |
| **5n** | 1250 | 1250 |

incubation at 37°C for 18–20 h, the MIC was defined as the lowest concentration of compound giving complete inhibition of visible growth. MIC values of the compounds are given in Table 2.

## 5. Results and discussion

The antibacterial and antifungal activities were evaluated by the disc diffusion method against eight representative bacteria and against *C. albicans*. Compounds **5f**, **5l**, **5m** and **5n** were found to be active against *S. aureus* and *S. epidermidis* and their MIC were determined by dilution technique (Table 2). This may show that compounds with $R' = CH_3$ are active and the compound **5f** with R and $R'$ both being $CH_3$ is the most active of the compounds.

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