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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL 4-OXOTHIAZOLIDINYL QUINOLINES AND TRIAZOLOQUINOLINES

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تم فى هذا البحث تشييد العديد من المركبات الثيازوليدينون المحملة على نواة الكينولين فى موضعى ٢،٣ . وكذلك تم تشييد مركبات ٤-ثيازوليدينايل-تريازولو (٤،٣-أ) كينولين.

وقد تم إثبات التركيب البنائى لهذه المركبات بواسطة التحليل الدقى ودراسة أطيافها فى الأشعة تحت الحمراء والرنين النووى المغناطيسى.

كما تمت دراسة تأثير هذه المركبات ضد ميكروب ستافيلوكوكس أوريس وأوريومينوزا هيدرفيلا.

Different thiazolidinone derivatives have been prepared, attached either to 2- or 3-position of quinoline or attached to the 4- position of triazolo[4,3-a]quinoline. The antimicrobial activity of most of the prepared compounds has been studied.

INTRODUCTION

Quinoline derivatives possess diverse pharmacological action including antimalarial[1,2], amoebicidal[3] and antibacterial activities[4,5]. In addition, some triazolo[4,3-a]quinoline derivatives exhibit bactericidal effect[6]. Moreover, different biological activities have been reported for thiazolidinone derivatives among them are antimicrobial[7-9], antidiabetic[10], anticonvulsant[9] as well as tuberculastic effects[11]. Motivated by the above findings, it was interesting in the present investigation to study the antimicrobial activity of certain thiazolidinone attached to quinoline and triazoloquinoline derivatives.

EXPERIMENTAL

All melting points were recorded in open glass capillaries and are uncorrected. The IR spectra were performed in nujol mulls, on Beckman 4210 spectrophotometer. The ^{1}H-NMR spectra were scanned on Varian EM-360L and GE NMR/QE-300 MHz spectrometers, using TMS as an internal standard. Microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University.

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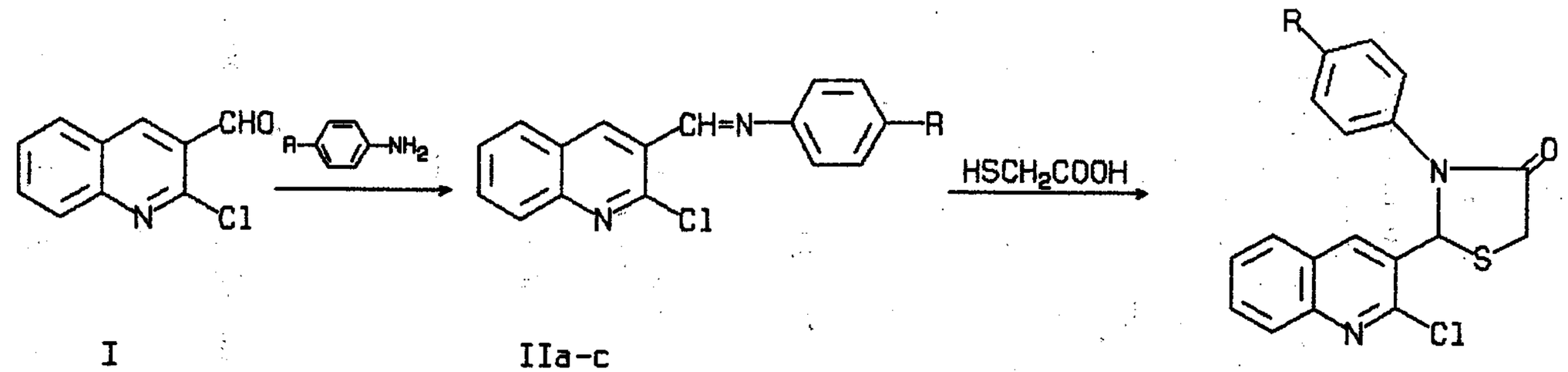
2-Chloro-3-(aryliminomethyl)quinolines(IIa-c)

To a solution of 2-chloroquinoline-3-carboxaldehyde[12] (I) (0.01 mol, 1.92 g) in ethanol (30 ml), the proper amine (0.01 mol) was added. The reaction mixture was heated under reflux for 1 hr., cooled and poured into cold water. The precipitate was filtered, washed with water and crystallized from ethanol (Table 1). IR for compound (IIb) cm^{-1}: 1630, 1620 (C=N); 1600, 1500 (C=C). ^{1}H-NMR (300 MHz) for compound (IIc) (DMSO-d_6), δppm: 7.41, 7.55 (two d each 2H, J= 8Hz, C_6H_4-Br); 7.72, 7.92 (two dd each 1H, J=7, 8Hz, quinoline C_6, C_7-H); 8.05, 8.25 (two d, each 1H, J= 8Hz, quinoline C_5, C_8-H); 8.35(s, 1H quinoline C_4-H); 8.91 (s, 1H, CH=N).

2-Chloro-3-(3-aryl-4-oxothiazolidin-2-yl) quinolines (IIIa-c)

1-Aryl-4-(3-substituted anilino-4-oxothiazolidin-2-yl)-1,2,4-triazolo[4,3-a]quinolines (VIa-f)

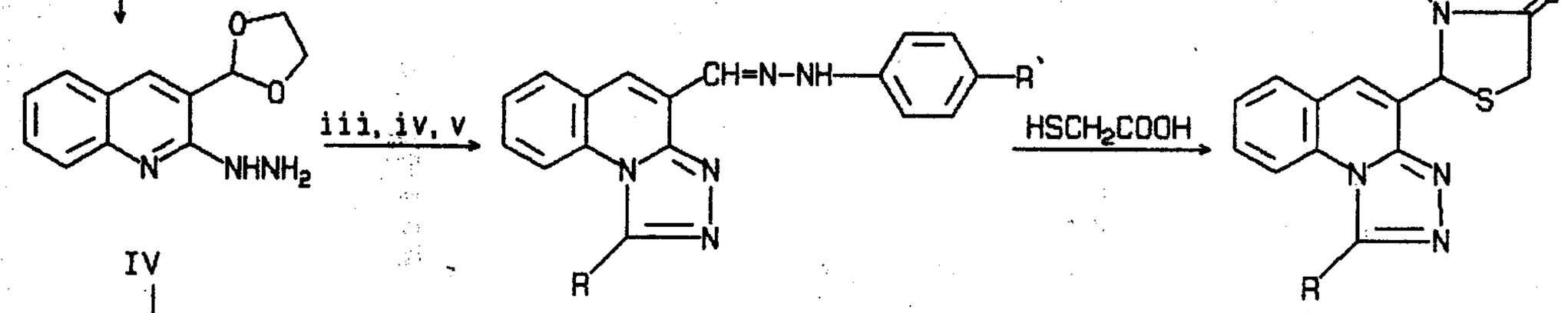
General procedure: A mixture of (IIa-c) or (Va-f)[13] (0.01 mol) and thioglycolic acid (0.012 mol, 1.1 g) in dry benzene (100 ml) was heated under reflux using Dean-Stark separator for 4 hrs. Benzene was evaporated under reduced pressure and the residue was crystallized from ethanol



I

IIa-c

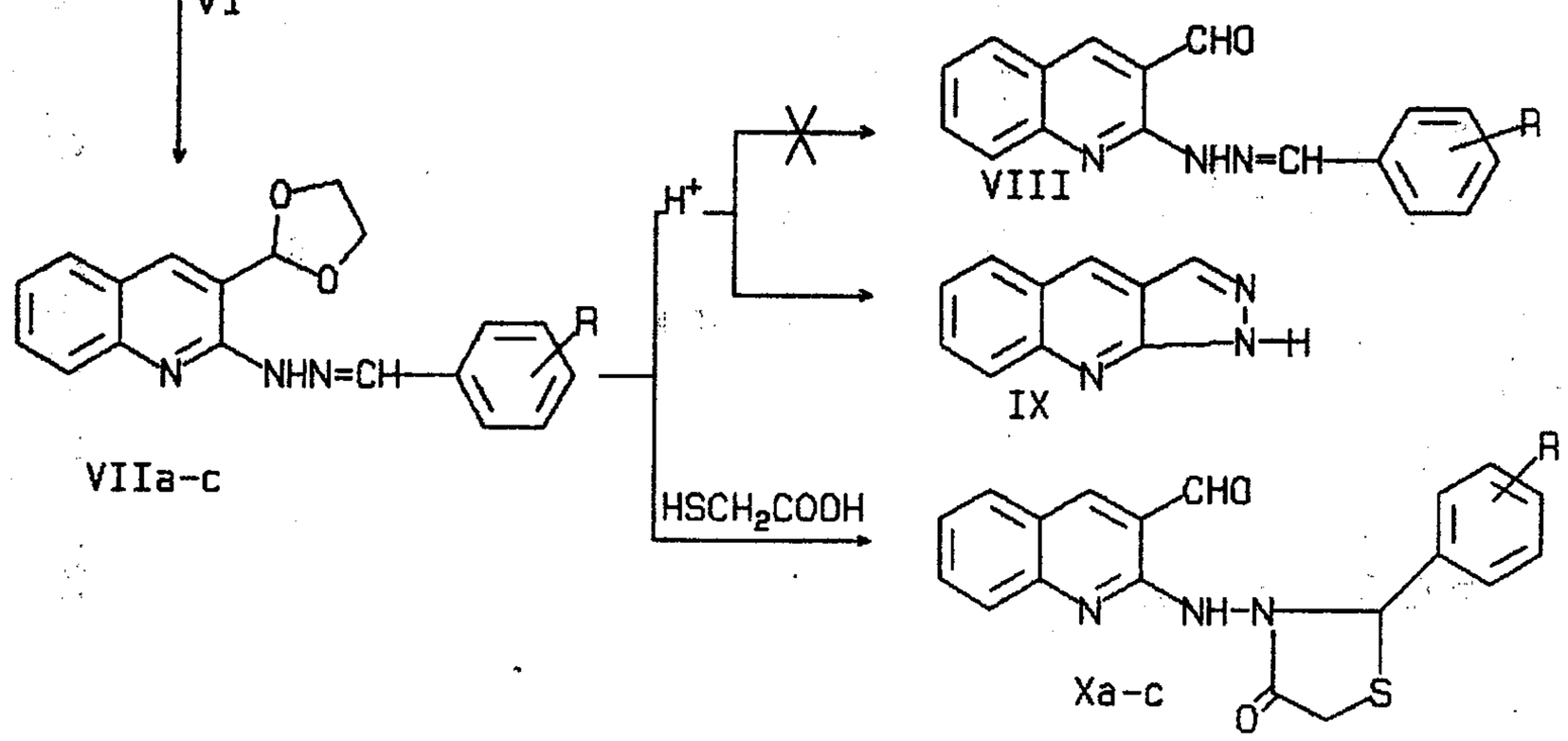
IIIa-c



IV

Va-f

VIa-f



VIIa-c

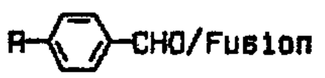
VIII

IX

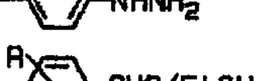
Xa-c

i = Ethylene glycol

ii = $N_2H_4.H_2O$

iii= 

iv = HCOOH

v = 

vi =

Table 1: 2-Chloro-3-(aryl iminomethyl) quinolines (IIa-c).

Comp. No	R	Yield (%)	M.P. (°C)	Molecular Formula (M. wt.)	Analyses Calcd./Found %		
					C	H	N
IIa	H	75	125-6	$C_{16}H_{11}ClN_2$ (266.73)	72.05 72.00	4.16 4.00	10.50 10.30
IIb	CH_3	80	95-6	$C_{17}H_{13}ClN_2$ (280.76)	72.73 72.40	4.67 4.40	9.98 9.40
IIc	Br	70	101-2	$C_{16}H_{10}BrClN_2$ (345.63)	55.60 56.00	2.92 3.10	8.11 7.60

Table 2: 2-Chloro-3-(aryl-4-oxothiazolidin-2-yl) quinolines (IIIa-c).

Comp. No	R	Yield (%)	M.P. (°C)	Molecular Formula (M. wt.)	Analyses Calcd./Found %			
					C	H	N	S
IIIa	H	60	151-2	$C_{18}H_{13}ClN_2OS$ (340.84)	63.43 63.20	3.84 3.10	8.22 8.40	9.41 9.80
IIIb	CH_3	65	115-6	$C_{19}H_{15}ClN_2OS$ (354.86)	64.31 64.80	4.26 4.10	7.89 8.10	9.04 8.70
IIIc	Br	65	112-4	$C_{18}H_{12}BrClN_2OS$ (419.74)	51.51 51.30	2.88 2.20	6.67 6.40	7.64 7.70

(Tables 2 and 3). IR for compound (IIIa) cm^{-1}: 1700 (C=O); 1650 (C=N) and 1610, 1500 (C=C). IR for compound (VIc) cm^{-1}: 1700 (C=O); 1650 (C=N); 1620, 1500 (C=C) and 1230, 1020 (C-O-C). ^{1}H-NMR (300 MHz) for compound (IIIc) (DMSO-d_6), δ ppm: 3.75, 3.90, 4.02, 4.05 (four d, J=14 Hz, 2H thiazolidinone C_5H_2 two chiral isomers); 6.44, 6.82 (two s, 1H, thiazolidinone C_2-H two chiral isomers); 7.35, 7.55 (two d, each 2H, J=8 Hz, C_6H_4-Br); 7.65, 7.8 (two t, each 1H, J=8 Hz, quinoline C_6, C_7-H); 7.92, 8.05 (two d, each 1H, J=8 Hz, quinoline C_5, C_8-H); 8.5 (s, 1H, quinoline C_4-H). ^{1}H-NMR (60 MHz) for compound (VIc) ($CDCl_3$), δ ppm: 3.9 (s, 3H, $OC\underline{H}_3$); 3.8-4.2 (m, 2H, thiazolidinone C_5-H_2); 5.9, 6.5 (two s, 1H, thiazolidinone C_2-H) (two chiral isomers); 7-8.4 (m, 14H, Ar-H), 9.8(s, 1H, NH, D_2O exchangeable).

Table 3: 1-Aryl-4-(3-substituted anilino-4-oxothiazolidin-1-yl)-1,2,4-trizolo[4,3-a]quinolines (VIa-f).

Comp. No	R	R^1	Yield (%)	M.P. (°C)	Molecular Formula (M. wt.)	Analyses Calcd./Found %			
						C	H	N	S
VIa	C_6H_5	H	60	159-160	$C_{25}H_{19}N_5OS$ (437.53)	68.63 69.10	4.38 4.00	16.01 15.80	7.33 7.10
VIb	C_6H_5	$COOCH_2CH_3$	60	135-6	$C_{28}H_{23}N_5O_3S$ (509.59)	66.00 66.50	4.55 4.10	13.74 13.40	6.29 6.20
VIc	$C_6H_4OCH_3$ (p)	H	55	141-2	$C_{26}H_{21}N_5O_2S$ (467.56)	66.79 67.10	4.53 4.10	14.98 15.30	6.86 6.60
VId	$C_6H_4OCH_3$ (p)	$COOCH_2CH_3$	60	149-50	$C_{29}H_{25}N_5O_4S$ (539.62)	64.55 64.30	4.67 4.80	12.98 13.20	5.96 5.60
VIe	C_6H_4OH (o)	H	40	161-2	$C_{25}H_{19}N_5O_2S$ (453.53)	66.21 66.70	4.22 3.80	15.44 15.80	7.07 7.00
VIf	C_6H_4OH (o)	$COOCH_2CH_3$	50	115-6	$C_{28}H_{23}N_5O_4S$ (525.59)	63.99 64.00	4.41 4.20	13.32 13.30	6.10 6.00

2-(2-Aryl-4-oxothiazolidin-3-yl)amino quinoline-3-carboxaldehydes (Xa-c)

To a solution of (VIIa-c)[13] (0.01 mol) in DMF, a few crystals of anhydrous zinc chloride and thioglycolic acid (0.012 mol, 1.1 g) was added. The reaction mixture was heated under reflux for 3 hrs., cooled and poured into ice-cold water (50 ml). The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 4). IR for compound (Xa) cm^{-1}: 3300 (ν NH); 1700 (C=O); 1680 (CHO); 1630 (C=N); 1540 (δ NH) and 1600, 1500 (C=C). ^{1}H-NMR (60 MHz) for compound (Xa) (DMSO-d_6) δ ppm: 3.3 (br. s, 1H, NH, D_2O exchangeable); 3.8-4.2 (m, 2H, CH_2 thiazolidinone C_5-H_2); 5.9, 6.5 (two s, 1H, thiazolidinone C_2-H) 7-8.2 (m, 9H, Ar-H); 8.5 (s, 1H, quinoline C_4-H); 10.1 (s, 1H, CHO).

Table 4: 2-(2-aryl-4-oxothiazolidin-3-yl)amino quinoline-3-carboxaldehydes (Xa-c).

Comp. No	R	Yield (%)	M.P. (°C)	Molecular Formula (M. wt.)	Analyses Calcd./Found %			
					C	H	N	S
Xa	H	50	110-11	$C_{19}H_{15}N_3O_2S$ (349.42)	65.31 65.00	4.33 4.00	12.03 12.20	9.18 9.00
Xb	OCH_3 (p)	65	121-2	$C_{20}H_{17}N_3O_3S$ (379.44)	63.31 64.00	4.52 3.70	11.07 10.80	8.45 8.80
Xc	OH (o)	65	132-3	$C_{19}H_{15}N_3O_3S$ (365.42)	62.45 62.60	4.14 4.00	11.50 11.90	8.77 9.10

Table 5: Antimicrobial testing.

Comp. NO.	Micro organisms	
	Staph. aureus	Arm. hydrophila
IIa	++	++
IIb	+++	+++
IIc	++	++
IIIa	+	+++
IIIb	+++	+++
IIIc	-	-
VIa	+	+
VIb	+	+
VIc	+	++
VId	+	-
VIe	-	+
VIf	-	++
Xa	+	-
Xb	+	+
Xc	+	++
Streptomycin sulphate	+++ ++	+++++

Preliminary antimicrobial testing

The preliminary antimicrobial testing of most of the prepared compounds has been performed by a modified method adapted by Baron and Finegold[14]. The microorganisms used were *Staphylococcus aureus* as Gram positive bacteria and *Arumonace hydrophila* as Gram negative bacteria which are pathogenic to both human and animals.

The tested compounds were dissolved in propylene glycol (1 mg/ml). One of the selected bacterial colonies was transferred into Meuller-Hintone broth and incubated at 35°C for 24 hr. 1 ml of inoculated Meuller-Hintone broth was added to 1 ml of the test compounds and incubated at 35°C for 24 hrs. The turbidity formed was compared against control. Streptomycin SO_4 (1 mg/ml) was used as reference standard. The results are shown in (Table 5).

RESULTS AND DISCUSSION

Schiff's bases, 2-chloro-3-(aryliminomethyl) quinolines (IIa-c), have been prepared by condensation of compound (I) with different aromatic amines. Cyclization of (IIa-c) with thioglycolic acid in benzene afforded 2-chloro-3-(3-aryl-4-oxothiazolidin-2-yl) quinolines (IIIa-c) in good yields. The previously prepared 1-substituted-1,2,4-triazolo[4,3-a]quinoline p-substituted phenylhydrazone 4-carboxaldehydes (Va-f)[13] underwent cyclization with thioglycolic acid in benzene to give 1-aryl-4-(3-substituted anilino-4-oxothiazolidin-2-yl)-1,2,4-triazolo[4,3-a]quinolines (VIa-f) in good yields. Treatment of 2-(arylidenehydrazino)3-(1,3-dioxolan-2-yl) quinolines (VIIa-c) with 60% formic acid afforded 1H-pyrazolo[4,3-b]quinoline (IX)[15] rather than 2-(arylidenehydrazino) quinoline-3-carboxaldehyde (VIII), i.e. instead of liberation of free aldehydic group, elimination of aromatic aldehyde took place with cyclization of the formed hydrazino derivatives to (IX) with the same m.p. and physical data as mentioned in literature[15]. Cyclization of compounds (VIIa-c) with thioglycolic acid in benzene went in vain. Therefore, these compounds were cyclized using thioglycolic acid in DMF and a pinch of zinc chloride to give 2-(2-aryl-4-oxothiazolidin-3-yl) aminoquinoline-3-carboxaldehydes (Xa-c) in good yields.

All the tested compounds showed lower activity than streptomycin. Compounds (IIb) and (IIIb) are selectively the most active against *Staph. aureus* and *Aram. hydrophila* while compound (IIIa) showed high activity against *Arum. hydrophila* only. Compounds (IIa) and (IIc) were moderately active. The other compounds showed no activity.

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REFERENCES

1- L.H.Schmidt, Antimicrob, Agents Chemother. 24(5), 615-52 (1983).
2- T.Singh, R.G.Stein and J.H.Biel, J. Med. Chem. 12, 801-3 (1969).
3- F.J.Salem J.Drug Res. 12, 101 (1980).
4- J.Frigola, J.Pares, J.Corbera, D.Vano, R.Merce, A.Torrens, J.Mas and E.Valenti, J. Med. Chem. 36(7), 801-10 (1993).

5- T.Okada, K.Ezumi, M.Yamakawa, H.Sato, T.Tsuji, T.Tsushima, K.Motokawa and Y.Komatsu, Chem. Pharm. Bull. 41(1), 126-31 (1993).
6- P.Sama, A.Carta, G.Paglietti, S.Zanetti and G.Fadda, Farmaco 47(7-8), 1001-19 (1992).
7- V.L.Panchhamia and A.R.Parkih, J.Inst. Chem. 63(6), 212-4 (1991) through C.A. 118, 191645b (1993).
8- K.Desai and A.J.Baxi, J.Indian Chem. Soc., 69(4), 212-4 (1992).
9- Sh.G.Donia and T.M. Ibrahim Bol. Soc., Quim Peru 58(2), 90-5 (1992) through C.A. 118, 101863u (1993).
10- M.Amir and E.Singh, Acta Pharm. 42(2), 133-7 (1992).
11- M.S.Khanna, Ch.P.Garg and R.P.Kapoor Indian J.Chem., Sect. B. 32(B), 364 (1993).
12- M.C.Otto, N.Bramha and T.Brian J.Chem. Soc. Perkin Trans I 1520 (1981).
13- M.A.Khalil, N.S.Habib, A.M.Farghaly and O.A.El-Sayed, Arch. Pharm. (Weinheim) 324, 249-53 (1991).
14- E.W.Koneman, S.D.Allen, V.R.Dowell and H.M.Sommers, Diagnostic Microbiology 2nd Ed., J.B. Lippincott Company, Philadelphia, London, New York, (1993).
15- A.M.Farghaly, N.S.Habib, A.A.B. Hazza and O.A.El-Sayed, Alex. J. Pharm. Sci., Vol. 111(1), March 84-86 (1989).