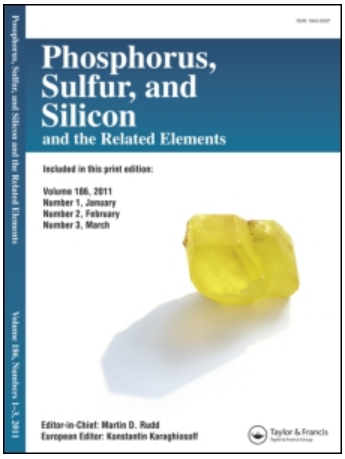

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THIENOPYRIDINONE ANTIBACTERIALS. PART II.[1] SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 2-CHLORO-7-CYCLOPROPYL-4,7-DIHYDRO-4-OXOTHIENO [2,3-b]PYRIDINE-5-CARBOXYLIC ACIDS

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The synthesis and properties of some new 7-cyclopropyl-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids and the 7-*tert*-butyl analogues, incorporating substituents at positions 2 and 3, are described. The antibacterial activity of these derivatives and of the parent 7-alkyl-2-chloro compounds, unsubstituted at position 3, has been evaluated against an assortment of micro-organisms. 2-Chloro-7-cyclopropyl-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid (**3a**) was found to possess leading *in vitro* activity among 4-thieno[2,3-*b*]pridinones known to date. However, none of the 3-nitro- or 3-amino-2-(4-methyl-1-piperazinyl) derivatives (**4–6**) showed interesting antibacterial activity.

Keywords: Functionalized 4-oxothieno[2,3-*b*]pyridines; synthesis; antibacterial activity

INTRODUCTION

The second generation "quinolones", such as norfloxacin (**1a**)[2] and ciprofloxacin (**1b**),[3,4] have stimulated considerable interest owing to their high potency and oral efficacy as broad-spectrum antibacterial agents.[5] Recently, several 2-(substi-

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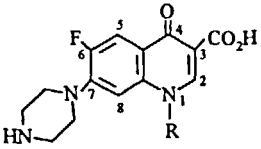
tuted)-7-ethyl4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids (**2**), potential bioisosteres of quinolones (**1**), have been prepared from 2-aminothiophene *via* the Gould-Jacobs method.[6–12] Notable examples that exhibit good level of antibacterial activity are compounds (**2a**)[6,7], (**2b**)[8] and (**2c,d**).[9,10]



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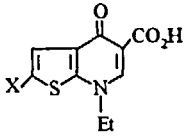

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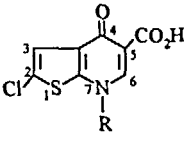


(**3**)

	R
a	Et
b	◁

	X
a	Cl
b	Me
c	CH = NOMe
d	CH = $NC_6H_4(OH)$-*o*

	R
a	◁
b	*t*-Bu
c	*n*-Pr
d	*i*-Pr

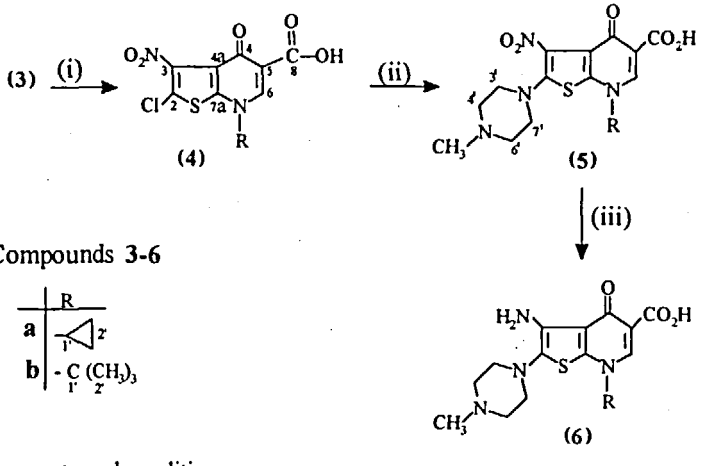
DIAGRAM I

Quite recently, we have described a novel versatile route for the synthesis of some 2-chloro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids (**3**) with a selected set of lower alkyl groups, including cyclopropyl, as appendages at the N-7 position.[1] The results of antibacterial screens against *Escherichia coli* have shown, as expected, that the 7-cyclopropyl derivative (**3a**) is more potent (*MIC* = 0.50 μ g / ml) [1] than the 7-ethyl analogue (**2a**)(MIC = 2.0 μg/ml). In the present study, compounds (**3a-d**) have been tested further against an assortment of micro-organisms by using the standard technique[13] (*vide infra),* and their *MICs* are compared with those of ofloxacin as the reference agent (TABLE II, *vide infra*).

Substitution at the 2- and 3-positions of the 4-oxothieno[2,3-*b*] pyridine moiety has not been sufficiently investigated and optimised. In extension to recent structure-activity relationship (SAR) studies,[6–10] we envisage to incorporate a piperazine substituent at the 2-position of the thieno[2,3-b]pyridine moiety. This is inferred from the fact that most of the potent quinolone antiinfectives are substituted (at the 7-position) by cyclic aliphatic amines, especially diamines such as piperazine (e.g compounds **1a,b**). Accordingly, the present work aims at obtaining selected set of 2-(4-methyl-1-piperazinyl)-4-oxothieno[2,3-*b*]pyridines (**5a,b** and **6a,b**) *(via* compounds **4a,b**/ SCHEME 1) for bioassay. Herein, their synthesis and properties are described.

SYNTHESIS

The requisite starting synthons, 2-chloro-4-oxothieno[2,3-*b*] pyridine-5-carboxylic acids (**3a,b**) have been prepared from methyl 3-(2,5-dichloro-thien-3-yl)-3-oxopropanoate[14] *via* a recently reported route. [1] Our initial approach involved the preparation of 2-(4-methyl-1-piperazinyl)-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids, unsubstituted at the 3-position, and performing electrophilic substitution reactions, thereon. However, attempts to bring about direct displacement of the 2-chloro substituent in compound (**3a**) by N-methylpiperazine or piperazine as nitrogen nucleophiles (in DMSO at 145–150 °C for several hours) have, thus far, been unsuccessful. To circumvent this problem, an alternative strategy was chosen such as to introduce, at C-3, a nitro group capable of activating the 2-position and promoting displacement of the chloride thereat. In a subsequent step, the nitro group is readily reduced to the amino group which is desirable as substituent at C-3 for SAR studies. This methodology works well for the preparation of the target compounds (**4–6**) and is outlined in SCHEME 1. The physical and analytical data for compounds (**4–6**) are shown in TABLE I. Their MS, ^1H and ^{13}C NMR spectral signals conform with the assigned structures, and are listed in the experimental.



SCHEME 1

TABLE I Physical and analytical data of compounds **4–6**

Compd. No	*Yield (%)*	*Mp (°C)*	*Mol. Formula (Mol. Mass)*	*% Analyses (Calcd. / Found)*			
				C	*H*	*N*	*S*
4a	73	268–269 (dec.)	$C_{11}H_7ClN_2O_5S$	41.98	2.24	8.90	10.19
			(314.70)	41.88	2.41	8.81	10.20
4b	75	264–265 (dec.)	$C_{12}H_{11}ClN_2O_5S$	43.58	3.35	8.47	9.69
			(330.75)	43.40	3.39	8.24	9.93
5a	46	270–271 (dec.)	$C_{16}H_{18}N_4O_5S$	50.79	4.79	14.81	8.47
			(378.41)	51.00	5.00	14.76	8.26
5b	38	212–213 (dec.)	$C_{17}H_{22}N_4O_5S$	51.76	5.62	14.20	8.13
			(394.45)	51.41	5.75	13.95	8.31
6a	71	218–219 (dec.)	$C_{16}H_{20}N_4O_3S$	55.16	5.79	16.08	9.20
			(348.42)	55.06	5.72	15.97	9.35
6b	88	189–190 (dec.)	$C_{17}H_{24}N_4O_3S$	56.02	6.64	15.37	8.80
			(364.47)	55.79	6.82	15.19	8.93

PHARMACOLOGICAL TESTS

The 7-alkyl-2-chloro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids **2a,3a-d** (DIAGRAM I) were evaluated for their in *vitro* antibacterial activity against eight representative Gram-positive and Gram-negative bacteria. These activities were determined by using conventional agar dilution procedures. The minimum inhibitory concentrations (*MICs*, μg / ml) were averaged from multiple experiments and recorded in TABLE II, wherein *MICs* for ofloxacin (as the reference agent) are also included for comparison. The data indicate that the activity is largely confined to Gram-negative bacteria, and that compound **(3a)** is the most active member of the present series. Here, the cyclopropyl group, appended at the N-7-position **(3a)**, did show the expected increase in potency (2–3 fold) relative to the N-7-ethyl analogue **(2a)**. Compared to ofloxacin, compound **(3a)** exhibited a rather low level of activity. The N-7-substituents confer influence onto the spectrum and extent of antibacterial potency in the following order :

cyclopropyl > ethyl, *t*-butyl > *n*-propyl > *i*-propyl

Such a trend parallels qualitatively that reported for the N-1-alkylquinolone counterparts. However, none of these thienopyridinones **(3a-d)** showed any interesting activity against *Ps. aeruginosa* and *B. bronchiseptica.*

Introduction of a nitro group at the 3-position resulted in a considerable overall decrease in the antibacterial activity of the derivatives **(4a, 4b)** as compared to their respective parent analogues **(3a, 3b)**. Replacement of the chlorine atom at 3-position with N-methylpiperazinyl group led to inactive products **(5a, 5b)** at 128 μg/ml. Similar results were also obtained for the respective 3-amino analogues **(6a, 6b)**.

TABLE II *In vitro* antibacterial activity *(MIC* values, in μg /ml) of the different thieno[2,3-b]pyridines **3–6**, and of ofloxacin (OFL) as the reference agent

Strains / *No.*	*OFL*	*2a*	*3a*	*3b*	*3c*	*3d*	*4a*	*4b*	*5a, 5b / 6a, 6b*
Staphylococcus aureus ATCC 9144	0.125	32	16	32	> 128	> 128	> 128	> 128	> 128
Streptococcus faecalis ATCC 11700	4	> 128	> 128	> 128	> 128	> 128	> 128	> 128	> 128
Bordetella bronchiseptica ATCC 4617	1	8	8	16	64	>128	> 128	> 128	> 128
Escherichia coli ATCC 10536	≤0.06	2	0.5	2	8	16	16	> 128	> 128
Klebsiella pneumoniae ATCC 10031	≤0.06	2	0.25	0.5	2	8	16	> 128	> 128
Enterobacter cloacae ATCC 13047	≤ 0.06	1	0.5	4	8	32	32	> 128	> 128
Proteus mirabilis. IP 54163	≤ 0.06	2	0.5	4	8	32	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 27853	1	128	64	128	> 128	>128	> 128	> 128	> 128

EXPERIMENTAL

Melting points were measured on an Electrothermal Mel. Temp. apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-WM 400 and 300 MHz instruments, with TMS as an internal reference. Electron-impact (EI) mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by M. H. W. Laboratories, Arizona, USA. The *MICs* were determined by the conventional agar dilution procedures according to the method of Mueller-Hinton at pH 7.4. Aqueous stock solutions (1000 μg/ml) of the test compounds were prepared with 0.1 N NaOH. Serial dilu-

tions were then made to obtain test concentrations ranging from 128 μ*g/ml* – 0.06 μ*g/ml*. The agar plates were inoculated with approximately 10^4 CFU per spot. The agar plates were then incubated at 37 °C for 18 h. The *MICs* were taken as the lowest concentrations of the test compounds that inhibit visible growth.

2-Chloro-7-cyclopropyl-4, 7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid (3a)[1]

This compound was prepared from methyl 2-(2,5-dichlorothien-3-yl)-3-oxopropanoate[14] following a recently reported procedure.[1]

7-*tert*-Butyl-2-chloro-4, 7-dihydro-4-oxothieno[2,3-b]pyridine-5-carboxylic acid (3b)[1]

The title compound was likewise prepared following a recently described method.[1]

2-Chloro-7-cyclopropyl-4, 7-dihydro-3-nitro-4-oxothieno[2,3-b] pyridine-5-carboxylic acid (4a)

A solution of compound **(3a)** (1.6 g, 6 mmol) in concentrated sulfuric acid (10 ml) was dropwise added to a stirred mixture of fuming nitric acid (1 ml) and concentrated sulfuric acid (5 ml) cooled to ~ –5 °C. Following the addition which took ~ 30 min., the resulting reaction mixture was allowed to warm to ~ 6 °C under stirring, and then poured onto ice (50 g). The precipitated solid product was collected by filtration, washed with water, dried and recrystallized from dimethylformamide / ethanol. ^{1}H NMR(DMSO-d_6) δ 1.31 (4H, m, H-2′), 3.92 (1H, m, H-1′), 8.72 (1H, S, H-6), 14.36 (1H, s, CO_2H) ; ^{13}C NMR (DMSO-d_6) δ7.5 (C-2′), 38.2 (C-1′), 112.9 (C-5), 119.5 (C-2), 123.3 (C-4a), 139.8(C-3),147.3 (C-6),150.6 (C-7a), 164.9 (C-8), 171.5 (C-4); EI-MS *m/z* (% relative abundance) 314 (8%, $M^{+\cdot}$), 270 (100), 223 (8), 192 (4), 160 (12), 115 (6), 94 (7), 69 (7), 53 (29), 41 (88).

7-*tert*-Butyl-2-chloro-4, 7-dihydro-3-nitro-4-oxothieno[2,3-b] pyridine-3-carboxylic acid (4b)

This compound was obtained by nitration of the precursor acid **(3b)** using the same experimental procedure described above for the preparation of compound **(4a)**. Recrystallization from dimethylformamide / ethanol yielded a pure sample

of **4b**. ^{1}H NMR (DMSO-d_6) δ1.81 (9H, s, H-2′), 8.82 (1H, s, H-1′), 14.27 (1H, s, CO_2H) ; ^{13}C NMR (DMSO-d_6) δ27.8 (C-2′), 68.0 (C-1), 111.8 (C-5), 121.9 (C-2), 122.4 (C-4a), 144.3 (C-6), 145.1 (C-3), 148.4 (C-7a), 165.0 (C-8), 170.8 (C-4). EI-MS *m/z* 330 (2%, $M^{+\cdot}$), 284 (2), 274 (31), 256 (66), 240(3), 226 (5), 210(11), 198 (10), 142 (12), 115 (11), 57 (35), 56 (41), 53 (65), 41 (100).

7-Cyclopropyl-4, 7-dihydro-2-(4-methyl-1-piperazinyl)-3-nitro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid (5a)

To a stirred solution of compound **(4a)** (1.1 g, 3.5 mmol) in dimethylformamide (5 ml) was added 1 -methylpiperazine (2.8 g, 28 mmol), and the reaction mixture was stirred for 30 min. at room temperature. The resulting orange-coloured precipitate was collected by suction filtration, washed successively with water, ethanol and ether. Compound **(5a)** was purified by successive soaking in small volumes (3 ml) of dimethylformamide, methanol, chloroform and ether. ^{1}H NMR(1% NaOD in D_2O) δ1.23 (4H, m, H-2′), 2.29 (3H, s, CH_3-N), 2.65 (4H, t, J = 4.7 Hz, H-4′ / H-6′), 3.40 (4H, t, J = 4.7 Hz, H-3′ / H-7′), 3.65 (1H, m, H-1′), 8.18 (1H, s, H-6); ^{13}C NMR(1% NaOD in D_2O) δ10.2 (C-2′), 39.7 (C-1′), 47.3 (CH_3-N), 56.2 (C-4′/C-6′), 56.4 (C-3′/C-7′), 123.8 (C-4a), 127.4 (C-5), 130.8 (C-3), 144.6 (C-6), 147.2 (C-2), 173.1 (C-8), 174.9 (C-4). EI-MS *m/z* 378 (2%, $M^{+\cdot}$), 320 (1), 274 (2), 256 (5), 207 (16), 191 (2), 179 (8), 158 (4), 57 (38), 44 (100).

7-tert-Butyl-4, 7-dihydro-2-(4-methyl-1-piperazinyl)-3-nitro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid (5b)

The title compound (TABLE I) was obtained by piperazinylation of **4b** (1.0 g, 3 mmol) following the same procedure described above in the preparation and purification of **5a**. ^{1}H NMR (1% NaOD in D_2O) δ 1.79 (9H, s, H-2′), 2.26 (3H, s, CH_3-N), 2.60 (4H, bt, H-4′/ H-6′), 3.31 (4H, bt, H-3′/ H-7′), 8.51 (1H, s, H-6); ^{13}C NMR (1% NaOD in D_2O) δ 30.9 (C-2′), 47.4 (CH_3-N), 56.1 (C-4′/C-6′), 56.3 (C-3′/C-7′), 68.9 (C-1), 125.4 (C-4a), 126.7 (C-5), 131.3 (C-3), 142.5 (C-2), 143.3 (C-6), 154.9 (C-7a), 172.9 (C-8), 175.2 (C-4). EI-MS *m/z* 394 (1%, $M^{+\cdot}$), 338 (1), 293 (2), 275 (4), 249 (4), 203 (5), 100 (7), 70 (8), 58 (20), 44 (100).

3-Amino-7-cyclopropyl-4, 7-dihydro-2-(4-methyl-1-piperazinyl)-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid (6a)

To a vigorously stirred solution of compound **(5a)** (1.16 g, 3 mmol) in concentrated hydrochloric acid (20 ml) was portionwise added stannous chloride dihy-

drate (3.6 g, 16 mmol) during 10 min. at room temperature. The resulting mixture was stirred for additional 1h. Water (15 ml) was then added to the stirred mixture until a clear solution is obtained, and stirring was continued for 30 min. The reaction mixture was cooled (ice-bath), and solid sodium carbonate was protionwise introduced, under stirring, until neutralization is reached. The resulting neutral solution was extracted with chloroform (4 × 40 ml) and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residual solid product was recrystallized from chloroform /n-hexane. ^{1}H NMR($CDCl_3$) δ 1.25 (4H, m, H-2′), 2.37 (3H, s, CH_3-N), 2.58 (4H, t, J = 4.8 Hz, H-4′ / H-6′), 2.94 (4H, t, J = 4.8 Hz, H-3′ / H-7′), 3.54 (1H, m, H-1′), 4.88 (2H, bs, NH_2), 8.57 (1H, s, H-6), 15.26 (1H, bs, CO_2H) ; ^{13}C NMR ($CDCl_3$) δ 7.6 (C-2′), 37.1 (C-1′), 46.2 (CH_3-N), 53.6 (C-4′/C-6′), 55.4 (C-3′/C-7′) 111.8 (C-5), 121.1 (C-4a), 124.2 (C-3), 134.5 (C-2), 147.8 (C-7a), 167.1 (C-8), 175.8 (C-4). EI-MS *m/z* 348 (76%, $M^{+\cdot}$), 302 (4), 278 (32), 260 (29), 245 (7), 234 (6), 219 (8), 191(5), 85 (14), 71 (87), 70 (30), 58 (24), 43 (100).

3-Amino-7-tert-butyl-4, 7-dihydro-2-(4-methyl-1-piperazinyl)-4-oxothieno [2,3-*b*]pyridine-5-carboxylic acid (6b)

This compound was produced via reduction of the 3-nitrothieno-pyridine derivative **(5b)** (1.18 g, 3 mmol) by the same experimental procedure as described above for the preparation of compound **(6a)** (TABLE I). Compound **(6b)** was recrystallized from chloroform / *n*-hexane. ^{1}H NMR ($CDCl_3$) δ 1.71 (9H, s, H-2′), 2.21 (3H, s, CH_3-N), 2.43 (4H, bt, H-4′/ H-6′), 2.82 (4H, t, J= 4.8 Hz, H-3′/ H-7′), 4.87 (2H, bs, NH_2), 8.66 (1H, s, H-6), 15.15 (1H, bs, CO_2H) ; ^{13}C NMR ($CDCl_3$) δ 28.8 (C-2′), 46.1 (CH_3-N), 53.3(C-4′/C-6′), 55.3 (C-3′/C-7′), 66.28 (C-1), 110.7 (C-5), 122.9 (C-4a), 123.4 (C-3), 133.5 (C-2), 141.6 (C-6), 143.3 (C-7a), 167.4 (C-8), 175.3 (C-4). EI-MS *m/z* 364 (66%, $M^{+\cdot}$), 308 (21), 290 (44), 262 (12), 238 (22), 220 (11), 205 (15), 191 (11), 179 (8), 85 (8), 71 (64), 70 (100), 56 (13), 43 (46).

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References

[1] El-Abadelah, M.M., Sabri, S.S. and Al-Ashqar, H.A (1997) *Heterocycles,* **45,** 255.
[2] Koga, H., Itoh, A., Murayama, S., Suzue, S. and Irikura, T (1980) *J. Med. Chem.,* **23,** 1358.
[3] Maurer, F. and Grohe, K (1986) *(Ger Offen,* 3, 435, 392 *(Chem. Abstr.,* **105,** 97158e (1986)).

[4] Wise, R., Andrews, J.M. and Edwards, L.J (1983) *Antimicrob. Agents Chemother.*, **23**, 559.
[5] Some of the recent publications and reviews include : Calas, M., Bompart, J., Giral, L. and Grassy, G (1991) *Eur. J. Med. Chem.*, **26**, 279; Chu, D.T.W. and Femandes, P.B (1991) *Adv. Drug Res.* **21**, 39; Vergin, H. and Metz, R (1991) *Drugs Today* **27**, 177; Wentland, M.P (1990) Structure-Activity of Fluoroquinolones. In : *The New Generation of Quinolones* (Siporin C., Heifetz C.L. and Domagala J.M., eds) Marcel Dekker, New York, pp. 1–43; Rosen, T (1990) The Fluoroquinolone Antibacterial Agents. In : *Progress in Medicinal Chemistry* (Ellis, G.R. and West, G.B., eds) Elsevier, New York Vol **27**, pp. 235 – 295; Fernandes, P.B. and Chu, D.T.W (1988) *Annu. Rep. Med. Chem.*, **23**, 133.
[6] Yamazaki, T., Matsubara, Y., Morishima, K. and Suenaga, I (1983) *Takeda Kenkyushoho,* **42**, 297.
[7] Brovic, G., Cotrait, M., Bompart, J. and Giral, L (1989) *Acta Crystallogr., C* **45**, 1983.
[8] Bompart, J., Giral, L., Malicorne, G. and Puygrenier, M (1987) *Eur. J. Med. Chem.*, **22**, 139, and refs therein.
[9] Bompart, J., Giral, L., Malicorne, G. and Puygrenier, M (1988) *Eur.* J. *Med. Chem.*, **23**, 457.
[10] Giral, L., Bompart, J. and Puygrenier, M (1985) Eur. Pat. EP., 161, 235 *(Chem. Abstr.,* **104**, 88515 w (1986)).
[11] Kuwada, Y., Meguro, K., Sato, Y. and Fugono, T(1976) Japan Kokai 76. 100. 092 *(Chem. Abstr.,* **86**, 189900h (1977)).
[12] Kuwada, Y., Meguro, K., Sato, Y. and Fugono, T(1975) Ger. Offen., 2, 435, 025 *(Chem. Abstr.,* **82**, 156252n (1975)).
[13] Cohen, M.A., Griffin, T.J., Bien, P.A., Heifetz, C.L. and Domagala, J.M (1985) *Antimicrob. Agents Chemother.*, **28**, 766.
[14] El-Abadelah, M.M., Kamal, M.R., Tokan, W.M. and Jarrar, S.O (1997) *J. Prakt. Chem.*, **339**, 284.