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Synthesis and antimicrobial activity of rhodanine derivatives

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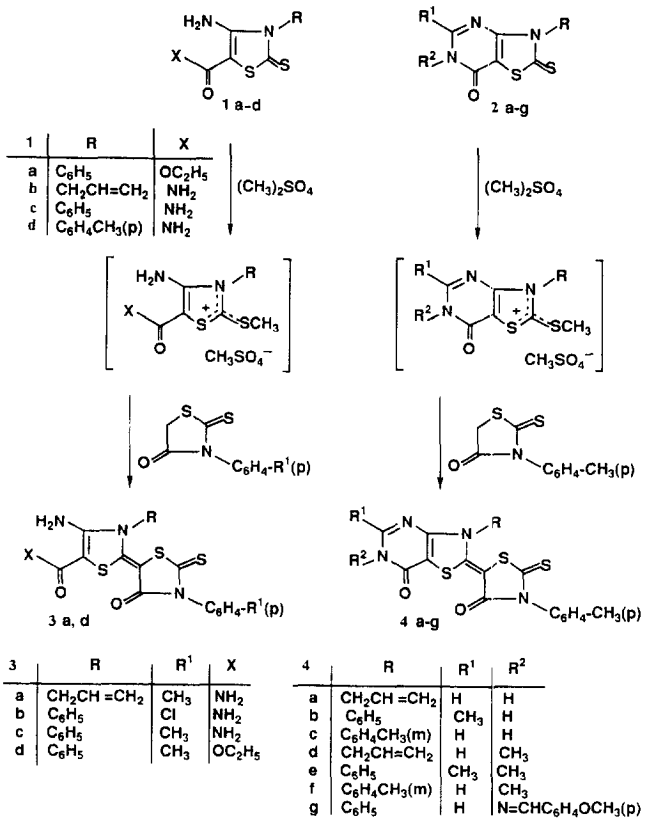
Introduction

The rhodanines, 2-thioxo-4-thiazolidinones, appear to be very important as far as biocidal potency is concerned, probably via incorporation of the N–C=S moiety, the importance of which has been stressed in many fungicides and bactericides [1–3]. Dithiazoles are also known to possess similar activities [4, 5]; furthermore, many thiazolo[4,5-*d*]pyrimidines are known to possess antiviral, antibacterial and antifungal activities [6, 7]. Encouraged by the above-mentioned fact and in connection with our work on the structural modifications of thiazolo[4,5-*d*]pyrimidines [8, 9], we planned to combine thiazole-2-thiones, or thiazolo[4,5-*d*]pyrimidines with rhodanines.

Chemistry

The dithiazoles **3a–d** were prepared by treating the appropriate thiazole-2(3*H*)-thiones **1a–d** [10] with dimethyl sulphate in boiling acetonitrile. The produced 2-methylthiothiazolium salt was then reacted with the selected rhodanines in the presence of triethylamine following the method reported by Gewald [11].

The rhodanine derivatives of thiazolo[4,5-*d*]pyrimidines **4a–g** were prepared from **2a–g** using the same principle (scheme 1).



1	R	X
a	C_6H_5	OC_2H_5
b	$CH_2CH{=}CH_2$	NH_2
c	C_6H_5	NH_2
d	$C_6H_4CH_3$(p)	NH_2

3	R	R^1	X
a	$CH_2CH{=}CH_2$	CH_3	NH_2
b	C_6H_5	Cl	NH_2
c	C_6H_5	CH_3	NH_2
d	C_6H_5	CH_3	OC_2H_5

4	R	R^1	R^2
a	$CH_2CH{=}CH_2$	H	H
b	C_6H_5	CH_3	H
c	$C_6H_4CH_3$(m)	H	H
d	$CH_2CH{=}CH_2$	H	CH_3
e	C_6H_5	CH_3	CH_3
f	$C_6H_4CH_3$(m)	H	CH_3
g	C_6H_5	H	$N{=}CHC_6H_4OCH_3$(p)

Scheme 1. Preparation of compounds **3a–d** and **4a–g**.

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Results and discussion

The structure of the prepared compounds was confirmed by IR, ^{1}H-NMR and in some cases by ^{13}C-NMR through the appearance of signals arising from the different groups and substituents on rhodanine and either the thiazole or thiazolopyrimidine rings.

The IR spectra of the dithiazoles showed two C=O absorption bands, one at 1660–1655 cm^{-1}, due to the rhodanine and the other at 1640–1630 cm^{-1} due to the amide functions or at 1665 cm^{-1} due to the ester function. Also the ^{13}C-NMR of compounds **3a,d** showed C=S at 187.7–189.5 ppm and two C=O signals at 163.6–165.7 ppm.

In their IR spectra compounds **4a–g** showed two C=O absorption bands, one due to rhodanine and the other to pyrimidone at 1700–1670 and 1675–1650 cm^{-1}, respectively. Compounds **4a–c** also showed NH at 3410 cm^{-1}. The ^{1}H-NMR of compounds **4a,c,d,f** showed a singlet at δ = 8.15–8.4 ppm due thiazolopyrimidine C_5-H, while the ^{1}H-NMR spectra of **4e** showed C_5-CH_3 as a singlet at δ 2.45 ppm. The N-CH_3 derivatives **4d,e,f** showed a singlet at δ 3.45–3.7 ppm due to the N-CH_3 moiety.

The ^{13}C-NMR spectra of compounds **4c,d** were characterized by the presence of the C_2-rhodanine C=S at 188.7–189.8 and two C=O bands, the C_4-rhodanine and the C_7 thiazolopyrimidine band at 155.5–155.7 and 165.3–165.4 ppm, respectively.

Investigation of the results of antimicrobial screening (table III) revealed that the most pronounced activity was the antifungal activity against *Aspergillus niger* and *Penicillium* sp with IZ 20–38 mm and MIC < 50 – < 25 μg/mL. Compound **4g** was the most active against *Aspergillus niger* while compound **4a** was the most active against *Penicillium* sp; they were only 5-fold less active than the standard antibiotic clotrimazole. It can be concluded that the presence of an alkyl group at position 3 of the thiazolopyrimidine ring **4a** is superior to that of other aromatic substituents; also the introduction of an arylideneamino group at position 6 of **4g** enhanced the antifungal activity.

Experimental protocols

Chemistry

Melting points were determined on Gallenkamp apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin–Elmer 1430 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390, TMS internal standard, δ (ppm), DMSO-d_6, 90 MHz. ^{13}C-NMR spectra were measured on Varian VXR-300 FT spectrometer. Elementary analyses were carried out at the microanalytical unit, Faculty of Science, University of Cairo, Egypt. All values of C, H, N and S were within ± 0.4% of theoretical values.

*Substituted 4-amino-5-carbamoyl (or ethoxycarbonyl)-2-(4-oxo-2-thioxothiazolidin-5-ylidene)-2,3-dihydrothiazoles **3a–d***

To a solution of the selected **1a–d** (10 mmol) in acetonitrile (20 mL), dimethyl sulphate (1.9 g, 1.45 mL, 15 mmol) was added. The reaction mixture was heated under reflux for 30 min, during which the 2-methylthiothiazolium salt was crystallized out and cooled. The appropriate rhodanine (10 mmol) and triethylamine (2 mL) were added under stirring. A bright yellow crystalline product was immediately formed. Stirring was continued for 30 min on a boiling water bath and the product then cooled, filtered, washed with EtOH, dried and recrystallized from aqueous DMF (table I). IR (**3a–d**) ν cm^{-1}: 3340–3370, 3330–3170 (NH), 1665 (C=O ester only for **3d**), 1660–1655 (C=O rhodanine), 1640–1630 (C=O amide for **3a–c**), 1590–1560 (δ NH). ^{1}H-NMR (**3a**) (CF_3COOH), δ (ppm) = 2.3 (S, 3H, CH_3), 4.8 (d, J = 12 Hz, 2H, $NCH_2CH{=}CH_2$), 5.0–5.3 (m, 2H, $NCH_2CH{=}CH_2$), 5.7–6.2 (m, 1H, $NCH_2CH{=}CH_2$), 7.0, 7.3 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$). ^{1}H-NMR (**3b**) (CF_3COOH), δ (ppm) = 6.8–7.9 (m, 9H, Ar-H). ^{1}H-NMR (**3c**) (CF_3COOH), δ (ppm) = 2.3 (s, 3H, CH_3), 6.5 (s, 2H, NH_2), 6.9, 7.2 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 7.3–7.7 (m, 5H, C_6H_5). 1H-NMR (**3d**) (CF_3COOH), δ (ppm) = 1.4 (t, J = 7 Hz,

Table I. Substituted 4-amino-5-carbamoyl (or ethoxycarbonyl)-2-(4-oxo-2-thioxothiazolidin-5-ylidene)-2,3-dihydrothiazoles **3a–d**.

Compound	*R*	*R^1*	*X*	*Mp (°C)*	*Yield (%)*	*Mol formula (mol wt)*
3a	$CH_2CH{=}CH_2$	CH_3	NH_2	245–247	83	$C_{17}H_{16}N_4O_2S_3$ (404.54)
3b	C_6H_5	Cl	NH_2	290–292	82	$C_{19}H_{13}ClN_4O_2S_3$ (460.99)
3c	C_6H_5	CH_3	NH_2	> 300	85	$C_{20}H_{16}N_4O_2S_3$ (440.57)
3d	C_6H_5	CH_3	OC_2H_5	> 300	80	$C_{22}H_{19}N_3O_3S_3$ (469.61)

Table II. Substituted 2-[4-oxo-2-thioxo-3-(4-tolyl)thiazolidin-5-ylidene]-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **4a–g**.

Compound	*R*	*R¹*	*R²*	*Mp (°C)*	*Yield (%)*	*Mol formula (mol wt)*
4a	$CH_2CH=CH_2$	H	H	283–285	75	$C_{18}H_{14}N_4O_2S_3$ (414.53)
4b	C_6H_5	CH_3	H	> 300	72	$C_{22}H_{16}N_4O_2S_3$ (464.59)
4c	$CH_3C_6H_4$ (m)	H	H	> 300	60	$C_{22}H_{16}N_4O_2S_3$ (464.59)
4d	$CH_2CH=CH_2$	H	CH_3	250–252	80	$C_{19}H_{16}N_4O_2S_3$ (428.56)
4e	C_6H_5	CH_3	CH_3	> 300	75	$C_{23}H_{18}N_4O_2S_3$ (478.62)
4f	$CH_3C_6H_4$ (m)	H	CH_3	295–297	65	$C_{23}H_{18}N_4O_2S_3$ (478.62)
4g	C_6H_5	H	$CH_3OC_6H_4CH=N$ (p)	> 300	75	$C_{29}H_{21}N_5O_3S_3$ (583.71)

3H, $COOCH_2CH_3$), 2.3 (s, 3H, CH_3), 4.4 (q, J = 7 Hz, $COOCH_2CH_3$), 7.0, 7.3 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 7.35–7.8 (m, 5H, C_6H_5). ^{13}C-NMR (**3a**), δ (ppm) = 21.6 (CH_3), 48.5 (NCH_2), 82.1 (C_5-thiazole), 83.4 (C_5-rhodanine), 117.1 (CH_2–CH=CH_2), 130.4 ($CH_2CH=CH_2$), 129.2 132.0, 134.3, 151.3 (*p*-tolyl), 139.2 (C_2-thiazole), 151.8 (C_4-thiazole), 165.0 (C=O amide), 165.7 (C_4-rhodanine), 187.7 (C_2-rhodanine). ^{13}C-NMR (**3d**) δ (ppm) = 15.3 ($COOCH_2CH_3$), 21.6 (CH_3); 60.7 ($COOCH_2$), 82.0 (C_5-thiazole), 83.4 (C_5-rhodanine), 129.1, 130.4, 131.3, 131.6, 133.3, 134.0, 151.4 (phenyl and *p*-tolyl), 139.4 (C_2-thiazole), 152.0 (C_4-thiazole), 163.6 (C=O ester), 165.6 (C_4-rhodanine), 189.5 (C_2-rhodanine).

*Substituted 2-[4-oxo-2-thioxo-3-(4-tolyl)thiazolidin-5-ylidene]-2,3-dihydrothiazolo[4,5-d]-pyrimidin-7(6H)-ones **4a–g***

The above compounds were prepared from the corresponding thiazolo[4,5-*d*]pyrimidines **2a–g** (10 mmol) and 4-(*p*-tolyl)rhodanine, as described for **3a–d.** The refluxing time in acetonitrile was 2 h (table II). IR (**4a–g**) ν cm^{-1}: 3410 (NH for **4a–c**), 1700–1670 (C=O rhodanine), 1675–1650 (C=O pyrimidine), 1650–1630 (C=N). ^{1}H-NMR (**4a**), δ (ppm) = 2.4 (s, 3H, CH_3), 5.0 (d, J = 12 Hz, 2H, $NCH_2CH=CH_2$), 5.2–5.3 (m, 2H, $NCH_2CH=CH_2$), 6.0–6.3 (m, 1H, $NCH_2CH=CH_2$), 7.2, 7.3 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 8.4 (s, 1H, thiazolopyrimidine C_5-H). ^{1}H-NMR (**4b**), δ (ppm) = 2.3 (s, 3H, $C_6H_4CH_3$), 2.5 (s, 3H, C_5-CH_3), 7.0, 7.7 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 7.2–7.5 (m, 5H, C_6H_5). ^{1}H-NMR (**4c**), δ (ppm) = 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.1–7.6 (m, 8H, Ar-H), 8.1 (s, 1H, thiazolopyrimidine C_5-H). ^{1}H-NMR (**4d**), δ (ppm) = 2.4 (s, 3H, CH_3), 3.7 (s, 3H, NCH_3), 5.0 (d, J = 12 Hz, 2H, $NCH_2CH=CH_2$), 5.2–5.5 (m, $NCH_2CH=CH_2$), 5.7–6.2 (m, 1H, $NCH_2CH=CH_2$), 6.8, 7.2 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 8.3 (s, 1H, thiazolopyrimidine C_5-H). ^{1}H-NMR (**4e**), δ (ppm) = 2.3 (s, 3H, CH_3), 2.4 (s, 3H, C_5-CH_3), 3.6 (s, 3H, NCH_3), 7.1, 7.6 (two d, J = 7 Hz, each 2H, $C_6H_4CH_3$), 7.2–7.4 (m, 5H, C_6H_5). ^{1}H-NMR (**3f**), δ (ppm) = 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 3.4 (s, 3H, NCH_3), 6.8–7.5 (m, 8H, Ar-H), 8.2 (s, 1H, thiazolopyrimidine C_5-H). ^{1}H-NMR (**4g**), δ (ppm) = 2.4 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 7.1–7.9 (m, 13H, Ar-H), 8.7 (s, 1H, CH=N), 9.0 (s, 1H, thiazolopyrimidine C_5-H). ^{13}C-NMR (**4c**), δ (ppm) = 20.5 (CH_3), 20.60 (CH_3), 87.1 (C_5-rhodanine), 103.7 (C_{7a}), 138.5 (C_2), 150.6 (C_{3a}), 155.7 (C_4-rhodanine), 156.0 (C_5), 165.4 (C_7), 189.8 (C_2-rhodanine), 126.9, 128.1, 129.4, 129.5, 130.1, 131.9, 132.9, 133.3, 139.7 150.1 (*m*-tolyl and *p*-tolyl). ^{13}C-NMR (**4d**), δ (ppm) = 20.6 (CH_3), 33.6 (NCH_3), 47.4 ($NCH_2CH=CH_2$), 85.7 (C_5-rhodanine), 103.0 (C_{7a}), 116.9 ($NCH_2CH=CH_2$), 131.2 ($NCH_2CH=CH_2$), 138.6 (C_2), 152.8 (C_5), 154.2 (C_{3a}), 155.5 (C_4-rhodanine), 165.3 (C_7), 188.7 (C_2-rhodanine), 127.4, 128.2, 129.3, 129.5, 132.9, 151.8 (*p*-tolyl).

Antimicrobial screening

The prepared compounds were evaluated for their antimicrobial activity using the agar diffusion technique [12]. A 1 mg/mL solution in DMF was used. The test organisms were *Staphylococcus aureus* (ATCC 29523), *Escherichia coli* (HP 101), *Proteus vulgaris* (local isolate), *Candida albicans* (NCTC 2708), *Aspergillus niger* and *Penicillium* sp (local isolates). Dimethylformamide showed no inhibition zones. The minimal inhibitory concentration (MIC) was measured using the two-fold serial dilution method. The reference antibiotics were streptomycin sulphate, ampicillin and clotrimazole. Inhibition zones (IZ) and MIC of these compounds are listed in table III.

Table III. Antimicrobial activity.

Compound	*S aureus*		*E coli*		*P vulgaris*		*C albicans*		*A niger*		*Penicillium sp*	
	IZ	*MIC*	*IZ*	*MIC*	*IZ*	*MIC*	*IZ*	*MIC*	*IZ*	*MIC*	*IZ*	*MIC*
3a	16	< 200	11	< 100	24	< 100	20	< 100	30	< 25	26	< 25
3b	13	< 200	12	< 100	15	< 100	16	< 100	30	< 25	34	< 25
3c	14	< 200	12	< 100	15	< 100	16	< 100	20	< 50	32	< 50
3d	16	< 200	11	< 200	16	< 100	20	< 100	26	< 25	34	< 25
4a	15	< 200	15	< 200	18	< 200	15	< 100	28	< 25	38	< 25
4b	15	< 200	14	< 200	20	< 200	22	< 100	30	< 25	32	< 50
4c	20	< 200	12	< 200	15	< 200	23	< 100	29	< 50	32	< 50
4d	14	< 200	13	< 200	20	< 100	24	< 100	30	< 25	30	< 50
4e	13	< 200	11	< 200	22	< 200	14	< 100	25	< 50	30	< 50
4f	15	< 200	11	< 200	20	< 200	24	< 100	24	< 50	26	< 50
4g	14	< 200	13	< 200	22	< 100	15	< 100	35	< 25	35	< 25
Ampicillin		1		–		–		–		–		–
Streptomycin		4		3		3		–		–		–
Clotrimazole		–		–		–		2		5		5

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