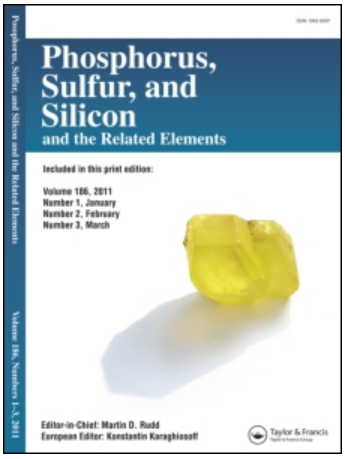

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PREPARATION OF NEW DERIVATIVES OF THIAZOLE, THIAZOLIDINE, AND THIAZOL-2-YLPYRAZOLO[3,4-D]PYRIMIDINE SULFONAMIDO CONJUGATES

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PREPARATION OF NEW DERIVATIVES OF THIAZOLE, THIAZOLIDINE, AND THIAZOL-2-YLPYRAZOLO[3,4-D]PYRIMIDINE SULFONAMIDO CONJUGATES

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*Several new thiazoles (**3–7**), thiazolylpyrazole carbonitrile (**10**,**11**), and Thiazolidine sulfonamido conjugate derivatives (**19–26**) were prepared starting with p-Piperidinesulfonylacetophenones (**1**,**2**). The structure of these compounds was elucidated on the bases of elemental analysis, IR, PMR, and mass spectra. The antimicrobial activities of some selected compounds are also reported.*

Keywords: *p*-Piperidinesulfonylacetophenones; thiazole; thiazolidine-containing piperidine sulfonamide; thiazolylpyrazol

INTRODUCTION

Due to considerable interest in their bioactivity, the syntheses of thiazole and their derivatives from thioacetamide derivatives have been explored with significant success.[1—15] The thiazolidine moiety occurs in different bioactive substances as an important pharmacophoric group, for instance, the imidazo[2,1-b]thiazole system in the main moiety of the well-known antihelmintic and immunomodulatory agent levamisole.[16,17] Thiazol[2,3-a]pyrimidines bear a structure analogous to levamisol and have been well studied as immunomodulatory, anticancer, analgesic, and psychotropic agents.[16—18] In the present article we detail the synthesis of thiazole, thiazolidine, and thiazolylpyrazolopyrimidine sulfonamido conjugates displaying improved biological properties with respect to the nonsulfonamido-conjugated thiazole

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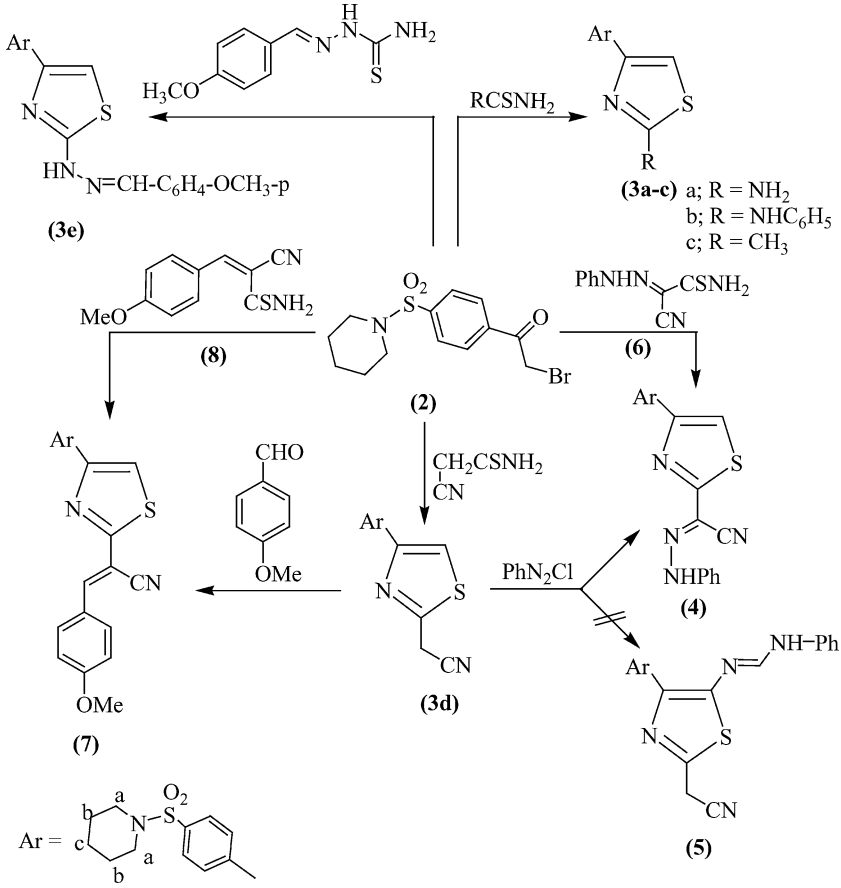
compounds. The antibacterial and antifungal screening of some selected compounds is also included.

RESULTS

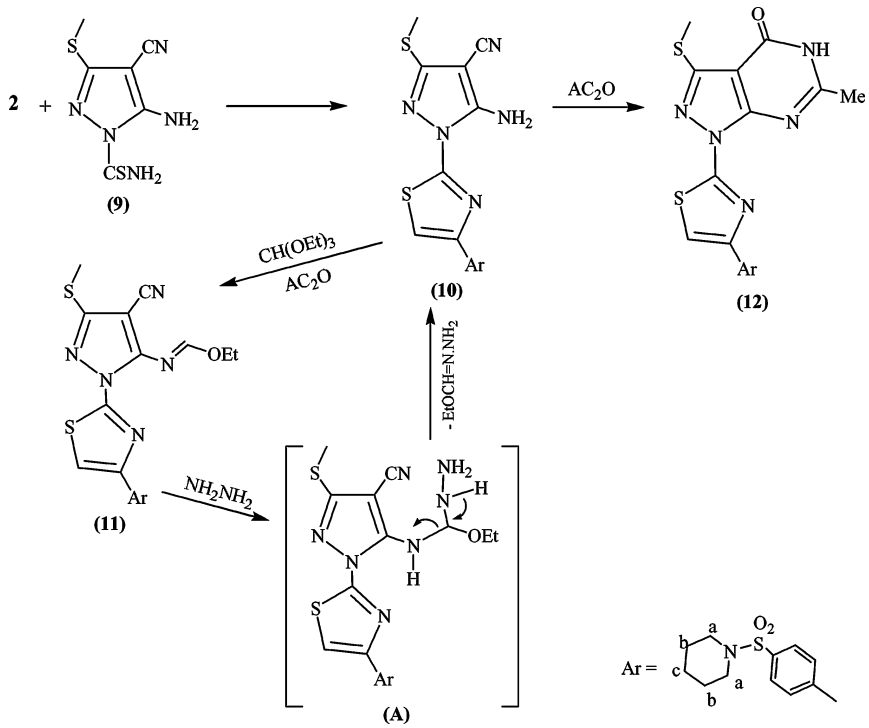
p-Piperidinosulfonylacetophenone (**1**)[19] and *p*-piperidinosulfonylacetophenacyl bromide (**2**)[20] were used as our starting materials. Thus, treatment of **2** with thiourea and thioacetamide compounds in refluxing ethanol afforded the corresponding thiazol-2-yl derivatives (**3a–d**) (Scheme 1). Also, when **2** was subjected to the reaction with *p*-anisaldehydethiosemicarbazone in boiling ethanol, the corresponding thiazol-2-yl derivative (**3e**) was obtained. The thiazole derivative **3d**



SCHEME 1

couples readily with benzene diazonium chloride in ethanolic sodium acetate to afford the coupling product for which two isomeric structures **4** or **5** seemed possible. PMR provided a firm support for structure **4** and ruled out the other possible isomer **5**, the lack of the signal due to methylene protons, and the appearance of the signal due to the H-thiazole at δ 7.7 ppm. Also, the structure **4** was further confirmed by an independent synthesis from the reaction of **2** with 2-phenylhydrazono-2-cyanoethanethioamide (**6**). On the other hand, **3d** was condensed with *p*-anisaldehyde in boiling ethanolic piperidine solution successfully to give the corresponding thiazol-2-ylacrylonitrile derivative (**7**), which was prepared independently from the reaction of **2** with *p*-methoxybenzylidenecyanothioacetamide (**8**) in refluxing ethanol (Scheme 1). Evidence for structures for the latter compounds were provided on the basis of elemental analysis (Table I) and spectral data.

Cyclocondensation of **2** with an equimolar amount of 5-amino-4-cyano-3-methylthio-pyrazole-1-thiocarboxamide (**9**)[21] in boiling ethanol yielded 5-amino-3-methylthio-1-[4-(4-piperidinosulfonylphenyl)-thiazol-2-yl]-1*H*-pyrazole-4-carbonitrile (**10**) (Scheme 2). Evidence for the



SCHEME 2

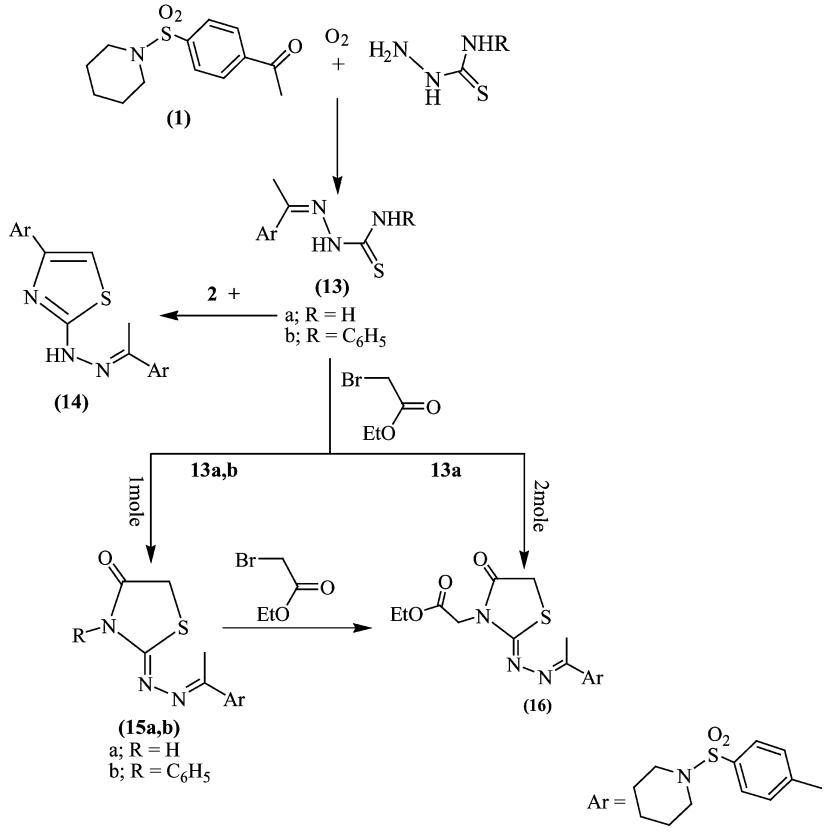
TABLE I Physical and Analytical Data for the Newly Prepared Compounds

Comp.	m.p (solvent)	Color (yield %)	M. formula (M. wt.)	Calc. (Found) C	Calc. (Found) H
3a	244 (Et./B.)	Yellow (79)	$C_{14}H_{17}N_3O_2S_2$ (323)	51.95 (52.01)	5.20 (5.26)
3b	213 (Et.)	Yellow (85)	$C_{20}H_{21}N_3O_2S_2$ (399)	60.10 (60.15)	5.20 (5.26)
3c	137 (Et./B.)	Yellow (80)	$C_{15}H_{18}N_2O_2S_2$ (322)	55.80 (55.90)	5.50 (5.59)
3d	171 (Et./B.)	Yellow (80)	$C_{16}H_{17}N_3O_2S_2$ (347)	55.16 (55.33)	4.85 (4.90)
3e	220 (Et./B.)	Yellow (79)	$C_{22}H_{24}N_4O_3S_2$ (456)	57.70 (57.89)	5.10 (5.26)
4	211 (Et./B.)	Yellow (70)	$C_{22}H_{21}N_5O_2S_2$ (451)	58.50 (58.54)	4.60 (4.66)
7	199 (Et./B.)	Yellow (80)	$C_{24}H_{23}N_3O_3S_2$ (465)	61.70 (61.91)	4.80 (4.98)
10	276 (Et./B.)	Yellow (70)	$C_{19}H_{20}N_6O_2S_3$ (460)	49.57 (49.57)	4.35 4.35)
11	207 (Et./B.)	Yellow (80)	$C_{22}H_{24}N_6O_3S_3$ (516)	51.06 (51.16)	4.55 (4.65)
12	321 Dioxan	Colorless (66)	$C_{21}H_{22}N_6O_3S_3$ (502)	50.15 (50.20)	4.28 (4.38)
13a	230 (Et./B.)	Pale yellow (80)	$C_{14}H_{20}N_4O_2S_2$ (340)	49.38 (49.41)	5.66 (5.88)
13b	201 (Et.)	Yellow (78)	$C_{20}H_{24}N_4O_2S_2$ (416)	57.67 (57.69)	5.65 (5.77)
14	285 (Et.)	Yellow (65)	$C_{27}H_{33}N_5O_4S_3$ (587)	55.17 (55.19)	5.52 (5.62)
15a	210 (Et./B.)	Yellow (80)	$C_{16}H_{20}N_4O_3S_2$ (380)	50.33 (50.53)	5.22 (5.26)
15b	220 (Et./B.)	Yellow (85)	$C_{22}H_{24}N_4O_3S_2$ (456)	57.77 (57.89)	5.16 (5.26)
16	156 (Et.)	Faint yellow (80)	$C_{20}H_{26}N_4O_5S_2$ (466)	51.47 (51.50)	5.48 (5.58)
19a	247 (Et./B.)	Yellow (75)	$C_{24}H_{26}N_4O_4S_2$ (498)	72.25 (72.36)	6.43 (6.53)
19b	215 (Et./B.)	Yellow (77)	$C_{30}H_{30}N_4O_4S_2$ (573)	62.62 (62.77)	5.12 (5.23)
19c	216 (Et.)	Yellow (77)	$C_{29}H_{27}ClN_4O_3S_2$ (579)	60.01 (60.16)	4.57 (4.67)
19d	232 (Et./B.)	Colorless (85)	$C_{29}H_{28}N_4O_3S_2$ (544)	63.87 (63.97)	5.04 (5.15)
20	201 (Et./B.)	Yellow (70)	$C_{28}H_{32}N_4O_6S_2$ (584)	57.33 (57.53)	5.41 (5.48)
22	196 (Et./B.)	Yellow (80)	$C_{14}H_{21}N_5O_2S_2$ (355)	47.21 (47.32)	5.79 (5.92)
23	210 (Et.)	Pale yellow (66)	$C_{22}H_{25}N_5O_2S_2$ (455)	57.99 (58.02)	5.31 (5.49)
24	210 (Et.)	Brown (66)	$C_{16}H_{21}N_5O_3S_2$ (395)	48.54 (48.61)	5.28 (5.32)
26	141 (Et./B.)	Yellow (82)	$C_{32}H_{33}N_5O_5S_2$ (631)	60.78 (60.86)	5.18 (5.23)

E.t, Ethanol; B, Benzene.

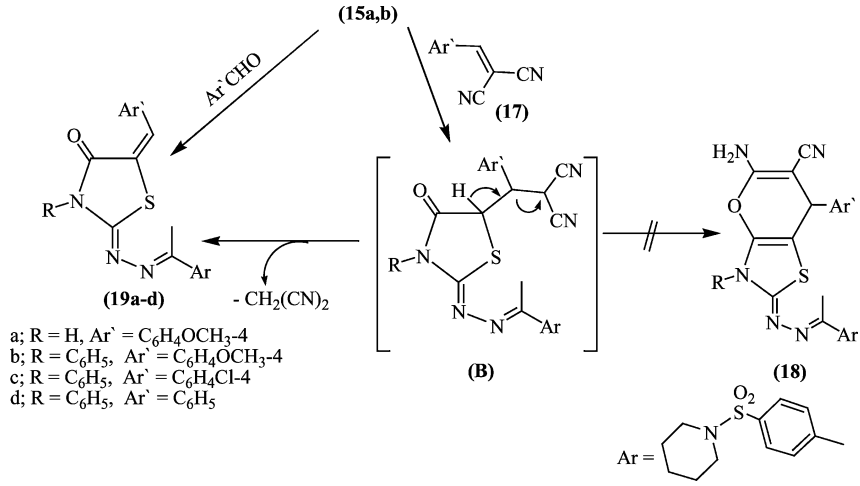
structure of **10** was provided on the basis of elemental analysis and spectral data. Treatment of **10** with triethylorthoformate in acetic anhydride under reflux gave the corresponding 5-ethoxymethyleneamino derivative (**11**). Compound **11** treated with hydrazine hydrate in stirred ethanol at room temperature led to the formation of a product that was found to be identical in all respects (m.p., mixed m.p., and spectral data) with **10**. The formation of **10** was assumed to proceed via addition of hydrazine to give the hydrazino intermediate (**A**) followed by elimination of ethyl formate hydrazone[21] (Scheme 2). Interaction of **10** with refluxing acetic anhydride yielded a single product that was identified as 1-(thiazol-2-yl)pyrazolo[3,4-d]pyrimidine-4-one derivative (**12**) on the basis of elemental analysis and spectral data (Scheme 2).

Condensation of *p*-piperidinosulfonylacetophenone (**1**) with thiosemicarbazide gave the corresponding thiosemicarbazones (**13a**,**b**) (Scheme 3). The structure of **13** was confirmed on the basis of elemental

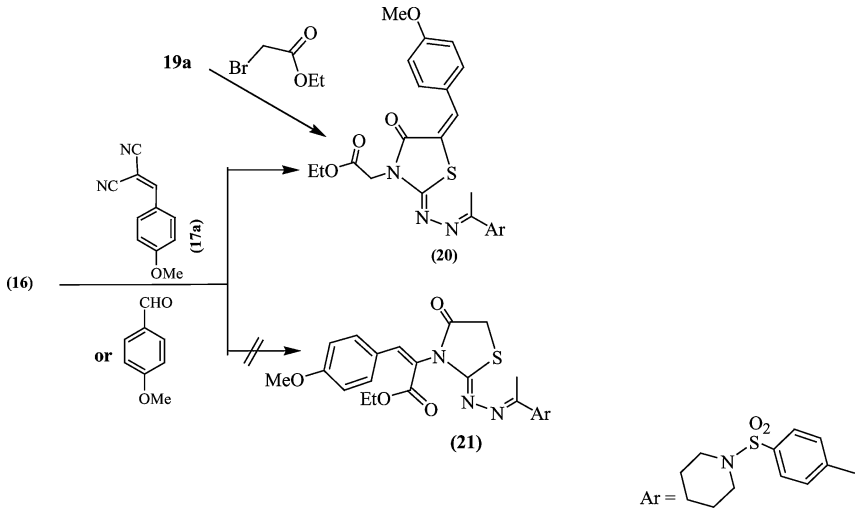


SCHEME 3

analysis and spectral data. The mass spectrum of **13b** gave a fragment peak at m/z (intensity %) 323 (30.1) ([M^+]-$C_6H_5NH_2$) instead of molecular ion peak. Treatment of **13a** with phenacyl bromide derivative **2** gave the corresponding 2-aminothiazole derivative **14** bearing two sulfonamide groups (Scheme 3). Cyclocondensation of **13a**,**b** with an equimolar ratio of ethyl bromoacetate afforded the corresponding 4-thiazolidinone (**15a**,**b**), respectively. Treatment of **13a** with two moles of ethyl bromoacetate gave N-ethoxycarbonylmethylthiazolidin-4-one derivative (**16**). The structure of **16** was further confirmed unequivocally by an independent synthesis from **15a** and ethyl bromoacetate in ethanolic sodium acetate solution (Scheme 3). Attempts to transform 4-thiazolidinone **15** into fused thiazolo[4,5-b]pyran compound **18** through Michael addition of **15** with arylidene malononitrile **17** were unsuccessful, and the only isolatable products were identified as 5-arylmethylidenethiazolidine-4-one derivatives (**19**), which were prepared from condensation of **15** with aromatic aldehydes. The formation of **19** from **15** and **17** can be explained by the addition of active methylene of **15** to active olefinic bond of **17** forming the intermediate (**B**), which undergoes spontaneous elimination of malononitrile to give the final product **19** (Scheme 4). Also, the thiazolidinone **16** reacted with *p*-methoxybenzylidenemalononitrile (**17a**) or p-methoxybenzaldeyde to give a single product with two possible isomeric structures (**20**, **21**). The absence of thiazole CH_2 proton signal at δ 3.8 ppm and the existance of CH_2 proton signal of acetate moiety at δ 4.7 ppm in its PMR spectrum provided firm support for the structure **20**



SCHEME 4



SCHEME 5

(Scheme 5). The structure **20** was further supported by an independent synthesis from the reaction of **19a** with ethyl bromoacetate.

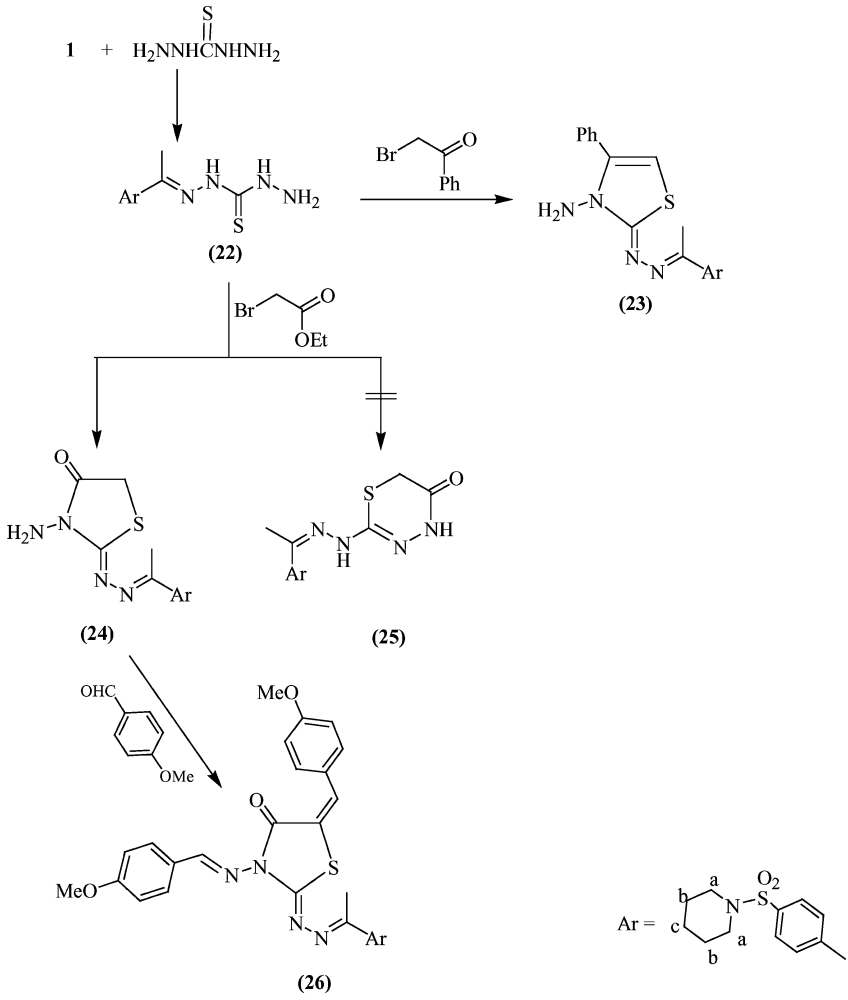
The structures of **13–20** were supported by correct elemental analysis (Table I) and spectral data.

Condensation of **1** with thiocarbohydrazide afforded thiocarbohydrazone derivative **22**. Cyclocondensation of **22** with equimolar amount of phenacyl bromide yielded 4-phenylthiazol-3-ylamine derivative **23** (Scheme 6). Also, **22** reacted with ethyl bromoacetate to give a single product. Two possible isomeric structures were proposed: 3-aminothiazolidin-4-one (**24**) and 1,3,4-thiadiazin-5-one (**25**) derivatives. The absence of NH signal and the existence of NH_2 signal at δ 4.7 ppm (PMR spectrum) provided firm support for the structure **24**. Further confirmation for structure **24** comes from its ready condensation with two moles of *p*-anisaldehyde to afford the corresponding 5-(4-methoxybenzylidene)-3-(4-methoxybenzylidene-amino)-thiazolidin-4-one derivative (**26**) (Scheme 6). This condensation supports the presence of free NH_2 and active CH_2 groups in **24**.

The above structures were established from elemental analysis (Table I) and spectral data.

ANTIMICROBIAL ACTIVITIES

The results of antimicrobial screening (Table II) show that the compound **15b** is the most active compound against *Klebsiella pneumo-*



SCHEME 6

nia (NCIMB-9111) (IZ 20 mm), while compounds **3b**, **16**, **19a**, **22** gave IZ 19 mm and compound **13a** gave IZ 18 mm. Also, the results indicated that compounds **16**, **13a** exhibited highest activity against *Rhizopus fungi* (IZ 24, 23 mm, respectively), while compounds **3b**, **3d**, **7**, **15b**, and **19a** gave IZ 18–20 mm. The compound **19d** exhibited highest activity against *Aspergillus fungigatus* (IZ 22 mm) while compounds **3a**,**b**,**d**, **19a**, and **22** gave IZ 19–20 mm. All remaining tested compounds are weakly active against all of the tested microorganisms. It seems

TABLE II Antimicrobial Activity of Some Compounds; Inhibition Zone Diameter (mm)

Compd. no.	Gram-positive			Gram-negative			Unicellar fungi		Filamentous fungi
	B. subtilis (NCTC-1040)	*S. aureus* (NCTC-7447)	*S. maxima* (ATCC-33910)	*K. peneumonia* (NCIMB-9111)	*Salmonella*	*P. aeruginosa* (ATCC-10145)	*C. albicans* (IMRU-3669)	*Rhizopus*	*A. fumigatus*
3a	14	15	16	13	16	16	19	17	19
3b	15	14	17	19	17	15	13	18	19
3e	13	13	12	14	12	14	12	16	17
7	14	13	17	16	15	15	19	18	17
13a	15	15	17	18	15	14	16	23	14
15a	14	13	17	13	15	12	16	12	13
15b	16	13	13	20	14	13	15	20	13
16	13	12	17	19	13	15	15	24	12
19a	12	13	14	19	14	14	14	20	20
19b	12	13	12	12	16	14	14	12	16
19c	13	13	12	10	12	13	12	12	17
19d	12	13	14	13	12	15	16	13	22
22	17	12	17	19	17	14	16	15	20
26	12	12	17	14	13	13	16	16	17
Ampicillin (AMD) 25 mg							24	25	25
Calforan 30 mg									

that most activity was exhibited by derivatives with thiazolidinone nucleus.

EXPERIMENTAL SECTION

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University. Ultraviolet spectra were recorded on Perkin Elmer Lambda-3B UV-visible spectrophotometer. IR spectra (KBr) were measured on a Fourier transform infrared (FTIR)/5300 spectrometer, ^{1}H NMR spectra on a Varian Mercury (300/75 MHz) spectrometer and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer.

Thiazol-2-yl Derivatives (3a–e)

A mixture of phenacyl bromide (**2**) (0.01 mol) and thiourea, thioacetamide compounds (0.01 mol) in ethanol (50 ml) was heated under reflux for 4 h. The separated solid was filtered off, washed with ethanol, and recrystallized from suitable solvent to give **3a–e** (Table I).

3a: IR (film) $\nu = 3426$, 3295 (NH_2), 2946 (CH-aliph.), 1630 cm^{-1} (C=N). MS (EI, 70 eV): m/z (%) = 323 (35.4) [M^+], 239 (5.7), 175 (68.6), 133 (8), 84 (100).

3b: IR (film): $\nu = 3309$ (NH), 2936 (CH-aliph.), 1595 cm^{-1} (C=N). MS (EI, 70 eV): m/z (%) = 399 (100) [M^+], 316 (28.25), 251 (70.36), 133 (0.25), 84 (4.11).

3c: IR (film): $\nu = 3100$ (CH-arom.), 2980 cm^{-1} (CH-aliph.). ^{1}H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.43$ (br, 2H, CH_2 (c), piperidine), 1.64 (t, 4H, $2CH_2$ (b), piperidine), 2.70 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 7.45 (s, 1H, CH-thiazole), 7.79 and 8.03 ppm (dd, 4H, AB-ArH; $J = 10.2$ Hz). MS (EI, 70 eV): m/z (%) = 322 (17.6) [M^+], 238 (10), 174 (38.5), 133 (8.3), 84 (100).

3d: IR (film): $\nu = 3090$ (CH-arom.), 2855 (CH-aliph.), 2251 cm^{-1} (CN). ^{1}H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.43$ (br, 2H, CH_2 (c), piperidine), 1.64 (t, 4H, $2CH_2$ (b), piperidine), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 4.30 (s, 2H, CH_2CN), 7.70 and 8.10 (dd, 4H, AB-ArH; $J = 8.4$ Hz), 7.80 ppm (s, 1H, CH-thiazole). MS (EI, 70 eV): m/z (%) = 347 (10) [M^+], 263 (6.6), 199 (20.4), 133 (5.4), 84 (100).

3e: IR (film): $\nu = 3260$ (NH), 3095 (CH-arom.), 2843 (CH-aliph.), 1603 cm^{-1} (C=N). ^{1}H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.35$ (m, 2H, CH_2 (c), piperidine), 1.59 (m, 4H, $2CH_2$ (b), piperidine), 2.95 (t, 4H, $2CH_2$ (a), piperidine), 3.82 (s, 3H, OCH_3), 6.80–7.98 ppm (m, 10H, (8ArH, CH=N and CH-thiazole)). MS (EI, 70 eV): m/z (%) = 456 (25) [M^+], 323 (9), 239 (10), 175 (60), 133 (12), 84 (100).

Phenylhydrazono{4-[4-(piperidine-1-sulfonyl)phenyl]-thiazol-2-yl}acetonitrile (4)

Method (a)

To a solution of thiazol-2-ylacetonitrile derivative (**3d**) (0.01 mol) in ethanol (20 ml) containing sodium acetate (0.08 mol), benzene diazonium chloride (0.01 mol) was added dropwise with stirring. The obtained product was collected and recrystallized to give compound **4** (Table I).

Method (b)

p-Piperidinosulfonylacetophenacylbromide (**2**) (0.01 mol) and 2-phenylhydrazono-2-cyanoethanethioamide (**6**) (0.01 mol) in ethanol (50 ml) was heated under reflux for 5 h, the obtained product was collected to give **4**, m.p. and mixed m.p. determined with authentic sample gave no depression (Table I). IR (film): $\nu = 3120$ (NH), 2215 cm^{-1} (CN). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.43$ (br, 2H, CH_2 (c), piperidine), 1.64 (t, 4H, $2CH_2$ (b), piperidine), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 7.10–7.40 (m, 5H, ArH), 7.70 (s, 1H, CH-thiazole), 7.90 and 8.00 (dd, 4H, AB-ArH; $J = 9.9$ Hz), 13.90 ppm (s, 1H, NH). MS (EI, 70 eV): m/z (%) = 451 (18) [M^+], 423 (1.7), 275 (3.1), 199 (1.9), 133 (2.6), 77 (100).

3-(4-Methoxyphenyl)-2-{4-[4-(piperidine-1-sulfonyl)-phenyl]thiazol-2-yl}acrylonitrile (7)

Method (a)

A mixture of 3d (0.01 mol), *p*-anisaldehyde (0.012 mol), and piperidine (1 ml) in ethanol (50 ml) was refluxed for 1 h to give **7** (Table I).

Method (b)

A mixture of phenacyl bromide (**2**) (0.01 mol) and *p*-methoxybenzylidene-cyanothioacetamine (**8**) (0.01 mol) in ethanol (50 ml) was heated under reflux for 4 h, the separated solid was filtered off, washed with ethanol and recrystallized to give **7**, m.p. and mixed m.p. determined with authentic sample gave no depression (Table I). IR (film): $\nu = 3110$ (CH-arom.), 2942 (CH-aliph.), 2212 cm^{-1} (CN). MS (EI, 70 eV): m/z (%) = 465 (100) [M^+], 381 (11.8), 317 (35.6), 133 (3.9), 84 (17.4).

5-Amino-3-methylsulfonyl-1-{4-[4-(piperidine-1-sulfonyl)-phenyl]thiazol-2-yl}-1H-pyrazole-4-carbonitrile (10)

A mixture of phenacyl bromide (**2**) (0.01 mol) and 5-amino-4-cyano-3-methyl-sulphonylpyrazole-1-thiocarboxamide (**9**)[21] (0.01 mol) in

ethanol (50 ml) was heated under reflux for 7 h. The separated solid was washed with ethanol and recrystallized to give **10** (Table I). IR (film): $\nu = 3399$, 3297 (NH_2), 3097 (CH-arom.), 2216 cm^{-1} (CN). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.25$ (m, 2H, CH_2 (c), piperidine), 1.64 (m, 4H, $2CH_2$ (b), piperidine), 2.6 (s, 3H, CH_3S), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 6.6 (s, 2H, NH_2), 7.36 (s, 1H, CH-thiazole), 7.80 and 7.90 ppm (dd, 4H, AB-ArH; $J = 7.8$ Hz).-MS (EI, 70 eV): m/z (%) = 460 (48.2) [M^+], 312 (20.6), 265 (23.3), 175 (3.3), 133 (4.1), 101 (4.9), 84 (100), 77 (3.8).

N-(4-Cyano-5-methylsulfonyl-2-{4-[4-(piperidine-1-sulfonyl)phenyl]thiazol-2-yl}-2H-(pyrazole-3-yl)-formimidic acid ethyl ester (11)

A mixture of 10 (0.01 mol) and triethyl orthoformate (0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 5 h and the separated solid was recrystallized to give **11** (Table I). IR (film): $\nu = 3092$ (CH-arom.), 2929 (CH-aliph.), 2222 cm^{-1} (CN).

Reaction of Compound 11 with Hydrazine Hydrate

A mixture of **11** (0.01 mol) and hydrazine hydrate (0.12 mol) in ethanol (40 ml) was stirred at room temperature for 2 h, and the solid that formed was recrystallized to give **10**. m.p. and mixed m.p. were determined with authentic sample gave no depression (Table I).

6-Methyl-3-methylsulfonyl-1-{4-[4-(piperidine-1-sulfonyl)phenyl]thiazol-2-yl}-1,5-dihydropyrazolo[3,4-d]-pyrimidin-4-one (12)

A mixture of **10** (0.01 mol) and acetic anhydride (30 ml) was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure and the separated solid was recrystallized to give **12** (Table I).-IR (film): $\nu = 3482$ (NH), 3094 (CH-arom.), 2934 (CH-aliph.), 1686 cm^{-1} (C=O).-MS (EI, 70 eV): m/z (%) = 502 (23) [M^+], 340 (23), 264 (17), 174 (10), 84 (100).

1-[4-(piperidine-1-sulfonyl)phenyl]ethanone Thiosemicarbazone and Its Phenyl Derivatives (13a,b)

A mixture of *p*-piperidinosulfonylacetophenone (**1**) (0.01 mol) and thiosemicarbazide or phenyl thiosemicarbazide (0.01 mol) in ethanol (50 ml) was heated under reflux for 5 h. The separated solid was recrystallized to give **13a**,**b** (Table I).

13a: IR (film): $\nu = 3431$, 3316 (NH_2), 3237 (NH), 2927 (CH), 1332 cm^{-1} (C=S). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.40$ (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.30 (s, 3H, CH_3), 3.00 (t, 4H, 2CH2 (a), piperidine), 6.4 (br, 2H, NH_2), 7.70 and 7.80 (dd, 4H, AB-ArH; $J = 8.4$ Hz), 8.70 ppm (s, 1H, NH).

13b: IR (film): $\nu = 3318$ (NH), 2937 (CH), 1292 cm^{-1} (C=S). MS (EI, 70 eV): m/z (%) = 323 (30.1) [$M^+ - C_6H_5NH_2$], 265 (15), 223 (21.9), 117 (33.8), 90 (7.5), 84 (100).

N-{1-[4-(Piperidine-1-sulfonyl)phenyl]ethylidene}-N′-{4-[4-(piperidine-1-sulfonyl)phenyl]thiazol-2-yl}hydrazine (14)

A mixture of **13a** (0.01 mol) and phenacyl bromide (**2**) (0.01 mol) in ethanol (50 ml) was heated under reflux for 8 h. The separated solid was recrystallized to give **14** (Table I). IR (film): $\nu = 3349$ (NH), 2935 (CH), 1556 cm^{-1} (C=N). MS (EI, 70 eV): m/z (%) = 587 (4.8) [M^+], 323 (9.5), 265 (11.2), 240 (4.3), 175 (20.6), 133 (4.3), 84 (100).

3-Substituted-2-({1-[4-(piperidine-1-sulfonyl)-phenyl]ethylidene}-hydrazono)thiazolidin-4-one (15a,b)

A mixture of **13a**,**b** (0.01 mol), ethyl bromoacetate (0.01 mol) and sodium acetate (0.08 mol) in ethanol (50 ml) was heated under reflux for 5 h. The separated solid was recrystallized to give **15a**,**b** (Table I).

15a: IR (film): $\nu = 3228$ (NH), 2933 (CH), 1726 cm^{-1} (C=O). MS (EI, 70 eV): m/z (%) = 380 (22.4) [M^+], 296 (2.5), 232 (11.4), 193 (16.2), 130 (25.6), 84 (100).

15b: IR (film): $\nu = 2932$ (CH), 1729 cm^{-1} (C=O). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.40$ (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.26 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 3.96 (s, 2H, CH_2), 7.30–7.50 (m, 5H, ArH), 7.70 and 7.90 ppm (dd, 4H, AB-ArH; $J = 8.7$ Hz).

[4-Oxo-2-({1-[4-(piperidine-1-sulfonyl)phenyl]-ethylidene}-hydrazono)thiazolidin-3-yl] Acetic Acid Ethyl Ester (16)

Method (a)

A mixture of **13a** (0.01 mol), ethyl bromoacetate (0.02 mol), and sodium acetate (0.08 mol) in ethanol (50 ml) was heated under

reflux for 8 h. The separated solid was recrystallized to give **16** (Table I).

Method (b)

A mixture of **15a** (0.01 mol), ethyl bromoacetate (0.02 mol), and sodium acetate (0.08 mol) in ethanol (50 ml) was heated under reflux for 8 h. The separated solid was recrystallized to give 16. m.p. and mixed m.p. determined with authentic sample gave no depression (Table I). IR (film): $\nu = 2940$ (CH), 1750 (CO-ester), 1727 cm^{-1} (C=O). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, CH_3-CH_2), 1.40 (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$-(b), piperidine), 2.40 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 3.80 (s, 2H, S-CH_2CO), 4.20 (q, 2H, CH_2-CH_3), 4.50 (s, 2H, N-CH_2-COOEt), 7.70 and 7.90 ppm (dd, 4H, AB-ArH; $J = 8.4$ Hz). MS (EI, 70 eV): m/z (%) = 466 (31.1) [M^+], 318 (4.2), 232 (6.4), 117 (100), 102 (32.3), 84 (85.9).

3,5-Disubstituted-2-({1-[4-(piperidine-1-sulfonyl)phenyl]-ethylidene}-hydrazono)- thiazolidin-4-one (19a–d)

Method (a)

A mixture of **15a**,**b** (0.01 mol), respective benzylidine malononitrile derivative (0.01 mol), and few drops of piperidine in ethanol (40 ml) was heated under reflux for 4 h. The separated solid was recrystallized to give **19a–d** (Table I).

Method (b)

A mixture of **15a** or **b** (0.01 mol), respective aromatic aldehyde (0.01 mol), and a few drops of piperidine in ethanol (40 ml) was heated under reflux for 4 h to give **19a–d**; m.p. and mixed m.p. determined with authentic sample gave no depression (Table I).

19a: IR (film): $\nu = 3113$ (NH), 2937 (CH), 1702 cm^{-1} (C=O).

19b: IR (film): $\nu = 2928$ (CH), 1709 (C=O), 1617 cm^{-1} (C=C). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.40$ (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.40 (s, 3H, CH_3), 2.90 (t, 4H, $2CH_2$ (a), piperidine), 3.80 (s, 3H, OCH_3), 7.00–8.00 ppm (m, 14H, (13ArH and =CH)).

19c: IR (film): $\nu = 2928$ (CH), 1708 cm^{-1} (C=O).

19d: IR (film): $\nu = 2935$ (CH), 1719 (C=O), 1613 cm^{-1} (C=C). MS (EI, 70 eV): m/z (%) = 544 (31.8) [M^+], 396 (2.4), 265 (6.9), 134 (100), 177 (24), 84 (39.4).

[5-(4-Methoxybenzylidene)-4-oxo-2-({1-[4-(piperidine-1-sulfonyl)phenyl]ethylidene}hydrazono)thiazolidin-3-yl] Acetic Acid Ethyl Ester (20)

Method (a)

A mixture of 16 (0.01 mol), *p*-methoxybenzylidenemalononitrile or *p*-anis-aldehyde (0.01 mol) and few drops of piperidine in ethanol (40 ml) was heated under reflux for 5 h. The separated solid was recrystallized to give **20** (Table I).

Method (b)

A mixture of **19a** (0.01 mol), ethyl bromoacetate (0.01 mol), and sodium acetate (0.08 mol) in ethanol (50 ml) was heated under reflux for 5 h. The separated solid was recrystallized to give **20**. m.p. and mixed m.p. determined with authentic sample gave no depression (Table I). IR (film): $\nu = 2932$ (CH), 1749 (CO-ester), 1706 cm^{-1} (CO).- ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.30$ (t, 3H, CH_3-CH_2), 1.40 (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.40 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 3.80 (s, 3H, OCH_3), 4.20 (q, 2H, CH_2-CH_3), 4.70 (s, 2H, CH_2-COOEt), 7.00 and 7.50 (dd, 4H, AB-ArH; $J = 8.7$ Hz), 7.70 (s, 1H, = CH), 7.70 and 8.00 ppm (dd, 4H, AB-ArH; $J = 8.7$ Hz).

N-{1-[4-(Piperidine-1-sulfonyl)phenyl]ethylidene}-thicarbohydrazone (22)

A mixture of acetophenone derivative (**1**) (0.01 mol) and thiocarbohydrazide (0.01 mol) in ethanol (50 ml) was heated under reflux for 4 h. The separated solid was recrystallized to give **22** (Table I). IR (film): $\nu = 3443$, 3263, 3170 (NH_2, NH), 1164 cm^{-1} (C=S). MS (EI, 70 eV): m/z (%) = 355 (3.7) [M^+], 323 (23), 265 (12.3), 249 (14.1), 223 (17.2), 117 (33), 84 (100).

4-Phenyl-2-({1-[4-(piperidine-1-sulfonyl)phenyl]-ethylidene}hydrazono)thiazol-3-ylamine (23)

A solution of **22** (0.01 mol) and phenacyl bromide (0.01 mol) in ethanol (30 ml) containing fused sodium acetate (0.02 mol) was heated under reflux for 3 h. The separated solid was recrystallized to give **23** (Table I). IR (film): $\nu = 3227$, 3113 (NH_2), 1587 cm^{-1} (C=N). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.20$ (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.50 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 4.70 (br, 2H, NH_2), 6.10 (s, 1H, CH-thiazole), 7.40–7.50 (m, 5H, ArH), 7.70–8.00 ppm (dd, 4H, AB-ArH; $J = 8.4$ Hz). MS (EI, 70 eV): m/z (%) = 455

(27.1) [M^+], 265 (26.3), 190 (100), 134 (37.4), 117 (23.7), 84 (70.5), 77 (38.3).

3-Amino-2-({1-[4-(piperidine-1-sulfonyl)phenyl]-ethylidene}hydrazono)thiazolidin-4- one (24)

A mixture of **22** (0.01 mol) and ethyl bromoacetate (0.01 mol) in ethanol (30 ml) containing fused sodium acetate (0.02 mol) was heated under reflux for 3 h. The obtained solid was recrystallized to give **24** (Table I). IR (film): $\nu = 3446$, 3240 (NH_2), 3095 (CH-arom.), 2851 (CH-aliph.), 1724 cm^{-1} (C=O). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.40$ (m, 2H, CH_2 (c), piperidine), 1.60 (m, 4H, $2CH_2$ (b), piperidine), 2.50 (s, 3H, CH_3), 3.00 (t, 4H, $2CH_2$ (a), piperidine), 3.80 (s, 2H, CH_2), 4.70 (s, 2H, NH_2; exchanged with D_2O), 7.70 and 8.00 ppm (dd, 4H, AB-ArH; $J = 10.3$ Hz). MS (EI, 70 eV): m/z (%) = 395 (25.1) [M^+], 265 (61.1), 117 (38.4), 84 (100).

5-(4-Methoxybenzylidene)-3-[(4-Methoxybenzylidene)-amino]-2-({1-[4-(piperidine-1-sulfonyl)phenyl]-ethylidene}hydrazono)thiazolidin-4-one (26)

A mixture of **24** (0.01 mol) and p-anisaldehyde (0.02 mol) in ethanol (30 ml) contains few drops of piperidine was heated under reflux for 4 h. The separated solid was recrystallized to give 26 (Table 1). IR (film): $\nu = 3098$ (CH-arom.), 2920 (CH-aliph.), 1718 cm^{-1} (C=O). ^1H NMR (300.069 MHz, $CDCl_3$): $\delta = 1.50$ (br, 2H, CH_2 (c), piperidine), 1.66 (br, 4H, $2CH_2$ (b), piperidine), 2.50 (s, 3H, CH_3), 3.00 (s, 4H, $2CH_2$ (a), piperidine), 3.87 and 3.88 (2s, 6H, $2OCH_3$), 7.80 (s, 1H, =CH), 9.20 (s, 1H, N=CH), 6.90–8.08 ppm (m, 12H, 3AB-ArH).

ANTIMICROBIAL SCREENING

The selected compounds were evaluated for their antimicrobial activity using the agar diffusion technique.[22,23] A mg/ml solution in dimethylformamide was used. The test organisms were Gram-positive *Bacillus subtilis* (NCTC-1040), *Staphylcococcus aureus* (NCTC-7447), *Sarcina maxima* (ATCC-33910); Gram-negative *Klebsiella peneumonia* (NCIMB-9111), *Salmonella, Pseudomonas aeruginosa* (ATCC-10145); Unicellular fungi *Candida albicans* (IMRU-3669); and Filamentous fungi *Rhizopus, Asperigillus fumigatus*. DMF showed no inhibition zones. The reference antibiotics were *Ampicillin* (*AMD*) and *Calforan*. The inhibition zones (IZ) of these compounds are listed in Table II.

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