Bull. Pharm. Sci., Assiut University Vol. 17, Part 1, July 1994, pp. 17-25

SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SOME NEW 1,3,4-OXADIAZOLES AND 2-SUBSTITUTED AMINO-1,3,4-OXADIAZOLE DERIVATIVES CONTAINING BENZIMIDAZOLE MOIETY

F.A. Ashour[1], S.A.M. El-Hawash, M.A. Mahran, A.H. Yousry* and A.F. Hamouda*

Pharmaceutical Chemistry Department, Faculty of Pharmacy, Alexandria University, Egypt
** Department of Microbiology, High Institute of Public Health, University of Alexandria, Egypt*

في هذا البحث تم تحضير مركبات جديدة من ١،٣،٤-اكساديازول و٢-مستبدلات أمينو ١،٣،٤-اكساديازول المحتوى على نواة البنزايميدازول وقد تم اختبار فاعلية هذه المركبات ضد البكتريا وثبت أن لمركب واحد من هذه المركبات فاعلية ضد بعض البكتريا. كما ثبت عدم فاعلية هذه المركبات ضد فطر الكانديدا البيكانس.

New 2-[4-(3-acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1H-bezimidazoles (V) and 2-[4-(3-acetyl-2-substituted-2,3-diydro-1,3,4-oxadiazol-5yl)phenoxymetyl]-1-methyl-1H-benzimidazoles (VI) were synthesized by cyclization of 2-[4-alkylidene or arylidenehydrazinocarbonyl)phenoxymethyl]-1H-benzimidazoles (III) or 2-[4-(alkylidene or arylidenehydrazinocarbonyl)phenoxymethyl]-1-methyl-1H-benzimidazoles (IV) with acetic anhydride.

New series of 2-[4-substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1H-benzimidazoles (IX) and 2-[4-substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1H-benzimidazoles (X) were obtained by cyclodesulfurization of 2-[4-(substituted-thiocarbamoylhydrazinocarbonyl)phenoxymethyl]-1H-benzimidazoles (VII) or 2-[4-(substitutedthiocarbamoylhydrazinocarbonyl)phenoxymethyl]-1-methyl-1H-benzimidazoles (VIII). The structure of the newly synthesized compounds were elucidated by elemental analysis, IR and ^{1}H-NMR spectra. Their antimicrobial activity was studied.

INTRODUCTION

Various compounds containing 1,3,4-oxadiazole moiety have been reported to exhibit antibacterial[1-3] and antifungal[3-6] activity. In addition, antibacterial[7,8] and antifungal[8-10] activities have been ascribed to several derivatives of benzimidazoles.

As a continuation of our research on the synthesis of oxadiazoles as antimicrobial agents[11], it was designed in the present investigation to synthesize new series of compounds containing an oxadiazole moiety attached to benzimidazole and evaluate their antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as nujol mulls on a Shimadzu IR 408 spectrometer. ^{1}H-NMR spectra were recorded on JEOL FX90Q 90 MHz spectrometer. Chemical shifts are reported in ppm. downfield from tetramethylsilane used as internal standard.Elemental analyses were carried out at the Microanalytical unit, University of Cairo, Egypt.

---

[1] To whom correspondence should be addressed

Received in 9/9/1993 & Accepted in 28/11/1993

4-(1-Methyl-1*H*-2-benzimidazolyl methyloxy) benzoic acid hydrazide (II):

A mixture of 2-[4-(ethoxycarbonyl) phenoxymethyl]-1-methyl-1*H*-benzimidazole[12] (0.3 g, 0.001 mole) and hydrazine hydrate (98%) (5 ml) was heated on a water bath for 3 hr. Water was then added and the precipitated solid was filtered, washed with water and crystallized from ethanol m.p. 217-18°C; yield (0.25 g, 80%). IR (cm^{-1}) 3400, 3300, 3205 (NH_2 and NH); 1675 (amide I band); 1520 (amide II band); Anal. for $C_{16}H_{16}N_4O_2$ Calcd. C:64.85, H: 5.44, N: 18.90, Found; C: 64.6, H: 5.4, N: 18.6.

2-[4-(Alkylidene or arylidenehydrazino-carbonyl)phenoxymethyl]-1*H*-benzimidazoles (III a-f) and 2-[4-(alkylidene or arylidene-hydrazinocarbonyl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (IV a-e):

To a solution of 0.01 mole of the acid hydrazide (I)[13] or (II) in ethanol (50 ml) was added 0.01 mole of the appropriate aldehyde or ketone and 2 drops of glacial acetic acid. The reaction mixture was heated under reflux for 3-4 hr (compound III c,d and IV c needed 10 hr.), concentrated and cooled to room temperature. The resulting product was filtered (in case of III c,d and IV c the products deposited after addition of drops of water), dried and crystallized from ethanol or aqueous ethanol (Table 1). The IR (cm^{-1}) of compounds (III a-f) showed 3300-3200 (br. NH), 1660-1640 (C=O), compounds (IV a-e) showed 3250-3150 (NH); 1650-1645 (C=O). ^{1}H-NMR of compound (III b) (DMSO-d_6) δ ppm; 3.7 (s, 3H, O$\underline{CH_3}$), 3.9 (s, 3H, O$\underline{CH_3}$), 5.45 (s, 2H, $\underline{CH_2}$), 6.9-7.95 (m, 11H, Ar-$\underline{H}$), 8.4 (br.s, 1H, N$\underline{H}$), 11.8 (s, 1H, N$\underline{H}$). Compound (III f) ^{1}H-NMR (DMSO-d_6) δ ppm; 2.3 (s, 3H, $\underline{CH_3}$), 5.35 (s, 2H, $\underline{CH_2}$), 7.05-7.85 (m, 12H, Ar-$\underline{H}$), 10.55 (s, 1H, N$\underline{H}$), 12.6 (s, 1H, N$\underline{H}$). Compound (IV d) ^{1}H-NMR (DMSO-d_6) δ ppm; 2.35 (s, 6H, 2$\underline{CH_3}$), 3.9 (s, 3H, N-C$\underline{H_3}$), 5.5 (s, 2H, $\underline{CH_2}$), 7.17-7.95 (m, 12H, Ar-$\underline{H}$), 10.43 (s, 1H, O=C-N$\underline{H}$).

2-[4-(3-Acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1*H*-benzimidazoles (V a-f) and 2-[4-(3-acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (VI a-e).

A mixture of the appropriate III a-f, or IV a-e (0.001 mole) and acetic anhydride (5 ml) was heated under reflux for 2 hr. The reaction mixture was concentrated, cooled, and the solid separated after addition of cold water was filtered, washed with water, dried and crystallized from the proper solvent (Table 2). The IR (cm^{-1}) of compounds (V a-f) showed 3200-3150 (NH), 1700-1680 (C=O); Compounds (VI a-e) showed 1670-1660 (C=O), ^{1}H-NMR of compound V f (DMSO-d_6)δ ppm, 1.92 (s, 3H, $\underline{CH_3}$), 2.56 (s, 3H, CO$\underline{CH_3}$), 5.52 (s, 2H, $\underline{CH_2}$), 7.36-8.24 (m, 12H, Ar-$\underline{H}$); 10.24 (s, 1H, N$\underline{H}$). Compound VI d ($CDCl_3$) δ ppm: 2.4 (s, 3H, $\underline{CH_3}$),2.45 (s, 3H, C_6H_4-$\underline{CH_3}$), 2.5 (s,3H, CO$\underline{CH_3}$), 3.8 (s, 3H,N-$\underline{CH_3}$), 5.4 (s, 2H, $\underline{CH_2}$),7.0-7.9 (m, 12H, Ar-$\underline{H}$).

2-[4-(Substitutedthiocarbamoylhydrazino-carbonyl)phenoxymethyl]-1-methyl 1*H*-benzimidazoles (VIII a-e).

Equimolar quantities of 4-(1-methyl-1*H*-benzimidazole-2-yl) methoxybenzoic acid hydrazide (0.01 mole) and the appropriate isothiocyanate (0.01 mole) were heated under reflux in ethanol (100 ml) for 1-8 hours. The excess ethanol was distilled and the crystalline solid, separated on cooling was collected and crystallized from the proper solvent (Table 3). The IR (cm^{-1}) of compounds (VIII a-e) showed 3200-3100 (NH); 1675-1670 (C=O); 1545-1540, 1335-1330, 1145-1140, 940-930 (N-C=S amide I, II, III and IV bands). ^{1}H-NMR of compound VIII e (DMSO-d_6) δ ppm showed 2.32 9s, 3H, C_6H_4-$\underline{CH_3}$), 3.92 (s, 3H, N-$\underline{CH_3}$), 5.68 (s, 2H, $\underline{CH_2}$), 7.28-8.28 (m, 12H, Ar-$\underline{H}$), 9.92, 10.08, 10.72 (3s, 3H, N$\underline{H}$ of thiosemicarbazide moiety, deuterium exchangeable).

Table 1: 2-[4-(Alkylidene or arylidenehydrazinocarbonyl)phenoxymethyl]-1*H*-benzimidazoles (III a-f) and 2-[4-(alkyidene or arylidenehydrazinocarbonyl)phenoxymthyl]-1-methyl-1*H*-benzimidazoles (IV a-e).

Compd. No.	R	R^1	R^2	Yield %	M.P. °C (cryst. solv.)	Mol. Formula (Mol. Wt.)	Analyses %	
							Calcd.	Found
III a	H	H	$-C_6H_5$	65	165° (A)	$C_{22}H_{18}N_4O_2$ (371.42)	reference 13	
b	H	H	$3,4-C_6H_3(OCH_3)_2$	86	230-31 (A)	$C_{24}H_{22}N_4O_4$ (430.47)	C 66.97 H 5.15 N 13.02	67.1 5.0 13.2
c	H	CH_3	$-CH_3$	64	238-39 (B)	$C_{18}H_{18}N_4O_2$ (322.37)	C 67.07 H 5.63 N 17.38	67.0 5.2 17.4
d	H	CH_3	$-C_2H_5$	62	195-96 (B)	$C_{19}H_{20}N_4O_2$ (336.40)	C 67.84 H 5.99 N 16.65	68.0 5.7 16.4
e	H	CH_3	$-C_6H_4CH_3$ (P)	78	214 (A)	$C_{24}H_{22}N_4O_2$ (398.47)	C 72.34 H 5.57 N 14.06	72.5 5.7 13.7
f	H	CH_3	$-C_6H_4Br$ (P)	74	278 (A)	$C_{23}H_{19}BrN_4O_2$ (463.34)	C 59.62 H 4.13	59.6 3.9
IV a	CH_3	H	$-C_6H_5$	76	195 (A)	$C_{23}H_{20}N_4O_2$ (384.44)	C 71.86 H 5.24 N 14.57	71.7 5.4 15.0
b	CH_3	H	$3,4-C_6H_3(OCH_3)_2$	78	202-4 (A)	$C_{25}H_{24}N_4O_4$ (444.49)	C 67.56 H 5.44 N 12.60	67.2 5.0 12.2
c	CH_3	CH_3	$-C_2H_5$	74	210 (B)	$C_{20}H_{22}N_4O_2$ (350.42)	C 68.55 H 6.33 N 15.99	67.9 6.6 15.6
d	CH_3	CH_3	$-C_6H_4CH_3$ (P)	79	230 (A)	$C_{25}H_{24}N_4O_2$ (412.50)	C 72.80 H 5.86 N 13.58	72.5 5.7 13.6
e	CH_3	CH_3	$-C_6H_4Br$ (P)	85	258 (A)	$C_{24}H_{21}BrN_4O_2$ (477.37)	C 60.39 H 4.43	60.7 4.3

A = Ethanol, B = Ethanol/H_2O.

Table 2: 2-[4-(3-Acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1*H*-benzimidazoles (V a-f) and 2-[4-(3-acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidaziles (VI a-e).

Compd. No.	R	R^1	R^2	Yield %	M.P. °C (cryst. solv.)	Mol. Formula (Mol. Wt.)	Analyses %	
							Calcd.	Found
V a	H	H	$-C_6H_5$	72	152-53 (A)	$C_{24}H_{20}N_4O_3$ (412.45)	C 69.89 H 4.89 N 13.58	69.5 4.9 13.3
b	H	H	$3,4-C_6H_3(OCH_3)_2$	76	164-5 (A)	$C_{26}H_{24}N_4O_5$ (472.51)	C 66.09 H 5.12 N 11.86	55.9 5.1 11.5
c	H	CH_3	$-CH_3$	68	166-7 (B)	$C_{20}H_{20}N_4O_3$ (364.41)	C 65.92 H 5.53 N 15.37	65.8 5.3 15.1
d	H	CH_3	$-C_2H_5$	65	200 (B)	$C_{21}H_{22}N_4O_3$ (378.43)	C 66.65 H 5.86 N 14.80	66.5 5.9 14.4
e	H	CH_3	$-C_6H_4CH_3$ (P)	82	190 (A)	$C_{26}H_{24}N_4O_3$ (440.51)	C 70.89 H 5.49 N 12.72	71.1 5.3 12.6
f	H	CH_3	$-C_6H_4Br$ (P)	85	250 (A)	$C_{25}H_{21}BrN_4O_3$ (505.38)	C 59.42 H 4.19 N 11.09	59.3 4.3 10.6
IV a	CH_3	H	$-C_6H_5$	78	157 (A)	$C_{25}H_{22}N_4O_3$ (426.48)	C 70.41 H 5.20 N 13.14	70.7 5.3 13.2
b	CH_3	H	$3,4-C_6H_3(OCH_3)_2$	75	183 (A)	$C_{27}H_{26}N_4O_5$ (486.53)	C 66.66 H 5.39 N 11.52	66.5 5.4 11.1
c	CH_3	CH_3	$-C_2H_5$	70	185 (B)	$C_{22}H_{24}N_4O_3$ (392.46)	C 67.33 H 6.16	67.2 6.1
d	CH_3	CH_3	$-C_6H_4CH_3$ (P)	85	165 (A)	$C_{27}H_{26}N_4O_3$ (454.53)	C 71.35 H 5.77 N 12.33	71.7 5.4 12.6
e	CH_3	CH_3	$-C_6H_4Br$ (P)	88	95 (A)	$C_{26}H_{23}BrN_4O_3$ (519.40)	N 10.79 Br 15.38	10.5 15.4

A= Ethanol/H_2O, B=$CHCl_3$/Pet. ehter 40-60°C.

Table 3: 2-[4-(Substitutedthiocarbomoylhydrazinocarbonyl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (VIII a-e).

Compd. No.	R^3	Yield %	M.P. °C (cryst. solv.)	Mol. Formula (Mol. Wt.)	Analyses %	
					Calcd.	Found
VIII a	n-C_4H_9	86	222-24 (A)	$C_{21}H_{25}N_2O_2S$ (411.53)	C 61.29 H 6.12 N 17.02 S 7.79	61.40 6.20 17.20 7.70
b	-C_6H_{11} (cyclo)	95	226-27 (A)	$C_{23}H_{27}N_5O_2S$ (437.58)	N 16.00 S 7.33	15.80 7.20
c	-$CH_2C_6H_5$	88	215-17 (A)	$C_{24}H_{23}N_5O_2S$ (445.55)	C 64.70 H 5.20 N 15.72	64.99 4.95 15.99
d	-C_6H_5	73	249-51 (B)	$C_{23}H_{21}N_5O_2S$ (431.52)	N 16.23 S 7.43	16.50 7.50
e	-$C_6H_4CH_3$ (p)	93	206-8 (B)	$C_{24}H_{23}N_5O_2S$ (445.55)	N 15.72 S 7.20	15.60 7.30

A= Ethanol, B=Ethanol/water.

2-[4-(2-Substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1*H*-benzimidazoles (IXa-e) and 2-[4-(2-substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (X a-e).

To a boiling stirred solution or suspension of the appropriate VII or VIII (0.001 mole) in ethanol (30 ml), finely powdered yellow HgO (0.2 g, 0.001 mole) was added portion wise, over a period of 30 min. The suspension was stirred and heated under reflux for 3-10 hours. The hot reaction mixture was filtered and the black precipitate was washed with boiling ethanol (2 ml). The filtrate and washings were combined, concentrated to a small volume and treated with drops of water. The precipitate formed was filtered, dried and crystallized from the proper solvent (Table 4). The IR of compounds (IX a-e) (cm^{-1}) showed 3400-3200 (NH), compounds (X a-e) showed 3440-3250 (NH). ^{1}H-NMR of compound IX c (DMSO-d_6) δ ppm; 4.56 (d, 2H, J=6 Hz, $\underline{CH_2}$-C_6-H_5), 5.52 (s, 2H, $\underline{CH_2}$-O), 7.36-8.08 (m, 13H, Ar-$\underline{H}$), 8.16 (br.s., 1H, N$\underline{H}$, deuterium exchangeable), 13 (br.s., 1H, N$\underline{H}$, deuterium exchangeable). ^{1}H-NMR of compound (X e) (DMSO-d_6) δ ppm; 2.4 (s, 3H, C_6H_5-$\underline{CH_3}$), 4.0 (s, 3H, N-$\underline{CH_3}$), 5.76 (s, 2H, $\underline{CH_2}$), 7.36-8.24 (m, 12H, Ar-$\underline{H}$), 10.96 (s, 1H, N$\underline{H}$), deuterium exchangeable).

Antimicrobial Testing

A) Inhibition Zone Measurement

Sterile Tryptic soy agar plates were prepared. The compounds to be tested were dissolved in dimethylformamide (10 mg/ml) and 20 μl each of these solutions were then dropped over the agar medium, and allowed to dry. The plates were then overplayed with 10 ml molten Tryptic soy agar inoculated with the test organism (20 μl of 24 hours Tryptic soy broth culture). The plates were incubated at 37° for 24 hours and the resulting inhibition zones were

measured. A control without the test compound was included for each organism. Amikacin (30 μg/ml) was used as a broad spectrum reference standard against the tested microorganisms (inhibition zone 17 mm. in diameter). Compounds which showed inhibition zones ≥ 17 mm in diameter were evaluated for their minimal inhibitory concentration (MIC).

B) Minimal inhibitory concentration (MIC) Measurement

The test organism was grown in Tryptic soy broth for 24 hours at 37°C. The compound to be tested was dissolved in dimethylformamide (500 μg/ml) and two fold serial dilutions were prepared using Tryptic soy broth. The tubes were then inoculated with 100 μl of the 24 hours test organism culture and were incubated at 37°C for 48 hours. The tubes showing turbidity were subcultured on Tryptic soy agar plates to confirm the presence or absence of bacterial growth.

RESULTS AND DISCUSSION

A- Chemistry

The new series of compounds were designed and synthesized comprising substituted oxadizole moiety joined to a substituted benzimidazole ring. It was hoped that some of the substituted isomers would yield a potent antibacterial or antifungal agents. Two substituted acid hydrazide I and II were selected as starting materials for this purpose.

The 4-(1*H*-2-benzimidazolyl methyloxy) benzoic acid hydrazide (I) was prepared according to a reported method[13] and the 4-(1-methyl-1*H*-2-benzimidazolyl methyloxy) benzoic acid hydrazide (II) was prepared from 2-[4-(ethoxycarbonyl)phenoxymethyl]-1-methyl-1*H*-benzimidazole[12] by reaction with hydrazine hydrate (Scheme 1). The 2-[4-(alkylidene or arylidenehydrazinocarbonyl)phenoxymethyl]-1*H*-benzimidazoles (III a-f) and 2-[4-(alkylidene or arylidenehydrazinocarbonyl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (IV a-e) were prepared by reaction of the acid hydrazide (I or II) with appropriate aldehydes or ketones. Cyclization of compounds (III a-f, IV a-e) with acetic anhydride gave 2-[4-(3-acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazole-5-yl)phenoxymethyl]-1*H*-benzimidazoles (V a-f) and 2-[4-(3-acetyl-2-substituted-2,3-dihydro-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (VI a-e).

The 2-[4-(butyl, cyclohexyl, benzyl, phenyl or p-tolyl-thiocarbamoylhydrazinocarbonyl) phenoxymethyl]-1*H*-benzimidazoles (VII) were prepared as reported[14]. The 2-[4-(substituted thiocarbamoylhydrazinocarbonyl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (VIII a-e) were prepared by reaction of (II) with the appropriate isothiocyanates. Compounds (VII) and (VIII) were converted to 2-[4-(2-substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1*H*-benzimidazoles (IX a-e) and 2-[4-(2-substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (X a-e) by cyclodesulfurization with freshly prepared yellow mercuric oxide.

The structures of the products were substantiated by microanalyses, IR and ^{1}H-NMR of representative examples.

B- Antimicrobial Activity

The newly prepared compounds were tested for *in vitro* activity against two Gram-negative bacilli (E. coli, K. pneumonia), Gram-positive cocci (Staphylococcus aureus: Oxford strain and penicillinase producer) and single strain of Candida albicans, using the agar diffusion method[15]. Amikacin (30 μg/ml) and 0.01% solution of nystatin were used as a reference standards (Table 5).

All the compounds showed no antibacterial potency (inhibition zone < 17 mm in diameter) against the tested Gram-negative bacilli and Gram-positive cocci except compound (IX e) which gave an inhibition zone of 22 mm and 20 mm in diameter to Gram-negative bacilli and Gram-positive cocci respectively, MIC was 15.625 (μg/ml). All the compounds were also found to lack the antifungal activity against the tested fungus (a single strain of Candida albicans).

Table 4: 2-[4-(2-Substitutedamino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1*H*-benzimidazoles(IX a-e) and 2-[4-(2-substituted amino-1,3,4-oxadiazol-5-yl)phenoxymethyl]-1-methyl-1*H*-benzimidazoles (X a-e).

Compd. No.		R	R^3	Yield %	M.P.°C (cryst. solv.)	Mol. Formula (Mol. Wt.)	Analyses %	
							Calcd.	Found
IX	a	H	$n\text{-}C_4H_9$	72	221-22 (A)	$C_{20}H_{21}N_5O_2$ (363.42)	C 66.10 H 5.82 N 19.27	66.3 5.7 19.3
	b	H	$-C_6H_{11}$ (cyclo)	76	204-5 (A)	$C_{22}H_{23}N_5O_2$ (389.46)	C 67.85 H 5.95	67.8 5.9
	c	H	$-CH_2C_6H_5$	83	188-90 (B)	$C_{23}H_{19}N_5O_2$ (397.44)	C 69.51 H 4.82 N 17.62	69.3 4.5 17.4
	d	H	$-C_6H_5$	82	260-61 (A)	$C_{22}H_{17}N_5O_2$ (383.41)	C 68.92 H 4.47 N 18.27	68.5 4.8 18.3
	e	H	$-C_6H_4CH_3$ (p)	50	240-2* (B)	$C_{23}H_{19}N_5O_2$ (397.44)	C 69.51 H 4.82 N 17.62	69.4 4.7 17.3
X	a	CH_3	$n\text{-}C_4H_9$	64	215-17 (A)	$C_{21}H_{23}N_5O_2$ (377.45)	C 66.83 H 6.14	67.2 6.0
	b	CH_3	$-C_6H_{11}$ (cyclo)	85	196-8 (B)	$C_{23}H_{25}N_5O_2$ (403.49)	C 68.47 H 6.25 N 17.36	68.2 6.2 17.2
	c	CH_3	$-CH_2C_6H_5$	78	197-99 (A)	$C_{24}H_{21}N_5O_2$ (411.47)	C 70.06 H 5.14 N 17.02	69.4 5.2 17.0
	d	CH_3	$-C_6H_5$	82	259-61 (A)	$C_{23}H_{19}N_5O_2$ (397.44)	C 69.51 H 4.82 N 17.62	69.58 4.93 17.70
	e	CH_3	$-C_6H_4CH_3$ (p)	89	211* (A)	$C_{24}H_{21}N_5O_2$ (411.47)	C 70.06 H 4.16 N 17.02	70.1 4.2 17.2

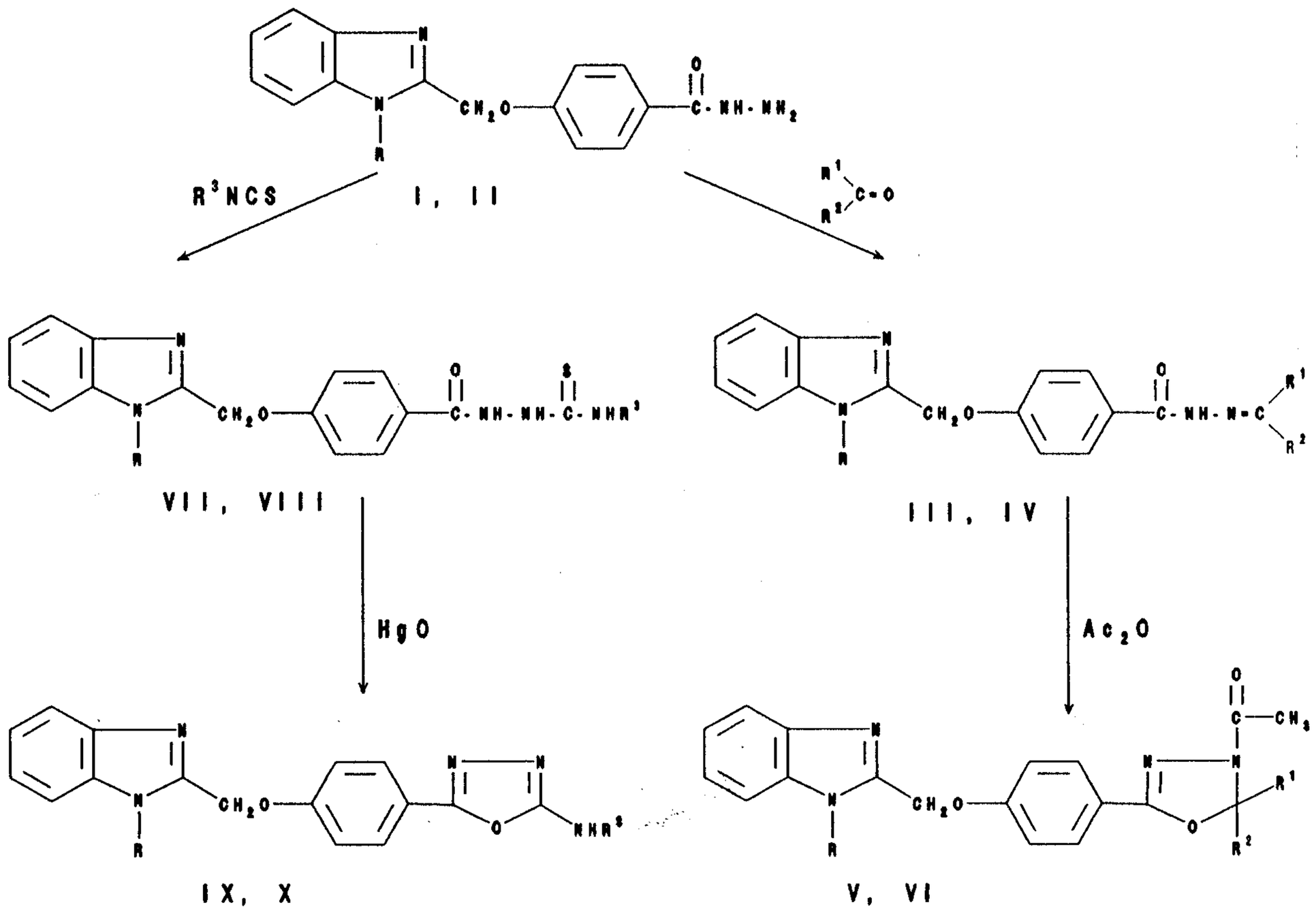
A = Ethanol, B=Ethanol/water.

* Melting with decomposition.

Table 5: Growth inhibition zones (mm) exhibited by the newly prepared compounds.

Compd.		S. aureus		E. Coli	K. Pneumonia	C. albicans
		Oxford	Penicillinase Producer			
II		-	-	-	-	-
III	a	13	-	-	-	-
	b	-	-	-	-	-
	c	-	-	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
	f	-	-	-	-	-
IV	a	-	-	-	-	-
	b	-	-	-	-	-
	c	-	-	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
V	a	-	-	-	-	-
	b	-	-	-	-	-
	c	-	-	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
	f	-	-	-	-	-
VI	a	-	-	-	-	-
	b	-	-	-	-	-
	c	9	10	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
VIII	a	16	14	-	-	-
	b	-	-	-	-	-
	c	-	-	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
IX	a	-	-	-	-	-
	b	-	-	-	-	-
	c	10	11	12	-	-
	d	-	-	-	-	-
	e*	20	20	22	22	-
X	a	-	-	-	-	-
	b	-	-	-	-	-
	c	-	-	-	-	-
	d	-	-	-	-	-
	e	-	-	-	-	-
Amikacin (30 μ/ml)		17	17	17	17	-
Nystatin (0.01%)		-	-	-	-	22

* MIC = 15.625 (μg/ml)



Scheme 1

REFERENCES

1. A.K.Sengupata and M.J.Garg, Antibact. Antifung. Agents. 9, 397 (1981).
2. K.H.Sinnur, S.Siddappa, Shivagogi, R.Purochit and G.Muralidhar, Indian J. Chem. Sect. B. 25B, 716 (1986).
3. K.P.Roda, R.N.Vansdadia, Parekh, Hansa, J. Indian Chem. Soc. 65, 44 (1988).
4. R.S.Sharma and S.C.Bahel, J. Antibact. Antifung. Agents, 10, 294 (1982).
5. H. Singh, A.R.Misra and L.D.S.Yadav, Indian J. Chem. Sect. B. 26B, 1000 (1987).
6. M.M.Dulta, B.N.Goswami and J.C.S.Kataky, J. Indian Chem. Soc. 64, 195 (1987).
7. G.Heywang, B.Baasner, G.Haenssier, W.Paulus, H.J.Santel, R.R.Schmidt and H.G.Schmitt, Ger.Offen (1988) De 3, 621, 265 C.A., 108, 221702f (1988).
8. S.Bahadur, M.Sazena and K.K. Pandey, J. Indian Chem. Soc., 58, 1018 (1981).
9. V.K.Mishra and S.C.Bahel, Indian J. Pharm. Sci., 47, 5 (1985).
10. A.C.Baillie, A.D.Buss, J.H.Parsons and P.E.Russel, Eur. Pat. EP 219, 192 (1987), C.A. 107, 134305g (1987).
11. F.A.Ashour and S.A.Al-Mazroa, Alex. J. Pharm. Sci., 4, 29 (1990).
12. F.A.Ashour, Alex. J. Pharm. Sci., 5, 16 (1991).
13. S.Bahadur and K.K.Pandy, Pharmazie, 34, 570 (1979).
14. F.A.Ashour and S.A.Al-Mazroa, IL Farmaco, 45, 1207 (1990).
15. J.E.Conti and S.L.Barriere "Manual antibiotics and infectious diseases" 1st. ed. Copyright, Leo and Febiger U.S.A. (1985).