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Synthesis of Mannich Bases of Some 2,5-Disubstituted 4-Thiazolidinones and Evaluation of Their Antimicrobial Activities*

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4-Carbethoxymethyl-2-[(α-chloropropionyl/α-bromobutyryl/α-chloro-(α-phenyl)acetyl)amino]thiazoles (**2a-c**) were synthesized by the reaction of 4-carbethoxymethyl-2-aminothiazole (**1**) with α-chloropropionyl chloride, α-bromobutyryl bromide and α-chloro-α-phenylacetyl chloride, respectively, which were then refluxed with ammonium thiocyanate to obtain 5-substituted 2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (**3a-c**). **3a-c** were stirred with formaldehyde and various secondary amines to gain 15 novel compounds with the structure 5-substituted 5-(N,N-disubstituted aminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (**4a-o**). The antibacterial activities of the compounds against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *K. pneumoniae* ATCC 4352, *P. aeruginosa ATCC 1539, S. typhi, Sh. flexneri* and *Pr. mirabilis* ATCC 14153 were tested using disk diffusion, while the antifungal activities of the compounds against *M. gypseum* NCPF-580, *M. canis*, *T. mentagrophytes, T. rubrum* and *C. albicans* ATCC 10231 were tested using microdilution.

Key Words: 2,5-Disubstituted 4-thiazolidinones, synthesis, Mannich bases, antimicrobial activity.

Introduction

It is recorded in the literature that 2-arylimino-4-thiazolidinone derivatives have various pharmacological activities such as antibacterial[1,2], antifungal[3], anticonvulsant[4,5] and anticancer[6]. In our literature search, we found that Mannich bases had antimicrobial activities[7−10] besides various other activities. In our previous work, we synthesized some thiazolidinone derivatives, which were shown to have antibacterial activity[11]. As

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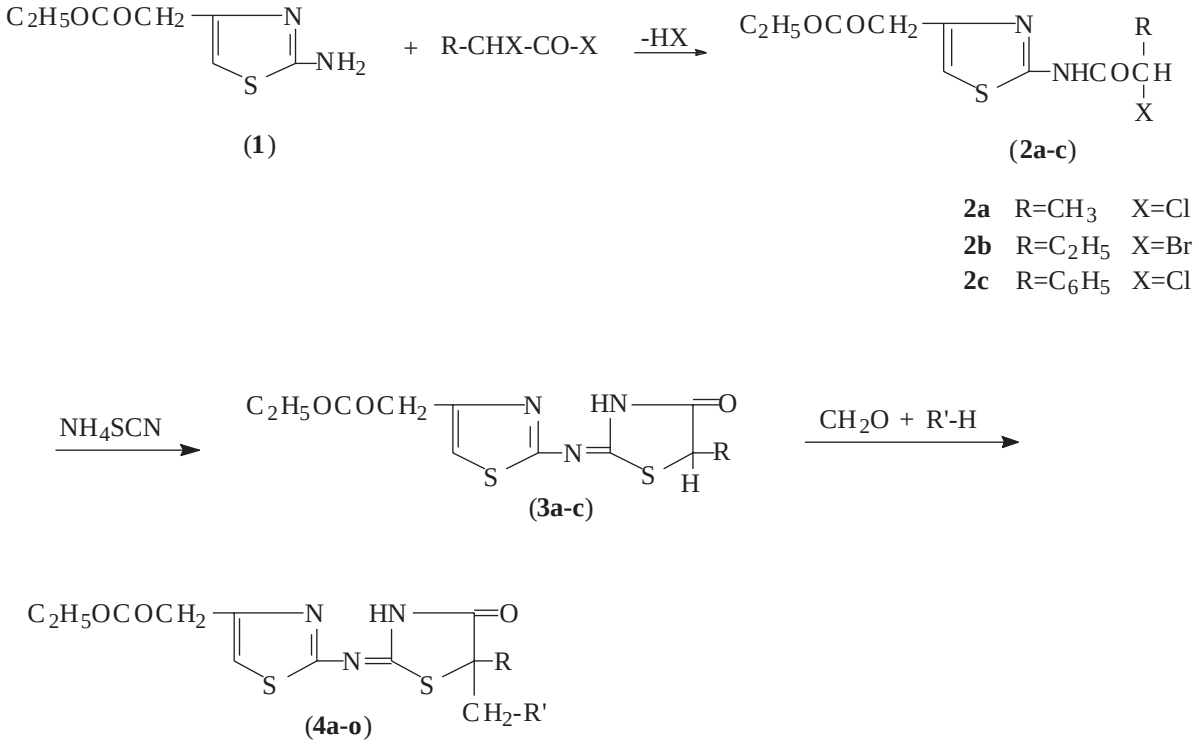
a continuation of our previous study on Mannich bases of 5-nonsubstituted 2-substituted-4-thiazolidinones where the tested compounds had shown significant antibacterial activity, we synthesized and characterized new Mannich bases of 5-substituted 2-thiazolylimino-4-thiazolidinones **(4a-o)** by refluxing 5-substituted 2[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones with formaldehyde and various secondary amines in order to screen the antimicrobial activity. The condensation reaction was run under reflux, so that the aminomethyl group was bonded to the 5-position[12,13] rather than to the 3-position[13−15]. The antimicrobial activities of the novel compounds against various microorganisms were investigated.

Chemistry

4-Carbethoxymethyl-2-[(α-haloacyl)amino]thiazoles (**2a-c**) were prepared by stirring various α-haloacyl halides with 4-carbethoxymethyl-2-aminothiazole (**1**) in dry benzene and dry pyridine for 1 h at room temperature. In the next stage of our study, to form the thiazolidinone ring, compounds **2a-c** were heated with ammonium thiocyanate in ethanol and 5-substituted 2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (**3a-c**) were obtained. In the last stage of our study, Mannich bases were synthesized by condensing the acidic C-5 hydrogen atom of thiazolidinone with formaldehyde and various secondary amines to obtain 15 novel compounds, 5-(N,N-disubstituted aminomethyl-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (**4a-o**) (Scheme 1, Table 1). The formulae of the compounds were confirmed by elemental analyses (Table 1), and their structures were determined based on IR, ^{1}H-NMR and EI mass spectral data.



Scheme 1

Table 1. Experimental data for compounds **4a-o**.

Compd.	Formula (M.W.)	Yield (%)	M.p. (°C)	Elem.Anal. (Calcd./found)		
				C	H	N
4a	$C_{16}H_{22}N_4O_4S_2$	90	wax	48.22	5.57	14.06
	(398.49)			49.24	5.92	13.58
4b	$C_{17}H_{24}N_4O_3S_2$	92	wax	51.49	6.10	14.13
	(396.51)			51.96	5.49	14.16
4c	$C_{18}H_{26}N_4O_3S_2$	85	wax	52.66	6.38	13.65
	(410.54)			53.29	5.94	13.32
4d	$C_{17}H_{24}N_4O_4S_2$	85	wax	49.49	5.86	13.58
	(412.51)			49.59	6.00	13.12
4e	$C_{19}H_{22}N_4O_3S_2.H_2O$	80	wax	52.27	5.54	12.84
	(436.54)			52.40	4.98	12.25
4f	$C_{21}H_{26}N_4O_3S_2.1/2H_2O$	80	wax	55.36	5.97	12.30
	(455.58)			55.11	6.02	11.88
4g	$C_{21}H_{24}N_4O_3S_2$	78	>300	56.73	5.44	12.60
	(444.55)			56.12	4.94	12.00
4h	$C_{22}H_{26}N_4O_3S_2.H_2O$	87	wax	55.44	5.92	11.76
	(476.60)			55.63	6.50	11.44
4i	$C_{23}H_{28}N_4O_3S_2.1/2H_2O$	85	wax	57.36	6.07	11.63
	(481.61)			57.38	6.50	11.37
4j	$C_{23}H_{28}N_4O_3S_2$	85	wax	58.45	5.97	11.86
	(472.60)			58.95	6.51	11.61
4k	$C_{23}H_{28}N_4O_3S_2$	75	wax	58.45	5.97	11.86
	(472.60)			58.10	6.72	11.32
4l	$C_{24}H_{30}N_4O_3S_2.H_2O$	78	wax	57.12	6.39	11.10
	(504.65)			56.97	6.49	10.80
4m	$C_{21}H_{24}N_4O_4S_2$	90	wax	54.76	5.25	12.17
	(460.55)			54.46	5.14	11.94
4n	$C_{27}H_{29}N_5O_3S_2$	86	wax	60.54	5.46	13.08
	(535.66)			60.91	5.19	13.02
4o	$C_{21}H_{20}N_4O_5S_2$	90	153-5	53.38	4.27	11.86
	(472.52)			53.32	4.31	11.57

Experimental

Melting points were measured on a Büchi 530 melting point apparatus in open capillaries and were uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. The compounds were checked for purity by TLC on silicagel HF_{254}. IR spectra were recorded on KBr disks using a Perkin-Elmer model 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker AC 200 (200 MHz) spectrometer using DMSO-d_6. EI/MS were determined on a VG Zab Spec (70 eV) mass spectrometer.

Synthesis of 4-Carbethoxymethyl-2-[(α-haloacyl)amino]thiazoles (2a-c)[16]

0.01 Mol of 4-carbethoxymethyl-2-aminothiazole (**1**) in 4 mL of dry benzene and 1 mL of dry pyridine was stirred with 0.01 mol (0.98 mL) of α-chloropropionyl chloride or 0.01 mol (1.22 mL) of α-bromobutyryl bromide or 0.01 mol (1.44 mL) of α-chloro-α-phenylacetyl chloride in 3 mL of dry benzene for 1 h at room

temperature. The crude product was washed with water to remove the acid and recrystallized from ethanol to obtain compound **2c** (**2a** and **2b** were not recrystallized).

Synthesis of 5-substituted 2-[(4-Carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (3a-c)[17]

0.05 Mol of 4-carbethoxymethyl-2-[(α-haloacyl)amino]thiazole (**2a-c**) and 0.1 mol (7.6 g) of ammonium thiocyanate in 50 mL of 96% ethanol were refluxed on a water bath for 1 h, left overnight, filtered and recrystallized from ethanol.

Synthesis of 5-substituted 5-(N,N-disubstituted aminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (4a-o)[18]

A solution of 0.5 mL of 37% formaldehyde and 0.002 mol of a secondary amine was added dropwise with vigorous stirring to a suspension of 0.002 mol of 5-substituted 2-[(4-carbethoxymethylthiazol-2-yl)imino-4-thiazolidinone (**3a-c**) in absolute ethanol. The mixture was refluxed for 4 h. Upon cooling, the crude compound was precipitated, filtered, dried and recrystallized from ethanol to obtain compounds **4g** and **4o** (the others were not recrystallized).

Spectral data of **4a**: IR [ν, cm^{-1}, KBr]: 3452 (N-H), 1732 (C=O, ester), 1700 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.21 (t, J=7.1 Hz, 3H, $\underline{CH_3}$-CH_2O), 1.52 (s, 3H, thiazolidinone C_5-CH_3), 2.61 (br.s, 2H, thiazolidinone C_5-$\underline{CH_2}$-R′), 3.46-3.59 (m, 4H, morpholine $C_{3,5}$-H), 3.73 (s, 2H, CO-CH_2), 4.10 (q, J=7.1 Hz, 4H, CH_2O and morpholine C_2-H), 4.67-4.69 (m, 2H, morpholine C_6-H), 7.21 (s, 1H, thiazole C_5-H), 12.00 (s, 1H, N-H).

Spectral data of **4b**: IR [ν, cm^{-1}, KBr]: 3424 (N-H), 1729 (C=O, ester), 1652 (C=O, lactam).

Spectral data of **4c**: IR [ν, cm^{-1}, KBr]: 3434 (N-H), 1732 (C=O).

Spectral data of **4d**: IR [ν, cm^{-1}, KBr]: 3444 (N-H), 1732 (C=O). ^{1}H-NMR [200 MHz , δ, ppm, DMSO-d_6]: 0.95 (t, J=7.2 Hz, 3H, thiazolidinone C_5-CH_2-$\underline{CH_3}$), 1.19 (t, J=7.1 Hz, 3H), 1.81-2.02 (m, 2H, thiazolidinone C_5-$\underline{CH_2}$-CH_3), 2.76 (s, 2H), 3.48-3.78 (m, 6H, CO-CH_2 and morpholine $C_{3,5}$-H), 4.04-4.14 (m, 4H, CH_2O and morpholine C_2-H), 4.69-4.77 (m, 2H, morpholine C_6-H), 7.23 (s, 1H), 11.90 (s,1H). EI/MS (70eV) [m/z (rel. int. %)]: 414 $(M+2)^+$ (3), 412 (M^+), (8), 313 (36), 284 (1), 280 (6), 240 (4), 212 (4), 211 (17), 166 (3), 138 (37), 114 (1), 100 (100), 86 (3), 73 (5), 72 (5), 71 (8), 56 (30), 45 (42), 42(30).

Spectral data of **4e**: IR [ν, cm^{-1}, KBr]: 3420 (N-H), 1725 (C=O).

Spectral data of **4f**: IR [ν, cm^{-1}, KBr]: 3440 (N-H), 1734 (C=O). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.06 (t, J=7.3 Hz, 9H, $\underline{CH_3}$-CH_2O and N-(CH_2-$\underline{CH_3}$)$_2$), 2.80 (q, J=7.3 Hz, 6H, thiazolidinone C_5-$\underline{CH_2}$-R′ and N-($\underline{CH_2}$-CH_3)$_2$), 3.57 (s, 2H), 3.93-3.99 (m, 2H), 7.24-7.33 (m, 6H, thiazole C_5-H and phenyl H's), 12.00 (br.s, 1H).

Spectral data of **4g**: IR [ν, cm^{-1}, KBr]: 3433 (N-H), 1734 (C=O, ester), 1654 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.05 (br.s, 3H), 1.72-1.75 (m, 4H, pyrrolidine $C_{3,4}$-H), 3.00 (s, 2H), 3.60 (s, 6H, CO-$CH_2$and pyrrolidine $C_{2,5}$-H), 3.96-3.97 (m, 2H), 7.00-7.50 (m, 6H), 12.04 (br.s, 1H).

Spectral data of **4h**: IR [ν, cm^{-1}, KBr]: 3404 (N-H), 1728 (C=O, ester), 1650 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.17 (t, J=6.6 Hz, 3H), 1.31-1.66 (m, 6H, piperidine $C_{3,4,5}$-H), 2.60

(s, 2H), 3.71 (s, 2H), 3.81-4.13 (m, 4H, piperidine $C_{2,6}$-H), 4.06 (q, J=7.4 Hz, 2H), 7.23-7.51 (m, 6H), 11.89 (br.s, 1H).

Spectral data of **4i**: IR [ν, cm^{-1}, KBr]: 3423 (N-H), 1732 (C=O, ester), 1648 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.00-1.19 (m, 6H, $\underline{CH_3}$-CH_2O and piperidine C_2-CH_3), 1.29-1.79 (m, 6H, piperidine $C_{3,4,5}$-H), 3.11 (s, 2H), 3.68 (s, 2H), 3.78-3.89 (m, 3H, piperidine $C_{2,6}$-H), 3.93-4.05 (m, 2H), 7.38 (br.s, 6H), 11.90 (s, 1H).

Spectral data of **4j**: IR [ν, cm^{-1}, KBr]: 3419 (N-H), 1731 (C=O, ester), 1650 (C=O, lactam). ^{1}H-NMR: [200 MHz, δ, ppm, DMSO-d_6] 0.89 (d, J=6.5 Hz, 3H, piperidine C_3-CH_3), 1.04-1.17 (m, 3H), 1.34-1.77 (m, 5H, piperidine $C_{3,4,5}$-H), 2.80 (s, 2H), 3.50-3.62 (m, 4H, piperidine $C_{2,6}$-H), 3.70 (s, 2H), 4.06 (q, J=7.1 Hz, 2H), 7.34-7.53 (m, 6H), 12.24 (br.s, 1H).

Spectral data of **4k**: IR [ν, cm^{-1}, KBr]: 3420 (N-H), 1733 (C=O). ^{1}H-NMR [200 MHz ,δ, ppm, DMSO-d_6]: 0.88 (d, J=5.5 Hz, 3H, piperidine C_4-CH_3), 1.05-1.15 (m, 3H), 1.72-2.09 (m, 5H, piperidine $C_{3,4,5}$-H), 2.84 (s, 2H), 3.51-3.61 (m, 4H, piperidine $C_{2,6}$-H), 3.70 (s, 2H), 4.05-4.10 (m, 2H), 7.18-7.42 (m, 6H), 11.77 (s, 1H).

Spectral data of **4l**: IR [ν, cm^{-1}, KBr]: 3420 (N-H), 1734 (C=O). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 0.88 (d, J=6.6 Hz, 6H, piperidine $C_{3,5}$-CH_3), 1.16 (t, J=8.3 Hz, 3H), 1.66-1.85 (m, 4H, piperidine $C_{3,4,5}$-H), 2.88 (s, 2H), 3.71 (s, 2H), 4.08 (q, J=7.2 Hz, 2H), 4.66-5.20 (2br.s, 4H, piperidine $C_{2,6}$-H), 7.18-7.46 (m, 6H), 12.15 (s, 1H).

Spectral data of **4m**: IR [ν, cm^{-1}, KBr]: 3444 (N-H), 1732 (C=O, ester), 1694 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.16 (t, J=7.0 Hz, 3H), 2.71 (s, 2H), 3.43-3.57 (m, 4H, morpholine $C_{3,5}$-H), 3.73 (s, 2H), 4.08 (q, J=8.4 Hz, 4H, $CH_2O$and morpholine C_2-H), 4.78-4.88 (m, 2H, morpholine C_6-H), 7.23 (s, 1H), 7.30-7.49 (m, 5H), 12.30 (br.s, 1H). EI/MS (70eV) [m/z (rel. int. %)]: 212 (2), 139 (3), 121 (8), 101 (58), 99 (78), 85 (25), 83 (23), 78 (7), 71 (17), 57 (42), 41 (92).

Spectral data of **4n**: IR [ν, cm^{-1}, KBr]: 3445 (N-H), 1732 (C=O, ester), 1648 (C=O, lactam).

Spectral data of **4o**: IR [ν, cm^{-1}, KBr]: 3450 (N-H), 1737 (C=O, ester), 1654 (C=O, lactam). ^{1}H-NMR [200 MHz, δ, ppm, DMSO-d_6]: 1.13 (t, J=7.1 Hz, 3H), 2.52 (s, 2H), 3.69 (s, 2H), 4.05 (q, J=7.1 Hz, 2H), 5.57 (s, 4H, succinimide $C_{2,3}$-H), 7.19 (s, 1H), 7.36-7.41 (m, 5H), 12.30 (s, 1H).

Microbiology

Antibacterial activity

The synthesized derivatives **4a-o** were screened for their in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi*, *Shigella flexneri* and *Proteus mirabilis* ATCC 14153 using disk diffusion[19]. Mueller-Hinton agar (Difco, Detroit, USA) was used for the bacterial strains. All of the compounds were inactive for antibacterial activity.

Antifungal activity

Study Design: Microdilution was used according to a standard protocol described by the NCCLS[20,21]. Five strains were tested each of the following species: *Microsporum gypseum* NCPF-580, *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Candida albicans* ATCC 10231.

Medium: RPMI 1640 broth with L-glutamine without sodium bicarbonate and 0.165 μ MOPS buffer (34.54 g/L) was used. The medium was adjusted to pH 7.0 at 25 °C. Sterility control of each bottle was performed before it was used.

Antifungal agents: Terbinafine was provided by the manufacturer as a standard powder. All drugs were dissolved in 100% dimethyl sulfoxide according to the NCCLS methods[20,21] . The final drug concentrations were 32 to 0.01 μg/mL for all drugs.

Preparation of inoculum: The preparation of inoculum suspensions was based mainly on the NCCLS guidelines[21] and as described previously[22−24]. For dermatophytes the final inoculum size was adjusted from 1.2 $\times$ 10^4 to 6 $\times$ 10^4 CFU/mL and for *C.albicans* it was approximately 1 $\times$ 10^3 to 5 x 10^3 CFU/mL[20,25,26].

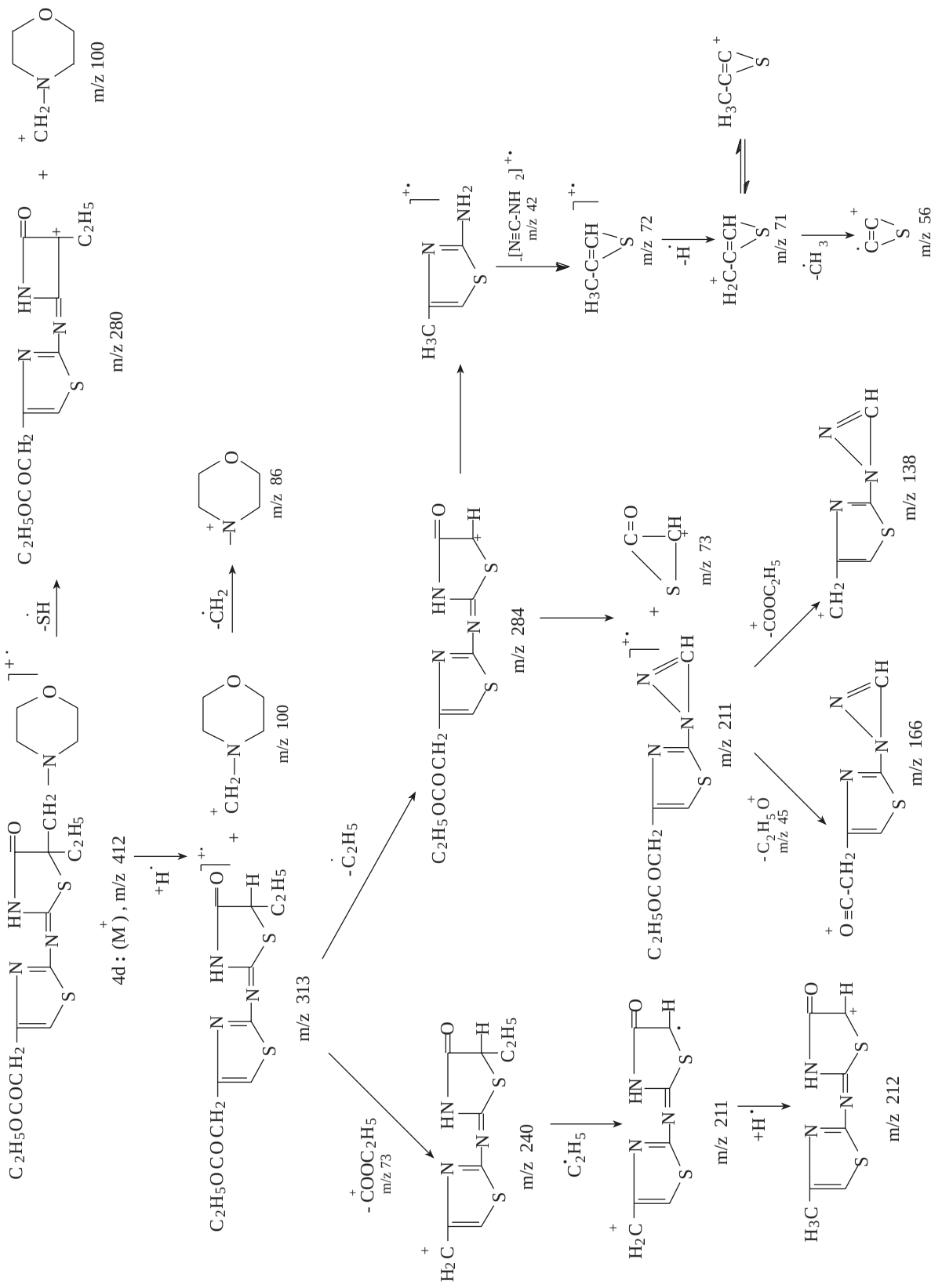
Test Procedure: The test procedure was applied according to the NCCLS protocols[20,21]. Microdilution plates (96 U-shaped) were prepared and frozen at -70 °C until needed. Each microdilution well containing 100 μL of the 2-fold drug concentration was inoculated with 100 μL of the final inoculum suspension. Two drug-free growth controls were included for each test plate, one without any drug (growth control) and the other with media containing an equivalent amount of solvent used to dissolve the drug (solvent control). For all drugs, the minimum inhibitory concentration (MIC) was defined as the lowest concentration showing 100% growth inhibition. All of the compounds (**4a-o**) were found to have antifungal activity against *M. gypseum*, *M. canis*, *T. mentagrophytes*, *T. rubrum* and *C. albicans*. MIC values of the compounds are given in Table 2.

Results and Discussion

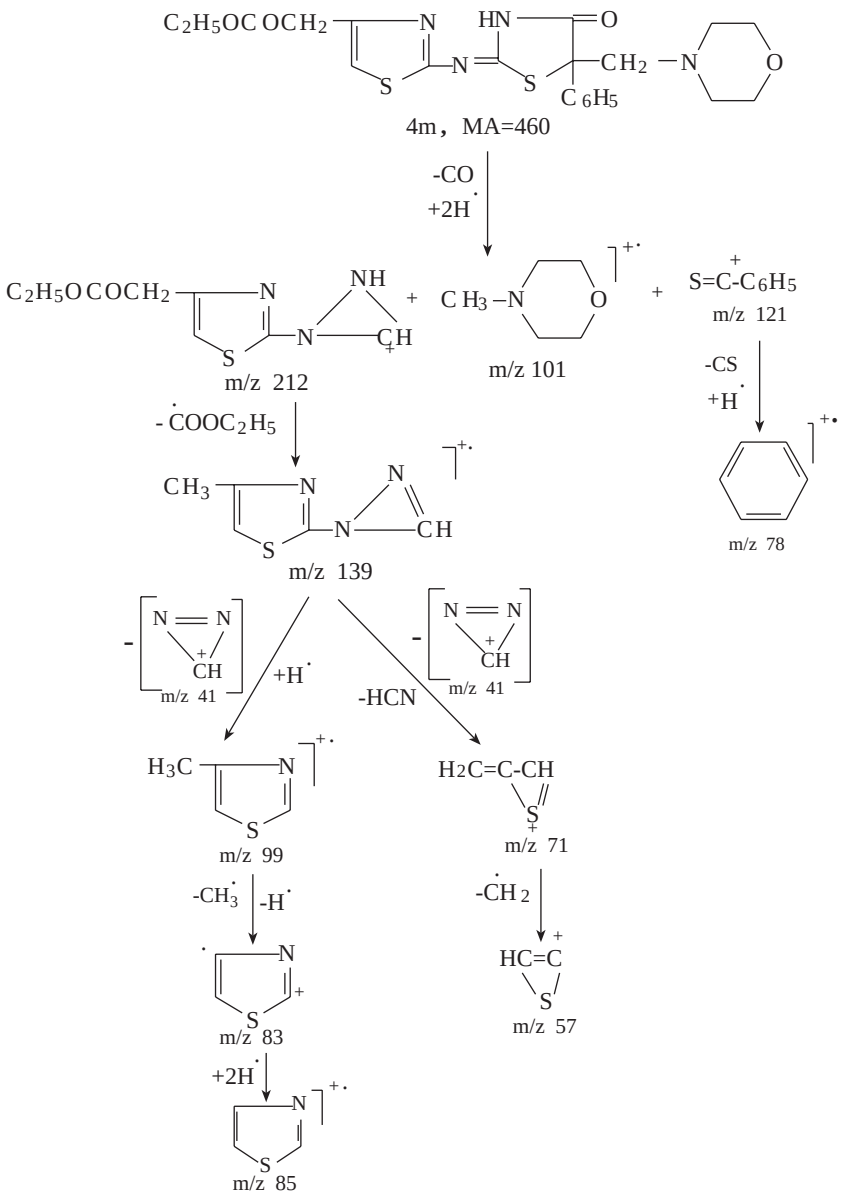
The title compounds were characterized based on their physical, analytical and spectral data. The spectral details of some of the representative compounds are given in the Experimental section.

In the IR spectra of compounds **4a-o** the N-H and C=O stretching bands of the ester and lactam groups were observed at 3452-3404, 1737-1725 and 1734-1648 cm^{-1}, respectively. The existence of the N-H stretching bands provided evidence that the bond was formed at the 5-position of the thiazolidinone rather than at the 3-position. The position of the bond was also confirmed by the ^{1}H-NMR spectra of the compounds. The singlet at 11.77-12.30 ppm in the spectrum of **4a-o** showed that the nitrogen still had a proton, which further supported the substitution at the 5-position. In addition, the absence of thiazolidinone C_5-H of **3a** in the ^{1}H-NMR spectrum of **4a** and the singlet assigned to the CH_3 group at 1.52, ppm which was a doublet in **3a**, prove that the proton at the 5-position of **3a** was replaced by the aminomethyl group.

The EIMS of 2 compounds, **4d** and **4m**, which were chosen as prototypes, were obtained. The MS of the compound **4d** showed a molecular ion peak (M^+) with low intensity, while the MS of compound **4m** did not show any molecular ion peak but did show peaks due to fragments, supporting the expected structures and in accordance with the fragmentation routes[27,28] (Schemes 2, 3).



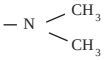
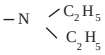
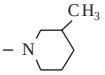
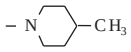
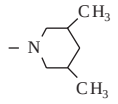
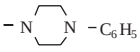
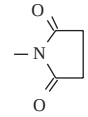
Scheme 2



Scheme 3

Experiments were performed to evaluate the antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, *Ps. aeruginosa*, *S. typhi*, *Sh. flexneri* and *Pr. mirabilis* using disk diffusion and the antifungal activity against *M. gypseum*, *M. canis*, *T. mentagrophytes*, *T. rubrum* and *C. albicans* using microdilution. The MIC values are given in Table 2. In the comparison of compound **4c** with compound **4h,** both bearing R^1=piperidine moiety, **4c** was found to be more active than compound **4h** against *M. canis*, *T. mentagrophytes* and *T. rubrum*. In the same way, when compounds **4d** and **4m** (both have R^1=morpholine) were compared, compound **4d** had a lower MIC value than compound **4m** against *M. gypseum*, *M. canis*, *T. mentagrophytes* and *T. rubrum*, indicating that the presence of ethyl groups in **4c** and **4d** caused potential antifungal activity when compared to phenyl groups in **4h** and **4m**. Compound **4e** (R^1=dimethylamine) was found to exhibit more activity than compound **4f** (R^1=diethylamine). Compound **4e** was also found to be more active than compounds **4g-4n** (R=C_6H_5, R^1=heterocyclic ring).

Table 2. MIC values (μg/mL) of compounds **4a-o**.

Compd.	R	R′	M. gypseum NCPF-580	M. canis	T. mentagrophytes	T. rubrum	C. albicans ATCC 10231
4a	CH_3		8	8	8	8	16
4b	C_2H_5		8	8	8	8	8
4c	C_2H_5		8	4	4	4	16
4d	C_2H_5		4	4	4	4	16
4e	C_6H_5		4	4	4	4	16
4f	C_6H_5		16	8	16	16	16
4g	C_6H_5		8	8	8	8	16
4h	C_6H_5		8	8	8	8	16
4i	C_6H_5		8	8	8	8	16
4j	C_6H_5		8	8	8	8	16
4k	C_6H_5		8	8	8	8	16
4l	C_6H_5		16	16	16	16	16
4m	C_6H_5		8	8	8	8	16
4n	C_6H_5		8	8	8	8	16
4o	C_6H_5		4	4	4	4	16
Terbinafine			≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	1

When compounds **4g** and **4o** (R=C_6H_5in both) were compared, **4o** (R^1=2,5-pyrrolidindione) was found to show more activity than **4g** (R^1=pyrrolidine) against *M. gypseum* NCPF-580, *M. canis*, *T. mentagrophytes* and *T. rubrum*. The dioxo groups on the 2,5-positions of the pyrrolidine ring led to enhanced activity. On the other hand, only the MIC value of compound **4b** was 8 μg/mL against *C. albicans* ATCC

10231, while the MIC values of the other compounds were 16 μg/mL.

All of the compounds tested in this study (**4a-o**) showed some antifungal activity against selected microorganisms when compared with terbinafine.

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