Department of Pharmaceutical Chemistry[1], Faculty of Pharmacy and Department of Microbiology[2], Medical Research Institute, Alexandria University, Egypt

Synthesis of some 3- and 4-substituted 1,5-diphenylpyrrolidine-2,4-diones as potential antimicrobial and antineoplastic agents Reactions with tetramic acid, part 5

M. N. S. Saudi[1], M. M. A. El Semary[1] and G. El Sawaf[2]

The condensation of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with the carboxyl compounds **2a**–**f** afforded the corresponding 3-arylidene-1,5-diphenylpyrrolidine-2,4-diones **3a**–**f**. Reaction of the parent compound **1** with isatin (**4**) yielded the condensation product **5** in an acidic medium, whereas compound **6** was obtained in an alkaline medium. The condensation of the primary amines **7a**–**f** with compound **1** afforded the corresponding 4-substituted amino-1,5-diphenyl-Δ^3-pyrrolin-2-ones **8a**–**f**. All the compounds synthesized were screened for their antimicrobial activity, and four compounds were selected for screening for their antineoplastic activity. The compounds tested showed both antimicrobial and antineoplastic activities.

1. Introduction

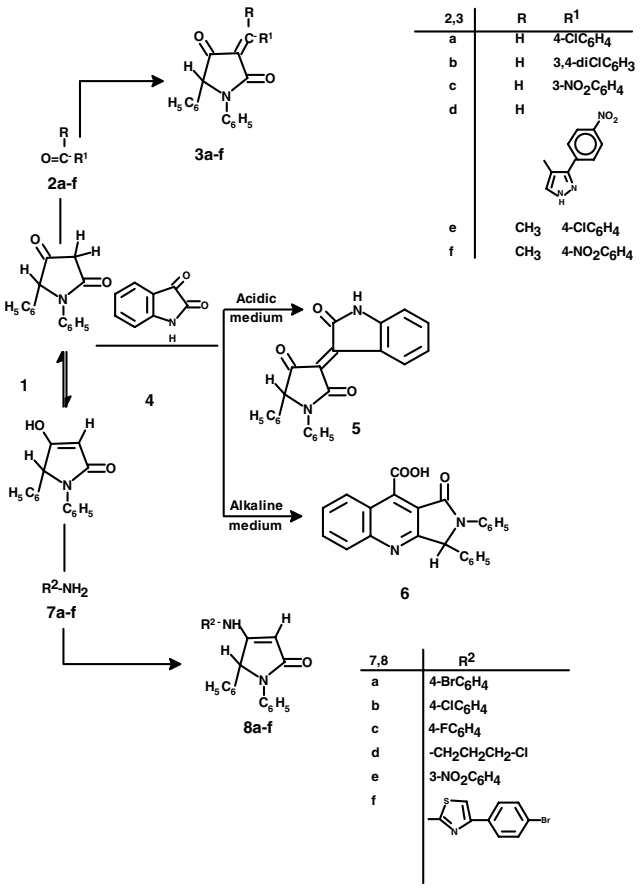
A number of antibiotics, mycotoxins and pigments which have been isolated from microorganisms involve the pyrrolidine-2,4-dione (4-hydroxy-Δ^3-pyrrolin-2-one; tetramic acid) nucleus as a main part of their structures [2–16]. Tenuazonic acid [2, 3] and magnesidin [12], which are considered the simplest members of this class of natural products, have shown antineoplastic, antiviral [17–20] or antimicrobial activities [21], respectively. Furthermore, such activities have been shown for many related synthetic pyrrolidine-2,4-diones [22–24] also. As part of a search for simple tetramic acid derivatives with potential antineoplastic and antimicrobial activities, this laboratory considered it would be useful to explore a variety of structural modifications of the basic nucleus. Thus various substituted 4-[1-(1*H*-benzimidazol-2-yl)alkylamino]-Δ^3-pyrrolin-2-ones were shown to exhibit antimicrobial activity [25]. In addition, the Mannich bases at C-3 of 1,5-diphenylpyrrolidine-2,4-dione showed considerable growth inhibitory effects against the Gram-positive *Streptococcus pyogenes* [26], while some of the 3-disubstituted methyl-4-hydroxy-1,5-diphenyl-Δ^3-pyrrolin-2-ones exhibited a degree of activity against some *Staph. aureus* strains [1]. The moderate anti-HIV-1 activity found with 3-(4-nitrobenzylidene)-1,5-diphenylpyrrolidene-2,4-dione synthesized in our laboratory [1] and the findings above encouraged us to synthesize a new series of 3-arylidene and 4-substituted amino derivatives to test their anticancer and antimicrobial activities.

2. Investigations and results

2.1. Synthesis of the compounds

The desired compounds were synthesized by the reactions outlined in the Scheme. Reaction of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with different carboxyl compounds **2a**–**f** yielded the corresponding 3-arylidene-1,5-diphenylpyrrolidine-2,4-dione derivatives **3a**–**f**. In the case of compounds **3a**–**c**, the reaction was done in acidic medium under reflux for 30 min. However, the use of 3-(*p*-nitrophenyl)pyrazol-4-aldehyde (**2d**) [27] or the appropriate acetophenone **2e** or **2f** to synthesize compounds **3d**, **3e** and **3f**, respectively, required prolonged reflux up to 10 h. On the other hand, the pH of the medium influenced the course of the reaction of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with isatin (**4**). In acidic medium, simple condensation between the C-3-active methylene of compound **1** and the C(3)=O of isatin (**4**) gave compound **5**. Its IR spectrum showed an NH band at 3320 cm^{-1} and three carbonyl bands at 1710, 1675 and 1660 cm^{-1}. In the ^{1}H-NMR spectrum, this compound **5** showed the isatin-NH as a singlet at δ 9.3 and a singlet at δ 5.35 for C_5-H in the tetramic acid residue. However, in a strong alkaline medium (30% aqueous NaOH), the reaction followed the

Scheme



Pfitzinger pathway [28] to form the 4-quinoline carboxylic acid derivative **6**. Its IR spectrum showed the broad OH band at 3600–3200 cm^{-1}, the carboxylic carbonyl band at 1680 cm^{-1} and C(2)=O band of tetramic acid moiety at 1669 cm^{-1}. Its ^1H NMR showed the 5-H at δ 5.4 and lacked the C-3-methylene signal of the tetramic acid part. On the other hand, reaction of 1,5-diphenylpyrrolidine-2,4-dione (**1**) with the appropriate primary amine **7a–f** yielded the corresponding 4-substituted amino-1,5-diphenyl-Δ^3-pyrrolin-2-ones **8a–f**. In case of 2-amino-4-(4-bromophenyl)thiazole (**7f**) [29] the reaction required a longer time of reflux. The IR spectra of those compounds showed NH bands at about 3340 to 3310 cm^{-1}. The ^1H NMR of some representative compounds showed NH singlets at about δ 8.8. Both IR and ^1H NMR data indicated that these compounds exist predominantly in the amino rather than the imino form.

2.2. Preliminary antimicrobial screening

2.2.1. MIC Testing [30]

Our new compounds were screened for their in vitro activities against *Staphylococcus aureus* strains (Gram-positive bacteria) and *Escherichia coli* strains, *Klebsiella* species strains, *Proteus* species strains and *Pseudomonas aeruginosa* strains (Gram-negative bacteria). The minimum inhibitory concentration (MIC) of our tested compounds was determined using microtiter plates. The compounds were dissolved in dimethyl-formamide to prepare a stock solution of 1 mg/ml. Two-fold serial dilutions were made in vertical rows of the microtiter plates. The media used were nutrient broth (DiFco) and Müller-Hinton agar plates (DiFco). To achieve the correct working inoculum of 10^7 cfu/ml, McFarland 0.5 turbidity standard was used. With the exception of compound **3a**, all the compounds tested showed activity against *Pseudomonas aeruginosa* strains. Compounds **3b** and **3e** showed activity against *Staphylococcus aureus* strains, but compound **8b** was the only one active against *E. Coli*. None of the compounds tested showed activity against both *Klebsiella* and *Proteus* species strains. The minimum inhibitory concentrations (MIC) in μg/ml of the effective compounds are given in Table 1.

Table 1: Minimum inhibitory concentration (MIC) in μg/ml of the most active compounds

Compd.	*S. aureus*	*E. coli*	*P. aeruginosa*
3b	250	–	125
3c	–	–	125
3d	–	–	125
3e	250	–	125
3f	–	–	500
5	–	–	500
6	–	–	500
8a	–	–	125
8b	–	500	500
8c	–	–	500
8d	–	–	125
8e	–	–	125
8f	–	–	125

2.2.2. Quality control

The following antibiotics and reference bacterial strains were used to evaluate effectively the precision and accuracy of the medium used.

- Gentamicin MICs with *Pseudomonas aeruginosa* strain ATCC 27853 used to test for cation concentration. (MIC range 1.0–4.0 μg/ml).
- Trimethoprim/sulfamethoxazole MICs with *Enterococcus faecalis* strain ATCC 29212 used to test for the presence of thymidine in the medium (MIC range <0.5/9.5 μg/ml).

These strains were obtained freeze-dried from the American Type Culture Collection, as a gift from Prof. M. Andreoni, Tor Vergata University, Rome, Italy.

2.3. Antineoplastic evaluation

Evaluation of anticancer activity was performed on 4 compounds corresponding to structures **3b, 3c, 8a** and **8c** (Scheme) at the National Cancer Institute (NCI), Bethesda, following the established *in vitro* disease oriented antitumor screening program against a panel of 60 human tumor cell lines [31]. Five concentrations (0.01–100 μM) of each compound were incubated with each cell line and were used to deduce the log concentration vs% growth inhibition curves. Response parameters GI_{50}, TGI and LC_{50} refer to the concentration of the agent in the assay that produced 50% growth inhibition, total growth inhibition, and 50% cytotoxicity, respectively. All the test compounds showed GI_{50} and TGI values $\leq$100 μM against leukemia, non-small cell lung cancer, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer subpanel cell lines (Tables 2 and 3). The four compounds tested showed total growth inhibition activity, but none of them showed cytotoxic activity.

The ratio obtained by dividing the compound's full panel MG-MID (μM) by its individual subpanel MG-MID (μM) is considered as a measure of compound selectivity. Ratios between 3 and 6 refer to moderate selectivity, ratios greater than 6 indicate high selectivity towards the corresponding cell line, while compounds meeting neither of these criteria are rated non selective [32]. The tested compound **8a** was found to exhibit moderate selectivity towards leukemia, non-small cell lung cancer, melenoma, renal cancer and breast cancer at the GI_{50} level with selectivity ratios of 6.1, 4.9, 5.7, 5 and 5.9, respectively. However, at the TGI level this compound was found to exhibit

Table 2: Median growth inhibitory concentration (GI_{50}, μM) of *in vitro* subpanel tumor cell lines

Compd.	Subpanel tumor cell lines [a]									
	I	II	III	IV	V	VI	VII	VIII	IX	MG-MID[b]
3b	15.4	3.17	16.8	17.4	14.5	15.5	16.7	14.3	17.4	19.4
3c	21.4	18.7	19.7	17.2	17.5	18.2	19.4	20.9	20.4	23.4
8a	1.32	1.64	5.62	3.60	1.43	2.99	1.59	3.28	1.38	8.1
8c	8.41	7.74	12.3	13.7	11.5	6.28	10.1	6.92	1.70	15.8

[a] I, leukemia; II, non-small cell lung cancer; III, colon cancer; IV, CNS cancer; V, melanoma; VI, ovarian cancer; VII, renal cancer; VII, prostate cancer; IX, breast cancer
[b] GI_{50} (μM) full panel mean-graph mid point (MG-MID) = the average sensitivity of all cell lines towards the test agent

Table 3: Total growth inhibitory concentration (TGI, μM) of in vitro subpanel tumor cell lines

Compd.	Subpanel tumor cell lines[a]									
	I	II	III	IV	V	VI	VII	VIII	IX	MG-MID[b]
3b	38.1	13.6	32.8	29.4	28.3	30.6	33.1	28.2	32.8	45.0
3c	45.7	33.0	32.7	37.8	32.7	34.1	35.0	44.0	41.8	53.7
8a	13.1	7.22	16.4	94.8	6.60	14.5	5.71	53.0	6.27	52.4
8c	41.0	27.2	27.5	40.9	27.5	26.9	31.1	50.3	17.3	48.9

[a] For subpanel tumor cell lines see footnote of table 2.
[b] TGI(μM) full panel mean-graph mid point (MG-MID) = the average sensitivity of all cell lines towards the test compound.

moderate selectivity towards leukemia and ovarian cancer with selectivity ratios of 4 and 3.6, respectively, while, high selectivity was shown towards non-small cell lung cancer, melanoma, renal cancer and breast cancer with selectivity ratios of 7.3, 7.9, 9.2 and 8.4, respectively.
In conclusion, the high degree of cell sensitivity and selectivity of compound **8a** raises the potential of its derivatization, in the hope of finding more active and selective antineoplastic agents.

3. Experimental

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded for KBr discs, using a Perkin-Elmer 421 spectrophotometer. The ^{1}H NMR spectra were recorded on a varian EM-390 (400 MHz) spectrophotometer, with TMS as an internal standard using DMSO-d_6 as solvent unless otherwise indicated. Chemical shifts were expressed in δ (ppm) values. Microanalytical data were obtained at the Microanalytical Unit, Faculty of Science, University of Alexandria, A.R. Egypt.

3.1. 3-Arylidene-1,5-diphenylpyrrolidine-2,4-diones 3a–f

A solution of 1,5-diphenylpyrrolidine-2,4-dione (**1**) [33] (0.5 g, 0.002 mol) and the appropriate carboxyl compound **2a–f** (0.002 mol) in ethanol (20 ml) was treated with 2 drops of concentrated sulfuric acid. The mixture was warmed for 30 min for compounds **3a–c**, or refluxed for 10 h for compounds **3d–f**, then the resulting yellow precipitate was filtered, washed with cold ethanol, dried and crystallized from the appropriate solvent. Melting points, % yields and IR spectral data of the compounds prepared are listed in Table 4.

Table 4: 3-Arylidene-1,5-diphenylpyrrolidine-2,4-dions 3a–f

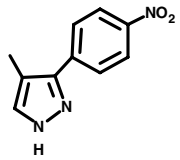
Compd.	R^1	R^2	Yield (%)	Melting point °C (cryst-solvent)	Molecular Formula (Molecular weight)	IR (cm^{-1})
3a	H	4-ClC_6H_4	70	204–205 (C_2H_5OH)	$C_{23}H_{16}ClNO_2$ (373.8)	1700 (C_4=O), 1646 (C_2=O), 1600 (C=C and aromatics)
3b	H	3,4-diClC_6H_3	65	210–212 (CH_3OH)	$C_{23}H_{15}Cl_2NO_2$ (408.3)	1694 (C_4=O), 1663 (C_2=O), 1590 (C=C and aromatics)
3c	H	3-$NO_2C_6H_4$	50	161–163 (CH_3OH)	$C_{23}H_{16}N_2O_4$ (384.4)	1690 (C_4=O), 1650 (C_2=O), 1598 (C=C and aromatics)
3d	H		42	198–199 ($(CH_3)_2CHOH$)	$C_{26}H_{18}N_4O_4$ (450.5)	3440 (NH); 1685 (C_4=O), 1650 (C_2=O), 1610 (C=N), 1596 (C=C and aromatics)
3e	CH_3	4-ClC_6H_4	35	174–176 (C_6H_6)	$C_{24}H_{18}ClNO_2$ (387.9)	1695 (C_4=O), 1645 (C_2=O), 1595 (C=C and aromatics)
3f	CH_3	4-$NO_2C_6H_4$	30	90–91 ($(CH_3)_2CHOH$)	$C_{24}H_{18}N_2O_4$ (398.4)	1690 (C_4=O), 1652 (C_2=O), 1591 (C=C and atomatics)

Table 5: 4-Substituted amino-1,5-diphenyl-Δ^3-pyrrolin-2-ones 8a–f

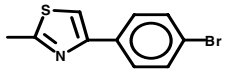
Compd.	R^3	Yield (%)	Melting point °C (cryst-solvent)	Molecular Formular (Molecular weight)	IR (cm^{-1})
8a	4-BrC_6H_4	65	190–91 (CH_3-OH)	$C_{22}H_{17}BrN_2O$ (405.3)	3340 (NH), 1657 (C_2=O), 1591 (C=C and aromatics)
8b	4-ClC_6H_4	55	188–89 (CH_3OH)	$C_{22}H_{17}ClN_2O$ (360.8)	3325 (NH), 1664 (C_2=O), 1595 (C=C and aromatics)
8c	4-FC_6H_4	60	196–97 (C_6H_6)	$C_{22}H_{17}FN_2O$ (344.4)	3320 (NH), 1659 (C_2=O), 1600 (C=C and aromatics)
8d	$-CH_2CH_2CH_2-Cl$	50	138–40 (C_6H_6)	$C_{19}H_{19}ClN_2O$ (326.8)	3460 (NH), 1647 (C_2=O), 1590 (C=C and aromatics)
8e	3-$NO_2C_6H_4$	53	234–35 (C_6H_6)	$C_{22}H_{17}N_3O_3$ (371.4)	3408 (NH); 1656 (C_2=O), 1594 (C=C and aromatics)
8f		30	153–55 ($(CH_3)_2CH-OH$)	$C_{25}H_{18}BrN_3OS$ (488.4)	3370 (NH); 1656 (C_2=O); 1615 (C=C and atomatics)

Table 6: ^{1}H NMR of 3-Arylidene-1,5-diphenylpyrrolidine-2,4-diones 3b-f and 4-substituted amino-1,5-diphenyl-Δ^3-pyrrolin-2-ones 8a, 8c and 8f

Compd.	^{1}H NMR δ (ppm)
3b	5.41 (s, 1 H, 5-H); 6.92–7.97 (m, 13 H, Ar.-H and 1 H, =CH–)
3c*	5.53 (s, 1 H, 5-H); 7.07–8.78 (m, 14 H, Ar.-H and 1 H, =CH–)
3d*	5.61 (s, 1 H, 5-H); 7.62–8.51 (m, 11 H, Ar.-H and 1 H, =CH–); 8.85 (s, 1 H, NH)
3e	2.50 (s, 3 H, CH_3); 5.35 (s, 1 H, 5-H); 6.94–7.47 (m, 14 H, Ar.-H)
3f	2.49 (s, 3 H, CH_3); 5.31 (s, 1 H, 5-H); 6.89–7.70 (m, 14 H, Ar.-H)
8a	5.30 (s, 1 H, 5-H); 6.00 (s, 1 H, 3-H); 6.78–7.56 (m, 14 H, Ar.-H); 8.80 (s, 1 H, NH)
8c	5.39 (s, 1 H, 5-H); 5.94 (s, 1 H, 3-H); 6.88–7.55 (m, 14 H, Ar.-H); 8.75 (s, 1 H, NH)
8f	5.50 (s, 1 H, 5-H); 6.22 (s, 1 H, 3-H); 7.02–8.00 (m, 15 H, Ar-H); 9.00 (s, 1 H, NH)

* In $CDCl_3$

3.2. Reaction of 1,5-diphenylpyrrolidine-2,4-dione (**1**) *with isatin* (**4**)

3.2.1. In acidic medium: 3-Isatin-3′-ylidene-1,5-diphenylpyrrolidine-2,4-dione (**5**)

A solution of compound **1** (0.25 g, 0.001 mol) and isatin (**4**) (0.15 g, 0.001 mol) in ethanol (10 ml) was refluxed for 10 h in presence of few drops of conc. sulfuric acid. The reaction mixture was then concentrated. After cooling, a reddish crystalline product was separated, filtered, dried and crystallized from benzene, m.p. 290–91 °C, yield 0.2 g (52.6%). IR (cm^{-1}): 3320 (NH); 1710 (C(4)=O, tetramic acid), 1675 (C(2)=O, isatin), 1660 (C(2)=O, tetramic acid), 1590 (C=C and aromatics).
^{1}H-NMR: δ 5.35 (s, 1 H, 5-H), 7.1–7.9 (m, 14 H, Ar.-H), 9.3 (s, 1 H, NH).
$C_{24}H_{16}N_2O_3$ (380.4)

3.2.2. In alkaline medium: 2,3-Dihydro-1-oxo-2,3-diphenyl-1H-pyrrolo-[3,4-b] quinoline-9-carboxylic acid (**6**)

Isatin (**4**) (0.15 g, 0.001 mol) was dissolved in an aqueous solution of NaOH (30%, 20 ml) and warmed until a clear solution was obtained. Then compound **1** (0.25 g, 0.001 mol) was added and the reaction mixture was refluxed for 15 h. After cooling, the solution was acidified with glacial acetic acid until a pale yellow precipitate was obtained. The product was filtered, washed with water, dried and crystallized from benzene-ethanol; m.p. >300 °C; yield 0.3 (78.9%). IR (cm^{-1}): 3600–3200 (br. OH), 1680 (–CO–OH), 1659 (C(4)=O), 1620 (C=N), 1593 (C=C and aromatics).
^{1}H NMR δ 5.6 (s, 1 H, 2-H), 6.9–7.8 (m, 14 H, Ar.-H).
$C_{24}H_{16}N_2O_3$ (380.4)

3.3. 4-Substituted amino-1,5-diphenyl-Δ^3-pyrrolin-2-ones **8a–f**

The appropriate amine **7a–f** (0.001 mol) was added to a solution of 1,5-diphenylpyrrolidine-2,4-dione (**1**) (0.25 g, 0.001 mol) in benzene (10 ml). The reaction mixture was refluxed for 1 h for compounds **8a–e** and for 5 h for compound **8f**. The benzene was removed under vaccum and the residue was crystallized from the appropriate solvent. Melting points, % yields and infrared spectral data of the compounds synthesized are recorded in Table 5.
The ^{1}H NMR data of some representative compounds are listed in Table 6.

Acknowledgement: The authors thank Professor Dr. Farid S. G. Soliman, Faculty of Pharmacy, University of Alexandria for his support and efforts.

* Part 4 [1]

References

1 Shams EL-Dine, S. A.; Soliman, F. S. G.; Ashour, F. A; Saudi, M. N. S.: Pharmazie **56**, 933 (2001)
2 Stickings, C. E.; Biochem. J. **72**, 332 (1959)
3 Poncet, J.; Jouin P.; Castro, B.; Nicolas, L.; Boutar, M; Gaudemer, A.: J. Chem. Soc. (Perkin Trans. 1), 611 (1990)
4 Shimshock, S. J.; Waltermire, R. E; De Shong; P.: J. Am. Chem. Soc. **113**, 8791 (1991)
5 Jones, R. C. F; Tankard, M.: J. Chem. Soc. (Perkin Trans 1) 240 (1991)
6 Holzapfel, C. W.: Tetrahedron **24**, 2101 (1968)
7 Holzapfel, C. W.; Hutchison, R. D; Wilkins, D. C.: Tetrahedron **26**, 5239 (1970)
8 Jones, R. C. F.; Begley, M. J.; Peterson, G. E; Sumaria, S.: J. Chem. Soc. (Perkin Trans 1) 1959 (1990)
9 Batelaan, J. G.; Barnick, J. W. F. K.; van der Baan, J. L; Bickelhaupt, F.: Tetrahedron Lett. 3107 (1972)
10 Schabacher, K; Zeeck, A.: Tetrahedron Lett. 2691 (1973)
11 Horvath, Gy.; Gyimesi, J; Méheshfalvi-Vajna, Zs.: Tetrahedron Lett. 3643 (1973)
12 Royles, B.: Chem. Rev. **95**, 1981 (1995)
13 Turos, E.; Audia, J. E; Danishefsky, S. J.: J. Am. Chem. Soc. **111**, 8231 (1989)
14 Rosen, T.; Fernandes, P. B.; Marovich, M. A.; Shen, L.; Mao, J; Pernet, A. G.: J. Med. Chem. **32**, 1062 (1989)
15 Brill, G. M.; McAlpine, J. B; Whittern, D.: J. Antibiot. **41**, 36 (1988); C.A. 108, 183342d (1988)
16 Ley, S. V.; Smith, S. C.; Woodward, P. R.: Tetrahedron **48**, 1145 (1992)
17 Shigeura, H. T; Gordon, C. N.; Biochemistry **2**, 1132 (1963)
18 Kaczka, E. A.; Gitterman, C. O.; Dulaney, E. L.; Smith, M. C.; Hendlin, D.; Woodruff, H. B.; Folers, K.: Biochem. Biophys. Res. Comm. **14**, 54 (1964)
19 Gitterman, C. O.; Dulaney, E. L.; Kaczka, E. A.; Cambell, G. W.; Hendlin, D; Woodruff, H. B.: Cancer Res. **24**, 440 (1964)
20 Miller, F. A.; Rightsel, W. A.; Sloan, B. J.; Ehrlich, J.; French, J. C; Bartz, Q. R.: Nature **200**, 1338 (1964)
21 Hoechst A.-G.: Brit. Pat. 1, 478, 643 (1977); C.A. **88**, 168480x (1978)
22 Harris, S. A.; Fisher, L. V; Folkers, K.: J. Med. Chem. **8**, 478 (1965)
23 Gitterman, C. O.: J. Med. Chem. **8**, 483 (1965)
24 Yuki, H.; Kariya, K; Hashimoto, Y.: Chem. Pharm. Bull. (Japan) **15**, 727 (1967)
25 Rida, S. M.; Soliman, F. S. G; Badawy, E. A. M.: Pharmazie **41**, 563 (1986)
26 Shams EL-Dine, S. A.; Kassem, M. G.; Soliman, F. S. G.; Saudi, M. N. S; Kader, O.: Il-Farmaco **46**, 1179 (1991)
27 Rainer, G.; Krüger, U; Klemm, K.: Arzneim-Forsch. **31**, 649 (1981)
28 Buu-Hoi, Ng. Ph.; Hoan, Ng.; Khôi, Ng. H; Xuong, Ng. D.: J. Org. Chem. **15**, 511 (1950)
29 Catsoulacos, P; Kallias, D.: J. Heterocycl. Chem. **16**, 763 (1979)
30 Working party of the British Society for Antimicrobial Chemotherapy (1991). A guide to antibiotic sensitivity testing. Journal of Antimicrobial Chemotherapy 27: Supplement D, 1–50.
31 Boyd, M. R.: Principles and Practices of Oncology **3** (10), 1 (1989)
32 Acton, E. M.; Narayanan, V. L.; Risbood, P. A.; Shoemaker, R. H.; Vistica, D. T; Boyd, M. R.: J. Med. Chem. **37**, 2185 (1994)
33 Soliman, F. S. G.: Pharmazie **32**, 572 (1977)

Received October 19, 2001
Accepted January 23, 2002

Dr. Manal N. S. Saudi
University of Alexandria
Department of Pharmaceutical Chemistry
Faculty of Pharmacy
Alexandria
Egypt