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SYNTHESIS AND BIOLOGICAL TESTING OF 2,4-DISUBSTITUTED THIAZOLE DERIVATIVES AS POTENTIAL ANTITUMOR ANTIBIOTICS

By

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تحضير مشتقات الثيازول واختبارها بيولوجياً كمضادات حيوية ضد الأورام

ح . الصباغ - و . النجار - ف . بدرية

تم تخليق مجموعة من مشتقات الثيازول واختبارها كمواد لها نشاط ضد البكتريا والأورام . واشتملت هذه المركبات على تلك المشتقات التي تحمل مجاميع أمين أو أسيتاميد أو ثيويوريدو في موقع رقم ٢ وكذلك التي تحمل مجاميع ثيوسيميكر بازون أو ١,٢,٤ - تريازول ثيون في موقع رقم ٤ . وقد ثبت أن لبعض المركبات التي تم إختيارها (وهي رقم ٥,٦,١٤,١٥) نشاط حيوي قوي وملحوظ ضد الأورام - وقد وجد أن تأثير هذه المركبات كمضادة للميكروبات يكون أساساً ضد بكتريا جرام الموجبة . وتذكر هذه الدراسة تفاصيل عملية تخليق المركبات ونتائج الدراسات الاسبكتروسكوبية والبيولوجية .

Key Words: Biological test, 2, 4-Disubstituted thiazoles, Antitumor, Antibiotics.

ABSTRACT

A series of thiazole derivatives bearing amino, acetamido or thioureido synthons at position 2- and thiosemicarbazone or 1,2,4-triazolethione moieties at position 4- have been synthesized and evaluated for their antimicrobial and antitumor activities. Some of the tested compounds (5,6,14 and 15) proved to possess a remarkable antitumor antibiotic activity. The antimicrobial potency is found mainly to be against Gram positive bacteria. The detailed synthesis, spectroscopic and biological data are reported.

INTRODUCTION

Bleomycin[1,2], mitomycin[3] and streptozocin[4] are known antineoplastic antibiotics containing an amide function. The antitumor activity of guanidinothiazolecarboxamides[5] and the groove binding property of distamycin[7,8] have been recently reported. Most of the aformentioned drugs have a thiazolecarboxamide moiety as a common structural feature. Thiazoles[9,10] mercaptotriazoles[11-14] and thiosemicarbazides[15,16] have long been reported to possess an antimicrobial activity. Cephalosporins containing thiazole and amide moieties proved to have an antibiotic activity against wide range of β-lactamase producing bacteria[17-19]. These observations prompted us to continue the earlier investigations[20-22] carried out in our laboratory with the hope to discover an active, less toxic compound.

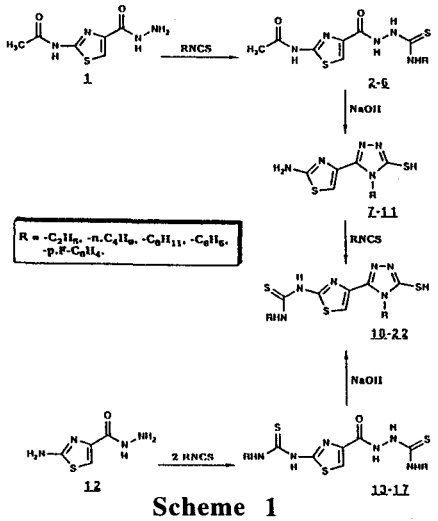
We wish to report here an efficient and easily reproducible synthesis of certain thiazole derivatives, bearing the functional groups believed to be responsible for antitumor antibiotic activity. It was rationalized to synthesize thiazole compounds incorporating an amino, acetylamino or the guanidino group isostere (thioureido function) at position 2- and a thiosemicarbazone or 1,2,4-triazolethione moieties at position 4-, to explore their antimicrobial and antitumor activities. Simple, cost efficient bioassays were used to evaluate the newly synthesized compounds. Antimicrobial testing was performed using the agar well diffusion assay[23]. Antitumor screening was carried out by the use of the potato disc assay[24] which is rapid, inexpensive, safe, animal sparing and statistically reliable as *in-vivo* prescreen.

Table 1
Physicochemical properties and recrystallization solvents of the newly synthesized compounds

No	R	mp° C	Yield %	Molecular Formulae
2	$-C_2H_5$	228-30	92	$C_9H_{13}N_5O_2S_2$
3	$-n.C_4H_9$	220-2	87	$C_{11}H_{17}N_5O_2S_2$
4	$-C_6H_{11}$	239-40	76	$C_{13}H_{19}N_5O_2$
5	$-C_6H_5$	203-5	83	$C_{13}H_{13}N_5O_2S_2$
6	$-p$-F-C_6H_4	185-6	89	$C_{13}H_{12}FN_5O_2S_2$
7	$-C_2H_5$	152-4	65	$C_7H_9N_5S_2$
8	$-n.C_4H_9$	274-5	72	$C_9H_{13}N_5S_2$
9	$-C_6H_{11}$	124-5	68	$C_{11}H_{15}N_5S_2$
10	$-C_6H_5$	308-10	62	$C_{11}H_8FN_5S_2$
11	$-p$-F-C_6H_4	284-5	60	$C_{11}H_8FN_5S_2$
13	$-C_2H_5$	229-30	88	$C_{10}H_{16}N_6OS_3$
14	$-n.C_4H_9$	175-6	94	$C_{14}H_{24}N_6OS_3$
15	$-C_6H_{11}$	159-60	86	$C_{18}H_{28}N_6OS_3$
16	$-C_6H_5$	179-80	89	$C_{18}H_{16}N_6OS_3$
17	$-p$.F-C_6H_4	186-7	95	$C_{18}H_{14}F_2N_6OS_3$
18	$-C_2H_5$	274-5	64	$C_{10}H_{14}N_6S_3$
19	$-n.C_4H_9$	258-60	66	$C_{14}H_{22}N_6S_3$
20	$-C_6H_{11}$	136-7	59	$C_{18}H_{26}N_6S_3$
21	$-C_6H_5$	223-5	73	$C_{18}H_{14}N_6S_3$
22	$-p$.F-C_6H_4	259-60	69	$C_{18}H_{12}F_2N_6S_3$

Chemistry

The synthesis of the compounds evaluated in this study is depicted in scheme I. 2-Amino and 2-acetamidothiazole-4-carboxyhydrazides (1, 12) were prepared according to known procedures[7,25,26]. The hydrazide 1 was treated with a variety of isothiocyantes to give the corresponding thiosemicarbazides 2-6, which were subsequently cyclized and deacetylated using NaOH solution to 1,2,4-triazole derivatives 7-11. The created 2-amino function was then utilized to introduce a thioureido moiety by allowing compounds 7-11 to react with another mole of isothiocyanate to yield the 2-(N-substituted thioureido) thiazole derivatives18-22. The synthesis of 18-22 was further confirmed through their preparation using an alternate route. The hydrazide 12 was treated with 2 moles of the isothiocyanate derivatives to afford 4-substituted-1-[2-(N-substituted - thioureido) - thiazole - 4-carbonyl] thiosemicarbazides 13-17, which were then cyclized using NaOH solution to give products identical to compounds 18-22 (Table 1, Scheme 1).



Scheme 1

EXPERIMENTAL

Melting points (°C., uncorrected) were recorded on a Fisher-Johns apparatus. ^{1}H NMR spectra were recorded on a Varian EM 360 (90 MHz) instrument using TMS as internal standard (chemical shift in δ, ppm). Microanalytical data (C, H, N, S) agreed with the proposed structures within the ±0.4 % of the theoretical values. Solvent evapoation was performed under reduced pressure using a Buchi Rotary Evaporator unless otherwise stated. Thin-layer chromatography was performed on percoated silica gel plates (60-F 254, 0.2 mm, EM Sciences; Inc.) and ultraviolet light (254 nm) was used to detect the UV absorbing compounds. The following organisms were used for the antimicrobial screeing: *staphylococcus aureus* ATCC 06538, Bacillus subitilis ATCC 6633, Escherichia coli ATCC 10536, Pseudomanas aeruginosa ATCC 15442, Candida albicans ATCC 1023 and Saccharmoyces cerevisiae ATCC 9763; also Agrobacterium tumefaciens was used for antitumor testing.

A-Synthesis

4-Alkyl or aryl-1-(2-acetamidothiazole-4-carbonyl)thiosemi-carbazides (2-6). The acid hydrazide 1 (0.5 g, 2.5 mmol) was treated with the appropriate alkyl or aryl isothiocyanate (3.5 mmol) in ethanol and the reaction mixture was heated under reflux for 2h and cooled. The separated solid was filtered, washed with aqueous ethanol and recrystallized from ethanol. ^{1}H NMR (DMSO-d_6), **2**: δ 0.9-1.1 (t, 3H, CH_2CH_3), 2.1 (s, 3H, $-COCH_3$), 3.2-3.6 (m, 2H, $-CH_2CH_3$), 7.8 (s, 1H, thiazole H), 8.0 (m, 1H, NH, exchangeable), 9.1 (br s, 1H, NH, exchangeable), 9.7 ((br s, 1H, NH, exchangeable), 12.2 ((br s, 1H, NH, exchangeable). **3**: δ 0.7-1.0 (m, 3H, $-N(CH_2)_3CH_3$), 1.1-1.8 (m, 4H, $-NCH_2(CH_2)_2CH_3$), 2.1 (s, 3H, $-COCH_3$), 3.2-3.6 (m, 2H, $-N-CH_2$), 7.8-8.1 (m, 2H, thiazole H & NH; exchangeable), 9.2 (m, 2H, NH; exchangeable), 11.2 (br s, 1H, NH, exchangeable). **4**: δ 1.2-2.3 (m, 13H, cyclohexyl H & $-COCH_3$), 3.2-3.4 (m, 1H, cyclohexyl H), 6.2-6.3 (m, 1H, NH; exchangeable), 7.7 (s, 1H, thiazole H), 9.3 (br s, 1H, NH, exchangeable), 10.4 (br s, 1H, NH, exchangeable), 13.1 (br s, 1H, NH, exchangeable), **5**: δ 2.2 (s, 3H, $-COCH_3$), 6.1 (br s, 1H, NH; exchangeable), 7.1-7.6 (m, 5H, ArH), 7.9 (s, 1H, thiazole H), 9.8 (br s, 1H, NH, exchangeable), 10.1 (br s, 1H, NH, exchangeable), 12.3 (br s, 1H, NH, exchangeable), **6**: δ 2.1 (s, 3H, $-COCH_3$), 6.3 (br s, 1H, NH, exchangeable), 7.4-7.6 (m, 2H, ArH), 7.9-8.3 (m, 3H, ArH

& thiazole H), 9.6 (br s, 1H, NH, exchangeable), 10.2 (br s, 1H, NH, exchangeable), 12.1 (br s, 1H, NH, exchangeable).

4-Alkyl or aryl-3-(2-aminothiazole-4-yl)-5-mercapto-1,2,4-triazoles (7-11). The thiosemicarbazides 2-6 (10 mmol) were refluxed in NaOH solution (2N, 30 ml)) for 3H, cooled, then neutralized to pH 6 using dilute hydrochloric acid to give the crude product, which was filtered, washed with water and recrystallized from aqueous ethanol. ^{1}H NMR ($CDCl_3$), **7**: δ 1.1-1.2 (t, 3H, CH_2CH_3), 3.3 (s, 1H, -SH, exchangeable), 3.4-3.7 (m, 2H, -CH_2CH_3), 7.3 (s, 1H, thiazole H), 7.5 (br s, 2H, NH_2, exchangeable), 8: d 0.8-1.0 (m, 3H, -$N(CH_2)_3CH_3$), 1.1-1.8 (m, 4H, -$NCH_2(CH_2)_2CH_3$), 3.3 (s, 1H, -SH, exchangeable), 4.2-4.5 (m, 2H, -N-CH_2), 7.2 (s, 1H, thiazole H), 13.8 (br s, 2H, NH_2, exchangeable). 9: δ 1.3-2.2 (m, 10 H, cyclohexyl H), 3.4-3.6 (m, 2H, cyclohexyl H & -SH; exchangeable), 6.5 (br s, 2H, NH_2; exchangeable), 7.9 (s, 1H, thiazole H). 10: δ 3.3 (s, 1H, -SH, exchangeable), 6.6 (br s, 2H, NH_2, exchangeable), 7.3-7.9 (m, 6H, Ar & thiazole H), **11**: δ 3.5 (s, 1H, -SH; exchageable), 7.4-7.5 (m, 3H, Ar H & thiazole H), 7.9-8.2 (m, 2H, ArH), 10.2 (br s, 2H, NH_2; exchangeable).

4-Alkyl or aryl-1-[2-(N-alkyl or aryl-thioureido)thiazol-4-carbonyl]thiosemi-carbazides (13-17). The acid hydrazide 12 (0.5g, 3.0 mmol) was treated with alkyl or aryl isothiocyanate (6.5 mmol) in ethanol and the reaction mixture was heated under reflux for 2h. The separated solid obtained upon cooling was filtered, washed with water and recrystallized from aqueous ethanol. ^{1}H NMR (DMSO-d_6), 13: d 0.8-1.1 (m, 6H, CH_2CH_3), 3.3-3.6 (m, 4H, CH_2CH_3), 7.7 (s, 1H, thiazole H), 7.9 (m, 2H, NH; exchangeable), 8.5 (br s, 2H, NH; exchangeable), 9.9 (br s, 1H, NH; exchangeable). **14**: d 0.9-1.2 (m, 6H, -$N(CH_2)_3$-CH_3), 1.4-2.0 (m, 8H, -$NCH_2(CH_2)_2$ CH_3), 3.3-3.5 (m, 4H, -N-CH_2), 5.9 (br s, 2H, NH; exchangeable), 7.7 (s, 1H, thiazole H), 9.2 (br s, 1H, NH; exchangeable), 13.2 (br s, 1H, NH; exchangeable), **15**: 1.0-2.1 (m, 20 H, cyclohexyl H), 3.0-3.2 (m, 2H, cyclohexyl H), 6.1 (m, 2H, NH: exchangeable), 7.7 (s, 1H, thiazole H), 7.9 (br s, 1H, NH; exchangeable), 9.3 (br s, 1H, NH, exchangeable), 10.5 (br s, 1H, NH; exchangeable), **16**: 5.7 (br s, 2H, NH; exchangeable), 7.2-7.5 (m, 10 H, ArH), 7.8 (s, 1H, thiazole H), 9.5 (br s, 1H, NH; exchangeable), 9.9 (br s, 1H, NH; exchangeable), 11.8 (br s, 1H, NH; exchangeable), **17**: 5.5 (br s, 2H, NH, exchangeable), 7.5-7.7 (m, 4H, ArH), 7.9-8.3 (m, 5H, Ar H & thiazole H), 8.9 (br s, 1H, NH; exchangeable), 9.9 (br s, 1H, NH; exchangeable), 10.1 (br s, 1H, NH; exchangeable).

4-Alkyl or aryl-3-[2-(N-alkyl or arylthioureido)thiazole-4-yl)-5-mercapto-1,2,4-triazoles (18-22). The thiosemicarbazides 13-17 (10 mmol) were refluxed in NaOH solution (2N, 30 ml) for 3h, then cooled and neutralized to pH 6 using dilute hydrochloric acid to give the crude product, which was filtered, washed with water and recrystallized from aqueous ethanol. The obtained products proved to be identical with those prepared by reacting compounds 7-11 (2.0 mmol) with alkyl or aryl isothiocyanate (3.0 mmol) in refluxing ethanol. ^{1}H NMR ($CDCl_3$), **18**: δ 1.0-1.1 (m, 6H, CH_2CH_3), 3.1 (s, 1H, -SH; exchangeable), 3.5-3.8 (m, 4H, -CH_2CH_3), 7.5 (s, 1H, thiazole H), 9.7 (m, 1H, NH; exchangeable), 11.2 (br s, 1H, NH; exchangeable). **19**: δ 0.8-1.0 (m, 6H, -$N(CH_2)_2CH_3$), 1.2-1.8 (m, 8H, -$NCH_2(CH_2)_2CH_3$), 3.4 (s, 1H, -SH; exchangeable), 4.0-4.4 (m, 4H, -NCH_2), 7.4 (s, 1H, thiazole H), 8.8 (br s, 1H, NH; exchangeable), 9.2 (m, 1H, NH; exchangeable), **20**: δ 1.2-2.1 (m, 20 H, cyclohexyl H), 3.3-3.5 (m, 3H, cyclohexyl H & -SH), 6.2 (br s, 1H, NH; exchangeable), 7.7 (s, 1H, thiazole H), 8.5 (m, 1H, NH; exchangeable), **21**: δ 3.2 (s, 1H, -SH; exchangeable), 7.2-7.8 (m, 11 H, ArH & thiazole H), 8.2 (br s, 1H, NH; exchangeable), 10.3 (m, 1H, NH; exchangeable). **22**: δ 3.4 (s, 1H, -SH; exchangeable), 6.6 (br s, 1H, NH; exchangeable), 7.2-7.4 (m, 5H, ArH & thiazole H), 7.8-8.1 (m, 4H, ArH), 9.2 (m, 1H, NH; exchangeable).

B-Antimicrobial testing

Nutrient agar plates were seeded using 0.1 ml of the diluted organisms. Cylindrical plugs were removed from the agar plate using a sterile cork borer, 100 ul of the tested compounds (1 mg/ml DMSO) and blank solvent were added to each well in triplicates. Plates of E. coli, S. aureus, B. subitilis and Ps. aeruginosa were incubated at 37 °C. While those of C. albicans and S. cerevisiae were incubated and was recorded as average diameter of the inhibition zone in mm.

C-Antitumor Screening

Fresh potato tubers were sterilized using sodium hypochlorite solution. Discs (0.5 cm thickness) were prepared in the laminar flow hood. The potato discs were then transferred to 1.5 % agar plates. Each plate contains 10 discs, three Petri dishes were used for each sample. A total of 1.0 mg of each compound was dissolved in 1.0 ml DMSO, then 0.5 ml of this solution was diluted with 1.5 ml of sterile distilled water, 2.0 ml of broth culture of A. tumfaciens strain B_6 (a 48h culture containing 5 x 10^9 cell/ml) were added to the solution aspectically. A solution of 0.5 ml DMSO, 1.5 ml sterile distilled water and 2.0 ml of A. tumefaciens was used as a control. Using disposable pipettes, one drop from each sample solution (≈ 0.05 ml) or the control was spread over the potato disc surface to be inoculated. Each plate was incubated at room temperature under dry condition for 14 days. The tumors were counted after staining with Lugol's iodine solution. Normal cell (starch containing cells) showed blue stain, while tumor cells (devoid of starch) exihibited no color. The results were expressed as positive or negative percentage inhibition of the number of tumor cells compared with the number of tumors on the control discs. Significant activity is indicated when the average of two independent assays give a consistent negative value of ca. 20% or greater inbibition.

D. Hemolytic Time Course

Samples were prepared at a concentration of 1 mg/ml in 0.9% NaCl solution (saline) and sonicated until homogeneous suspension obtained. A 100 µl solution of 1% red cells suspension was mixed with 100 µl of 1% suspension of each compound in 96-well microtiter plate. The mixture was incubated for 30 minutes at 37 °C. The hemolysis was observed at each 5 minuted up to 60 minutes and monitored against a control mixture of red cells suspension in saline solution. The hemolysis activity was

observed using a microtiter plate reader at 540 nm-background at 630 nm. The value percent hemolysis was the ratio of absorbance at 540 nm, to that caused by hypotonicity. Figure 1 shows the hemolytic time course for the tested compounds. Fresh human blood samples were obtained by vein puncture. The blood was made incoagulable by addition of isotonic sodium citrate solution. RBCs suspensions were prepared daily in buffered isotonic solution. (4 parts 0.9% NaCl + 1 part of buffer) by washing the red cells three times with buffered saline solution (centrifuged at 1500 g for 5 minutes). Sodium phosphate (0.15 M) buffer, pH 7.0 was used unless otherwise specified.

RESULTS AND DISCUSSION

All of the prepared compounds, and starting materials 1,12, were subjected to antimicrobial and antitumor screening. Compounds 7-11 and 18-22 showed no activity towards the tested microorganisms as well as against crown gall tumors. On the other hand, compounds 2-6 and 13-17 exhibited variable activities in both assays, as shown in Table 2. It was concluded that all the thiosemicarbazone derivatives showed almost poor or no activity towards Gram negative bacteria (*Ps. aeruginosa* and *E. coli*) and marginal activity against *C. albicans* and *S. cerevisiae*. The tested Gram positive bacteria in this assay, *S. aureus* and *B. subitilis*, were very sensitive to most of these thiosemicarbazones. Compounds 2,3,4,16 and 17 proved to have weak or moderate activity, while 5,6,14 and 15 exhibited very strong activity. The activity of the latter compounds were comparable to ciprofloxacine (100 µg/disc) with inhibition zones 26 and 24 mm. for S. aureus and B. subitilis respectively. The antitumor activity results were in consistent with the antimicrobial results i.e. the four potent compounds were able to inhibit ca. 20% of the crown gall tumor in two successive determinations as listed in Table 2. These results initiated another study to discolse the mechanism of action of the active compounds (5,6,14 and 15). RBCs are the site of numerous metabolic activities designed to maintain cellular intergrity and to transport oxygen and carbon dioxide. The cell membrane permeability properties control the volume of the red cell and prevent colloid osmotic hemolysis. Many drugs have been shown to possess potent hemolytic activities[27] through increasing the cell membrane permeability or diminishing the production of ATP required for active transport which may lead to colloid osmotic hemolysis[28]. So, a blood hemolysis test could be used as a measure to determine if the active compounds in this study can alter the cell membrane permeability or not. The hemolytic activity against RBCs at concentration ranged from 0.06-1.0 mg/ml was evaluated for compounds 5,6,14 and 15. Compound 6 (0.125 mg/ml) showed 50% hemolysis after 20 min. at 0.25, 0.125 and 0.25 mg/ml respectively (Figure 1). This hemolytic study revealed that compounds 5,6,14 and 15 exert their activity -most probably-through altering the cell membrane permeability.

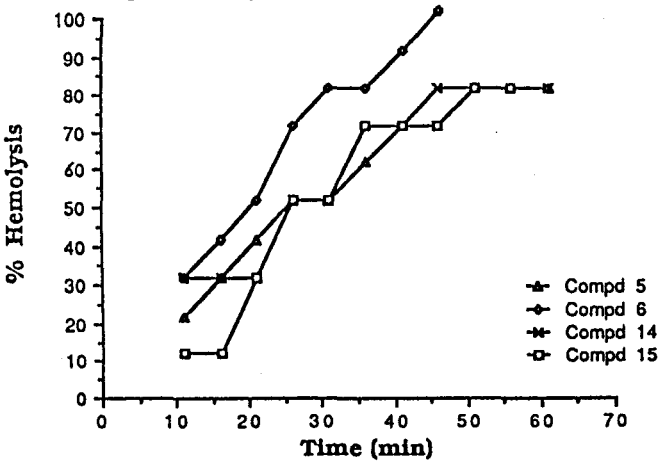
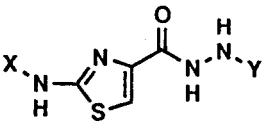


Fig. 1 Hemolytic time course for compounds 5, 6, 14 & 15.

Table 2

Antimicrobial and antitumor screening results for compounds 2-6 and 13-17.Table 1
Physicochemical properties and recrystallization solvents of the newly synthesized compounds.



No	Substitution		Antimicrobial Screening*		Antitumor testing	
		Y	S. aureus	B. subitilis	% inhibition**	Average
1	CH_3CO-	H	7	7	-7, -13	-10
2	CH_3CO-	-CSNH-C_2H_5	9	8	-15, -13	-14
3	CH_3CO-	-CSNH-n-C_4H_9	9	10	-10, -12	-11
4	CH_3CO-	-CSNH-C_6H_{11}	7	9	-8, -16	-12
5	CH_3CO-	-CSNH-C_6H_5	18	16	-18, -22	-20
6	CH_3CO-	-CSNH-*p*-FC_6H_4	26	22	-20, -24	-22
12	H	H	7	8	-4, -8	-6
13	-CSNH-C_2H_5	-CSNH-C_2H_5	9	13	-13, -11	-12
14	-CSNH-n-C_4H_9	-CSNH-n-C_4H_9	19	12	-24, -16	-20
15	-CSNH-C_6H_{11}	-CSNH-C_6H_{11}	27	29	-22, -18	-20
16	-CSNH-C_6H_5	-CSNH-C_6H_5	8	9	-6, -12	-9
17	-CSNH-*p*-FC_6H_4	-CSNH-*p*-FC_6H_4	11	10	-14, -14	-14

* Inactive (inhibition zone < 6 mm), weak activity (6-10 mm), moderate activity (11-15 mm), high activity (> 15 mm), solvent: DMSO (5 mm).

** Antitumor activity is assumed when the crown gall tumor inhibition is ca. 20% or more, calculation based on the average results of two independent determinations.

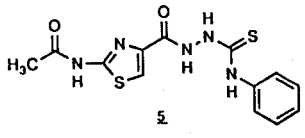
A tentative stucture-activity relatioship (SAR) could be deduced as follows:

1. An amide moiety at position 4- of the thiazole ring is essential for both antibacterial and antitumor activities. Cyclization of the active thiosemicarbazones 2-6 and 13-17 with the loss of the amide function led to the inactive 1,2,4-thriazolethiones 7-11 and 18-22.

2. -CSNH-alkyl group is essential for activity as evidenced by the conversion of the inactive hydrazides 1 and 12 into active compounds such as 5,6,14 and 15. Compound 6(-CSNH-C_6H_4-F) proved to be more active than 5 (-CSNH-C_6H_5) due to the presence of F-atom at 4-position.

3. Comparing compounds 2,3 and 4 (-CSNH-ethyl, -CSNH-butyl and -CSNH-cyclohexyl) to 5 and 6 (-CSNH-phenyl and -CSNH-p. F-phenyl) in the 2-acetamido series, implies that aromatic substitution has a significant contribution to the activity more than aliphatic substitution. This conclusion proved to be the opposite of what was found in the 2-thioureido series: i-aliphatic substitution (15,-CSNH-cyclohexyl) proved to be more active than aromatic substitution (16, -CSNH-phenyl), ii-the activity increases as the number of carbon of the alkyl group increases (cyclohexyl > butyl > ethyl : 15 > 14 > 13).

4. The substitution at 2-position (acetamido or thioureido) showed no great difference in activity, which suggests that they act as an anchoring group to help the active moiety (4-amido function) in attacking the active site or enzyme(s) involved.



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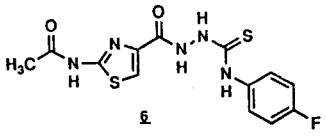

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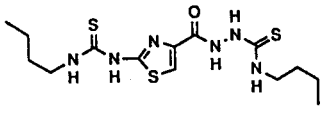

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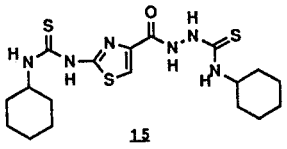

15

The overall results indicated that compounds 6 and 15 deserve further in-vivo and preclinical investigations as antitumor Gram positive antibacterial agents.

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