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Synthesis, Characterization and In-vitro Antifungal Evaluation of Some Dithiocarbamic Acid Derivatives

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Abstract

Some new *N*, *N*-disubstituted dithiocarbamates derived from α-acetonaphthone and their precursors, potassium salts of dithiocarbamic acid, were prepared and evaluated for antifungal activity.

Synthesis involved the reaction of α-chloro-2-acetonaphthone or α-chloro-4-methoxy-1-acetonaphthone with the potassium salts of *N*, *N*-disubstituted dithiocarbamic acid (**5a**–**g**). Compounds **5a**–**g** were readily produced by reaction of equivalent amounts of the appropriate secondary amine, potassium hydroxide and carbon disulphide. The purity of the final derivatives, *N*, *N*-disubstituted dithiocarbamates **6a**–**g** and **7a**–**g**, was determined by elemental analyses and TLC, and assignment of structures was confirmed by IR, ^{1}H NMR,^{13}C NMR and MS.

Preliminary evaluation of the antifungal activity of derivatives **5a**–**g**, **6a**–**g** and **7a**–**g** was determined in-vitro at a 2·5 or 5·0% concentration against different fungal species using tolnaftate as a reference drug. The potassium salts **5a**–**g** were the most potent derivatives of the tested series. Compounds **5a**–**e** showed significant broad spectrum antifungal activity. Combination of the dithiocarbamate with acetonaphthonyl moiety, represented by the **6a**–**g** and **7a**–**g** series, resulted in a decrease in or complete loss of antifungal activity in certain derivatives. Compounds derived from 4-methoxy-1-acetonaphthone (**7a**–**g**) were generally superior to their 4-nonsubstituted congeners (**6a**–**g**). The morpholino dithiocarbamate derivative **7e** was equipotent or superior to the reference drug against the tested dermatophytes species and *Rhodotorula rubra* at a 5% concentration. In addition, **7e** exhibited inhibitory activity against *Chrysosporium tropicum*, *Emericella nidulans*, *Penicillium aurantiogriseum* and *Aspergillus sydowii*. Some derivatives of both series showed selective activity against certain fungi, (e.g. **6f** against *Phoma glomerata* and *Scopulariopsis acremonium*; **6g** against *Emericella nidulans* and *Phoma glomerata*; **7c** against *Geotrichum candidum* and *Mucor circinelloides*; **7d** against *Geotrichum candidum*, *Penicillium aurantiogriseum* and *Rodotorula rubra* and **7f** against *Mucor circinelloides*).

Antifungal activity is related to a substructural fragment of the molecule, the pharmacophore. Such moieties include divalent sulphur attached to an electron-deficient carbon atom (Caujolle et al 1995; Klimesová et al 1996). This was the basis for the synthesis of numerous sulphur-containing compounds with antifungal activity against various fungal species (Al-Nakib et al 1992; Papakonstantinou-Garoufalia et al 1992; Foroumadi et al 1998). Of these derivatives the potassium salts of *N*, *N*-disubstituted carbamodithioic acid (Shah et al 1997) and their esters (Ates et al 1995; Gürsoy et al 1996; Noguer & Marty 1997) showed potent antifungal activity.

Several naphthaline-containing compounds also have antifungal activity and some are well known antimycotic agents (Artico et al 1992; Nussbaumer et al 1993; Auzzas et al 1998). Tolnaftate (Figure 1) is a topical antifungal agent that incorporates both a naphthaline nucleus and an *N*, *N*-disubstituted

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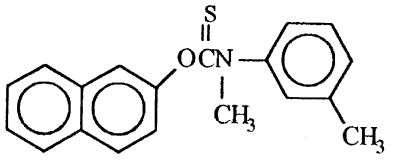


Tolnaftate (1)

Figure 1. Structure of tolnaftate.

thiocarbamate moiety (Weinberg 1996). It is assumed that the dithiocarbamate moiety could be considered an isosteric group for the thiocarbamate function. Some potassium salts of *N*, *N*-disubsti-tuted dithiocarbamic acid (**5a**–**g**) and their combination with acetonaphthones (**6a**–**g** and **7a**–**g**) were therefore synthesized as potential antifungal agents.

In the first group, **6a**–**g**, the variable dithiocarbamate moiety was linked at C-2 of the naphthaline nucleus through an acetyl spacer, while in the second series, **7a**–**g**, the dithiocarbamate residue attached to the α-carbon of 4-methoxy-1-acetonaphthone. The interdependence of the antifungal activity on these structural variations is discussed.

Materials and Methods

Chemistry

Tolnaftate was obtained from Cairo Co. for Drugs and Chemical Industries, Cairo, Egypt. All reagents and chemicals were of reagent grade. Melting points were determined in open-glass capillaries on an electrothermal melting-point apparatus (Fa. Sturat Scientific, UK) and are uncorrected. Precoated silica gel 60 F-254 plates (Merck) were used for thin-layer chromatography (TLC) and spots were detected by UV. Elemental analysis (C, H and N) was performed at the Department of Chemistry, Assiut University, Assiut, Egypt. IR spectra (KBr discs) were recorded on a Schimadzu-408 Spectrophotometer. ^{1}HNMR spectra were determined on a Varian EM-60 Spectrometer in d_6-DMSO or $CDCl_3$ using tetramethylsilane (TMS) as internal standard and chemical shifts are in δ ppm.^{13}CNMR spectra were recorded on a Varian Gemini-300 spectrometer at the Research Institute for Wakan-Yaku, Toyama, Japan. d_6-DMSO was used as a solvent and chemical shifts are in δ ppm relative to TMS. MS were obtained using a Shimadzu GC/MS Spectrometer QP-5000 (Shimadzu Co. Kyoto, Japan) at the Institute of Pharmaceutical Chemistry, Vienna University, Vienna, Austria.

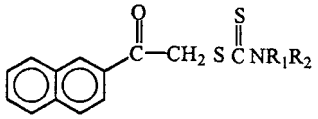
*α-Chloro-2-acetonaphthone (**3**) and α-chloro-4-methoxy-1-acetonaphthone (**4**).* To a suspension of anhydrous aluminum chloride (2·4 g, 0·018 mol) in dried methylene chloride (50 mL) was added chloroacetylchloride (2·03 g, 0·018 mol). The resulting mixture was slowly added at room temperature to naphthaline (**1**) or 1-methoxynaphthaline (**2**; 0·015 mol) dissolved in dried methylene chloride (25 mL). The reaction mixture was stirred overnight at ambient temperature, poured gradually onto ice and acidified with concentrated HCl with vigorous stirring. The aqueous layer was further extracted with methylene chloride (2 × 50 mL) and the combined organic extracts were washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The oily residue obtained was crystallized from ether–petroleum ether to give a pale-yellow crystalline product. Compound **3**: mp 64–66°C, reported mp 65–66°C (Synch 1956) and compound **4**: mp 68–69°C, reported mp 70·5–71°C (Jacobs et al 1946).

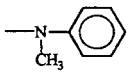
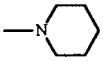
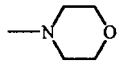
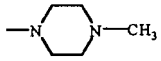
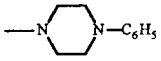
*Potassium dithiocarbamates **5a**–**g**.* Potassium hydroxide (0·03 mol) was dissolved in ethanol (250 mL) with constant stirring and the appropriate secondary amine (0·03 mol) was added. The reaction mixture was cooled in an ice bath and CS_2 (0·03 mol) was added dropwise and the stirring was continued for 1 h at ambient temperature. Ethanol was distilled off under reduced pressure and the residue was triturated with anhydrous diethylether until precipitation of the products was complete and then filtered to give quantitative yields of the potassium dithiocarbamate derivatives **5a**–**g**.

*α-Acetonaphthonyl N,N- disubstituted dithiocarbamate derivatives **6a**–**g** and **7a**–**g**.* Equimolar amounts of α-chloro-2-acetonaphthone (**3**) or α-chloro-4-methoxy-1-acetonaphthone (**4**) and the corresponding potassium dithiocarbamate derivatives (**5a**–**g**) were refluxed in ethanol (**5b**–**f**) or acetonitrile (**5a**) for 1 h. After cooling, the reaction mixture was evaporated under reduced pressure and the products were washed well with water, and crystallized from the appropriate solvent. Tables 1 and 2 summarize the physicochemical properties of the synthesized compounds.

Reaction of **5a** and **3** in ethanol gave compound **10**: yield 65%; mp 91–93°C (methanol) which was identified as *O*-ethyl α-2-acetonaphthonylcarbonodithioic acid ester.[1] HNMR ($CDCl_3$, δ ppm): 1·5 (t, 3H, J = 7 Hz, CH_2CH_3); 4·6 (q, 2H J = 7 Hz, CH_2CH_3); 4·8 (s, 2H, $COCH_2$–); 7·5–8·1 (m, 6H, naph-H3-8) and 8·5 (s, 1H, naph-H1). ^{13}CNMR (d_6-DMSO, δ ppm): 13·4 (CH_3); 42·6 ($COCH_2S$); 70·3 (OCH_2); 123·3 (naph-C-3); 126·7 (naph-C-7); 127·4 (naph-C-5); 128·1 (naph-C-4); 128·5 (naph-C-6); 129·3 (naph-C-8); 130·1 (naph-C-1); 131·8 (naph-

Table 1. Physicochemical data of compounds **6a–g**.



Compound	$-NR_1R_2$	Yield (%)	Mp (°C)	Formula (MW)	Elemental analysis (%)		
					C	H	N
6a		62	167–169[a]	$C_{20}H_{17}NOS_2$ (351·48)	67·98 (68·35)	4·70 (4·88)	4·40 (3·99)
6b	$-N(C_2H_5)_2$	78	82–84[b, c]	$C_{17}H_{19}NOS_2$ (317·09)	64·69 (64·32)	5·97 (6·03)	3·88 (4·41)
6c		92	140–141[b]	$C_{17}H_{17}NOS_2$ (315·45)	64·25 (64·75)	5·08 (5·44)	4·45 (4·44)
6d		95	114–116[a, c]	$C_{18}H_{19}NOS_2$ (329·09)	65·31 (65·75)	6·00 (5·82)	3·87 (4·24)
6e		93	134–136[b, c]	$C_{17}H_{17}NO_2S_2$ (331·45)	61·33 (61·62)	5·40 (5·18)	3·83 (4·23)
6f		91	162–165[a]	$C_{18}H_{20}N_2OS_2$ (344·49)	62·46 (62·76)	5·42 (5·85)	8·60 (8·13)
6g		94	182–184[b]	$C_{23}H_{22}N_2OS_2$ (406·56)	68·18 (67·95)	5·50 (5·45)	6·54 (6·89)

Recrystallization solvent: [a]methanol-acetone, [b]ethanol. [c]Reported melting points of compounds: **6b** 74°C; **6d**, 105–106°C; **6e**, 130–131°C (Erdogan et al 1988). [d]Calculated values are in parentheses.

C-9); 132·7 (naph-C-2); 134·8 (naph-C-10); 191·7 (C = O); 212·7 (C = S). Elemental analysis: found: C, 60·00; H, 4·84; calculated for $C_{15}H_{14}O_2S_2$, (290·394); C, 59·98; H, 4·40.

Reaction of **5a** with **4** gave the corresponding analogue **11**: yield 63%; mp 74–77°C (methanol) which was identified as *O*-ethyl α-[1-(4-methoxy)-acetonaphthonyl]carbonodithioic acid ester. ^{1}HNMR ($CDCl_3$, δ ppm): 1·3 (t, 3H, J = 7 Hz, CH_2CH_3); 4·0 (s, 3H, OCH_3); 4·6 (q overlapped with s, 4H $COCH_2$ and OCH_2CH_3); 6·8 (d, 1H, J = 9 Hz, naph-H3); 7·5–7·9 (m, 2H, naph-H6, H7); 8·2 (d, 1H, J = 8 Hz, naph-H2); 8·4 (dd, 1H, J = 8, 3 Hz, naph-H5) and 9·0 (dd, 1H, J = 8, 4 Hz, naph-H8). Elemental analysis: found: C, 61·57; H, 5·16; calculated for $C_{16}H_{16}O_3S_2$; (320·419); C, 62·04; H, 4·86.

Evaluation of in-vitro antifungal activity

The fungal species were previously isolated from cases of human dermatophytosis (Moubasher et al 1992). The fungi were grown in sterilized 9-cm Petri dishes containing Sabouraud's Dextrose Agar (SDA) supplemented with 0·05% chloramphenicol to suppress bacterial contamination (Al-Doory 1980). From these cultures, agar discs (10 mm diam.) containing spores and hyphae were transferred aseptically to screw-topped vials containing 20 mL sterile distilled water. After thorough shaking, 1-mL samples of the spore suspension were pipetted into sterile Petri dishes, followed by the addition of 15 mL liquified SDA medium which was then left to solidify.

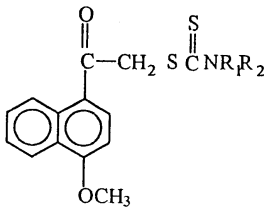
The tested compounds and tolnaftate were dissolved in dimethylsulphoxide to give 2·5 or 5·0% concentrations. Antifungal activity was determined according to the method reported by Bauer et al (1966) using 3-mm diameter filter-paper discs (Watmann No. 3) loaded with 10 μL of the solution under investigation (250 or 500 μg/disc, 2·5% or 5% concn, respectively). The discs were placed on the surface of the fungal cultures which were then incubated at 30°C. The diameter of the inhibition zone around each disc was measured.

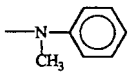
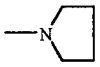
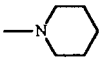
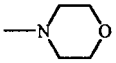
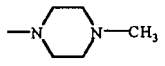
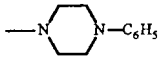
Results and Discussion

Synthesis and characterization

The synthetic pathway for synthesis of the title compounds **5a–g**, **6a–g** and **7a–g** is illustrated in

Table 2. Physicochemical data of compounds **7a–g**.



Compound	$-NR_1R_2$	Yield (%)	Mp (°C)	Formula (MW)	Elemental analysis (%)		
					C	H	N
7a		57	175–176[a]	$C_{21}H_{19}NO_2S_2$ (381·09)	66·61 (66·13)	5·14 (5·02)	3·00 (3·67)
7b	$-N(C_2H_5)_2$	72	127–129[b]	$C_{18}H_{21}NO_2S_2$ (347·10)	62·35 (62·22)	6·00 (6·09)	3·35 (4·03)
7c		89	145–147[c]	$C_{18}H_{19}NO_2S_2$ (345·50)	63·12 (62·59)	5·40 (5·55)	4·14 (4·06)
7d		93	169–171[c]	$C_{19}H_{21}NO_2S_2$ (359·50)	63·50 (63·49)	6·30 (5·89)	3·56 (3·09)
7e		94	138–140[c]	$C_{18}H_{19}NO_3S_2$ (345·50)	59·50 (59·81)	5·13 (5·30)	4·11 (3·87)
7f		92	141–143[c]	$C_{19}H_{22}N_2O_2S_2$ (374·11)	61·31 (60·93)	5·90 (5·92)	7·23 (7·48)
7g		96	163–165[c]	$C_{24}H_{24}N_2O_2S_2$ (436·13)	65·60 (66·04)	5·36 (5·55)	6·50 (6·42)

Recrystallization solvent: [a]methanol-ethylacetate, [b]ethanol, [c]ethanol-dioxan. [d]Calculated values are in parentheses.

Figure 2. The precursors α-chloro-2-acetonaphthone (**3**) and α-chloro-4-methoxy-1-acetonaphthone (**4**) were obtained by Friedel-Craft's acylation of the corresponding naphthaline (**1**) or its 1-methoxy derivative (**2**), respectively. To obtain the final compounds **6a–g** and **7a–g**, it was necessary to prepare the potassium salts of *N*, *N*-disubstituted dithiocarbamic acid **5a–g** by the reaction of the appropriate amines with CS_2 and KOH at room temperature. The potassium salts were refluxed with **3** or **4** to afford the final compounds **6a–g** and **7a–g**, respectively. Physical data are given in Tables 1 and 2 .

Reaction of potassium *N*-methyl-*N*-phenyldithiocarbamate (**5a**) with **3** or **4** in ethanol resulted in the formation of the corresponding *O*-ethyl carbonodithioic acid ester **10** or **11** instead of the expected α-acetonaphthonyl-*N*-methyl-*N*-phenyldithiocarbamate derivative **6a** or **7a** (Figure 3). The reaction proceeds through a second-order mechanism as reported for carbonyl and the corresponding nitrogen and sulphur analogues (March 1984). The delocalization of the lone pair of electrons on the aryl nitrogen of compounds **6a** and **7a** renders the

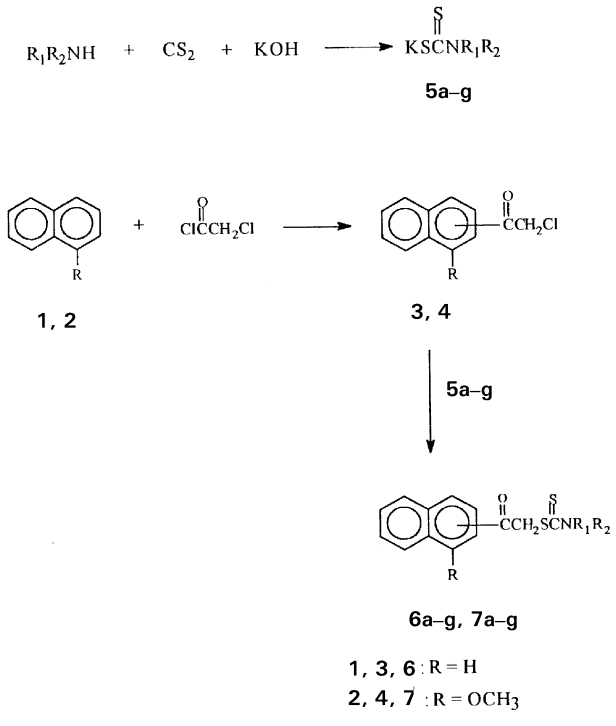


Figure 2. Synthetic pathway for the synthesis of compounds **5a–g**, **6a–g** and **7a–g**.

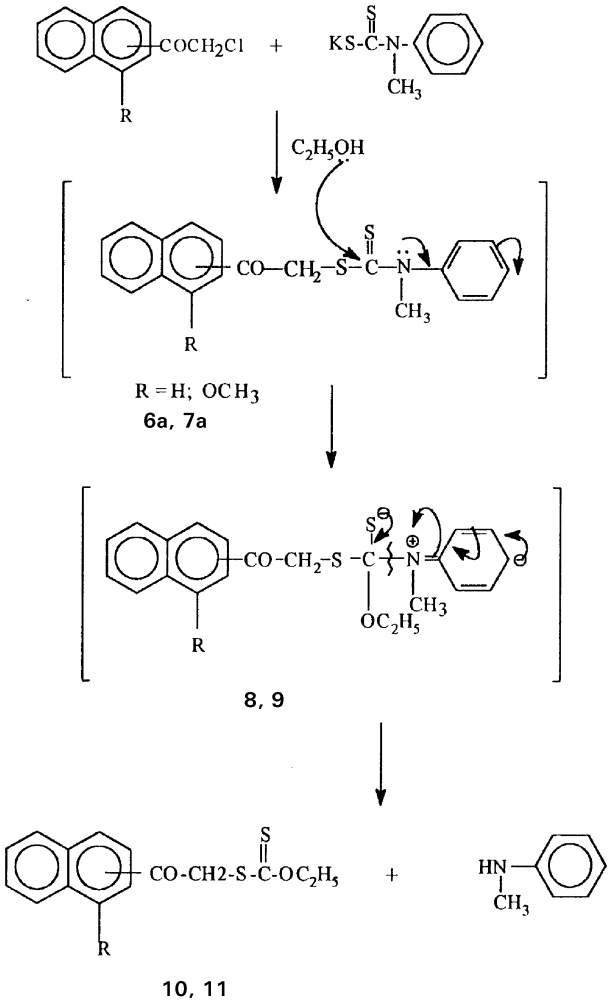


Figure 3. Suggested mechanism for formation of compounds **10** and **11**.

positive charge at the C atom of the thiocarbonyl group of **6a** or **7a** more pronounced, facilitating the nucleophilic attack of ethanol to give the intermediate **8** or **9**, respectively. Cleavage of the C−N bond of the latter compounds leads to the formation of compounds **10** and **11**. When acetonitrile was used instead of ethanol, the desired products α-acetonaphthonyl-*N*-methyl-*N*-phenyl dithiocarbamate derivatives **6a** and **7a** were obtained in reasonable yields. In the case of the aliphatic and alicyclic amines, localization of the lone pair of electrons on the amine nitrogen increased the C−N bond character and ensured the formation of the desired compounds **6b**–**g** and **7b**–**g** regardless of the solvent used.

The structures of *O*-ethyl carbonodithioic acid esters **10** and **11** were confirmed by elemental analyses and spectral data. ^{1}HNMR spectra showed the signals characteristic for CH_2CH_3 group, in addition to the other signals of the acetonaphthone moiety. The spectra of compound **11** also revealed a singlet at $\delta \sim 4$ ppm, due to methoxy protons. ^{13}CNMR of compound **10** showed CH_3 at $\delta \sim 13{\cdot}4$ ppm and two signals at $\delta \sim 42{\cdot}5$ and 70·3 ppm assigned to the methylene C-atoms, CH_2S and OCH_2, respectively. The spectra also revealed five quaternary C-atoms, three of which are characteristic for naphthaline C-atoms (C-9, C-2 and C-10 at $\delta \sim 131{\cdot}8$, 132·7 and 134·8 ppm, respectively). The downfield shifted signals at $\delta \sim 191{\cdot}7$ and 212·7 ppm are characteristic for C=O and C=S, respectively. Chemical shifts of the remaining C-atoms of the naphthaline ring appeared as expected.

Compounds **6b**, **6d** and **6e**, which were previously synthesized, showed higher melting points than the reported values (Erdogan et al 1988). The purity of these compounds was assessed by TLC and elemental analyses (Table 1), and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and MS.

The IR spectra of compounds **6a**–**g** and **7a**–**g** showed the characteristic stretching vibrations at 1650–1683 cm^{-1} (C=O) and 1222–1276 cm^{-1} (C=S), in addition to out-of-plane bending vibration of the naphthaline ring. In ^{1}HNMR spectra, the signals of the respective H-atoms were assigned on the basis of chemical shifts, multiplicities and coupling constants. The spectra showed upfield shifted signals at $\delta \sim 1{\cdot}2$–$4{\cdot}3$ ppm due to amine protons, and a singlet signal at $\delta \sim 5$ ppm assigned to the CH_2S group. The spectra of compounds **7a**–**g** revealed an additional signal due to OCH_3 which appeared as a separate singlet at $\delta \sim 4$ ppm (**7a**, **7c** and **7g**) or overlapped with the amine moiety in other derivatives (**7b** and **7d**–**f**). The signals of the naphthaline nucleus in the two series, **6a**–**g** and **7a**–**g**, appeared as expected at different δ values due to variation in the substitution pattern in both series. The chemical shifts in the same series were almost identical whatever the type of substitution of the amine moiety.

For ^{13}CNMR data, the signals in the proton decoupled spectra were assigned to their specific carbon atoms by comparison of their chemical shifts with similar compounds and application of some additivity rules (Kalinowski et al 1984; Silverstein & Webster 1998). The carbonyl and thiocarbonyl C atoms were easily identified by their low intensity and characteristic downfield-shifted signal at $\delta \sim 192$–197 ppm. The acetyl carbonyl C atom appeared upfield relative to its isoster, thiocarbonyl C atom. The chemical shifts of the latter in the different compounds varied according to the type of the adjacent amine moiety. The C atoms of

the naphthaline nucleus resonate in the aromatic region at different δ-values. However, it is easy to recognize the quaternary C atoms by their low intensity. The spectra also revealed signals in the upfield region at $\delta \sim 65-11$ ppm assigned to methoxy (**7b** and **7f**) and amine C atoms. The C atoms of the *N*, *N*-diethylamino group of compound **7b** were nonequivalent and appeared at different chemical shifts. This may be attributed to the slow rate of rotation around the hindered C = N bond as has been observed for similar compounds (Kalinowski et al 1984). In all compounds, the signal of the α-C atom of the spacer overlapped with the peaks of the solvent (d_6-DMSO), except for compound **7b** where it was downfield shifted to $\delta \sim 45$ ppm due to the hindered rotation around C = N bond.

The mass spectra of compounds **6c**, **6e**, **6f** and **7d–g** showed molecular ion peaks which confirmed their molecular weights and generated ionic fragments that verified their structures. The major fragmentation pathway involved cleavage of the C–S bond of the dithiocarbamate moiety which was in accordance with the literature (Capan et al 1993). The proposed fragmentation pattern of compound **6c** under electron impact is depicted in Figure 4 as a representative example.

Antifungal screening

The filter-paper disc method (Bauer et al 1966) was used for evaluation of the in-vitro antifungal activity of compounds **5a–g**, **6a–g** and **7a–g** against various fungal species using SDA. The results are summarized in Tables 3 and 4 . The screening of the potassium salts **5a–g** for potential antifungal activity was based on the previously reported antimycotic activity of some sodium salts of dithiocarbamic acid against different *Candida* species (Shah et al 1997). In this series, compounds **5a–e** displayed broad spectrum antifungal activity at both concentrations (2·5 and 5·0%) against all the tested fungi (Table 3). Potassium salts derived from *N*-methylaniline (**5a**) and morpholine (**5c**) had greater antifungal activity than the reference drug, tolnaftate.

Combination of the potassium salts **5a–g** with a naphthaline nucleus through an acetyl spacer resulted in the derivatives **6a–g** and **7a–g**. These modifications led to a drastic decrease in, or

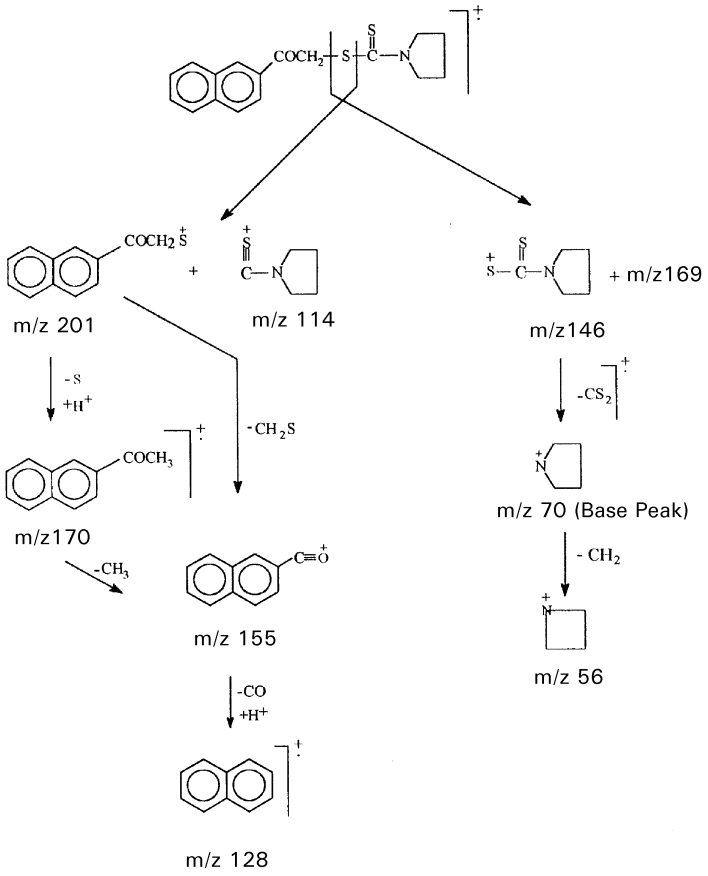


Figure 4. Mass fragmentation of compound **6c**.

Table 3. Antifungal activity of some potassium salts of *N*, *N*-disubstituted dithiocarbamic acid derivatives and tolnaftate.

Fungal species	Inhibition zone (mm)														
	5a		**5b**		**5c**		**5d**		**5e**		**5f**[b]	**5g**		Tolnaftate	
	2·5%	5%	2·5%	5%	2·5%	5%	2·5%	5%	2·5%	5%	2·5%	2·5%	5%	2·5%	5%
Aspergillus alutaceus	22	40	8	35	20	40	10	15	–	8	–	–	12	18	20
Aspergillus fumigatus	20	30	10	15	12	35	10	15	8	15	10	–	–	–	–
Aspergillus niger	18	30	5	10	15	40	10	18	10	12	–	–	–	18	23
Aspergillus sydowii	10	35	10	20	10	40	15	25	7	10	–	–	12	–	–
Aspergillus terreus	20	30	8	12	15	35	12	20	6	10	10	–	–	10	15
Botryotrichum piluliferum	25	40	25	40	20	60	12	20	10	35	–	–	–	10	30
Candida albicans	18	30	6	8	15	35	8	15	10	14	18	–	12	–	–
Chrysosporium tropicum	20	45	20	40	12	50	8	15	10	12	–	–	10	10	12
Emericella nidulans	20	40	18	20	15	45	18	30	20	28	12	10	20	15	20
Fusarium oxysporum	18	30	12	30	15	40	10	20	12	15	10	–	–	–	–
Geotrichum candidum	17	30	10	20	12	40	15	30	10	30	10	–	15	16	18
Microsporum canis	20	35	20	25	20	50	10	30	25	40	20	–	10	25	30
Microsporum gypseum	25	40	15	35	25	60	12	30	15	30	–	–	15	12	15
Nectrio haematococca	15	20	8	20	10	40	–	10	–	10	–	–	10	–	10
Penicillium funiculosum	10	30	10	20	10	40	–	10	–	12	–	–	10	–	–
Stachybotrys chartarum	12	30	10	20	18	45	15	25	12	32	15	–	–	–	–
Trichophyton gourvilli	20	50	20	30	15	50	15	30	20	30	7	–	15	35	40
Trichophyton mentagrophytes	20	40	25	40	20	60	18	30	20	45	20	–	10	23	26
Trichophyton rubrum	16	30	10	15	10	40	10	15	10	14	–	–	12	7	10
Trichothecium roseum	20	50	15	32	10	50	10	15	10	25	20	–	10	–	–

[b]Not determined at 5%; –, inactive.

Table 4. Antifungal activity of *N*, *N*-disubstituted dithiocarbamate derivatives and tolnaftate.

Fungal species		Inhibition zone (mm)			
		Compounds		Tolnaftate	
		2·5%	5%	2·5%	5%
Aspergillus alutaceus	**7e**	–	12	18	20
Aspergillus sydowii	**7e**	10	15	–	–
Chrysosporium tropicum	**7e**	12	15	10	12
Emericella nidulans	**6g**	ND	11	12	15
	7e	16	20		
Geotrichum candidum	**7c**	ND	8	–	–
	7d	ND	8		
Microsporum canis	**7e**	10	35	25	30
Microsporum gypseum	**7e**	10	30	12	15
Mucor circinelloides	**7c**	ND	6	ND	10
	7f	ND	10		
Penicillium aurantiogriseum	**7d**	ND	11	–	–
	7e	ND	25		
Phoma glomerata	**6f**	ND	8	–	30
	6g	ND	13		
Rhodotorula rubra	**7d**	ND	10	ND	18
	7e	ND	32		
Scopulariopsis acremonium	**6f**	ND	8	–	–
Trichophyton gourvilli	**7e**	10	40	35	40
Trichophyton mentagrophytes	**7e**	10	30	23	26

ND, not determined; –, inactive.

complete loss of antifungal activity in certain derivatives. In the series **6a**–**g**, **6f** exhibited weak and selective activity against *Phoma glomerata* and *Scopulariopsis acremonium*, whereas **6g** showed weak activity against *Emericella nidulans* and *Phoma glomerata* (Table 4). Introduction of a methoxy group at C-4 and shifting the dithiocarbamate moiety to C-1 of the naphthaline nucleus, resulting in **7a**–**g**, led to partial restoration of activity (Table 4). The morpholino deri-

vative **7e** showed equipotent or superior activity against the tested dermatophytic species *Aspergillus alutaceus* and *Rhodotorula rubra* compared with tolnaftate. Compound **7e** also revealed inhibitory activity against *Pencillium aurantiogriseum* and *Aspergillus sydowii*; tolnaftate showed no activity against either of these fungi. Compound **7c** exhibited weak and selective activity against *Geotrichum candidum* and *Mucor circinelloides*. Some efficacy of compound **7d** was found against *R. rubra*, *P. aurantiogriseum* and *G. candidum*. The latter two fungi were not sensitive to tolnaftate. Compound **7f** was equipotent with the reference drug against *Mucor circinelloides*. The derivatives **6a–e**, **7a**, **7b** and **7g** were completely inactive against all the tested fungal isolates listed in Tables 3 and 4 .

In conclusion, potassium salts of *N*, *N*-disubstituted dithiocarbamic acid displayed higher and broad spectrum activity against true dermatophytes, as well as opportunistic nondermatophyte fungal species among all the tested compounds. Combination of these derivatives with a naphthaline nucleus through an acetyl spacer resulted in a drastic decrease or complete loss of antifungal activity of some derivatives in comparison with tolnaftate. Derivatives **6a–g** were much less active than their congeners **7a–g**, which may be attributed to the presence of the methoxy group in **7a–g**. The morpholino analogue **7e** was the most active compound in the series **7a–g**.

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