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SYNTHESIS OF SOME NEW BENZIMIDAZOLE DERIVATIVES WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

A series of 2-aminomethylbenzimidazole (**I**) and 2-benzimidazolone (**II**) derivatives were synthesized. Imidazo-and pyrazino-derivatives (**IIIa-g**) were obtained from the reaction of compound (**I**) with acetic anhydride, glycine, carbon disulfide, chloroform, dibromoethane, phenacylbromide or diethyloxalate. Condensation of compound (**I**), acid hydrazide (**VII**) or compound **II** with some aldehydes or some amines, the Schiff's bases (**IVa-b**), (**VIIIa,b**) or (**Va-c**) respectively were produced. In addition, compound (**II**) was reacted with acetic anhydride to afford the diacetyl derivatives (**IX**) which was condensed with hydrazine, urea or thiourea to yield a triazolo-or triazino-derivatives **X** and **XIa,b** respectively. The prepared compounds were tested against some fungi and bacteria. Some of these compounds were found to have antimicrobial activity.

INTRODUCTION

Currently, benzimidazole derivatives are an object of sustained interest due to the vast range of their potential activities as antitumour agents[1-5] (e.g. pyrrolo[1,2-a]benzimidazole) and cardiotonic agents[6,7] (e.g. azobenzimidazole and pimobendan), as well as antibacterial, antifungal agents[8,11] (e.g. clemizole, penicillin and benomyl) and anthelmintic agents[12,13] (e.g. cambendazole). Also, compounds containing imidazole, triazole and pyrazine rings were found to have antibacterial and antifungal activities. Miconazole and related derivatives together with ketoconazole and metronidazole belong to the class of imidazole, fluconazole, intraconazole and terconazole are the most important drugs of triazole family[14,16]. In addition, azomethine containing compounds were documented to have antimicrobial activity[17].

The aim of the present research was to develop novel synthetic benzimidazole derivatives and to examine the antimicrobial activity.

Chemistry :

Thus, compound (**I**) was prepared according to reported procedures in the literature[18]. Imidazo-(1,5-a) benzimidazole derivatives (**IIIa-d**) were obtained by the reaction of 2-aminomethylbenzimidazole (**I**) with acetic anhydride or glycine in dil HCl solution and with carbon disulfide[19] or chloroform in KOH solution. Also, via the reaction of compound (**I**) with phenacylbromide, dibromoethane[20] or diethyloxalate[21-23] in KOH solution or by fusion, the pyrazino (1,2-a) benzimidazole derivatives (**IIIe-g**) were obtained. The azomethine containing compounds (**VIa-b**) were synthesized by condensation of the p-nitrobenzaldelyde or m-hydroxybenzaldehyde with compound (**I**). On the other hand, compound (**II**) was produced according to reported method[24]. Compound (**II**) was reacted with ethanolamine, isopropanolamine or p-aminobenzoic acid to afford Schiff's bases (**Va-c**). Compound (**Ve**) was reacted with $EtOH/H_2SO_4$ to give the corresponding ester (**VIa**) which then was condensed with hydrazine hydrate to yield acid hydrazide (**VII**). Compound (**VII**) was reacted with some aldehydes to obtain Schiff's bases (**VIIIa,b**). Also, compound **II** was reacted with acetic anhydride to give diacetyl-benzimidazolone **IX** which was condensed with hydrazine, urea or thiourea to afford triazolo-derivative (**X**) or triazino-derivatives (**XIa,b**). The sequence of the reaction adopted for the prepared compounds is illustrated in Scheme 1.

EXPERIMENTAL

All melting points were determined on Stuart Scientific Melting Point Apparatus SMP2 and were uncorrected. IR spectra were measured as KBr discs on Schimadzu IR 408 instrument. The ^{1}HNMR spectra were measured using 390 L spectrophotometer for solution in DMSO-d_6 using TMS as an internal standard. TLC was performed on glass plates coated with silica gel G eluted with a mixture of n-butanol, acetic acid, water (4:1:1) using ninhydrin or Dragendorff's reagent as spraying agent.

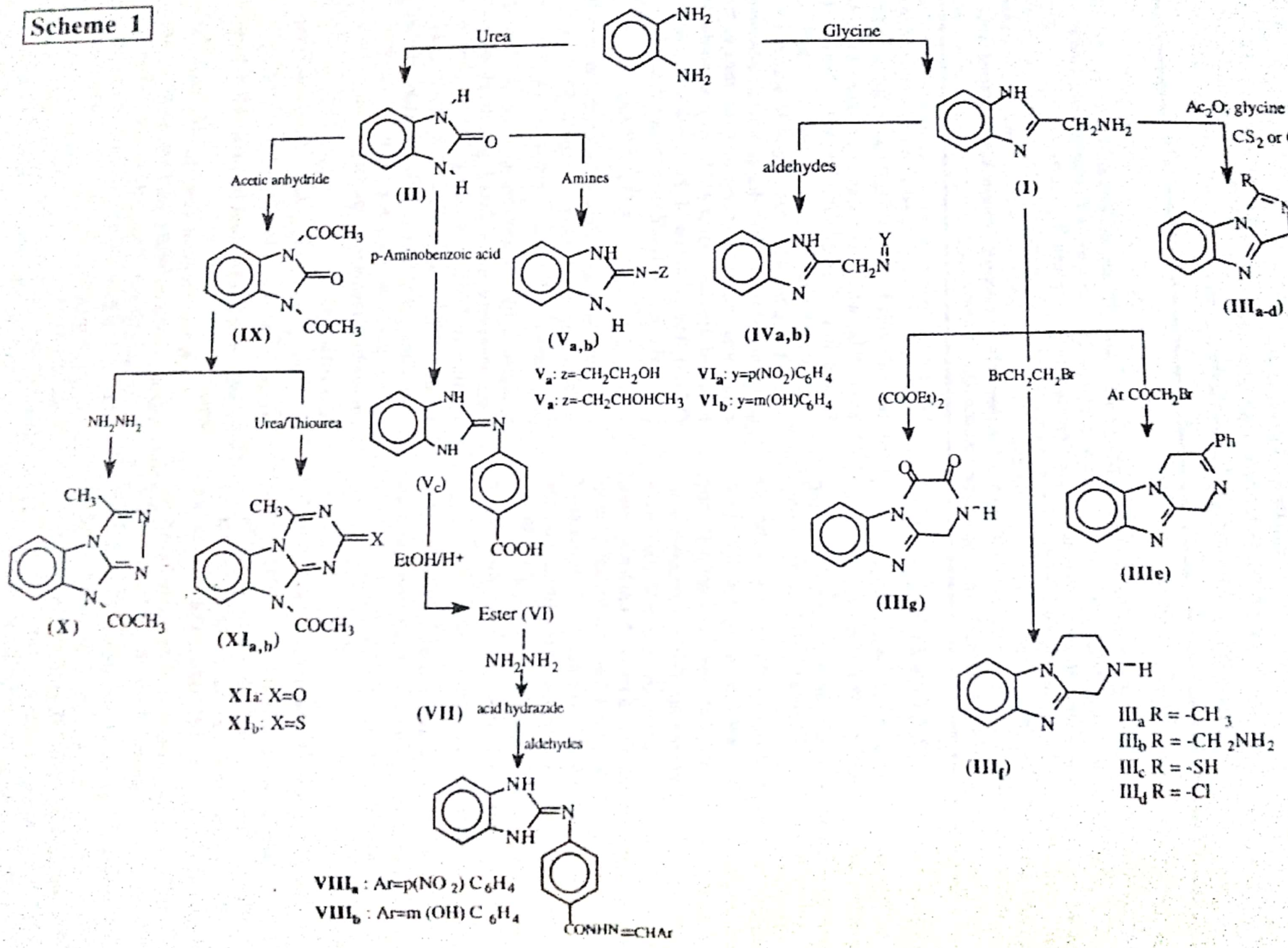
A. Synthesis:

Synthesis of 2-aminomethy lbenzimidazole **I** was carried out according to reported method[18].

Synthesis of 1-substiuted-imidazo-(1,5-a) benzimidazole (IIIa):

A few drops of conc. H_2SO_4 were added to a mixture of 0.01 mole of compound **I** and acetic anhydride (10 ml). The reaction mixture was heated at 80°C for 4 hr then cooled. The mixture was neutralized with sod. carbonate solution. A white needle crystalline product was collected by filtration and washed with aqueous sod. carbonate, then with water. The product gave negative ninhydrin reaction (Table 1). IR spectrum (ν, cm^{-1}), 3090 (Ar), 2950 (CH_3), 1640 (C = N). ^{1}HNMR spectrum (δ, ppm-DMSO-d_6): 2.2 (s, 3H,CH_3), 3.4 (s,2H,CH_2), 7.76 (m,ArH).

Scheme 1


Urea
Glycine
Acetic anhydride
Amines
p-Aminobenzoic acid
aldehydes
Ac2O; glycine or
CS2 or CHCl3
(II)
(I)
(IX)
(Va,b)
(IVa,b)
(IIIa-d)
NH2NH2
Urea/Thiourea
(COOEt)2
BrCH2CH2Br
Ar COCH2Br
(X)
(XIa,b)
(Vc)
EtOH/H+
Ester (VI)
(VII)
acid hydrazide
aldehydes
(IIIg)
(IIIe)
(IIIf)
XIa: X=O
XIb: X=S
Va: z=-CH2CH2OH
Va: z=-CH2CHOHCH3
VIa: y=p(NO2)C6H4
VIb: y=m(OH)C6H4
VIIIa : Ar=p(NO2) C6H4
VIIIb : Ar=m (OH) C6H4
IIIa R = -CH3
IIIb R = -CH2NH2
IIIc R = -SH
IIId R = -Cl

Zagazig J. Pharm. Sci., December 1995,
Vol. 4, No. 2, pp. 198-203

Synthesis of 1-aminomethyl-imidazo-(1,5-a)benzimidazole (IIIb) :

A 0.01 mole of the compound **I** was dissolved in 10 ml of HCl. To this solution a 0.01 mole of glycine in 5 ml of HCl was added. The reaction mixture was refluxed for 6hr then cooled. The mixture was neutralized with Na_2CO_3 carbonate solution and filtered. The product was washed with water and air dried giving positive ninhydrin reaction (Table 1). IR spectrum (ν, cm^{-1}); 3330 (NH_2), 3080 (Ar), 2950 (CH_3), 1640 (C=N). ^{1}HNMR spectrum (σ ,DMSO-d6): 3 (s,2H,CH_2), 4.1 (t,2H,CH_2N), 5.5 (s,br., NH_2), 7-7.5 (m,ArH).

Synthesis of 1-mercaptoimidazo-(1,5-a)-benzimidazole (IIIc):

Compound **I** (0.01 mole) was dissolved in 0.02 mole KOH solution in 30 ml ethanol-water mixture (2:1). The solution was treated with CS_2 (3 ml). The mixture was refluxed for 4 hr[19]. Most of the solvent was distilled off and the crude product was dissolved in water and filtered. The filtrate was acidified with HCl. The separated crystalline product was filtered off and washed with water; yield 67%, m.p. 250°C.

The same product **(IIIc)** was obtained by stirring a mixture of CS_2 (3 ml) and compound I (0.01 mole) dissolved in 0.02 mole KOH solution for 20 hr at room temperature, then neutralized with dil. HCl, filtered and washed with water. (Table 1). IR spectrum (ν, cm^{-1}), 3100 (SH), 3050 (Ar), 1630 (C=N). ^{1}HNMR spectrum (δ, ppm-DMSO-d_6): 3.3 (s, 2H, CH_2), 2.9 (s, 1H, SH), 7.5-8.2 (Ar, H).

1-Chloro-3H-imidazo-(1,5-a)benzimidazole (IIId) :

A 0.01 mole of compound **1** dissolved in 0.02 mole KOH in 20 ml ethanol water mixture (3:2) was added to 5 ml chloroform. The reaction mixture was refluxed for 19 hr. Then cooled and filtered. The filtrate was evaporated and the product was recrystallized form aqueous ethanol. (Table 1. IR spectrum (ν, cm^{-1}): 1630 (C=N). ^{1}HNMR spectrum (δ. ppm-DMSO-d_6): 3.3 (s, 2H, CH_2) 7-7.5 (ArH).

Synthesis of pyrazino-(1,6-a) benzimidazole derivatives (III e-g):

A 0.01 mole of the compound **I** was dissolved in 30 ml of KOH (0.02 mole) solution in ethanol-water mixture (3:2). This solution was added to 0.01 mole of phenacylbromide, dibromoethane[20] (30 ml) or diethyl oxalate (0.1 mole)[21-23] separately. The reaction mixture was refluxed for 15-25 hr then cooled and filtered. The crystalline product was washed with dil. HCl and crystallized from aq. ethanol.

The same was also produced by heating a mixture of compound I and diethyloxalate at 140°C for 4 hr. IR spectrum (ν, cm^{-1}): 3400-3150 (OH/NH), 1730 (C=O), 1630 (C=N)

1.2-Dioxo-2H-pyrazino-(1,6-a)benzimidazole(III g):

^{1}HNMR spectrum of **(IIIg)** (δ, ppm, DMSO-d_6), 3.3 (s, 2H, CH_2), 6.3 (s,br NH), 7.5-8 (m,ArH)

^{1}HNMR of perhydropyrazino(1,6-a)benzimidazole (IIIf): 3.3 (s,2H, CH

2), 3.6 (t, 4H, CH_2CH_2),4.3 (s,br., NH), 7.5-8 (m,ArH). Reaction of 2-aminomethyl benzimidazole **I** with aldehydes **(IVa,b).** 2-N (substituted benzylidenyl) aminomethylbenzimidazole. A 0.01 mole of the compound **I** dissolved in 20 ml 1N HCl was added to solution of the desired aldehyde (0.01 mole) in 5-ml ethanol (p-nitrobenzaldehyde or m-hydroxybenzaldehyde). The mixture was heated at 100°C for 9hr, then cooled and neutralized with Na_2CO_3 solution. The crystalline product was collected and washed with water. (Table 1). IR spectra (ν, cm^{-1}): 3350 (NH), 1640 (C=N) and 1510 (NO_2) for compound **(VIa)** 3450 (OH), 3330 (NH), 1635 (C=N) for compound **(VIb)** ^{1}HNMR spectrum (δ ppm, DMSO-d_6) 3,5 (s,2H, CH_2) 6.6 (s,br, OH), 7.5-8 (ArH), 8.5 (s,1H, HN), 9.7 (s, 1H, CH=N). The compound 2-Benzimidazolone **(II)** was prepared according to reported method[24].

Schiff's bases (Va,b) :

Equimolecular amounts of compound II and amines (ethanolamine or isopropanolamine) was fused for 1/2 hr then cooled. The crude product was recrystallized from aq. ethanol. (Table 1) yield 70%, m.p. 321, 310°C for compound **Va** and **Vb,** respectively. 2-(2-Hydroxyethyl)imino-3H-benzimidazole (va): IR spectrum (ν, cm^{-1}): 3500-3250 (OH, NH) 3070 (ph), (aliph.), 1620 (C=N). ^{1}HNMR spectrum (δ, DMSO-d6\ 3.3 (t,t, 4H, J=3 cps, CH_2CH_2) 5.3 (s,1H,OH), 7.5-8 (m,ArH), 8.3 (s, NH).

2-(4-Carboxyphenyl) mino-3H-benzimidazole (Vc) :

To a mixture of compound **II** (0.01 mole) and p-aminobenzoic acid (0.01 mole) gl. acetic acid (20 ml) was added. The mixture was refluxed for 9 hr then cooled and neutralized by cold solution of $(Et)_3N$. The crystalline proluct was filtered and recrystallized from water: yield 90%, m.p. 280°C (compound Vc). IR spectrum (ν, cm^{-1}): 3500-2500 (br. COOH), 1710 (C=O) 1620 (C=N). ^{1}HMR (δ, DMSO-d_6): 7.3-8.2 (m,ArH), 8.3 (s, NH), 13.1 (s, COOH).

Table 1: Melting points, Yield and Elemental Analyses of the Prepared Compounds.

Compd. No.	yield %	m.p.C°	Mol. Formula	Analyses % (Calcd / found)		
				C	H	N
IIIa	65	153	$C_{10}H_9N_3$	70.2 70.5	5.3 5.0	24.6 24.1
IIIb	68	193	$C_{10}H_{10}N_4$	64.5 65.0	5.4 5.9	30.1 29.5
IIIc	78	251	$C_9H_7N_3S$	57.1 56.7	3.7 4.1	22.2 22.5
IIId	55	70	$C_9H_6ClN_3$	56.54 56.0	3.14 2.70	21.98 21.3
IIIe	67	260	$C_{16}H_{13}N_3$	77.7 77.2	5.3 5.0	17.0 17.4
IIIf	50	60	$C_{10}H_{11}N_3$	69.36 69.8	6.3 6.0	24.3 24.0
IIIg	73	210	$C_{10}H_7N_3O_2$	59.7 59.5	3.5 3.8	20.9 20.4
IIIh	70	180	$C_{15}H_{12}N_4O_2$	64.3 64.8	4.3 4.0	20.0 20.4
IIIi	75	240	$C_{15}H_{13}N_3O$	71.7 72.1	5.2 5.5	16.7 16.3
Va	78	321	$C_9H_{11}N_3O$	61.02 61.5	6.21 6.6	23.72 24.1
VII	90	219	$C_{14}H_{13}N_5O$	62.92 62.4	4.86 4.3	26.21 25.7
VIIIa	70	300	$C_{21}H_{16}N_6O_3$	63.0 63.4	4.0 4.3	21.0 20.6
X	80	286	$C_{11}H_{10}N_4O$	61.68 61.2	4.67 4.3	26.16 25.7

Table 2: Antimicrobial Activity of Tested Compounds.

Compd. No	Inhibition Zones		
	A.niger	*S. aureus*	*E.coli*
IIIa	+++	-	-
IIIb	+++	++	++
IIIe	+++	++	++
IIIf	+++	-	-
IIIg	+++	-	-
IIIh	++	++	-
Va	+	-	-
Vb	+	+	-
VIIIa	++	+	+
VIIIb	++	+	-
X	++	+	-
XIa	-	+	-
XIb	-	-	-
Thiabendazole	++++	++++	++++

++++ highly active +++ active ++ moderatly active

To the compound **Vc** ethyl alcohol (60 ml) and few drops of conc. H_2SO_4 were added. The reaction mixture was refluxed for 5 hr then cooled and poured into cold Na_2CO_3 solution to give crystalline product: yield 85%, m.p. 119°C compound **(VI).** To compound (VI) hydrazine hydrate (20 ml) was added. The mixture was refluxed at 100°C for 4 hr. cooled and filtered. The product was recrystallized from water (Table 1); 2-(4-Carbohydrazide phenyl)mino-3H-benzimidazole **VII :** IR spectrum (ν, cm^{-1}): 3400-3000 (NH, NH_2), 1720 (C=O), 1600 (C=N).

Reaction of compound VII with aldehydes (VIIIa,b):

To a solution of compound **VII** (0.01 mole) in gl. acetic acid (10 ml) an aldehyde (p-nitro-benzaldehyde or m-hydroxybenzaldehyde (0.01 mole) was added. The reaction mixture was heated at 100°C for 3 hr., cooled and neutrallized by 10% Na_2CO_3 solution. The crystalline product was recrytallized from methanol; yield 75%, m.p. 300°C and 105°C for compound **VIIIa** and **VIIIb,** respectively (Table 1).

3-Hydroxybenzylidenyl(carbohydrazidephenyl)imin o-3H-benzimidazole (VIIIb):

IR spectrum (ν, cm^{-1}): 3400-3200 (OH, NH), 3050 (ph), 1710 (C=O), 1620 (C=N). ^{1}HNMR spectrum (δ, DMSO-d_6): 4.3 (s, 1H, OH), 7.3-8 (m, ArH), 8.3 (s, NH), 9.6 (s, 1H, NHCO), 10.3 (s, 1H, N=CN).

1,3 Diacetyl-2-benzimidazolone (IX) :

To compound **II** (0.01 mole), acetic anhydride (5 ml) was added. The reaction mixture was refluxed for 5 hr then cooled and filtered. The product was washed with Na_2CO_3 solution and recrystallized from water; yield 90%, m.p. 144C. IR spectrum (ν, cm^{-1}): 3050 (Ar), 2950 (CH_3), 1730 (C=O). ^{1}HNMR (δ, DMSO-d_6): 2 (s, 6H, CH_3CO), 7.5-8 (m, 4H, ArH).

4-Acetyl-1-methyltriazole (3,4-a)benzimidazole (Xa):

Equimolar amount of compound **IX** and hydrazine hydrate (0.01 mole) were fused at 150°C for 1/2 hr, cooled. The crude product was crystallized from aq. ethanol: Yield 80%, m.p. 286°C. IR spectrum (ν, cm^{-1}): 3050 (ph), 2970 (CH_3), 1710 (C=O), 1640 (C=N). ^{1}HNMR spectrum (δ, DMSO-d_6): 2 (s,3H, CH_3CO), 2.5 (s, 3H, CH_3), 7.3-7.8 (m, ArH).

4-Acetyl-1-methyl-3-oxo-or 3-thiotriazino (1,6-a) benzimidazole (Xa,b):

To a solution of compound **IX** (0.01 mole) in ethanol (20 ml) urea or thiourea (0.01 mole) was added. The reaction mixture was refluxed for 9 hr. at 100°C, cooled and filtered. The product was recrystallized from ethanol ; yield 65%, m.p. 304°C and 236°C for compound **XIa** and **XIb,** respectively (Table 1).

4-Acetyl-1-methyl-3-oxo-triazino(1,6-a) benzimidazole (XIb):

IR spectrum (ν, cm^{-1}): 3050 (Ar), 2950 (CH_3), 1720 (C=O), 1620 (C=N). ^{1}HNMR spectrum (δ, DMSO-d_6): 1.9 (s, 3H, CH_3CO), 2.6 (s, 3H, CH_3), 7.3-8 (m,ArH).

B. Antimicrobial activity :

The antifungal and antibacterial activities of the new compounds were determined against *A. niger* and *S. aureus* and *E. coli* using agar diffusion method[25,26]. The result of thiabendazole was included for comparison. The results shown in Table 2, indicated that compounds **IIIa-h, VIIIa,b** and **X** were found to have antifungal activity. Also, a significant antibacterial activity was observed for compounds $III_{b\text{-}f}$ and III_h.

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تشييد بعض مشتقات البنزيميدازول الجديده ذات النشاط المتوقع ضد الميكروبات

نبويه شرف الدين

قسم الكيمياء الصيدلية - كلية الصيدله - جامعة طنطا - طنطا - مصر

تم فى هذا البحث تشييد سلسلة مشتقات المركب ٢-أمينو بنزايميدازول (١) بتفاعله مع كل من أستيك أنهيدريد، جليسين، هذا بالإضافة الى سلسلة مشتقات أخرى كربون داى سلفيد، كلوروفورم، داى بروموايثان، فيناسيل بروميد وداى ايثيل أوكسلات. للمركب ٢-بنزايميدازولون (١١) بتفاعله مع بعض الامين والاسيتك انهيدريد والذى تفاعل أيضا مع الهيدرازين، اليوريا والثيويوريا. وقد تم دراسة تأثير هذه المركبات المشيده على بعض الميكروبات وقد أظهرت الدراسه التأثير الايجابى لبعض هذه المركبات على