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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL IMIDAZOLYLMERCAPTOACETYLTHIOSEMICARBAZIDE AND 4-THIAZOLIDINONE ANALOGS

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Abstract

In this study, new imidazolylmercaptoacetylthiosemicarbazides were synthesized from the reaction of (4,5-diphenyl-1H-imidazole-2-yl) mercaptoacetic acid hydrazide with appropriate alkyl/aryl isothiocyanates in absolute ethanol. From the cyclization of thiosemicarbazide derivatives with ethyl bromo acetate, 4-thiazolidinone derivatives were obtained. Analytical and spectral data (IR, NMR, EIMS) confirmed the proposed structures. The synthesized compounds were tested for in vitro antimicrobial activity using the disc diffusion method. None of the compound showed significant activity against the selected microorganism.

Key words: *Imidazolylmercaptoacetylthiosemicarbazides; 4-Thiazolidinones; Antimicrobial activity*

Yeni İmidazolilmerkaptoasetiltiyosemikarbazid ve 4-tiyazolidinon analoglarının sentez ve antimikrobiyal etkilerinin incelenmesi

Bu çalışmada, (4,5-difenil-1H-imidazol-2-il)merkaptoasetik asid hidrazid'inin uygun alkil/aril izotiyosiyanatlarla absolü etanollü ortamda reaksiyonundan yeni imidazolilmerkaptoasetil tiyosemikarbazidler sentezlenmiştir. Tiyosemikarbazid türevlerinin etil bromo asetat ile siklizasyonu sonucu 4-tiyazolidinon türevleri elde edilmiştir. Analitik ve spektral veriler (IR, NMR, EIMS) amaçlanan yapıları doğrulamıştır. Sentezlenen bileşiklerin disk difüzyon yöntemi kullanılarak in vitro antimikrobiyel etkileri araştırılmıştır. Maddelerin hiçbiri seçili mikroorganizmalara karşı belirgin bir etki göstermemiştir.

Anahtar kelimeler: *Imidazolilmerkaptoasetiltiyosemikarbazidler; 4-Tiyazolidinonlar; Antimikrobiyel aktivite*

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INTRODUCTION

Resistance of pathogenic bacteria to available antibiotics is quickly becoming a major problem in the community and hospital based healthcare settings. The search for novel agents to combat resistant bacteria has become one of the most important areas of antibacterial research today. (1). Recently reported that substituted thiazolidinones inhibit the MurB enzyme, integral component in bacterial peptidoglycan biosynthesis, at the low micromolar level (Figure 1.) (2,3). Mercaptoimidazole derivatives have also been reported to show bactericidal and fungucidal activity (4,5).

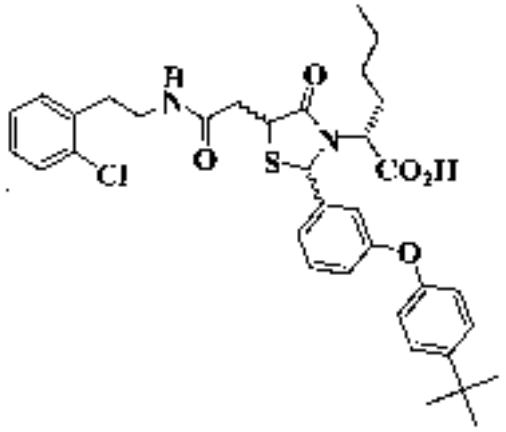


Figure 1. Structure of MurB enzyme inhibitor (IC_{50}=12 μM)

In view of the above considerations and in continuation of our previous work on imidazoles, thiosemicarbazides and thiazolidinones of pharmaceutical interest (6,7), we report here on the synthesis, characterization and antimicrobial evaluation of new 1-(4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetyl-4-alkyl/aryl-3-thiosemicarbazides (**5-10**) and 2-[(4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetyl]hydrazone-3-alkyl/aryl-4-thiazolidinones (**11-15**) derivatives featuring a imidazole nucleus.

EXPERIMENTAL

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. Elemental analyses were performed on Carlo Erba 1106 elemental analyzers (Milan, Italy). IR (KBr) and ^{1}H-NMR (DMSO-d_6, $CDCl_3$) spectra were run on Perkin Elmer 1600 FT-IR (Norwalk, CT, USA) and Bruker AC 200 (200 MHz) instruments (Rheinstetten, Germany), respectively. EIMS (70 eV) were recorded on VG Zab Spec (Manchester, England).

*1-(4,5-diphenyl-1H-imidazole-2-yl)mercaptoacetyl-4-alkyl/aryl-3-thiosemicarbazides (**5-10**)*

A mixture of **4** (5 mmol) in absolute ethanol (20 ml) and an appropriately substituted isothiocyanate (5 mmol) were refluxed for 3-4 h. The prepicitate that formed after cooling was collected by filtration and recrystalyzed from ethanol.

*2-[(4,5-diphenyl-1H-imidazole-2-yl)mercaptoacetyl]hydrazone-3-alkyl/aryl-4-thiazolidinones (**11-15**)*

To a suspension of thiosemicarbazides (5 mmol) in 50 ml absolute ethanol, ethyl bromoacetate (5.5 mmol) and anhydrous sodium acetate (20 mmol) were added. The reaction mixture was refluxed on a water bath for 3h, cooled, poured over crushed ice and allowed to stand overnight. The precipitate obtained was filtered and recrystallized from ethanol.

Antimicrobial activity

Disk diffusion method was used for antimicrobial activity [8]. The cultures of bacteria were prepared in 4 ml Mueller-Hinton Broth (Difco) 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 rocki0ng the plate. Excess suspension was pipetted off. The surface of the medium was allowed to dry for 15 min at room temperature. The 200 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 inhibition zone was measured.

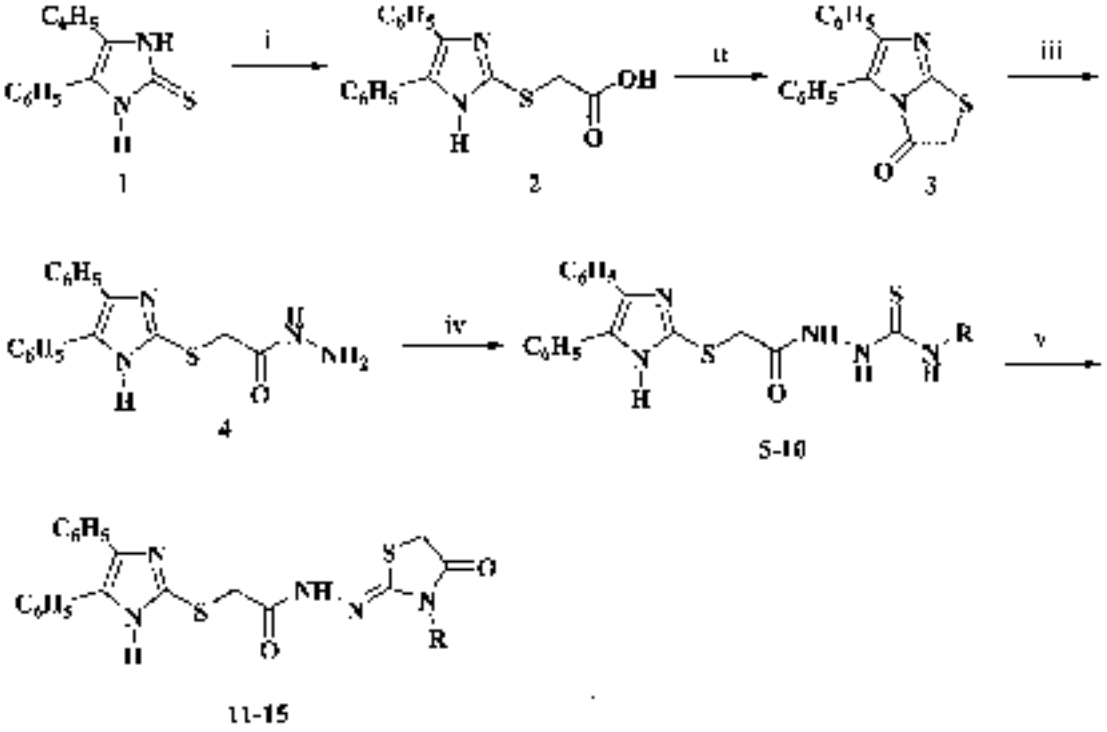
RESULT AND DISCUSSION

Chemistry

The synthesis of the new compounds was carried out as outlined in Scheme 1. The starting compounds **1-4** were prepared according to the literature methods. Thus 4,5-diphenyl-1*H*,3*H*-imidazole-2-thione **1** (9) was reacted with chloroacetic acid in alkaline medium to afford (4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetic acid **2** (6). Treatment of **2** with acetic anhydride gave 5,6-diphenylimidazo[2,1-b]thiazole-3-one **3** (10). This compound was reacted with hydrazine hydrate in boiling ethanol to furnish (4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetic acid hydrazide **4** (11). Compound **4** reacted with appropriate alkyl/aryl isothiocyanates in ethanol to give thiosemicarbazides **5-10**. Thiosemicarbazide derivatives were cyclized with ethyl bromoacetate in the presence of anhydrous sodium acetate to yield the corresponding 4-thiazolidinone derivatives **11-15**. Some characteristics and spectral data of the compounds are presented in Table 1 and 2.

The IR spectra of compounds **5-10** displayed the imidazole, amide and thioamide NH bands about 3336-3264 and 3267-3151 cm^{-1} region. The amide C=O and the thioamide C=S streching bands of the same compounds were observed at about 1684-1677 cm^{-1} and 1202-1186 cm^{-1}, respectively (7).

Thiazolidinone derivatives **11-15** displayed the imidazole and amide NH bands about 3471-3291 and 3193-3160 cm^{-1}. The exocyclic amide C=O absorbed in the 1689-1670 cm^{-1} region (12-14). Additional C=O absorptions in the 1734-1703 cm^{-1} region which were characteristic for thiazolidinones further confirmed cyclization to the expected structures.



Scheme 1. i) NaOH, EtOH, $ClCH_2COOH$, 3h; ii) $(CH_3CO)_2O$, 1h; iii) $NH_2NH_2.H_2O$, EtOH; iv) RNCS, EtOH, 3-4h; v) $BrCH_2COOEt$, abs. EtOH, 3h.

Table 1. Physical data of compounds **5-15**

Comp.	R	Formula (M.W.)	Yield %	Mp ºC	Analysis Calcd./Found C	H	N
5	CH_2-CH=CH_2	$C_{21}H_{21}N_5OS_2$ (423.56)	78	201-3	59.55 59.65	4.99 5.10	16.53 16.86
6	C_6H_{11}	$C_{24}H_{27}N_5OS_2.C_2H_5OH$ (511.70)	87	193	61.02 61.00	6.49 6.72	13.68 14.12
7	4-$CH_3C_6H_4$	$C_{25}H_{23}N_5OS_2.C_2H_5OH$ (519.68)	93	198	62.40 61.88	5.62 5.46	13.48 13.47
8	4-ClC_6H_4	$C_{24}H_{20}ClN_5OS_2.C_2H_5OH$ (540.10)	89	192	57.82 57.70	4.85 4.96	12.96 13.05
9	4-FC_6H_4	$C_{24}H_{20}FN_5OS_2.C_2H_5OH$ (523.65)	79	174	59.63 59.31	5.00 5.13	13.37 13.53
10	4-$NO_2C_6H_4$	$C_{24}H_{20}N_6O_3S_2.C_2H_5OH$ (550.65)	99	158	56.71 56.58	4.76 4.64	15.26 14.93
11	C_2H_5	$C_{22}H_{21}N_5O_2S_2$ (451.57)	69	186	58.51 58.26	4.68 4.74	15.51 15.00
12	CH_2-CH=CH_2	$C_{23}H_{21}N_5O_2S_2$ (463.58)	95	114	59.59 59.00	4.56 4.81	15.10 15.11
13	C_6H_5	$C_{26}H_{21}N_5O_2S_2.½C_2H_5OH$ (522.64)	84	192	62.05 61.45	4.62 4.64	13.40 13.77
14	4-ClC_6H_4	$C_{26}H_{20}ClN_5O_2S_2.C_2H_5OH$ (580.12)	80	170	57.97 57.50	4.52 4.26	12.07 11.96
15	4-FC_6H_4	$C_{26}H_{20}FN_5O_2S_2.H_2O$ (535.62)	97	193	58.30 59.52	4.14 4.10	13.08 13.20

Table 2. Spectral data of the compounds

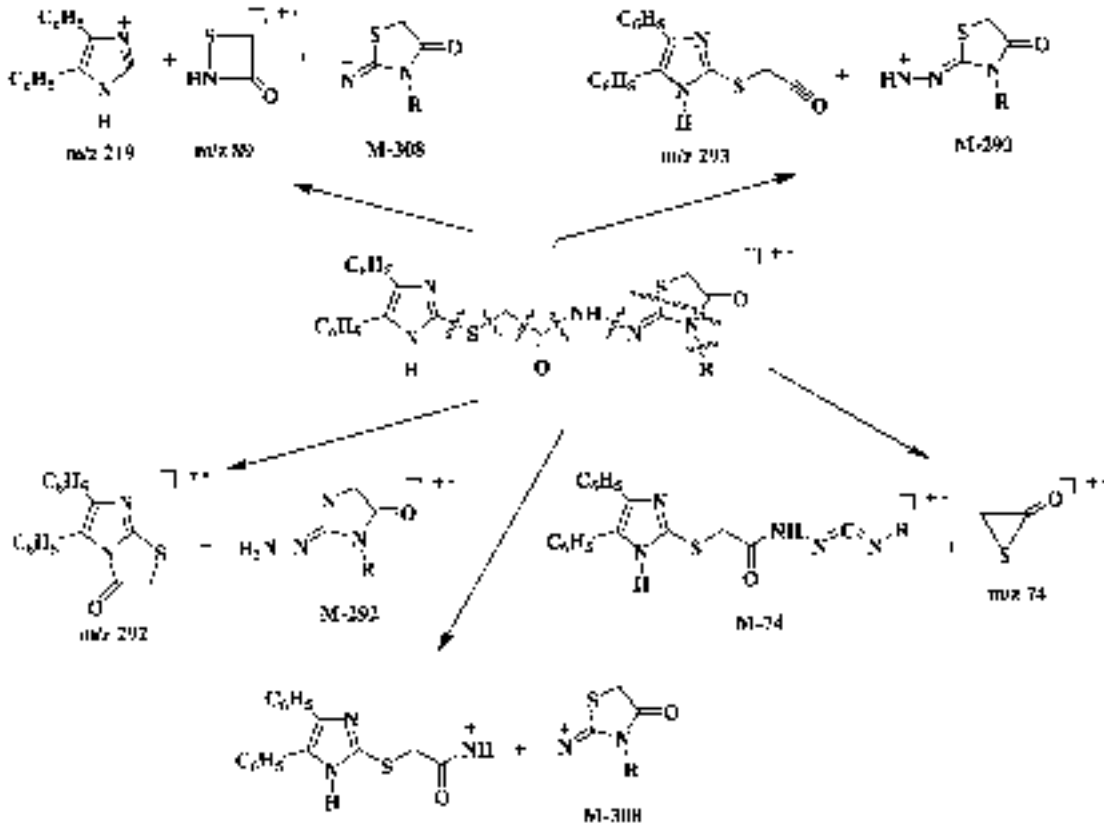
Comp.	IR ν cm^{-1}	^{1}H-NMR δ (ppm)
5	3336, 3267 (N-H) 1677 (C=O)	(DMSO-d_6+$CDCl_3$, 400 MHz): 12.40 (s, 1H, imidazole NH); 10.35 (s, 1H, CONH); 9.05 (s, 1H, NH); 7.96 (s, 1H, N<u>H</u>CH_2); 7.29 and 7.28 (2s, 10H, ar); 5.65 (m, 1H,-C<u>H</u>=CH_2); 5.01 (d, J:17.2 Hz, 1H, =CH_2); 4.94 (d, J:10.3, 1H, =CH_2); 3.88 (s, 2H, N-CH_2); 3.77 (s, 2H, SCH_2)
6	3447 (OH) 3330, 3157 (N-H) 1684 (C=O)	(DMSO-d_6+$CDCl_3$, 400 MHz): 12.65 (s, 1H, imidazole NH); 10.14 (s, 1H, CONH); 9.20 (s, 1H, NH); 7.30-7.48 (m, 11H, N<u>H</u>CH_2 and ar); 4.34 (br.s, 1H, CH_3CH_2O<u>H</u>); 3.90 (2s, 2H, SCH_2); 3.46 (br.s, 2H, CH_3C<u>H</u>$_2$OH); 1.80-0.94 (m, 11H, cyclohex.); 1.07 (m, 3H, C<u>H</u>$_3CH_2$OH)
7	3462 (OH) 3275, 3163 (N-H) 1679 (C=O)	(DMSO-d_6, 400 MHz): 12.79 (s, 1H, imidazole NH); 10.52 (s, 1H, CONH); 9.54 (s, 2H, NH); 7.34-7.11 (m, 12H, ar); 7.20 (d, J:8.1 Hz, 2H, ar); 4.26 (br. s, 1H, CH_3CH_2O<u>H</u>); 3.90 (s, 2H, SCH_2); 3.46 (br.q, 2H, CH_3C<u>H</u>$_2$OH); 2.21 (s, 3H, CH_3); 1.01 (t, J:7 Hz, 3H, C<u>H</u>$_3CH_2$OH)
8	3462 (OH) 3268, 3162 (N-H) 1678 (C=O)	(DMSO-d_6, 400 MHz): 12.70 (s, 1H, imidazole NH); 10.45 (s, 1H, CONH); 9.78 (s, 2H, NH); 7.54-7.25 (m, 14H, ar); 4.33 (br.s, 1H, CH_3CH_2O<u>H</u>); 3.95 (s, 2H, SCH_2); 3.46 (br.q, 2H, CH_3C<u>H</u>$_2$OH); 1.07 (br.s, 3H, C<u>H</u>$_3CH_2$OH)
9	3462 (OH) 3272, 3173 (N-H) 1678 (C=O)	(DMSO-d_6, 400 MHz): 12.68 (s, 1H, imidazole NH); 10.42 (s, 1H, CONH); 9.71 (s, 2H, NH); 7.38-7.24 (m, 12H, ar); 7.07 (t, J: Hz, 2H, ar); 4.32 (br.s, 1H, CH_3CH_2O<u>H</u>); 3.94 (s, 2H, SCH_2); 3.45 (br.q, 2H, CH_3C<u>H</u>$_2$OH); 1.07 (br. s, 3H, C<u>H</u>$_3CH_2$OH)
10	3487 (OH) 3264, 3151 (N-H) 1679 (C=O)	(DMSO-d_6, 400 MHz): 13.08 (s, 1H, imidazole NH); 12.17 (s, 1H, CONH); 10.85 (s, 2H, NH); 8.05 (d, 2H, ar); 7.66-7.24 (m, 12H, ar); 4.26 (br.s, 1H, CH_3CH_2O<u>H</u>); 3.90 (s, 2H, SCH_2); 3.40 (q, J:6.9 Hz, 2H, CH_3C<u>H</u>$_2$OH); 1.01 (t, J:7 Hz, 3H, C<u>H</u>$_3CH_2$OH)
11	3330, 3165 (N-H) 1703, 1670 (C=O)	(DMSO-d_6, 400 MHz): 12.65 (br.s, 1H, imidazole NH); 10.62 (s, 1H, CONH); 7.38-7.26 (m, 10H, ar); 3.98 (s, 2H, thiaz. SCH_2); 3.94 (s, 2H, SCH_2); 3.66 (q, J:6.82 Hz, 2H, NC<u>H</u>$_2CH_3$); 1.11 (t, J:6.9 Hz, 3H, NCH_2C<u>H</u>$_3$)
12	3471, 3193 (N-H) 1710, 1672 (C=O)	(DMSO-d_6+$CDCl_3$, 300 MHz): 12.41 (s, 1H, imidazole NH); 11.24 (s, 1H, CONH); 7.57-7.27 (m, 10H, ar); 5.89-5.79 (m, 1H,-C<u>H</u>=CH_2); 5.22 (d, J:17.1 Hz, 1H, =CH_2); 5.16 (d, J:10.4, 1H, =CH_2); 4.33 (br.s, 2H, N-CH_2); 3.83 (s, 2H, thiaz. SCH_2); 3.67 (s, 2H, SCH_2)
13	3291 (N-H) 1734, 1689 (C=O)	(DMSO-d_6, 300 MHz): 12.24 (br.s, 1H, imidazole NH); 10.65 (s, 1H, CONH); 7.28-6.62 (m, 15H, ar); 3.92 (s, 2H, thiaz. SCH_2); 3.90 (s, 2H, SCH_2); 3.22 (q, J:6.9 Hz, 1H, CH_3C<u>H</u>$_2$OH); 0.83 (t, J:6.9 Hz, 1.5H, C<u>H</u>$_3CH_2$OH)

14	3435 (N-H) 1726, 1686 (C=O)	(DMSO-d_6 +$CDCl_3$, 300 MHz): 12.17 (s, 1H, imidazole NH); 11.26 (s, 1H, CONH); 7.41 (d, J:8.7 Hz, 2H, ar); 7.28 (d, J:8.7 Hz, 2H, ar); 7.53-7.26 (m, 10H, ar); 3.97 (br.s, 1H, $CH_3CH_2O\underline{H}$); 3.80 (s, 2H, thiaz. SCH_2); 3.79 (s, 2H, SCH_2); 3.62 (q, J:6.6 Hz, 2H, $CH_3C\underline{H}_2OH$); 1.17 (t, J:6.8 Hz, 3H, $C\underline{H}_3CH_2OH$)
15	3439, 3160 (N-H) 1723, 1680 (C=O)	(DMSO-d_6, 300 MHz): 12.64 (br.s, 1H, imidazole NH); 10.58 (s, 1H, CONH); 7.41-7.25 (m, 15H, ar); 4.11 (s, 2H, thiaz. SCH_2); 3.90 (s, 2H, SCH_2)

The ^{1}H-NMR spectrum of **5-10** displayed the methylene protons of the SCH_2CO group at about 3.77-3.95 ppm as a singlet. In the cyclic product **11-15**, the methylene protons of the exocyclic SCH_2CO group absorbed at about 3.67-3.94 ppm whereas the methylene protons of the endocyclic SCH_2CO group absorbed at about 3.80-4.11 ppm (13,15,16). N^4-H, N^2-H and N^1-H protons of **5** and **6** which are N^4-alkylsubstituted derivatives resonated as singlets at about 7.30-7.96, 9.05-9.20 and 10.14-10.35 ppm, respectively. The N^4-H and N^2-H protons of **7-10** which are N^4-arylsubstituted derivatives resonated as singlets at about 9.54-10.85 ppm. The N^1-H and imidazole N-H protons absorbed as singlets at about 10.42-12.17 and 12.40-13.08 ppm, respectively. The CONH and imidazole N-H protons of the cyclic products **11-15** were observed at about 10.58-11.26 ppm and 12.17-12.65 ppm, respectively.

The EIMS of thiosemicarbazide derivatives **8** and **9** did not show the molecular ions presumably due to the instability of the molecular ions under EI conditions. Excessive fragmentation involving the cleavage of the thioamide linkage and hydrogen migration yielded ions at m/z 324 and isothiocyanates which were accordance with the literature (17,18).

Compounds **11-15** which are thiazolidinone derivatives fragmented via a common pathway. Thus rupture of the amide bonds or hydrogen migration accompanying the cleavage of the cited bond yielded ions at m/z 293 or 292. The rupture of the N-N bond yielded the ion at m/z 308 whereas cleavage of the thioether and N-N bonds led to the ions at m/z 219 and M-308 (7,19,20) (Scheme 2). These ions further fragmented to yield ions at m/z 265, 264, 252, 251, 234, 233, 208, 207, 193, 192, 178, 119, 118, 117 and 89.



Scheme 2. The proposed fragmentation of the 4-thiazolidinones

Microbiology

Selected members from both series **8**, **9**, **14** and **15** were investigated for antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Escherichia coli* ATCC 8739 and *Candida albicans* ATCC 10231 using the disc diffusion method, but no significant activity was encountered.

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