Benzo[b]thiophenes, Part I: Synthesis and Antimicrobial Activity of Benzo[b]thienyl-1,3,4-oxadiazole, -1,2,4-triazoline, and -thiazoline Derivatives

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Four new series of benzo[b]thiophene derivatives bearing various thiosemicarbazide, 1,3,4-oxadiazole, 1,2,4-triazoline, and thiazoline moieties have been synthesized and evaluated for antimicrobial activity.

Benzo[b]thiophene, 1. Mitt.: Synthese und antimikrobielle Wirkung von Benzo[b]thienyl-1,3,4-oxadiazol-, -1,2,4-triazol- und -thiazolin-Derivaten

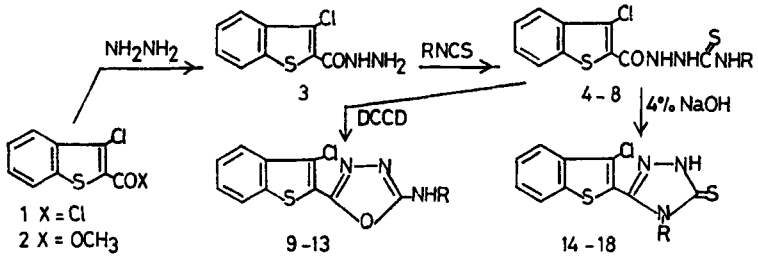
Vier neue Serien von Benzo[b]thiophen-Derivaten mit verschiedenen Thiosemicarbazid-, 1,3,4-Oxadiazol-, 1,2,4-Triazolin- und Thiazolin-Resten wurden synthetisiert und auf antimikrobielle Wirksamkeit geprüft.

Biologically active benzo[b]thiophenes have been largely explored and well reviewed[1-6]. Some of them possess remarkable herbicidal[7], pesticidal[8], and microbicidal[9-11] activities.

Within our studies on biologically active heterosulfur compounds[12], we adopted the benzo[b]thiophene system as a carrier for different thiosemicarbazide and azole moieties in four new groups as potential antimicrobial agents. The study makes use of the good lipophilicity and the low level of toxicity of benzo[b]thiophene[1b] in potentiating the bactericidal properties of the selected thiosemicarbazides and the azoles. The designed compounds, namely: 3-chloro-2-(1'-substituted thiocarbamoylhydrazinocarbonyl)benzo[b]thiophenes (**4-8**), 2-(substituted amino)-5-(3-chloro-2-benzo[b]thienyl)-1,3,4-oxadiazoles (**9-13**), 1*H*-4-substituted-5-thio-3-(3-chloro-2-benzo[b]thienyl)-1,2,4-triazolines (**14-18**), and 3-chloro-2-[(3',4'-disubstituted-2',3'-dihydrothiazol-2'-ylidene)hydrazinocarbonyl]benzo[b]thiophenes (**19-32**) (Schemes 1, 2) were synthesized and evaluated for antimicrobial activity.

The 3-chloro-2-chlorocarbonylbenzo[b]thiophene (**1**), required as starting material, was prepared by reacting cinnamic acid with $SOCl_2$ in the presence of catalytic amounts of pyridine[13a]. The acid chloride **1** was then reacted with hydrazine hydrate to give the acid hydrazide **3** in poor yield which could be significantly improved by converting the acid chloride **1** into the ester **2** and treating the latter with hydrazine hydrate (Scheme 1). Subsequent treatment of 3-chloro-2-hydrazinocarbonylbenzo[b]thiophene (**3**) with the selected isothiocyanate derivatives provided the 3-chloro-2-(1'-substituted thiocarbamoylhydrazinocarbonyl)benzo [b] thiophenes **4-8** in high yields (Scheme 1, Table 1). In their IR-spectra, **4-8** showed vibrational bands due to NH, C=O and NCS amide I, II, III, and IV bands[14]. The ^{1}H-NMR-spectra of compounds **4** and **5**, as representative examples for the thiosemicarbazides, showed N-H-signals for the thiosemicarbazide moiety.

The thiosemicarbazides **4-8** were then cyclodesulfurized with dicyclohexylcarbodiimide (DCCD)[15-17], to produce the 2-(substituted amino)-5-(3-chloro-2-benzo[b]thienyl)-1,3,4-oxadiazoles **9-13** in good yields (Scheme 1, Table 2).



	R
4, 9, 14	$CH_2C_6H_5$
5, 10, 15	C_6H_5
6, 11, 16	$C_6H_4Cl(p)$
7, 12, 17	$C_6H_4CH_3(p)$
8, 13, 18	$C_6H_4OCH_3(p)$

Scheme 1

Boiling the thiosemicarbazides **4-8** with 4% aqueous NaOH in ethanol furnished the corresponding 1*H*-4-substituted-5-thio-3-(3-chloro-2-benzo[b]thienyl)-1,2,4-triazolines **14-18**

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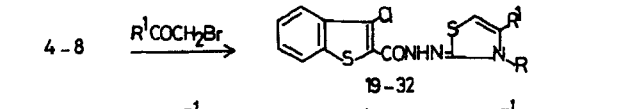

	R	R¹		R	R¹
19	$CH_2C_6H_5$	C_6H_5	26	$C_6H_4Cl(p)$	$C_6H_4C_6H_5(p)$
20	"	$C_6H_4NO_2(p)$	27	$C_6H_4CH_3(p)$	C_6H_5
21	"	$C_6H_4C_6H_5(p)$	28	"	$C_6H_4NO_2(p)$
22	C_6H_5	C_6H_5	29	"	$C_6H_4C_6H_5(p)$
23	"	$C_6H_4NO_2(p)$	30	$C_6H_4OCH_3(p)$	C_6H_5
24	"	$C_6H_4C_6H_5(p)$	31	"	$C_6H_4NO_2(p)$
25	$C_6H_4Cl(p)$	$C_6H_4NO_2(p)$	32	"	$C_6H_4C_6H_5(p)$

Scheme 2

in high yields (Scheme 1, Table 3). Various 3-chloro-2-[(3',4'-disubstituted-2',3'-dihydrothiazol-2'-ylidene)hydrazinocarbonyl]benzo[*b*]thiophenes **19-32** were prepared by reacting the thiosemicarbazide derivatives **4-8** with phenacyl bromide or the appropriate 4-substituted phenacyl bromide (Scheme 2).

The IR- and ^{1}H-NMR-spectra of the products were consistent with the assigned structures. The benzo[*b*]thienyl-oxadiazole derivatives **9-13** lacked the C=O and NCS amide bands and showed the C=N, C-O-C absorptions. The benzo[*b*]thienyl-triazolines **14-18** showed absorptions due to C=N and NCS amide functions indicating that they exist in the triazolinethione rather than in the mercaptotriazole form. The spectra of the thiazoline derivatives **19-32** showed bands for C=O, C=N, and NH functions and lacked the NCS amide bands. The ^{1}H-NMR-spectra of the oxazoles **11** and **12** lacked the two NH-signals of the thiosemicarbazide group. The triazoline derivatives **14** and **18** showed a highly deshielded signal at 14.08-14.25 ppm assigned for the NH proton of the triazoline ring. Compounds **25** and **29** showed the thiazoline-H at 6.08-6.29 ppm. In addition, all products showed the C-4-, C--5-, C-6-, and C-7-protons of benzo[*b*]thiophene[18].

Experimental Part

Melting points: *Griffin* melting point apparatus, uncorrected.- IR spectra (KBr): Shimadzu spectrophotometer.- ^{1}H-NMR spectra: Varian EM 360L, 60 MHz, TMS as internal standard.- Microanalyses: Microanalytical Unit, Faculty of Sciences, Cairo University, Egypt.

3-Chloro-2-chlorocarbonylbenzo[b]thiophene (**1**)

1 was prepared in 71% yield according to lit.[13a]; m.p. 113-115°C; lit.[13a]: 113.5-115°C and 114.4-115.1°C[13b].

Methyl 3-chlorobenzo[b]thiophene-2-carboxylate (**2**)

3-Chloro-2-chlorocarbonylbenzo[*b*]thiophene (**1**) (10 g, 0.04 mole) in absol. MeOH (100 ml) was heated under reflux for 1 h. The clear solution was concentrated and left to cool to room temp. to deposit white shiny needles of methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (**2**) in almost quantitative yield (9 g), m.p. 62-63°C.- IR: 1720 (C=O), 1590 and 1510 (C=C aromatic), 1230 (C-O-C vas), 1090 and 1060 cm^{-1} (C-O-C vs).- $C_{10}H_7ClO_2S$ (226.5) Calc. C 53.0 H 3.09 S 14.1 Found 53.3 H 3.00 S 13.8.

3-Chloro-2-hydrazinocarbonylbenzo[b]thiophene (**3**)

A solution of ester **2** (9 g, 0.039 mole) in methanol (100 ml) was heated with hydrazine hydrate (7 g, 0.14 mole) under reflux for 1 h. The mixture, containing the product partially separated, was left to cool to room temp., filtered and the product was crystallized from a large volume of methanol giving 8.5 g of compound **3**, m.p. 169-171°C, yield 94%.- IR: 3290 (NH), 1630 (C=O), 1590 and 1510 cm^{-1} (C=C aromatic).- $C_9H_7ClN_2OS$ (226.5) Calc. C 47.7 H 3.09 N 12.4 Found C 48.0 H 3.00 N 12.5.

3-Chloro-2-(1'-substituted thiocarbamoylhydrazinocarbonyl)benzo[b] thiophenes **4-8**

A solution of the acid hydrazide **3** (1 g, 4.4 mmole) in hot ethanol (40 ml) was cooled to 60°C and treated with a solution of the pertinent isothiocyanate (4.4 mmole) in ethanol (5 ml). An immediate precipitate was formed. The mixture was stirred at 60°C for further 30 min and the product was filtered and crystallized from acetone. Table 1.- IR: 3300; 3150 (NH); 1625-1620 (C=O); 1590; 1500 (C=C); 1530; 1350-1345; 1255-1250; 950-930 cm^{-1} (NCS amide I, II, III, IV bands).- ^{1}H-NMR of **4** ($CDCl_3$+DMSO-d_6): δ (ppm) = 4.78 (d, 2H, J = 4 Hz, CH_2), 7.28 (s, 5H, Ar-H), 7.38-7.60 (m, 2H, H-5 and H-6, benzothiophene), 7.68-7.99 (m, 2H, H-4 and H-7, benzothiophene), 7.99-8.40 (m, 2H, NH-NH), 11.12 (s, broad, 1H, $NHCH_2C_6H_5$).- ^{1}H-NMR of **5** ($CDCl_3$+DMSO-d_6): δ (ppm) = 7.10-7.78 (m, 7H, Ar + H-5 and H-6, benzothiophene), 7.78-8.10 (m, 2H, H-4 and H-7, benzothiophene), 9.78 (s, 1H, NHCS), 10.20 (s, broad, 1H, NHCO), 10.48 (s, 1H, NHC_6H_5).

Table 1: 3-Chloro-2-(1-substituted thiocarbamoylhydrazinocarbonyl)benzo[*b*]thiophenes **4-8**

Compd No.	Yield %	Mp °C	Molecular Formula	Analysis% C	H	N	Calc/Found
4	83	192-94	$C_{17}H_{14}ClN_3OS_2$ (375.5)	54.32 54.70	3.72 3.90	11.18 11.10	
5	91	236-38	$C_{16}H_{12}ClN_3OS_2$ (361.5)	53.11 53.70	3.31 3.50	11.61 11.60	
6	86	226-28	$C_{16}H_{11}Cl_2N_3OS_2$ (396)	48.40 48.40	2.77 2.80	10.60 10.70	
7	99	228-29	$C_{17}H_{14}ClN_3OS_2$ (375.5)	54.32 54.60	3.72 3.60	11.18 11.50	
8	92	192-94	$C_{17}H_{14}ClN_3OS_2$ (391.5)	52.10 52.40	3.57 3.80	10.72 10.40	

2-(Substituted amino)-5-(3-chloro-2-benzo[b]thienyl)-1,3,4-oxadiazoles **9-13**

A solution of the thiosemicarbazides **4-8** (300 mg) and 1.5 molar equivalent of DCCD in hot 1:1 v/v absol. methanol-dry acetone was heated under reflux for 4 h. The product, which either precipitated immediately or after cooling to room temp., was filtered and crystallized from the proper solvent. Table 2.- IR: 3400-3350 (NH); 1680-1660 (C=N); 1580; 1510-1490 (C=C); 1250-1230 and 1080-1070 cm^{-1} (C-O-C vas and vs).- ^{1}H-NMR of **11** (DMSO-d_6): δ (ppm) = 7.28 (d, 2H, J = 6 Hz, Ar-H *meta* to Cl), 7.51 (d, 2H, J = 6 Hz, Ar-H *ortho* to Cl), 7.41-7.76 (m, 2H, H-5 and H-6, benzothiophene, overlaping with the d at 7.51), 7.80-8.30 (m, 2H, H-4 and H-7, benzothiophene), 10.78 (s, broad, 1H, NH).- ^{1}H-NMR of **12** (DMSO-d_6): δ (ppm) = 2.28 (s, 3H, tolyl CH_3), 7.01 (d, 2H, J = 6 Hz, Ar-H *ortho* to CH_3), 7.45 (d, 2H, J = 6 Hz, Ar-H *meta* to CH_3), 7.00-7.60 (m, 2H, H-5 and H-6, benzothiophene, overlaping with the d at 7.45) 7.72-8.00 (m, 2H, H-4 and H-7, benzothiophene), 10.38 (s, 1H, NH).

1H-4-Substituted 5-thio-3-(3-chloro-2-benzo[b]thienyl)-1,2,4-triazolines **14-18**

A solution of the substituted thiosemicarbazide **4-8** (250 mg) in a mixture of 4% aqueous NaOH (2.5 ml) and ethanol (0.5 ml) was heated under reflux for 1 h. The clear solution was left to cool to room temp. and acidified with 10% aqueous HCl. The precipitate was filtered and crystallized from the proper solvent. Table 3.- IR: 3400-3250 (NH); 1600 (C=N); 1590; 1510-1490 (C=C); 1550-1520; 1380-1360; 1270-1250; 980-970 cm^{-1} (NCS amide I, II, III, IV bands).- ^{1}H-NMR of **14** ($CDCl_3$+DMSO-d_6): δ (ppm) = 5.29 (s, 2H, CH_2), 6.80-7.20 (m, 5H, Ar-H), 7.39-7.58 (m, 2H, H-5 and H-6, benzothiophene), 7.70-7.98 (m, 2H, H-4 and H-7, benzothiophene), 14.08 (s, broad, 1H, NH).- ^{1}H-NMR of **18** ($CDCl_3$+DMSO-d_6): δ (ppm) = 3.80 (s, 3H, OCH_3), 6.92 (d, 2H, J = 6 Hz, Ar-H *ortho* to OCH_3), 7.26 (d, 2H, J = 6 Hz, Ar-H *meta* to OCH_3), 7.40-7.68 (m, 2H, H-5 and H-7, benzothiophene), 14.25 (s, broad, 1H, NH).

3-Chloro-2-[(3',4'-disubstituted 2',3'-dihydrothiazol-2'-ylidene)hydrazinocarbonyl]benzo[b]thiophenes **19-32**

A solution of equimolar amounts of the thiosemicarbazides **4-8** (200 mg) and the proper *p*-substituted phenacyl bromide in absol. methanol or a mixture of 2:1 v/v absol. methanol-dry acetone (20 ml) was heated under reflux for 3 h and concentrated to half volume. The product, which separated either upon cooling to room temp. or after addition of some drops of water, was filtered and crystallized from the proper solvent. Table 4.- IR: 3400-3300 (NH); 1670-1660 (C=O); 1645-1630 (C=N); 1600-1590; 1510-

Table 2: 2-Substituted amino-5-(3-chloro-2-benzo[*b*]thienyl-1,3,4-oxadiazoles **9-13**

Compd No.	Yield %	Mp°C (cryst.solvent)[a]	Molecular Formula	Analysis% C	H	Calc/Found N
9	81	211-12 (A)	$C_{17}H_{12}ClN_3OS$ (341.5)	59.73 60.20	3.51 4.40	12.29 11.90
10	74	247-48 (B)	$C_{16}H_{10}ClN_3OS$ (327.5)	58.62 58.60	3.05 3.30	12.82 13.00
11	91	279-280 (C)	$C_{16}H_9Cl_2N_3OS$ (362)	53.03 52.80	2.48 2.80	11.60 11.80
12	88	245-46 (A)	$C_{17}H_{12}ClN_3OS$ (341.5)	59.73 60.00	3.51 4.00	12.29 12.50
13	80	249-250 (B)	$C_{17}H_{12}ClN_3O_2S$ (357.5)	57.06 57.20	3.35 3.50	11.74 11.30

a) Crystallization solvents: (A) = MeOH, (B) = acetone, (C) = dioxane.

Table 3: 1*H*-4-Substituted 5-thio-3-(3-chloro-2-benzo[*b*]thienyl)-1,2,4-triazolines **14-18**

Compd No.	Yield %	Mp°C (cryst.solvent)[a]	Molecular Formula	Analysis% C	H	Calc/Found N
14	92	195-96 (A)	$C_{17}H_{12}ClN_3S_2$ (357.5)	57.06 57.30	3.35 3.00	11.74 11.50
15	97	256-57 (B)	$C_{16}H_{10}ClN_3S_2$ (343.5)	55.89 55.70	2.91 2.70	12.22 12.00
17	97	202-204 (B)	$C_{16}H_9Cl_2N_3S_2$ (378)	50.79 50.60	2.38 2.60	11.11 11.50
17	97	231-32 (A)	$C_{17}H_{12}ClN_3S_2$ (357.5)	57.06 57.20	3.35 3.30	11.74 11.60
18	96	257-58 (C)	$C_{17}H_{12}ClN_3OS_2$ (373.5)	54.61 55.00	3.21 3.40	11.24 11.50

a) Crystallization solvents: (A) = EtOH, (B) = EtOH-acetone, (C) = dioxane.

Table 4: 3-Chloro-2-[(3',4'-disubstituted 2',3'-dihydrothiazol-2'-ylidene)hydrazinocarbonyl]benzo[*b*] thiophenes **19-32**

Compd No.	Yield %	Mp°C (cryst.solvent)[a]	Molecular Formula	Analysis% C	H	Calc/Found N
19	99	205-206 (A)	$C_{25}H_{18}ClN_3OS_2$ (475.5)	63.09 63.40	3.78 4.20	8.83 9.20
20	83	208-209 (B)	$C_{25}H_{17}ClN_4O_3S_2$ (520.5)	57.63 57.50	3.26 3.00	10.75 10.50
21	72	249-250 (C)	$C_{31}H_{22}ClN_3OS_2$ (551.5)	67.45 67.50	3.98 4.00	7.61 7.40
22	55	170-72 (D)	$C_{24}H_{16}ClN_3OS_2$ (461.5)	62.40 62.10	3.46 3.20	9.10 9.00
23	93	120-23 (E)	$C_{24}H_{15}ClN_4O_3S_2$ (506.5)	56.86 57.00	2.96 3.20	11.05 10.60
24	98	214-16 (F)	$C_{30}H_{20}ClN_3OS_2$ (537.5)	66.97 67.00	3.72 3.50	7.81 7.80
25	92	220-22 (A)	$C_{24}H_{14}Cl_2N_4O_3S_2$ (541)	53.23 53.60	2.58 3.00	10.35 10.50
26	94	207-208 (A)	$C_{30}H_{19}Cl_2N_3OS_2$ (572)	62.93 62.50	3.32 3.10	7.34 7.10
27	79	120-22 (D)	$C_{25}H_{18}ClN_3OS_2$ (475.5)	63.09 63.40	3.78 4.00	8.83 8.50
28	79	225-26 (E)	$C_{25}H_{17}ClN_4O_3S_2$ (520.5)	57.63 57.50	3.26 3.40	10.75 10.80
29	65	233-35 (G)	$C_{31}H_{22}ClN_3OS_2$ (551.5)	67.45 67.20	3.98 4.00	7.61 7.50
30	96	150-52 (D)	$C_{25}H_{18}ClN_3O_2S_2$ (491.5)	61.03 61.40	3.66 3.50	8.54 8.30
31	73	188-190 (A)	$C_{25}H_{17}ClN_4O_4S_2$ (536.5)	55.91 60.20	3.16 3.50	10.43 10.20
32	83	219-221 (G)	$C_{31}H_{22}ClN_3O_2S_2$ (567.5)	65.55 65.70	3.87 3.80	7.40 7.00

a) Crystallization solvents: (A) = dioxane-H_2O, (B) = dioxane-EtOH, (C) = dioxane, (D) = EtOH-H_2O, (E) = EtOH-acetone, (F) = acetone-H_2O, (G) = acetone.

1490 cm^{-1} (C=C).- ^{1}H-NMR of **25** ($CDCl_3$+DMSO-d_6): δ (ppm) = 6.29 (s, 1H, thiazoline), 6.87-7.97 (m, 5H, H-4, H-5, H-6, and H-7, benzothiophene + NH), 7.21 (d, 2H, J = 6 Hz, Ar-H *meta* to Cl), 7.75 (d, 2H, J = 6 Hz, Ar-H *ortho* to Cl), 8.01 (d, 2H, J = 6 Hz, Ar-H *meta* to NO_2) and 8.18 (d, 2H, J = 6 Hz, Ar-H *ortho* to NO_2).- ^{1}H-NMR of **29** ($CDCl_3$): δ (ppm) = 2.29 (s, 3H, tolyl CH_3), 6.08 (s, 1H, thiazoline), 7.03-7.24 (m, 4H, Ar-H, tolyl group), 7.24-7.58 (m, 11H, H-5, H-6, benzothiophene + biphenyl-Hs), 7.69-7.91 (m, 3H, H-4, H-7, benzothiophene + NH).

Antimicrobial Screening

All new compounds were *in vitro* tested for antimicrobial activity by the single disc diffusion method[19], using three strains of *Staphylococcus aureus*, three strains of *Escherichia coli*, and three strains of *Candida albicans* as test organisms. The products showed no singificant activity against the microorganisms used. Only 1*H*-4-*p*-tolyl-5-thio-3-(3-chloro-2-benzo[*b*] thienyl)-1,2,4-triazoline (**16**) and the *p*-chlorophenyl derivative **17** showed weak activity against two strains of *Staph. aureus* with an inhibition zone diameter of 10 mm. In the MIC test[20], compounds **16** and **17** showed no inhibition of growth up to a concentration of 1 mg/ml.

References

1 a) E. Campaigne, D.R. Knapp, E.S. Neiss, and T.R. Bosin, Adv. Drug Res. *5*, 1 (1970). b) T.R. Bosin and E.E. Campaigne, Adv. Drug Res. *11*, 191 (1977).

2 E. Lilly and Co., Ger. Offen 3, 433, 475 (1983); C.A. *103*, 92840v (1985).

3 a) P. Chatelain, M. Clayes, W. Van Drosser, and J. Roba, Arch. Int. Pharmacodyn. Ther. *268*, 271 (1984); C.A. *101*, 401 (1984). b) P. Chatelain, A.J. Friedhoff, E. Meller, T. Mennini, H. Gorissen, and J. Roba, Arzneim. Forsch. *34*, 754 (1984).

4 a) D.W. Roberston, J.H. Krushinski, E.E. Beedle, V. Wyss, G. Don Pollock, and J.S. Hayes, Eur. J. Med. Chem.-Chim. Ther. *21*, 223 (1986). b) Y. Amemiya, A. Terada, K. Wachi, H. Miyazawa, N. Hatakeyma, K. Matsuda, and T. Oshima, J. Med. Chem. *32*, 1265 (1989).

5 a) M.S. Manhas, S.G. Amin, S.D. Sharma, B. Dayal, and A.K. Bose, J. Heterocycl. Chem. *16*, 371 (1979). b) E. Lilly and Co., US 4,418,068 (1983); C.A. *100*, 156501h (1984).

6 G. Guerrera, L. Salerno, M.A. Siracusa, G. Ronsisvalle, A. Caruso, M.G. Leone, and A. Felice, Il Farmaco, Ed. Sci. *45*, 29 (1990).

7 K.S. Denko, Japan Kokai JP 6011, 466 (1983); C.A. *103*, 22451v (1985).

8 L.S. Fuller, J.W. Pratt, and F.S. Yates, Manuf. Chem. Aerosol News *49*, 58 (1978); C.A. *89*, 141687d, (1978).
9 A. Stuetz (Sandoz patent G.m.b.H.), Ger. Offen DE 3,316,093 (1983); C.A. *100*, 85436c (1984).
10 a) M. Raga, C. Palacin, J.M. Castello, and J.A. Ortiz, Eur. J. Med. Chem.- Chim. Ther. *21*, 329 (1986). b) R. Foguet, M. Moreno-Manas, M.M. Raga, M.R. Cuberes, J.M. Castello, and J.A. Ortiz, Eur. Pat. 151, 477 (1985); C.A. *104*, 19591f (1986).
11 B. Venugopalan, C.P. Bapat, N.J. de Souza, D.K. Chatterjee, and N.J. Iyer, Eur. J. Med. Chem.-Chim. Ther. *24*, 611 (1989).
12 Omaima M. AboulWafa, Hamida Abou-Shleib, and A. Mohsen M.E. Omar, Alex. J. Pharm. Sci. *4*, 168 (1990); C.A. *114*, 207166b (1991).
13 a) T. Higa and A.J. Krubsack, J. Org. Chem. *40*, 3037 (1975). b) A.J. Krubsack and T. Higa, Tetrahedron Lett. *1968*, 5149.
14 A. Mohsen M.E. Omar and S.A. Osman, Pharmazie, *28*, 30 (1973).
15 A. Mohsen M.E. Omar, N.S. Habib, and Omaima M. AboulWafa, a) Synthesis *1977*, 864; b) Pharmazie *35*, 503 (1980).
16 El-Sebaii A. Ibrahim, A. Mohsen M.E. Omar, N.S. Habib, O.M. AboulWafa, and J. Bourdais, J. Heterocycl. Chem. *19*, 761 (1982).
17 A. Mohsen M.E. Omar and O.M. AboulWafa a) J. Heterocycl. Chem. *21*, 1415 (1984) and *23*, 1339 (1986); b) Alex. J. Pharm. Sci. *2*, 21 (1988); C.A. *110*, 192718z (1989).
18 R.M. Scrowston, Adv. Heterocycl. Chem. *29*, 171 (1981).
19 A.W. Bauer, W.M.M. Kirby, J.C. Sherris, and M. Turck, Am. J. Clin. Path. *45*, 493 (1966).
20 J.G. Collee, J.P. Duguid, A.G. Fraser, and B.P. Marmin, Practical Medical Microbiology: Laboratory control of antimicrobial therapy, 13th Ed., p. 162, London, Churchill Livingstone 1989. [Ph912]