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REACTIONS OF 2,3-DICHLOROMALEIC ANHYDRIDE[1]: III REACTIONS WITH BINUCLEOPHILES ([4+2]CYCLOCONDENSATION) FOR SYNTHESIS OF COMPOUNDS WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

The reaction of 2,3-dichloromaleimides 1a-f with binucleophiles, viz, o-aminophenol (2a) and o-phenylenediamine (2b) is described. Products isolated were dependent on both pH and the used reaction solvents. Many of the novel, fused pyrroloquinoxalines and maleimides showed remarkable antimicrobial activities.

INTRODUCTION

Numerous derivatives of maleimides have been recently developed and tested as potential fungicidal agents, where they showed valuable activity[1-4]. In addition, the authors started to reinvestigate thoroughly the chemistry of 2,3-dichloromaleimides which may be considered as key intermediates to many interesting compounds of potential antimicrobial value[5,6]. This has urged the synthesis of new maleimides as well as other fused heterocyclic ring systems through [4+2] cyclocondensation of 2,3-dichloromaleimides with the binucleophiles viz. o-aminophenol **2a** and o-phenylenediamine **2b** (Figure 1).

The bactericidal and fungicidal activities of N-substituted maleimides and several of their derivatives are well known[7-9]. It has been reported that some of these compounds are useful as industrial biocides, antifouling agents or agricultural fungicides[7,8,10]. Moreover, the nucleoside antibiotic showdomycin is a maleimide derivative. Showdomycin [2-(ß-D- ribofuranosyl) maleimide] is produced by Streptomyces showdoensis and possesses moderate activity against gram-positive and gram-negative bacteria and is cytotoxic to tumour cells[11].

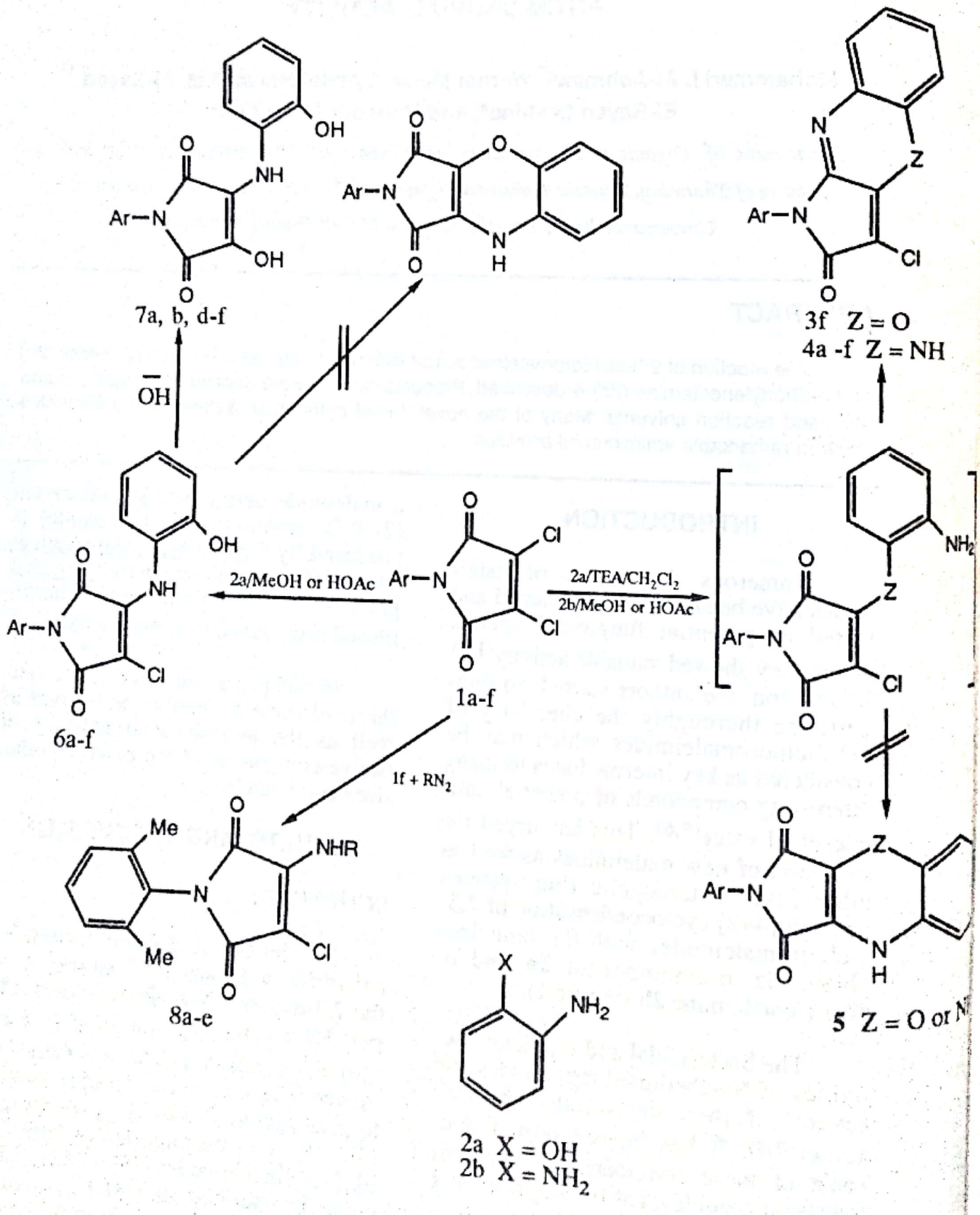
In this paper, we describe the synthesis of some maleimide derivatives as well as the antimicrobial activity of twelve compounds of the newly synthesized compounds.

RESULTS AND DISCUSSION

SCHEME 1 :

Imidation of 2,3-dichloromaleic anhydride with aromatic amines gives the 2,3-dichloro-N-arylmaleimides (**1a-f**)[12,13]. Cyclocondensation of (**1f**) with (**2a**) was conducted in basic solution using methylene chloride and triethylamine to give pyrrolo[3,2-b] [1,4]benzoxazine (**3f**) instead of the expected pyrrolo [3,4-b] [1,4]-benzoxazine (5) (Z=O). This could be ascribed first to the favoured nucleophilic attack at position # 2 via the

Figure 1:


7a, b, d-f
3f Z = O
4a -f Z = NH
2a/MeOH or HOAc
2a/TEA/CH2Cl2
2b/MeOH or HOAc
1a-f
6a-f
1f + RN2
8a-e
5 Z = O or N
2a X = OH
2b X = NH2

oxyanion formed in basic solution, followed by cyclocondensation with the amino group either at position # 1 or at position # 3 depending on the type of the products obtained. Thus, product (**3f**) enjoys the aromatic π sextet and therefore it will be formed easier than the relatively unstable dihydro product (**5**) (Z=O).

On the other hand, reaction of (**1a-f**) with (**2a**) in neutral or acidic solution proceeded differently. It reacts first through the amino group to afford the uncyclized products (**6a-f**). Further cyclization through the phenolate anion to give (**5**) was now prevented due to the diminished electrophilicity of position # 3 being conjugated with nitrogen. So trials to affect cyclization of compound (**6**) into (**5**) using sodium hydroxide resulted in hydrolytic cleavage at position # 3 to give products (**7**).

The structure of the intermediates **6 and 7** was established based on elemental, chemical and spectral data. Thus, the solubility in sodium hydroxide solution revealed the presence of a phenolic hydroxyl group. Compounds **6** showed two strong absorption bands in their IR spectra at 1700-1720/1650-1670 cm^{-1} due to the unsymmetrical C=O at positions # 1 and # 4, respectively. The carbonyl at position # 4 is affected by the positive electronic effects of the amino substituent. On the contrary, compounds **7** showed one broad absorption band due to the quite similar carbonyl groups.

SCHEME 2 :

With **2b**, the 2,3-dichloromaleimides (**1a-f**) were simultaneously cyclocondensed to give the pyrrolo [2,3-b]-quinoxalines (**4a-f**) rather than the expected pyrrolo [3,4-b]-quinoxalines (**5**) (Z=NH) confirming a similar reaction pathway to **2a** in basic solution. This would be parallel to the relatively higher stability enjoyed by the quinoxalines **4** being aromatic in nature. The structure of the products (**4a-f**) was proved by both elemental and spectral data (also by ^{13}C-NMR for 4f and MS for 4b) and by alternative synthesis. Thus, reacting the maleimides (**6a-f**) with **2b** resulted in S_N2-displacement reaction via Michael-type with consequent expulsion of the substituents at position # 2 to afford the previously obtained pyrroloquinoxalines (**4a-f**). In the same way, the maleimides (**8a-e**) bearing five different substituted phenylamino residues at position # 2 gave the same cyclization product (**4f**).

Antimicrobial Activity :

Twelve of the new, chemically synthesized compounds, (**4a and f**), (**6b, d, e, and f**), (**7a, b and d**) and (**8a, b and e**) (Table 1), have been investigated for their antimicrobial activity employeing the disc-plate agar diffusion method(**14**) against seven strains of microorganisms. These microorganisms are: Staphylococcus aureus, Sarcina lutea, Bacillus subtilis, Neisseria sp., Escherichia coli, Pseudomonas aeruginosa and Saccharomyces cerevisiae. Most of the compounds showed variable degrees of antimicrobial activity against all of these microorganisms.

Table (2) shows the antimicrobial activity of the 12 synthesized chemical compounds against the 7 microorganisms, representing Gram's positive and Gram's negative bacteria as well as a yeast (Saccharomyces cerevisiae). Compounds (**6f and 8e**), showed a wide spectrum antimicrobial activity. They also could inhibit the growth of Pseudomonas aeruginosa. Compounds (**8a and b**) showed the most pronounced antimicrobial activity against all of the tested microorganisms, except Pseudomonas aeruginosa, where they did not show any antimicrobial activity. In a descending order, compounds, (**8b, 8a, 6f and 8e**) showed the highest activity against E. coli, but compounds (**8e, 8b and 6f**) were more active against Neisseria sp. Compounds (**6f, 8e and 8b**) produced the largest inhibition zone in plates seeded with the yeast Saccharomyces cerevisiae. Other compounds showed either a very low antimicrobial activity against most of the tested microorganisms or only

Table (1): Microbiologically tested compounds, codes, and their chemical structure

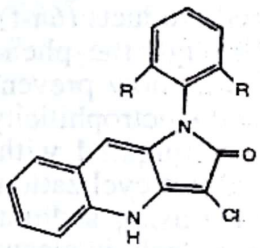
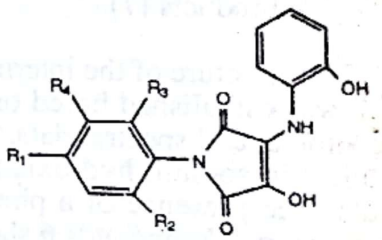
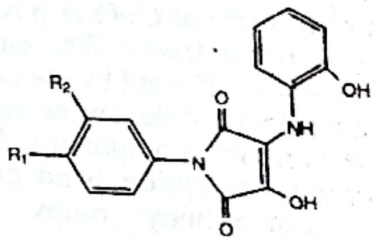
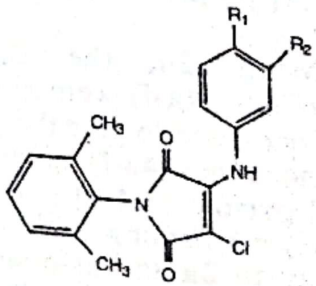
Code	Chemical Formula	Molecular weight	Chemical Structure
4a	$C_{16}H_{10}N_3O$	295.702	
4f	$C_{18}H_{14}ClN_3O$	325.78	
6b	$C_{16}H_{10}ClN_2O_3$	349.17	
6d	$C_{17}H_{13}ClN_2O_3$	328.75	
6e	$C_{17}H_{13}ClN_2O_3$	344.75	
6f	$C_{18}H_{15}ClN_2O_3$	342.78	
7a	$C_{16}H_{12}N_2O_4$	296.28	
7b	$C_{16}H_{11}ClN_2O_4$	330.72	
7d	$C_{17}H_{14}ClN_2O_4$	310.30	
8a	$C_{18}H_{15}ClN_2O_2$	326.78	
8b	$C_{18}H_{14}ClN_2O_2$	361.22	
8e	$C_{19}H_{17}ClN_2O_3$	356.80	

Table (2): Comparison between the antimicrobial activity of the synthesized compounds (a) against seven tested microorganisms by the disc agar diffusion method, expressed as X^2 (mm^2) (b)

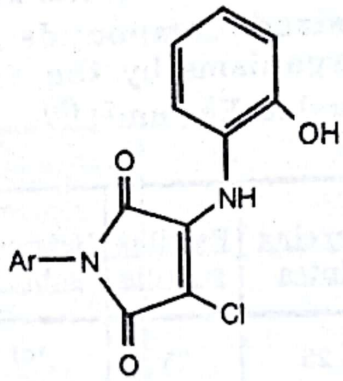
Code	Staph aureus	Sarcina lutea	Bacillus subtilis	Neisseria subtilis	E. coli	Ps. aeruginosa	Yeast
4a	100	25	25	-(c)	25	-	-
4f	49	-	4	-	16	-	-
6b	16	16	25	-	16	-	20
6d	25	100	-	-	9	-	16
6e	-	36	56	-	16	-	9
6f	81	81	81	16	100	16	81
7a	16	9	9	-	25	-	-
7b	4	9	16	9	25	-	-
7d	25	25	25	4	16	-	36
8a	36	225	64	25	100	-	9
8b	100	196	9	36	121	-	49
8e	64	100	64	56	81	16	49

(a) Compounds were dissolved in dimethyl formamide (1 mg/ml). Then filter paper discs were saturated with the solution, dried in air and then applied to the surface of the agar plates seeded with the microorganisms.

(b) X is the distance between the edge of the disc and the outer edge of the inhibition zone. Diameter of the disc = 5mm. The figures in this table are the mean value of 3 different parallel measurements, performed under the same conditions.

(c) (-) means no zone of inhibition.

Table (4): 3-Chloro-2-(2-hydroxyphenylamino)-N-substituted phenyl maleimides (6a-f)



Parameters			Compound's Number*					
			6a (1)	6b (1)	6c (1)	6d (1)	6e (1)	6f (1)
Yield (%)			78	85	81	76	91	89
M.P. (°C)			190-1	156-7	150-1	178-9	184-5	208-9
Mol. Formula			$C_{16}H_{11}ClN_2O_3$	$C_{16}H_{11}ClN_2O_3$	$C_{16}H_{10}ClN_2O_3$	$C_{17}H_{13}ClN_2O_3$	$C_{17}H_{13}ClN_2O_3$	$C_{18}H_{15}ClN_2O_3$
Mol. Weight			314.72	349.17	349.17	328.75	344.75	342.78
Elem. Anal. (%)	C	Calculated	61.06	55.03	55.03	62.11	59.22	63.07
		Found	60.92	55.30	54.83	61.90	58.87	63.23
	H	Calculated	3.42	2.88	2.88	3.98	3.80	4.41
		Found	3.39	2.71	2.91	3.68	3.78	4.10
	N	Calculated	8.90	8.02	8.02	8.52	8.12	8.17
		Found	8.57	7.90	8.20	8.72	7.90	8.91
IR (KBr) cm^{-1}	C=O		1710-1650	1720-1650	1720-1650	1720-1660	1720-1670	1700-1650
	OH		3360	3380	3380	3360	3380	3380
	NH		3340	3340	3340	3320	3340	3340
^{1}H-NMR** (δ ppm) (multiplicity)	CH_3					2.15 (s)	3.85 (s)	2.1 (s)
	H_{arom}		6.7-7.5 (m)	6.9-7.7 (m)	6.9-7.7 (m)	6.8-7.4 (m)	6.8-7.4 (m)	6.9-7.4 (m)
	NH		9.35 (s)	9.45 (s)	9.45 (s)	9.32 (s)	9.35 (s)	9.45 (s)
	OH		9.75 (s)	9.85 (s)	9.85 (s)	9.75 (s)	9.75 (s)	9.85 (s)

(*) Solvent of crystallization is : (1) CH_3OH, (2) C_2H_5OH, or (3) C_2H_5OH/H_2O.

(**) Dissolved in DMSO-d_6 and the intensities agree with the proposed arrangement.

showed a low activity against some selective strains from the tested groups of microorganisms.

Table (3) shows the minimum inhibitory concentrations (MIC, µg/ml) for compounds 6f and 8e against the tested microorganisms. From this table, compound 8e is more active against all the tested microorganisms than compound 6f. The relative activity between the two compounds differ from one microorganism to another. For example, compound 8e is about 6.2, 3.7, 3.6, 2.3, 1.8, 1.5 and 1.3 times active as compound 6f against E. coli, B. subtilis, Staph. aureus, Serratia liquea, Saccharomyces cerevisiae, Neisseria sp. and Pseudomonas aeruginosa, respectively.

The chlorine atom at position 3 in the heterocyclic ring might play an active role in the antimicrobial activity of the reported compounds. Replacement of chlorine at position 3 with a hydroxyl group (compare compounds 6 and 8 with compounds 7) or with a C-C bond (compounds 4) strongly reduces the antimicrobial activity of the synthesized compounds. Also, substitution in the N-aryl of the maleimide or in the anilinyl group at position 2 could highly affect the antimicrobial activity of the products. Para or ortho substitution with an electron donor groups such as CH_3 or OCH_3 could lead to an increase in electron density in the heterocyclic ring. That possibly enhances antimicrobial activity of the chlorine at position 3 of the maleimide nucleus (compare compounds 6f and 8e with other compounds).

EXPERIMENTAL

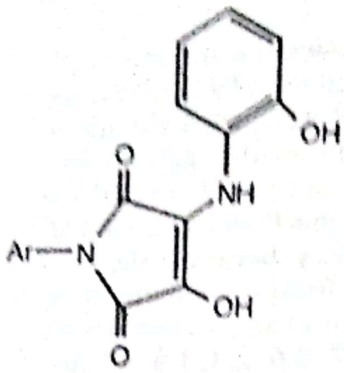
All analyses, (except the antimicrobial activity) were carried out at Bonn University, Bonn, West Germany. Melting points (Gallenkamp apparatus) are uncorrected values. Microanalyses were carried in the Microanalytical Center of the Institute of Organic and Biochemistry. IR spectra (KBr) were performed using a Perkin-Elmer 298 instrument. NMR spectra were determined using a Varian T-60 and a Varian XL300

Table (3): Minimum inhibitory concentration (MIC) of synthesized compounds with broad spectrum of antimicrobial activity against the seven tested microorganisms by the cup-plate agar diffusion method (*)

Microorganisms	MIC (µg/ml DMF)	
	Compound (6f)	Compound (8e)
Staphylococcus aureus	479	132
Serratia liquea	447	251
Bacillus subtilis	337	90
Neisseria sp.	562	376
Escherichia coli	692	112
Pseudomonas aeruginosa	794	603
Saccharomyces cerevisiae	474	209

(*) Compounds were dissolved in dimethyl formamide (1 mg/ml) and a two-fold serial dilution in DMF was made. Antimicrobial activity of DMF, if there was, was compensated. Diameter of the cup in the agar medium = 8mm. The figures in this table are the mean value of 3 different parallel measurements, performed under the same conditions.

Table (3): 3-Hydroxy-2-hydroxyphenylamino)-N-substituted phenyl maleimides (7a, b, d-f)



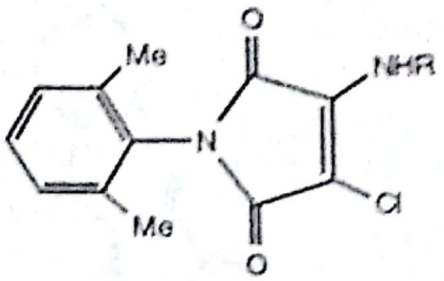
Parameters			Compound's Number*				
			7a (2)	7b (4)	7d (4)	7e (1)	7f (3)
Yield (%)			87	85	88	81	83
M.P. (°C)			204-5	193-4	187-8	175-6	196-8
Mol. Formula			$C_{16}H_{12}N_2O_4$	$C_{16}H_{11}ClN_2O_4$	$C_{17}H_{14}N_2O_4$	$C_{17}H_{14}N_2O_5$	$C_{18}H_{16}N_2O_4$
Mol. Weight			296.28	330.72***	310.30	326.30	324.33
Elem. Anal. (%)	C	Calculated	64.86	58.10	65.80	62.57	66.66
		Found	64.95	58.00	65.79	62.66	66.60
	H	Calculated	4.08	3.55	4.54	4.32	4.97
		Found	3.99	3.51	4.62	4.32	4.86
	N	Calculated	9.45	8.47	9.03	8.58	8.64
		Found	9.42	8.45	8.95	8.51	8.73
IR (KBr) cm^{-1}	C=O		1640	1640	1650	1650	1640
	OH		3395	3390	3395	3390	3395
	NH		3300	3300	3300	3300	3300
^{1}H-NMR** (δ ppm) (multiplicity)	CH_3				2.15 (s)	3.80 (s)	
	$OH_{aliph.}$		3.30 (br,s)	3.30 (br,s)	3.10 (br,s) 6.	3.30 (br,s)	
	H_{arom}		6.7-7.6 (m)	6.7-7.8 (m)	6.7-7.5 (m)	6.7-7.5 (m)	
	OH_{arom}		8.10 (s)	8.10 (s)	8.10 (s)	8.10 (s)	
	OH		10.2 (s)	10.2 (s)	10.2 (s)	10.2 (s)	9.75 (s)

(*) Solvent of crystallization was : (1) CH_3OH, (2) CH_3CN, (3) C_2H_5OH/H_2O or (4) CH_3CN/H_2O

(**) Dissolved in DMSO-d_6 and the intensities agree with the proposed arrangement.

(***) MS m/z (M^+) for 7b calculated was 330.73, observed was 330.038, 7.5%; m/z M^+ (132.00, 100%) base peak.

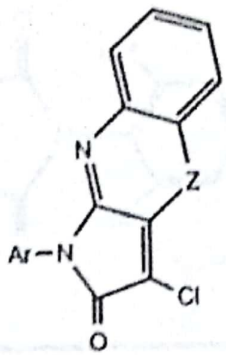
Table (6): 3-Chloro-N(2,6-dimethylphenyl)-2-substituted aminomaleimides (8a-e).



Parameters			Compound's Number*				
			8a	8b	8c	8d	8e
R			C_6H_5	m-ClC_6H_4	p-ClC_6H_4	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$
Yield (%)			83	89	86	90	84
M.P. (°C)			198-9	173-4	160-1	178-9	161-2
Mol. Formula			$C_{18}H_{15}ClN_2O_2$	$C_{18}H_{14}Cl_2N_2O_4$	$C_{18}H_{14}Cl_2N_2O_2$	$C_{19}H_{17}ClN_2O_2$	$C_{19}H_{17}ClN_2O_3$
Mol. Weight			326.78	361.22	361.22	340.80	356.80
Elem. Anal. (%)	C	Calculated	66.16	59.85	59.85	66.96	63.95
		Found	65.77	59.63	59.58	66.61	63.82
	H	Calculated	4.62	3.90	3.90	5.02	4.80
		Found	4.62	4.03	3.77	5.10	4.96
	N	Calculated	8.57	7.75	7.75	8.22	7.85
		Found	8.46	7.63	7.61	8.13	7.78
IR (KBr) cm^{-1}	2 C=O		1710 & 1650	1710 & 1650	1710 & 1650	1710 & 1650	1700 & 1650
	NH		3300	3260	3260	3280	3300
	$CH_{arom.}$ & aliph.		3060-2900	3060-2900	3060-2900	3060-2900	3060-2900
	C=C		1600 & 1540	1600 & 1510	1600	1600	1600
	C-OCH_3						1180
^{1}H-NMR** (δ ppm) (multiplicity)	6H (2 CH_3)		2.15 (s)	2.15 (s)	2.15 (s)	2.15 (s)	2.15 (s)
	3H (CH_3 or OCH_3)					1.85 (s,CH_3)	3.90 (s,OCH_3)
	Harom		7.1-7.6 m,5H	7.1-7.7 m,7H	7.1-7.7 m,7H	6.8-7.6 m,7H	6.9-7.6 m,7H
	NH		10.15 (s)	10.20 (s)	10.20 (s)	10.00 (s)	10.00 (s)

(*) Solvent of crystallization is ethanol.
(**) Dissolved in DMSO-d_6 and the intensities agree with the proposed arrangement.

Table (7): 3-Chloro-1-substituted phenyl-1H-pyrrolo [2,3-b]quinoxaline-2(4H)-one (4a-f).



Parameters			Compound's Number*					
			4a (1)	4b (1)	4c (1)	4d (2)	4e (3)	4f (2)
Yield (%)			82	57	51	63	56	56
M.P. (°C)			>300	>300	>300	>300	>300	>300
Mol. Formula			$C_{16}H_{10}N_3O$	$C_{16}H_9Cl_2N_3O$	$C_{16}H_9Cl_2N_3O$	$C_{17}H_{12}ClN_3O$	$C_{17}H_{12}ClN_3O_2$	$C_{18}H_{14}ClN_3O$
Mol. Weight			295.702	330.17***	330.17	309.75	325.75	325.78
Elem. Anal. (%)	C	Calculated	64.98	58.20	58.20	65.91	62.68	66.77
		Found	65.13	58.32	57.87	65.81	62.55	66.50
	H	Calculated	3.40	2.74	2.74	3.90	3.71	4.35
		Found	3.31	2.84	2.78	3.89	3.74	4.36
	N	Calculated	14.20	12.72	12.72	13.56	12.90	12.98
		Found	13.98	12.59	12.65	13.00	13.05	12.93
IR (KBr) cm^{-1}	C=O		1660	1665	1660	1660	1660	1660
	C=N		1620	1620	1620	1630	1620	1630
	NH		3200	3225	3200	3210	3200	3250
^{1}H-NMR** (δ ppm) (multiplicity)	CH_3					2.40 (s)	3.90 (s)	2.00 (s)
	H_{arom}					7.2-7.65 (m)	7.1-7.7 (m)	7.2-7.45 (m)
	NH					12.90 (br,s)	12.90 (br,s)	12.90 (br,s)

(*) Solvent of crystallization is : (1) CH_3OH, (2) C_2H_5OH, or (3) C_2H_5OH/H_2O.

(**) Dissolved in DMSO-d_6 and the intensities agree with the proposed arrangement. ^{13}C-NMR (δ ppm) for 4f : 163.959, 146.493, 137.263, 133.195, 131.326, 130.469, 128.746, 128.588, 127.967, 127.519, 127.177, 123.296, 116.086, 83.511, 17.648.

(***) MS m/z (M^+) for 4b : Calcd. 1330.17, found : 329.921; 0.1%; m/z (M^+) 323.00, 100% base peak.

instrument at the Institute of Pharmaceutical Chemistry using d_6-DMSO as a solvent, TMS as an internal standard, and D_2O to trace NH and OH protons. The mass spectrum (MS) was made using a Kratos DS-50 mass spectrometer at the Institute of Organic and Biochemistry. Antimicrobial activity was performed at the Department of Microbiology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt.

3-Chloro-1-(2,6-dimethylphenyl)-pyrrolo[3,2-b][1,4]benzoxazin-2(1H)-one (3f) :

To a solution of **(1f)** (2.7 g, 10 mmol) in methylene chloride (40 ml), o-aminophenol **(2a)** (1.09 g, 10 mmol) was added followed by addition of 1 ml of triethylamine. The reaction mixture was stirred for 12 hours and then filtered. The filtrate was concentrated under reduced pressure and the residue was crystallized from aqueous ethanol; mp 234-235°C; yield 2.66 g (82%). $C_{18}H_{13}ClN_2O_2$ (324.8); Calcd : C: 66.6, H: 4.03, and N: 8.6; found : C: 66.7, H:3.89, and N: 8.7. The IR spectrum showed absorption at 1680 cm^{-1} for (C=C), and at 1620 cm^{-1} for (C=N).

3-Chloro-2-(2-hydroxyphenylamino)-N-substituted phenylmalemides (6a-f):

General Procedure: To a mixture of 2,3-dichloro-N-substituted phenylmaleimides **(1a-f)**[12,13] in glacial acetic acid or methanol (30 ml), a solution of o-aminophenol **(2a)** (1.96 g, 18 mmol) in glacial acetic acid or methanol (20 ml) was added dropwise while stirring. After refluxing the reaction mixture for 2h, it was concentrated under reduced pressure, cooled and diluted with water. The obtained solid was filtered, washed with distilled water and crystallized from the appropriate solvent (Table 4).

3-Hydroxy-2-(2-hydroxyphenylamino)-N-substituted phenylmaleimides (7a, b, d-f):

General Procedure : A solution of **(6a-e)** (10 mmol) in 2N sodium hydroxide (40 ml) was stirred for 1h at room temperature and then filtered. The filtrate was acidified with dilute hydrochloric acid, where a precipitate was obtained. The precipitate was filtered and crystallized from the suitable solvent (Table 5).

3-Chloro-N-(2,6-dimethylphenyl)-2-substituted aminomaleimides (8a-e):

To a solution of **(1f)** (8.1 g, 30 mmol) in glacial acetic acid (40 ml), the proper primary aromatic amines (28 mmol) in glacial acetic acid (20 ml) were added dropwise while stirring under reflux for one hour. The reaction mixture was then concentrated under reduced pressure, cooled, diluted with ice-cold water and filtered. Excess acid was washed with water (3x100 ml) and the products were crystallized from ethanol (Table 6).

3-Chloro-1-substituted phenyl-1H-pyrrolo[2,3-b]quinoxaline-2 (4H)- ones (4a-f):

General Procedure : To a solution of **(1a-f)** or (6a-f) (5 mmol) in acetic acid or methanol (30 ml), o-phenylenediamine **(2b)** (1.5 g, 14 mmol) was added while stirring. After refluxing for 1 hour, the reaction mixture was cooled and filtered. The separated product was crystallized from DMF/water (Table 7). The obtained yields were calculated based on **(1a-f).** By repeating the same experimental methodology using compounds **(8a-f)** as substrates, only the product **(4f)** was obtained.

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تفاعلات ٢ ,٣-ثنائى كلور حمض الماليك اللامائى: ٣
- التفاعلات مع محبات الانوية الثنائية (الاضافة الحلقية ٤٠٢)
لتحضير مركبات لها تأثير مضاد للميكروبات

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فى هذا البحث تم وصف تفاعل ٢ ,٣-ثنائى كلوروالماليميدات (١ أ-و) مع محبات الانوية الثنائية مثل الامينوفينول المجاور (٢أ) وكذلك الفنيلين ثنائى الامين المجاور (٢ب).

وقد تم فصل نواتج هذه التفاعلات بالاعتماد على تركيز أيون الهيدروجين وكذلك محلول التفاعل. وقد وجد أن كثير من المركبات الجديدة مثل بيرولوكينو اوكسالين ومشتقات المالبميدات لها تأثير ملحوظ كمضادات للميكروبات.