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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW TRIAZOLE AND THIADIAZOLE DERIVATIVES OF 4(3*H*)-QUINAZOLINONES

4(3H)-KİNAZOLİNONLARIN YENİ TRİAZOL VE TİYADİAZOL TÜREVLERİNİN SENTEZİ VE ANTİMİKROBİYAL ETKİLERİ

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In order to test their antimicrobial activity new 3-[(3 - ethyl - 4 (3H) - quinazolinon - 2 - yl) mercapto-methyl]-4-alkyl/aryl-1,2,4-triazoline-5-thiones and 2-[(3-ethyl-4(3H)-quinazolinon-2-yl)mercaptomethyl] -5-alkyl/arylamino-1,3,4-thiadiazoles were synthesized from the reaction of 1-[(3-ethyl-4(3H)-quinazolinon-2-yl) mercaptoacetyl]-4-alkyl/arylthiosemicarbazides with 10% Na_2CO_3 solution and conc. H_2SO_4, respectively. Analytical and spectral data (IR, ^{1}H-NMR, EIMS) confirmed the proposed structures. The synthesized compounds were tested for in vitro antibacterial activity against Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeroginosa ATCC 1539, Salmonella typhi, Shigella flexneri and proteus mirabilis using the disc diffusion method and for in vitro antifungal activity Trichophyton rubrum, Microsporum canis and Microsporum gypseum NCPF 580 using the microdilution method. All the compounds were inactive against tested bacteria whereas all compounds showed varying degrees of inhibition against tested fungi.

Keywords :*4(3H)-Quinazolinone; 1,2,4-Triazoline-5-thione; 1,3,4-Thiadiazole; Antimicrobial activity*

Antimikrobiyal etkilerini araştırmak için yeni 3-[(3-etil-4(3H)-kinozolinon-2-il)merkaptometil]-4-alkil /aril - 1,2,4 - triazolin - 5 -tiyonlar ve 2-[(3-etil-4 (3H)-kinazolinon-2-il)merkaptometil]-5-alkil/arilamino -1,3,4 -tiyadiazoller 1 - [(3 - etil - 4 - (3H) -kinazolinon - 2 - il) merkaptoasetil] - 4 - alkil /ariltiyosemikarbazidlerin sırasıyla %10 Na_2CO_3 çözeltisi ve der. H_2SO_4 ile reaksiyonundan sentezlenmiştir. Analitik ve spektral veriler (IR, ^{1}H-NMR, EIMS) amaçlanan yapıları doğrulamıştır. Sentez edilen bileşikler disk difüzyon yöntemi kullanılarak Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 4352, Pseudomonas aerognosa ATCC 1539, Salmonella typhi, Shigella flexneri ve Proteus mirabilis'e karşı in vitro antibakteriyel etkileri ve mikrodilüsyon yöntemi kullanılarak Trichophyton rubrum, Microsporum canis ve Microsporum gypseum NCPF 580'e karşı in vitro antifungal etkileri araştırılmıştır. Tüm bileşikler araştırılan bakterilere karşı inaktiftir, oysa tüm bileşikler araştırılan mantarlara karşı değişen derecelerde inhibisyon göstermiştir.

Anahtar kelimeler: *4(3H) - Kinazolinon; 1, 2,4 - Triazolin-5-tiyon; 1,3,4-Tiyadiazol; Antimikrobiyal etki*

Introduction

The derivatives incorporating the 4(3*H*)-quinazolinone ring system are interesting compounds due to their biological properties. A large spectrum of pharmacological activity is reported for these ligands. The sedative-hypnotic drugs methaqualon and mecloqualone, diuretics phenquizone and quinatozone are currently being used in therapy. Moreover, there have been several reports on the antibacterial and antifungal activity of 4(3*H*)-quinazolinone thiosemicarbazides and their cyclized products (1,2). Antimycobacterial activity has been demonstrated for some 1,2,4-triazoline-5-thiones (3) and 1,3,4-thiadiazoles (4). Based on these findings, some new 3 - [(3 - ethyl-4(3*H*)-quinazolinon - 2 - yl) mercaptomethyl] -4 -alkyl/aryl-12,4-triazoline-5-thiones **2a-j** and 2 - [(3 - ethyl - 4 (3*H*) - quinazolinon - 2 - yl) mercoptomethyl] - 5 - alkyl/arylamino-1,3,4-thiadiazoles 3a-e were synthesized and tested for antimicrobial activity against bacteria and fungi.

Materials and Methods

a.Chemistry

Melting points were estimated with a Büchi 530 melting point apparatus (Flawil, Switzerland) in open capillaries and were uncorrected. IR spectra were recorded on KBr discs, using a Perkin-Elmer Model 1600 FT-IR spectrometer (Norwalk, Connecticut, USA). ^{1}H-NMR spectra were obtained on Bruker AC200 (200 MHz) (Rheinstatten, Germany) spectrophotometer using

[D_6]DMSO or $CDCl_3$. EIMS were determined on a VG Zab Spec (70 eV) mass spectrometer (Manschester, England). Starting materials were purchased from E. Merck (Darmstadt, Germany).

3 - [(3 - Ethyl - 4 (3H) - quinazolinon - 2 - yl)mercaptomethyl]-4-alkyl/aryl-1,2,4-triazoline-5-thiones **2a-j**

To a solution of 1 (0.0025 mol) in 25 ml of C_2H_5OH, 25 ml of Na_2CO_3 solution (10%) was added. The mixture was refluxed for 3 h and after cooling was neutralized with CH_3COOH (10%). The precipitate formed was recrystallized from ethanol.

Spetral data of **2a**; IR [υ, cm^{-1}, KBr]:3406 (NH), 1670 (C=O), 1245 (C=S). ^{1}H-NMR [200 MHz, [D_6]DMSO]: δ =1.28 (3H, t, J:7.1 Hz, $NCH_2C\underline{H}_3$);3.60 (3H, s, $N\text{-}CH_3$); 4.10 (2H, q, J:7.1 Hz, $NC\underline{H}_2CH_3$); 4.69 (2H, s, SCH_2); 7.47 (1H, t, J:7.5 Hz, quin. 6-H); 7.51 (1H, d, J:8.1 Hz, quin. 8-H); 7.80 (1H, t, J:7.7 Hz, quin. 7-H); 8.07 (1H, dd, J: 7.9, 1.2 Hz, quin. 5-H); 13.57 (1H, s, NH). EI (70 eV) [m/z (rel.int. %)]: 333 (M^+, 100), 205 (99), 173(24), 162(52), 146(61), 128(34), 119(47).

Spetral data of **2e**; IR [υ, cm^{-1}, KBr]:3454 (NH), 1660 (C=O), 1245 (C=S). ^{1}H-NMR [200 MHz, [D_6]DMSO]: δ =1.21-1.81 (10H, m, cyclohex.);1.29(3H, t, J:7.0 Hz, $NCH_2C\underline{H}_3$); 4.12 (H, q, J:7.0 Hz, $NC\underline{H}_2CH_3$); 4.55 (1H, br. s, cyclohex. 1-H); 4.84 (2H, s, SCH_2); 7.48 (1H, t, J:7.6 Hz, quin. 6-H); 7.50 (1H, d, J:6.9 Hz, quin. 8-H); 7.81 (1H, t, J: 7.9 Hz, quin. 7-H); 8.09 (1H, d, J:7.8 Hz, quin. 5-H); 13.65 (1H, s, NH). EI (70 eV) [m/z (rel.int. %)]: 401 (M^+, 56), 205 (100), 196(10), 173(18), 162(37), 146(29), 119(37).

Spetral data of **2h**; IR [υ, cm^{-1}, KBr]:3447 (NH), 1682 (C=O), 1241 (C=S). ^{1}H-NMR [200 MHz, [D_6]DMSO]: δ =1.22 (3H, t, J:7.0 Hz, $NCH_2C\underline{H}_3$);4.00 (2H, q, J:7.1 Hz, $NC\underline{H}_2CH_3$); 4.60 (2H, s, SCH_2); 7.33-7.56 (6H, m, 4-C_6H_4Cl, quin. 6-H and quin. 8-H); 7.79 (1H, t, J:6.9 Hz, quin. 7-H); 8.05 (1H, dd, J:8.0, 1.0 Hz, quin. 5-H); 13.91 (1H, s,NH). EI (70 eV) [m/z (rel.int. %)]: 429 (M^+, 3 (431, 1)], 224[7(226, 4)], 205(30), 173(12), 162(17), 146(21), 119(44), 55(100).

Spetral data of **2j**; IR [υ, cm^{-1}, KBr]:3447 (NH), 1684 (C=O), 1242 (C=S). ^{1}H-NMR [200 MHz, [D_6]DMSO]: δ =1.13 (3H, t, J:7.0 Hz, $NCH_2C\underline{H}_3$); 1.98 (3H, s, 4-$C_6H_4C\underline{H}_3$); 3.90 (2H, q, J:7.1 Hz, $NC\underline{H}_2CH_3$); 4.49 (2H, s,SCH_2); 7.07 (2H, d, J:8.2 Hz, 4-$C_6H_4C\underline{H}_3$ 2-H); 7.22 (2H, d, J:8.3 Hz, 4-$C_6H_4C\underline{H}_3$ 3-H); 7.25 (1H, d, J:8.4 Hz, quin.8-H); 7.39 (1H, t, J:7.4 Hz, quin. 6-H); 7.70 (1H, t, J:7.7 Hz, quin. 7-H); 7.95 (1H, dd, J:7.6, 1.3 Hz, quin. 5-H); 1374 (1H, s, NH). EI (70 eV) [m/z (rel.int. %)]: 409 (M^+, 98), 205(100), 204 (46), 173(22), 162(45), 146 (42), 119(43).

2-[(3-Ethyl-4(3H)-quinazolinon-2-yl)mercaptomethyl] -5-alkyl/arylamino-1,3,4-thiadiazoles ***3a-e***

1 (0.0025 mol) was added portionwise to H_2SO_4 (96 %)(5.3 ml) cooled in an ice bath with constant stirring. After dissolution, the reaction mixture was further agitated for 30 min. at room temperature, poured over crushed ice and neutralized by saturated Na_2CO_3 solution. The precipitate thus obtained was washed with water and recrystalized from ethanol.

Spectral data of **3a**; IR [υ, cm^{-1}, KBr]:3447 (NH), 1687 (C=O). ^{1}H-NMR (200 MHz, [D_6]DMSO]: δ =1.25 (3H, t, J:7.0 Hz, $NCH_2C\underline{H}_3$);4.05 (2H, q, J:7.2 Hz, NCH_2CH_3); 4.83 (2H, s, SCH_2); 7.43-7.58 (5H, m, 4-C_6H_4Br and quin. 6-H); 7.66 (1H, d, J:8.2 Hz, quin. 8-H); 7.84 (1H, t, J:6.9 Hz, quin. 7-H); 8.10 (1H, d, J: 8.0, 1.0 Hz, quin. 5-H); 10.36 (1H, s, NH). EI (70 eV) [m/z (rel.int. %)]:473 (M^+, 19 (475,20)], 268 [11(270, 10)], 205 (58), 173(11), 162(35), 146(39), 119(52), 58(100).

Spectral data of **3b**; IR [υ, cm^{-1}, KBr]:3465 (NH), 1678 (C=O). ^{1}H-NMR (200 MHz, [$CDCl_3$]: δ =1.30 (3H, t, J:7.1 Hz, $NCH_2C\underline{H}_3$);4.08 (2H, q, J:6.9 Hz, $NC\underline{H}_2CH_3$); 4.83 (2H, s, SCH_2); 7.15 (2H, d, J:8.4 Hz, 4-C_6H_4Cl 2-H) 7.39 (1H, t, J:7.4 Hz, quin. 6-H); 7.53 (2H, d, J:8.3 Hz, 4-C_6H_4Cl 3-H); 7.62 (1H, d, J: 8.1 Hz, quin. 8-H); 7.67 (1H, t, J:7.2 Hz, quin. 7-H); 8.13 (1H, d, J:7.9 Hz, quin. 5-H); 9.95 (1H, s, NH).. EI (70 eV) [m/z (rel.int. %)]:429 (M^+, 23 (431,11)], 224 [11(226, 6)], 206 (100), 205(82), 173(33), 162(39), 146(32), 119(59).

Spectral data of **3b**; IR [υ, cm^{-1}, KBr]:3465 (NH), 1678 (C=O). ^{1}H-NMR (200 MHz, [$CDCl_3$]: δ =1.30 (3H, t, J:7.1 Hz, $NCH_2C\underline{H}_3$);4.08 (2H, q, J:6.9 Hz, $NC\underline{H}_2CH_3$); 4.83 (2H, s, SCH_2); 7.15 (2H, d, J:8.4 Hz, 4-C_6H_4Cl 2-H) 7.39 (1H, t, J:7.4 Hz, quin. 6-H); 7.53 (2H, d, J:8.3 Hz, 4-C_6H_4Cl 3-H); 7.62 (1H, d, J: 8.1 Hz, quin. 8-H); 7.67 (1H, t, J:7.2 Hz, quin. 7-H); 8.13 (1H, d, J:7.9 Hz, quin. 5-H); 9.95 (1H, s, NH).. EI (70 eV) [m/z (rel.int. %)]:429 (M^+, 23 (431,11)], 224 [11(226, 6)], 206 (100), 205(82), 173(33), 162(39), 146(32), 119(59).

Spectral data of **3b**; IR [υ, cm^{-1}, KBr]:3447 (NH), 1685 (C=O). ^{1}H-NMR (200 MHz, [D_6] DMSO]: δ =1.27 (3H, t, J:7.1 Hz, $NCH_2C\underline{H}_3$); 2.50 (3H, s, 4-$C_6H_4C\underline{H}_3$); 4.08 (2H, q, J:6.9 Hz, $NC\underline{H}_2CH_3$); 4.83 (2H, s, SCH_2) 7.11 (2H, d, J:8.1 Hz, 4-C_6H_4 $C\underline{H}_3$ 2-H); 7.46 (2H, d, J:8.2 Hz, 4-$C_6H_4CH_3$ 3-H); 7.51 (1H, t, J: 7.5 Hz, quin. 6-H); 7.69 (1H, d, J:8.2 Hz, quin. 8-H); 7.87 (1H, t, J:7.4 Hz, quin. 7-H); 8.13 (1H, d,J:7.9 Hz, quin. 5-H); 10.09 (1H, s, NH). EI (70 eV) [m/z (rel.int. %)]:409 (M^+, 93), 205 (100), 204 (65), 173(10), 162(33), 146(31), 119(41).

b.Microbiology

Antibacterial Activity

Disc diffusion method was used for antimicrobial activity. The cultures of bacteria were prepared in 4 ml Mueller-Hinton Broth (Buyyon) at 37°C. After 24 h incubation, the turbidity of culture suspension was adjusted with sterile Mueller-Hinton Broth in order to obtain a turbidity comparable to a No 1 Mc Farland turbidity standard. One milliliter of this suspension was pipetted onto the Mueller-Hinton Agar (Difco) plate and distributed evenly over the surface of the medium by gently rocking the plate. Excess suspension was pipetted off. The surface of the medium was allowed to dry for 15 min at room temperature. The 160 µg compound impregnated disks 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 the diameter of the zone of inhibition was measured.

Antifungal Activity

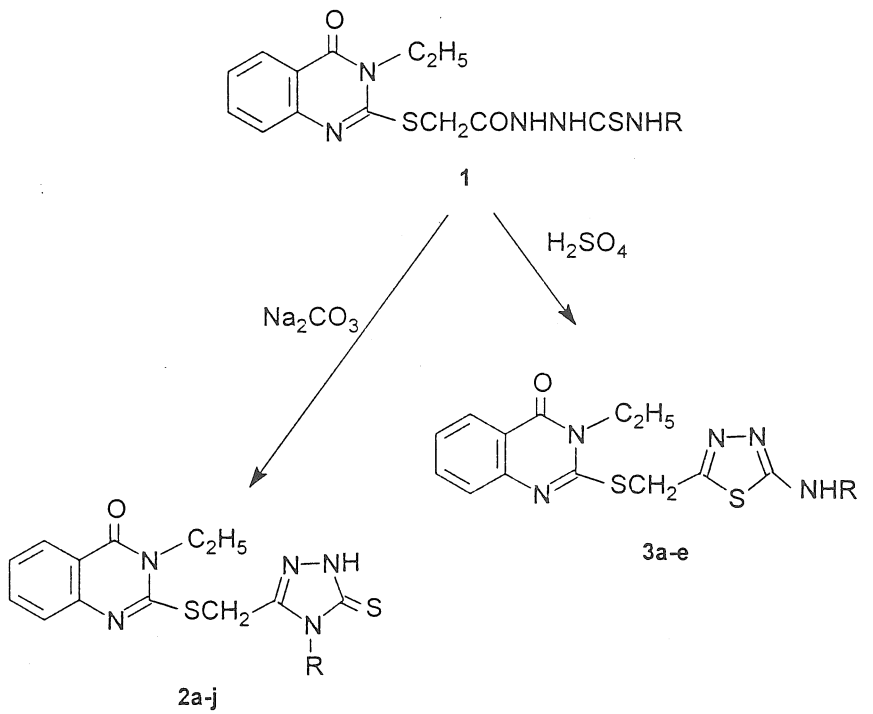
All the compounds to be tested were dissolved in DMSO at a concentration 4000 µg/ml and the final concentration was reduced to 200 µg/ml with sterile distilled water. No effect of DMSO (5%) was observed upon growth of dermatophytes. The dermatophyte strains which were grown on slant medium of Sabouraud (Difco) were transferred to 3.5 ml nutrient broth (NB, Diagnostic Pasteur) and incubated for three to five days at 25°C. At the end of the incubation period these strains were transferred into screwcapped bottles containing sterilized beads and shaken for 4-5 min in a vortex (IKA-VF, Germany). The suspensions of the cultures were adjusted to have an absorbance degree of 0.6 at 450 nm in the spectrophotometer. Eight different dilutions between 25-0.2 µg/ml were prepared in microplates by serial dilutions from top to bottom. Then all the wells except the 12th wells (positive control) were filled with 10 ml of the standardized strains. These plates were incubated at 25°C for five ofr six days.

The minimum concentration at which no growth was observed was taken as the MIC value. It should be noted, however, that these techniques leave a variable number of broken hyphae and therefore even an identical optical density of such hyphal suspensions could lead to a considerable variation in the number of viable cells; this would obviously prevent proper standardization of the inoculum.

Results and Discussion

To prepare the title compounds, we started with 1 - [(3 - ethyl - 4 (3*H*) - quinazolinon-2-yl)mercaptoacetyl]-4-alkyl/arylthiosemicarbazides **1a-k** synthesized as described previously (5,6). As it is well known cyclodehydration of 1-acyl or 1-aroyl-3-thiosemicarbazides in the presence of a strong base or a strong mineral acid leads to 1,2,4-triazoline-5-thiones or 2-amino-1,3,4-thiadiazoles. Reaction of **1** with 10% Na_2CO_3 solution in ethanol and conc. H_2SO_4 at 0-4°C afforded the triazole derivatives **2a-j** and thiadiazole derivatives **3a-e**, respectively (Scheme 1 and Table 1). The structures of new products were confirmed by analytical and spectral data (IR, ^{1}H-NMR, EIMS).

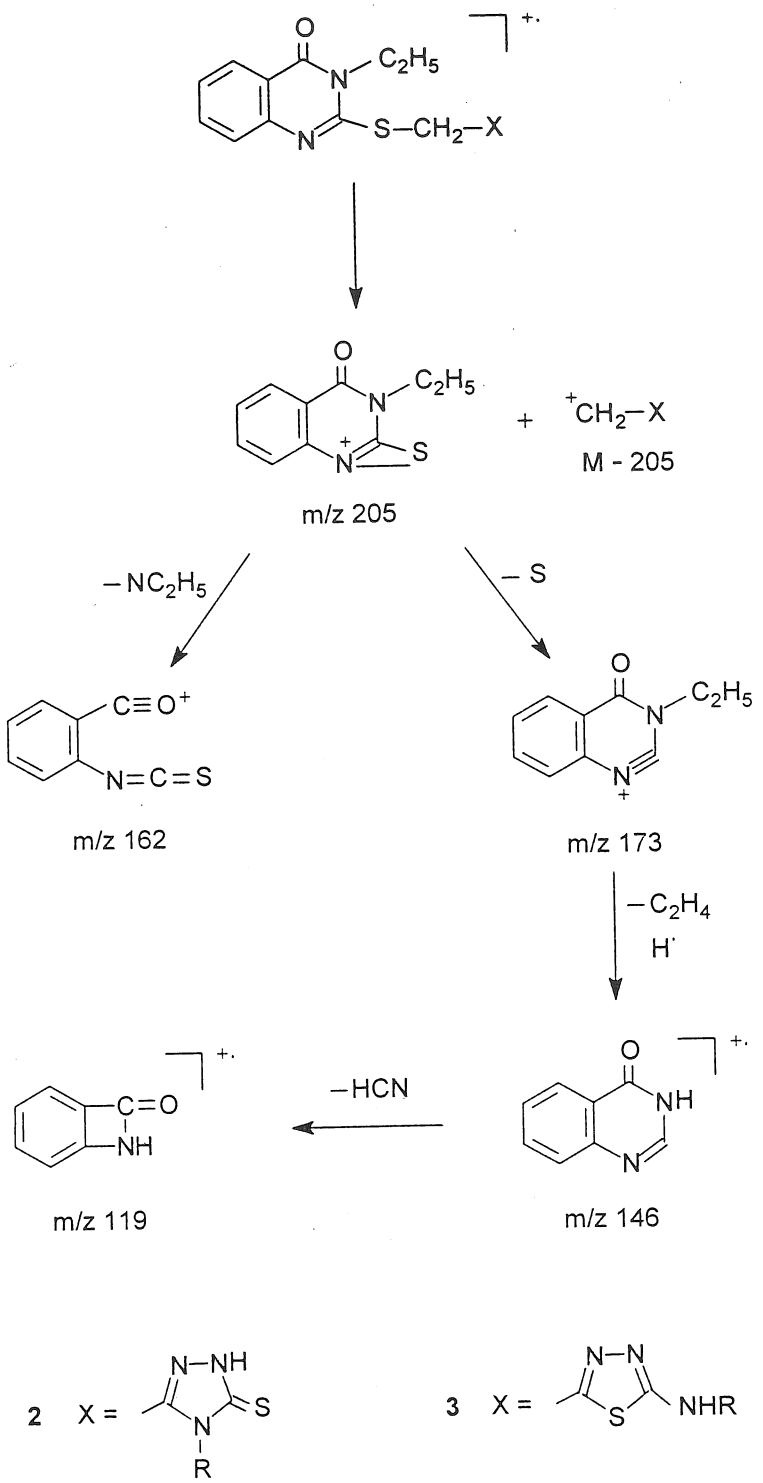
In the IR spectra absence of the thiosemicarbazide C=O stretchings and in the ^{1}H-NMR spectra absence of resonances assigned to the N_1-H and N_2-H signals of the thiosemicarbazides provided confirmatory evidence for triazole and thiadiazole of formation. The tautomerism encountered in 1,2,4-triazoline-5-thiones attracted our interest like that of previous researchers and the thione-thiole tautomerism which concerns the sulphur atom at five position of **2a-j** was investigated. Absence of absorption bands



Scheme 1

Table 1. Physical constants of **2a-j** and **3a-e**

Comp.	R	Yield (%)	m.p. °C	Formula (M.W.)	Analysis (calc./found)		
					C	H	N
2a	CH_3	81	185-8	$C_{14}H_{15}N_5OS_2.H_2O$ (351.45)	47.84 47.64	4.87 5.04	19.92 19.36
2b	C_2H_5	71	182-7	$C_{15}H_{17}N_5OS_2.½H_2O$ (356.47)	50.54 49.95	5.08 5.25	19.64 18.92
2c	CH_2-CH=CH_2	75	172	$C_{16}H_{17}N_5OS_2.½H_2O$ (368.48)	52.15 51.52	4.92 5.37	19.00 18.96
2d	n-C_3H_7	70	178-9	$C_{16}H_{19}N_5OS_2$ (361.49)	53.16 53.06	5.29 5.62	19.37 19.45
2e	cycl-C_6H_{11}	64	230-3	$C_{19}H_{23}N_5OS_2$ (401.55)	56.83 56.43	5.77 6.14	17.44 17.78
2f	C_6H_5	74	220-1	$C_{19}H_{17}N_5OS_2$ (395.51)	57.70 58.20	4.33 4.48	17.70 17.67
2g	4-C_6H_4Br	87	201-4	$C_{19}H_{16}BrN_5OS_2$ (474.41)	48.10 47.97	3.40 3.49	14.76 14.59
2h	4-C_6H_4Cl	65	204-5	$C_{19}H_{16}ClN_5OS_2$ (429.95)	53.07 53.14	3.75 3.79	16.29 15.90
2i	4-C_6H_4F	56	209-13	$C_{19}H_{16}FN_5OS_2$ (413.50)	55.18 54.97	3.90 3.87	16.93 16.55
2j	4-$C_6H_4CH_3$	80	195-6	$C_{20}H_{19}N_5OS_2$ (409.53)	58.65 58.52	4.67 4.87	17.10 17.05
3a	4-C_6H_4Br	92	213-5	$C_{19}H_{16}BrN_5OS_2$ (474.41)	48.10 47.85	3.40 3.59	14.76 14.92
3b	4-C_6H_4Cl	85	220-3	$C_{19}H_{16}ClN_5OS_2$ (429.95)	53.07 52.96	3.75 4.05	16.29 16.32
3c	4-C_6H_4F	99	212-5	$C_{19}H_{16}FN_5OS_2$ (413.50)	55.18 55.55	3.90 3.80	16.93 16.97
3d	4-$C_6H_4CH_3$	79	199-201	$C_{20}H_{19}N_5OS_2$ (409.53)	58.65 59.04	4.67 4.75	17.10 17.31
3e	4-$C_6H_4NO_2$	89	246-7	$C_{19}H_{16}N_6O_3S_2.½H_2O$ (449.50)	50.76 50.75	3.81 3.37	18.69 18.24



Scheme 2

and signals of the SH group in the IR and ^{1}H-NMR spectra and presence of bands in the 1248-1210 cm^{-1} region of the C=S group in the IR spectra proved that the compounds were in thione from in the solid state (7). Furthermore, in the IR spectra of **2** and **3** the NH and lactam C=O bands were observed in the 3474-3222 cm^{-1} and 1688-1642 cm^{-1} regions, respectively (8,9). In the ^{1}H-NMR spectra of 2 and 3 SCH_2 protons resonated as singlets in the δ 4.60-4.84 ppm region (10), the NH signals appeared at δ 13.57-13.91 ppm in 2 and δ 9.95-10.36 ppm in **3** as singlets, respectively(11). EIMS of **2** and **3** displayed a common fragmentation route. In this route, m/z 205 and M-205 fragments were formed by the cleavage of the SCH_2 bond and confirmed the structures of **2** and **3** (Scheme 2) (5, 12, 13).

2a-j and **3a-d** were evaluated for in vitro antibacterial activity against *Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeroginosa ATCC 1539, Salmonella typhi, Shigella flexneri* and *Proteus mirabilis* using the disc diffusion method (14). The preliminary results indicated that all of the tested compounds were inactive against the test organisms. Antifungal activites were investigated against *Trichophyton rubrum, Microsporum canis* and *Microsporum gypseum* NCPF 580 using the microdilution method and compared with that of ketoconazole (15). As can be seen in Table 2 **2d**, **2h** and **2i** showed inhibition against *Tricophyton rubrum* at a concentration of 12.5 μg/ml while **2g** exhibited inhibition against *Microsporum canis* at the same concentration. The preliminary antifungal screening results indicated that 1,2,4-triazoline-5-thiones were generally more effective than 1,3,4-thiadiazoles against the tested fungi and that among 1,2,4-triazoline-5-thiones the most effective compounds were the compounds having propyl and halogenated phenyl function at the 4-position.

Table 2. MIC values (mg/ml) of **2a-j** and **3a-d**

Compound	Fungi*		
	A	B	C
2a	25	25	25
2b	25	25	25
2c	25	25	25
2d	12.5	25	25
2e	25	25	25
2f	25	25	25
2g	25	12.5	25
2h	12.5	25	25
2i	12.5	25	25
2j	25	25	25
3a	25	25	25
3b	25	25	25
3c	25	25	25
3d	25	25	25
ketoconazole	0.4	1.6	1.8

* A=*Tricophyton rubrum*, B=*Microsporum canis*, C=*Microsporum gypseum* NCPF-580

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