Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

Synthesis, reactions and biological activity of some new thieno[2,3-*f*]-1,3-benzodioxoles

E. A. Bakhite and Sh. M. Radwan

The reaction of 7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbonyl chloride (**2**) with some aromatic or heterocyclic amines gave the corresponding 6-(aryl or heterocyclyl) carbamoyl-7-chlorothieno [2,3-*f*]-1,3-benzodioxoles (**3a–c**, **4a**, **b** and **5**). Compound **2** was also reacted with potassium thiocyanate, ethanol or sodium azide to afford the isothiocyanto compound **6**, the ester **7** and the acid azide **9**, respectively. Hydrazinolysis of **7** gave the carbohydrazide **8**. The compounds **6**, **8** and **9** were used as precursors in the synthesis of the target heterocycles, 7-chlorothieno[2,3-*f*]-1,3-benzodioxoles substituted with a variety of moieties at position-6 (**10–15**, **17**, **19–26**, **28–31**). Also, 2-methyl-1,3-dixolo[5,6][1]benzothieno[2,3-*c*]quinolin-6(5 *H*)-one (**33**) was prepared. The antibacterial and antifungal activities of some selected compounds were also reported.

1. Introduction

The benzodioxole ring system is distributed widely in nature and is found in numerous natural products such as safrole and piperonal, as well as in a multitude of alkaloids [1]. As a consequence, it found applications in chemotherapy. Thus, many 1,3-benzodioxole derivatives are reported to be useful as antitumor drugs [2, 3], endothelin receptor antagonists [4–7] or tuberclostatics [8]. On the other hand, the well known antibacterial agent, oxolinic acid contains a 1,3-benzodioxole moiety [9, 10]. The 1,3-dioxolane nucleus is found in a major antifungal drug, ketoconazole [1]. Encouraged by the above findings and as a continuation of our previous work on condensed thiophenes [11–14], we report herein the synthesis and reactions of some thienobenzodioxoles as new molecules in this field. The target compound might possess enhanced biological and pharmaceutical properties owing to their incorporation of a thiophene ring and other pharmacophores such as thiazole, oxadiazole, thiadiazole or sulphanilamide moieties. The antibacterial and antifungal testing of some selected compounds is hereby included.

2. Investigations, results and discussion

2.1. Chemistry

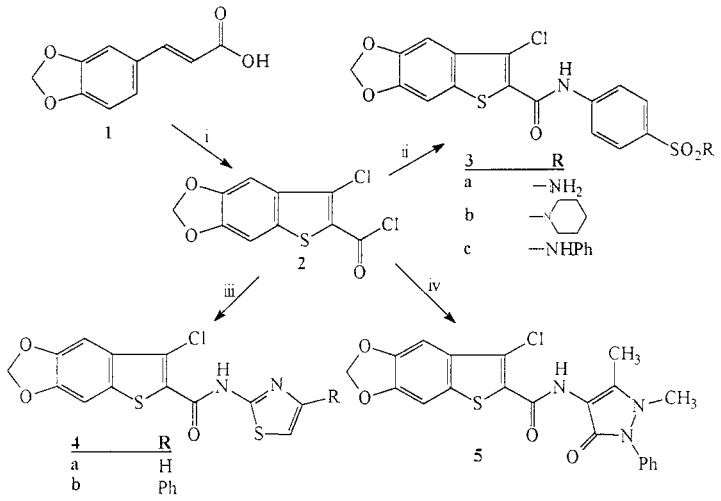
The starting material, 7-chlorothieno [2,3-*f*]-1,3-benzodioxole-6-carbonyl chloride (**2**) was prepared by the reaction of 3,4-methylenedioxycinnamic acid (**1**) with thionyl chloride in the presence of a catalytic amount of pyridine [15].

The direct condensation of **2** with some sulphanilamides, 2-aminothiazoles or 4-aminophenazone afforded 6-(aryl or heterocyclyl) carbamoyl-7-chlorothieno[2,3-*f*]-1,3-benzodioxoles (**3a–c**, **4a**,**b** and **5**, respectively) (Scheme 1).

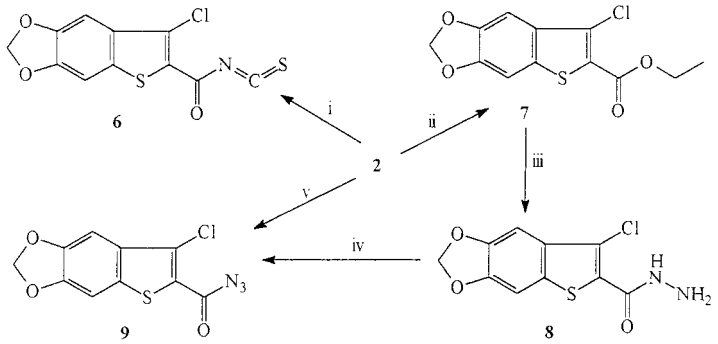
Compound **2** was also reacted with potassium thiocyanate to give 7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbonyl isothiocyanate (**6**) in nearly quantitative yield. Ester **7** was obtained by refluxing of **2** in absolute ethanol. The reaction of **7** with hydrazine hydrate yielded 7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbohydrazide (**8**) which in turn, was reacted with nitrous acid to give the corresponding acid azide **9**. The latter compound (**9**) can be also prepared by direct interaction of **2** with sodium azide (Scheme 2).

7-Chloro-6-functionally-thieno[2,3-*f*]-1,3-benzodioxoles **6**, **8** and **9** were employed as precursors in the synthesis of other new thienobenzodioxoles.

Scheme 1



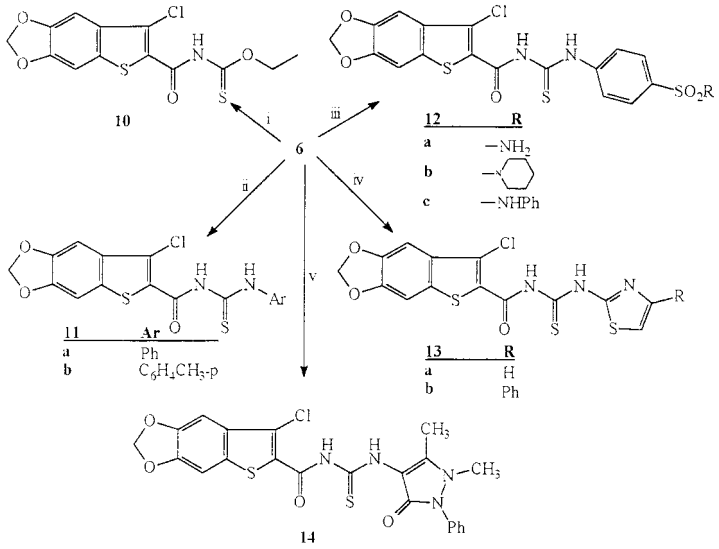
Scheme 2



i: KSCN, ii: C_2H_5OH; iii: $N_2H_4.H_2O$; iv: $NaNO_2$ / AcOH; v: NaN_3.

Heating of the isothiocyanatocarbonyl derivative **6** in absolute ethanol resulted in the formation of the ethyl thiocarbamate **10**. Reaction of **6** with aniline or *p*-toluidine in refluxing dry benzene gave the *N*-aryl-*N*′-(7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbonyl)thioureas **11a**, **b**. In a similar manner, compound **6** was reacted with sulphanilamide and its derivatives to afford the corresponding thioureas **12a**–**c**. Also, the reaction of **6** with some heterocyclic amines namely 2-aminothiazole, 2-amino-4-phenylthiazole or 4-aminophenazone led to the formation of *N*-(7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbonyl)-*N*'-heterocyclylthioureas **13a**, **13b** and **14**, respectively (Scheme 3).

Scheme 3



i: C_2H_5OH; ii: Aniline or p-toluidine; iii: $H_2NC_6H_4$-SO_2R-p;
iv: 2-Aminothiazole or 2-amino-4-phenylthiazole; v: 4-Aminophenazone.

Compound **13b**, in turn, underwent a ring closure reaction on treatment with PCl_5 in $POCL_3$. In view of earlier reports [16, 17], the product of the above reaction was found to be the thiazolo[3.2-*b*]-1,2,4-thiadiazoline derivative **15**, instead of the expected thiazolo[3,2-*a*]-s-triazine-7-thione **16** (Scheme 4).

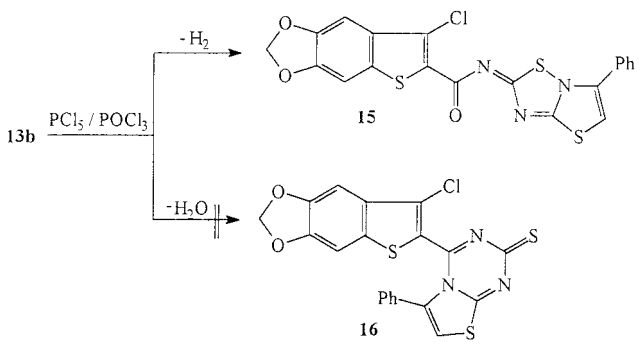
When compound **6** was allowed to react with ethyl glycinate in heated pyridine, the product was identified as *N*-(7-chlorothieno[2.3-*f*]-1,3-benzodioxole-6-carbonyl)-*N*′-ethoxycarbonylmethylthiourea (**17**), not as the thiohydantion **18**. An attempt to cyclize **17** into **18** failed and the ester **17** was recovered unchanged (Scheme 5).

On treatment of **6** with cyanoacethydrazide, the promising addition product **19** was obtained. Refluxing of **19** in glacial acetic furinshed the thiadiazole derivative **20** [18] (Scheme 6).

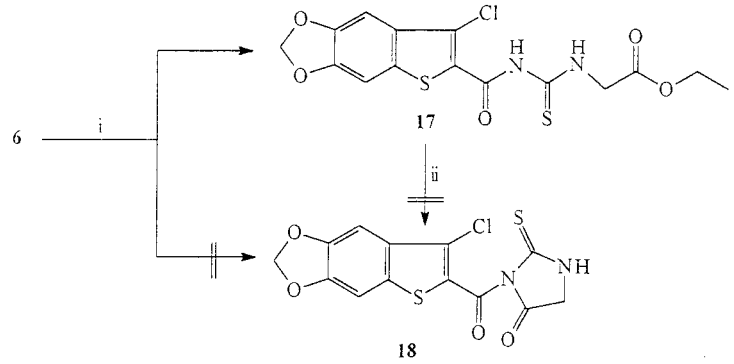
The reaction of **6** with 3-methyl-1-phenyl-2-pyrazolin-5-one by refluxing in dry benzene or toluene in the presence of triethylamine gave a yellow crystalline product with a m.p. >300 °C. Based on the elemental and spectral analyses, the structure of this product was assigned as **21**, not **22**. However, the conversion of the triethylammonium salt **21** into compound **22** was achieved by treating **21** with dilute hydrochloric acid (Scheme 7).

The cyclocondensation of **8** with acetylacetone afforded 1-(7-chlorothieno[2,3-*f*]-1,3-benzodioxole-6-carbonyl)-3,5-dimethyl-1 *H*-pyrazole (**23**). Also, the interaction of **8** with

Scheme 4

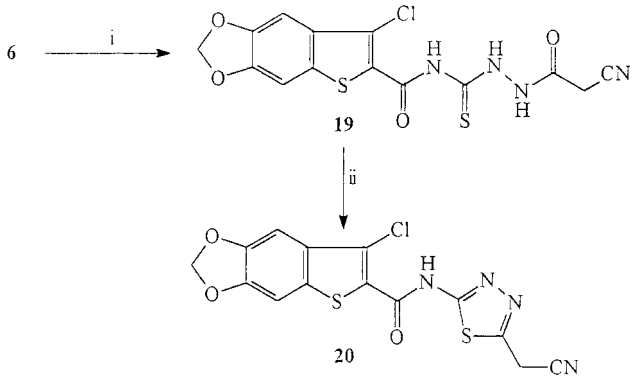


Scheme 5



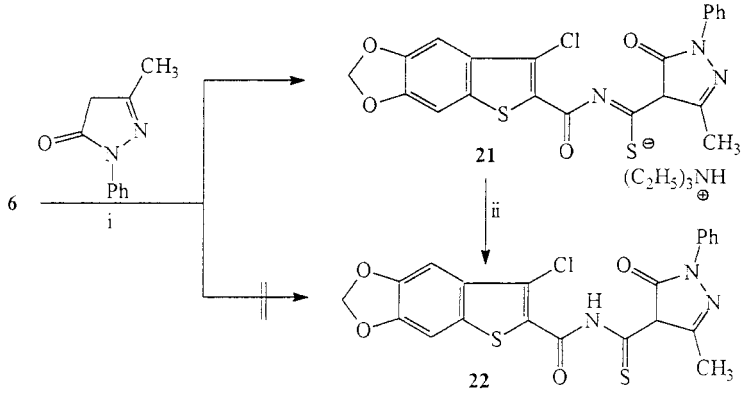
i: $HCl.H_2NCH_2CO_2Et$ / Pyridine; ii: AcOH / Heat.

Scheme 6



i: $CNCH_2CONHNH_2$; ii: AcOH / Heat.

Scheme 7



i: $(C_2H_5)_3N$; ii: dil. HCl.

carbon disulphide furnished 2-(7-chlorothieno[2,3-*f*]-1,3-benzodioxol-6-yl)-1,3-4-oxadiazole-5 (4*H*)-thione (**24**) in a good yield. Compound **24** was reacted with phenacyl bromide or ethyl chloroacetate to give the corresponding S-alkylated products **25a**, **b**. On treatment of the ester **25b** with hydrazine hydrate, the s-triazolo [3,4-*b*][1,3,4]-thiadiazine derivative **26** was obtained (Scheme 8).

The carboxylic acid azide **9** underwent Curtius rearrangement into the isocyanate intermediate **27** when heated in ethanol or dry toluene. Thus, refluxing of **9** in absolute ethanol afforded the ethyl carbamate **28**. On heating of **9** with *p*-toluidine, some sulpanilamides or 4-aminophenazone in dry toluene, the corresponding urea derivatives **29**, **30a–c** and **31** were obtained in good yields (Scheme 9).

On the other hand, in 1995, Gakhar et al. [15] reported that the photocyclization of 7-chloro-6-*p*-tolylcarbamoylthieno[2,3-*f*]-1,3-benzodioxole (**32**) affords 2-methyl-1,3-dioxolo[5,6][1]benzothieno[2,3-*c*] quinolin-6(5*H*)-one (**33**). In this investigation, a successful attempt to cyclize **32** into **33** was achieved by heating **32** with anhydrous $AlCl_3$ in chlorobenzene [19] (Scheme 10). The characterization data of **33** were in agreement with those reported before [15].

The structural formula of all the synthesized compounds was established and confirmed on the basis of their elemental analyses, IR and ^1H NMR spectral data (Table 1). Moreover, the MS of compounds **3c**, **5**, **7**, **28** and **29** were recorded and showed the corresponding molecular ion

Table 1: Characterization data of the synthesized compounds

Compd.	Mp (°C)/ (Yield %)	Mol. formula* (M.Wt.)	IR (cm^{-1})	^{1}H NMR (δ; ppm)
3a	>300 (85)	$C_{16}H_{11}ClN_2O_5S_2$ (410.8)	3380 (NH); 3300, 3200 (NH_2); 1640 (CO); 1340, 1160 (SO_2)	
3b**	282–284 (90)	$C_{21}H_{19}ClN_2O_5S_2$ (479.0)	3370 (NH); 1640 (CO); 1340, 1160 (SO_2)	(DMSO-d_6): 10.6 (s, 1 H, NH); 7.3–8.0 (m, 6 H, Ar–H); 6.2 (s, 2 H, OCH_2O); 2.7–3.0 [t, 4 H, $N(CH_2)_2$]; 1.3–1.7 [m, 6 H, $(CH_2)_3$].
3c	275–277 (92)	$C_{22}H_{15}ClN_2O_5S_2$ (486.9)	3380, 3200 (2 NH); 1630 (CO); 1340, 1160 (SO_2)	–
4a	243–245 (83)	$C_{23}H_7ClN_2O_3S_2$ (338.8)	3370 (NH); 1630 (CO)	(DMSO-d_6): 11.5 (s, 1 H, NH); 7.9 (d, 1 H, CH thiazole); 7.5 (d, 1 H, CH thiazole); 7.3 (s, 1 H, Ar–H); 7.2 (s, 1 H, Ar–H): 6.1 (s, 2 H, OCH_2O).
4b	240–241 (85)	$C_{19}H_{11}ClN_2O_3S_2$ (414.9)	3380 (NH); 1640 (CO)	(TFA): 7.6–7.8 (m, 5 H, Ar–H); 7.4 (s, 1 H, CH thiazole); 7.2 (s, 1 H, Ar–H): 7.1 (s, 1 H, Ar–H); 5.9 (s, 2 H, OCH_2O).
5**	223–225 (77)	$C_{21}H_{16}ClN_3O_4S$ (441.9)	3400 (NH); 1630 (CO)	($CDCl_3$): 10.5 (s, 1 H, NH), 7.0–7.7 (m, 7 H, Ar–H); 6.1 (s, 2 H, OCH_2O); 3.6 (s, 3 H, NCH_3); 2.5 (s, 3 H, CH_3)
6	175–176 (98)	$C_{10}H_4ClN_2O_3S_2$ (285.7)	2000–1900 (NCS); 1670 (CO)	($CDCl_3$): 7.2 (s, 1 H, Ar–H); 7.0 (s, 1 H, Ar–H); 6.0 (s, 2 H, OCH_2O)
7**	130–131 (83)	$C_{12}H_9ClO_4S$ (284.7)	1700 (CO	($CDCl_3$): 7.2 (s, 1 H, Ar–H); 7.0 (s, 1 H, Ar–H); 6.0 (s, 2 H, OCH_2O); 4.2–4.5 (q, 2 H, OCH_2); 1.3–1.5 (t, 3 H, CH_3)
8	276–277 (90)	$C_{10}H_7ClN_2O_3S$ (270.7)	3400–3200 (NH, NH_2); 1670 (CO)	(DMSO-d_6): 9.2 (s, 1 H, NH); 7.2 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 6.0 (s, 2 H, OCH_2O); 4.4 (br, 2 H, NH_2)
9	160 (dec.) (75)	$C_{10}H_4ClN_3O_3S$ (281.7)	2120 (N_3); 1660 (CO)	($CDCl_3$): 7.2 (s, 1 H, Ar–H); 6.1 (s, 2 H, OCH_2O)
10	160–161 (78)	$C_{13}H_{10}ClNO_4S_2$ (343.8)	3370 (NH); 1680 (CO)	(DMSO-d_6): 11.8 (s, 1 H, NH); 7.5 (s, 1 H, Ar–H); 7.3 (s, 1 H, Ar–H); 6.2 (s, 2 M, OCH_2O); 4.3–4.6 (q, 2 H, OCH_2); 1.2–1.4 (t, 3 H, CH_3)
11a	230–231 (90)	$C_{17}H_{11}ClN_2O_3S_2$ (390.9)	3350, 3200 (2 NH); 1630 (CO)	–
11b	221–222 (95)	$C_{18}H_{13}ClN_2O_3S_2$ (404.9)	3350, 3200 (2 NH); 1630 (CO)	(DMSO-d_6): 11.2 (s, 1 H, NH); 10.0 (s, 1 H, NH); 7.0–7.6 (m, 6 H, Ar–H); 6.2 (s, 2 H, OCH_2O); 2.3 (s, 3 H, CH_3)
12a	255–256 (84)	$C_{17}H_{12}ClN_3O_5S_3$ (469.9)	3480, 3380, 3300, 3230 (2 NH, NH_2); 1630 (CO)	–
12b	242–243 (86)	$C_{22}H_{20}ClN_3O_5S_3$ (538.0)	3350, 3200 (2 NH); 1630 (CO)	(DMSO-d_6): 12.0 (s, 1 H, CONH); 7.0–8.0 (m, 7 H, Ar–H and CSNH); 6.2 (s, 2 H, OCH_2O); 2.7–3.0 [t, 4 H, $N(CH_2)_2$]; 1.3–1.7 [m, 6 H, $(CH_2)_3$]
12c	240–241 (85)	$C_{23}H_{16}ClN_3O_5S_3$ (546.0)	3350, 3220 (3 NH); 1640 (CO)	–
13a	261–262 (80)	$C_{14}H_8ClN_3O_3S_3$ (397.9)	3350, 3100 (2 NH); 1630 (CO)	(TFA): 7.9 (d, 1 H, CH thiazole); 7.5 (d, 1 H, CH thiazole); 7.3 (s, 1 H, Ar–H); 7.2 (s, 1 H, Ar–H); 6.2 (s, 2 H, OCH_2O)
13b	240–242 (83)	$C_{20}H_{12}ClN_3O_3S_3$ (474.0)	3370, 3100 (2 NH); 1630 (CO)	(TFA): 7.5–7.8 (m, 5 H, Ar–H); 7.4 (s, 1 H, CH thiazole); 7.3 (s, 1 H, Ar–H); 7.2 (s, 1 H, Ar–H); 6.1 (s, 2 H, OCH_2O)
14	254–255 (75)	$C_{22}H_{17}ClN_4O_4S_2$ (501.0)	3350, 3200 (2 NH); 1660, 1630 (2 CO)	(TFA): 7.4–7.9 (m, 5 H, Ar–H); 7.2 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 6.1 (s, 2 H, OCH_2O); 3.6 (s, 3 H, NCH_3); 2.5 (s, 3 H, CH_3)
15	260–261 (60)	$C_{20}H_{10}ClN_3O_3S_3$ (472.0)	1660 (CO)	(DMSO-d_6): 7.6–7.8 (m, 5 H, Ar–H); 7.4 (s, 1 H, CH thiazole); 7.2 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 5.9 (s, 2 H, OCH_2O)
17	221–222 (78)	$C_{15}H_{13}ClN_2O_5S_2$ (400.8)	3350, 3200 (2 NH); 1730, 1640 (2 CO)	(DMSO-d_6): 11.0 (s, 1 H, NH); 10.7 (t, 1 H, NH); 7.6 (s, 1 H, Ar–H); 7.3 (s, 1 H, Ar–H); 6.2 (s, 2 H, OCH_2O); 4.5 (d, 2 H, NCH_2CO); 4.0–4.3 (q, 2 H, OCH_2); 1.1–1.4 (t, 3 H, CH_3)

Table 1: Continued

Compd.	Mp (°C)/ (Yield %)	Mol. formula* (M.Wt.)	IR (cm^{-1})	^1H NMR (δ; ppm)
19	260–261 (90)	$C_{14}H_9ClN_4O_4S_2$ (396.8)	3360, 3220, 3100 (3 NH); 2250 (C≡N); 1670, 1640 (2 CO)	–
20	243–244 (73)	$C_{14}H_7ClN_4O_3S_2$ (378.8)	3170 (NH); 2250 (C≡N); 1640 (CO)	(DMSO-d_6): 12.7 (br, 1 H, NH); 7.3 (s, 1 H, Ar–H); 7.2 (s, 1 H, Ar–H); 6.3 (s, 2 H, OCH_2O); 4.5 (s, 2 H, CH_2CN)
21	>300 (88)	$C_{27}H_{29}ClN_4O_4S_2$ (573.1)	1660, 1630 (2 CO)	(TFA): 7.4–7.8 (m, 7 H, Ar–H); 6.2 (s, 2 H, OCH_2O); 3.2–3.6 (7 H, 3 CH_2 and CH pyrazole); 3.1 (s, 3 H, CH_3); 1.3–1.6 (t, 9 H, 3 CH_3)
22	>300 (95)	$C_{21}H_{14}ClN_3O_4S_2$ (471.9)	3400 (NH); 1660, 1630 (2 CO)	(TFA): 7.5–7.9 (m, 7 H, Ar–H); 6.3 (s, 2 H, OCH_2O); 3.2 (s, 4 H, CH_3 and CH pyrazole)
23	230–231 (80)	$C_{15}H_{11}ClN_2O_3S$ (334.8)	1660 (CO)	($CDCl_3$): 7.3 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 6.1 (s, 3 H, OCH_2O and CH pyrazole); 2.7 (s, 3 H, CH_3); 2.3 (s, 3 H, CH_3)
24	261–262 (78)	$C_{11}H_5ClN_2O_3S_2$ (312.7)	3300 (NH); 1320 (C=S)	–
25a	195–196 (70)	$C_{19}H_{11}ClN_2O_4S_2$ (430.9)	1680 (CO)	(DMSO-d_6): 6.8–7.8 (m, 7 H, Ar–H); 6.0 (s, 2 H, OCH_2O); 5.0 (s, 2 H, SCH_2)
25b	167–168 (80)	$C_{15}H_{11}ClN_2O_5S_2$ (398.8)	1720 (CO)	(DMSO-d_6): 7.6 (s, 1 H, Ar–H); 7.3 (s, 1 H, Ar–H); 6.2 (s, 2 H, OCH_2O); 4.3 (s, 2 H, SCH_2); 3.9–4.2 q, 2 H, OCH_2); 1.1–1.3 (t, 3 H, CH_3)
26	>300 (87)	$C_{13}H_7ClN_4O_3S_2$ (366.8)	3300 (NH); 1700 (CO)	(DMSO-d_6): 11.6 (s, 1 H, NH); 7.3 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 6.0 (s, 2 H, OCH_2O); 4.2 (s, 2 H, SCH_2)
28**	137–138 (73)	$C_{12}H_{10}ClNO_4S$ (299.7)	3350 (NH); 1710 (CO)	(DMSO-d_6): 7.5 (s, 1 H, Ar–H); 7.1 (s, 1 H, Ar–H); 6.1 (s, 2 H, OCH_2O); 4.1–4.4 (q, 2 H, OCH_2); 1.2–1.4 (t, 3 H, CH_3)
29**	260–261 (86)	$C_{17}H_{13}ClN_2O_3S$ (360.8)	3350–3100 (NH); 1630 (CO)	(DMSO-d_6): 9.8, 9.0 (2s, 2 H, 2 NH); 7.0–7.5 (m, 6 H, Ar–H); 6.1 (s, 2 H, OCH_2O); 2.3 (s, 3 H, CH_3)
30a	251–252 (85)	$C_{16}H_{12}ClN_3O_5S$ (425.8)	3500–3200 (2 NH, NH_2); 1630 (CO)	–
30b	260–261 (87)	$C_{21}H_{20}ClN_3O_5S_2$ (494.0)	3350–3100 (2 NH); 1630 (CO)	(DMSO-d_6): 9.7, 8.9 (2s, 2 H, 2 NH); 7.1–8.0 (m, 6H, Ar–H); 6.2 (s, 2 H, OCH_2O); 2.8–3.0 [t, 4 H, $N(CH_2)_2$]; 1.4–1.8 [m, 6 H, $(CH_2)_3$]
30c	238–240 (85)	$C_{22}H_{16}ClN_3O_5S_2$ (502.0)	3400–3100 (3 NH); 1630 (CO)	–
31	275–277 (86)	$C_{21}H_{17}ClN_4O_4S$ (456.9)	3350–3100 (2 NH); 1640, 1630 (2 CO)	(TFA): 7.1–7.8 (m, 7 H, Ar–H); 6.1 (s, 2 H, OCH_2O); 3.6 (s, 3 H, NCH_3); 2.5 (s, 3 H, CH_3)
33	>300 (77)	$C_{17}H_{11}ClNO_3S$ (309.3)	3250, 3130 (NH) 1670 (CO)	(TFA): 7.2–7.9 (m, 5 H, Ar–H); 6.3 (s, 2 H, OCH_2O); 2.4 (s, 3 H, CH_3)

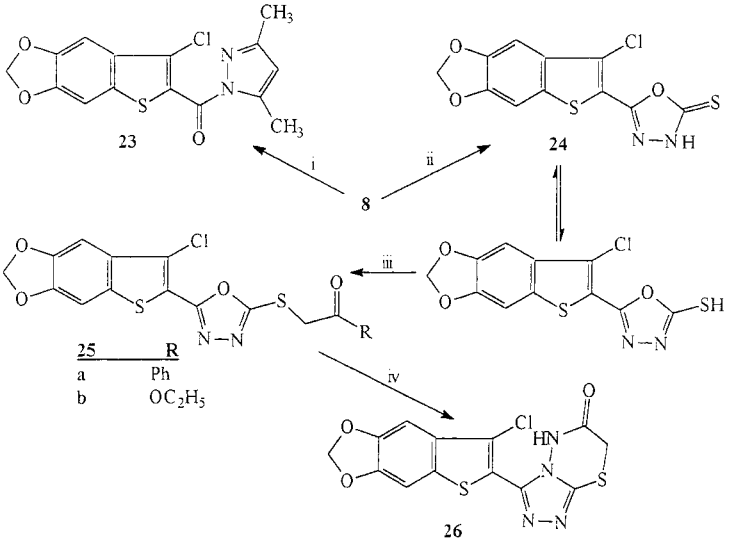
* Satisfactory elemental analyses were obtained for all compounds; ** Ms of **3b**. m/z, fragment, r.i.: 480, M + 1, 4; 479, M, 10; 478, M–H, 15; 238, **A**–H, 100; ** MS of **5**: 443, M + 2, 8; 442, M + 1, 35; 441, M, 48; 440, M–H, 100; 405, M–H–Cl, 48; 239, **A**, 5; 238, **A**–H, 45; ** MS of **7**: 285, M + 1, 6; 283, M–1, 13; 262, M–22, 100; 238, **A**–H, 3. ** MS of **28**: 299, M, 100; 297, M–2 H, 19; 254, M–OC_2H_5, 42; 227, **B** + H, 35; 226, **B**, 5; ** MS of **29**: 361, M, 26; 359, M–2H, 100; 254, M–$NHC_6H_4CH_3$, 64; 226, **B**, 90.

Table 2: Antibacterial and antifungal activities of some selected compounds (diameter of inhibition zone)

Compd.	*Staph. aureus*	*Sarcina* spp.	*Pseud. aeurginosa*	*Bacillus cereus*	*Asp. fumigatus*	*Asp. niger*	*Asp. temcus*	*Fusar. solani*
5	–	–	–	–	–	–	–	–
6	8	11	–	18	–	–	–	–
7	13	12	11	24	10	11	9	9
8	–	7	–	7	–	–	–	–
10	12	11	–	13	–	–	–	–
14	–	–	–	–	–	–	–	–
17	–	–	–	–	–	–	–	–
19	–	8	–	–	–	–	–	–
25b	17	18	–	11	–	–	–	–
28	–	–	–	–	–	–	–	–
31	–	–	–	–	–	–	–	–
33	–	9	–	–	–	–	–	–
Tioconazole (Tyrosyd®)	7	22	–	21	16	14	22	12

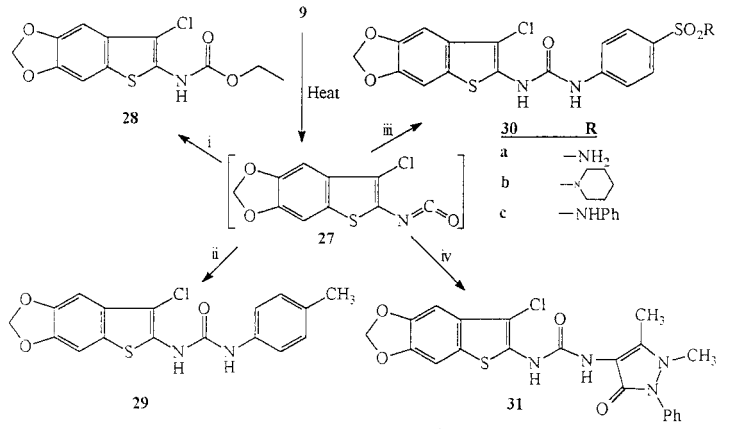
–: no inhibition zone

Scheme 8



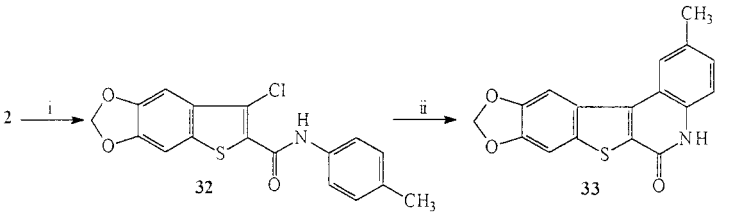
i:Acetylacetone; ii: CS_2; iii:$BrCH_2COPh$ or $ClCH_2COOEt$/AcONa; iv:$N_2H_4.H_2O$

Scheme 9



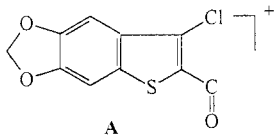
i: C_2H_5OH; ii: p-Toluidine; iii: $H_2NC_6H_4$-SO_2R-p; iv: 4-Aminophenazone.

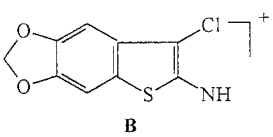
Scheme 10



i: p-Toluidine; ii: hν or $AlCl_3$ / C_6H_5Cl.

peaks (Table 1). The MS of **3c**, **5** and **7** showed also a peak at m/z = 238 due to the fragment **A**-H, whilst those of **28** and **29** exhibited a peak at m/z = 226 equivalent to the fragment **B**.





2.2. Biological activity

Some of the prepared compounds were screened *in vitro* for their antimicrobial activities against four strains of bacteria (*Staphylococcus aureus, Sarcina* spp., *Pseudomonas aeruginosa, Bacillus cereus*) and four strains of fungi (*Aspergillus fumigatus, Aspergillus niger, Aspergillus temcus, Fusarium solani*) using the filter paper disc method [20, 21]. The results revealed that only seven compounds (**6**, **7**, **8**, **10**, **19**, **25b** and **33**) possess a considerable antibacterial activity and only one compound (**7**) exhibits anti-

fungal activity. The other compounds tested were inactive against all the microorganisms used (Table 2). However, concerning the structure-action relationship it is observed that the three compounds which contain an antipyrine moiety (**5**, **14** and **31**) exhibit no antibacterial or antifungal activity, the thiourea derivatives **14** and **17** were inactive against all strains but the related thiosemicarbazide **19** showed a weak activity against *Sarcina* spp. The thiocarbamate **10** possesses a moderate activity against *Staphylococcus aureus, Sarcina* spp. and *Bacillus cereus* whilst the carbamate derivative **28** showed no activity against all species. Among the three esters tested (**7**, **17** and **25b**) only (**17**) was inactive against all the microorganisms since it contains thiourea residue. The ester **7** showed the highest activity against all bacterial and fungal species under study.

3. Experimental

Melting points are uncorrected and were measured on a Fisher-John apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer using KBr discs, ^{1}H NMR spectra on a Varian EM 390 90 MHz NMR spectrometer using TMS as internal reference, and MS on a Jeol JMS-600 apparatus. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer and the results were in an acceptable range. The characterization data of all the synthesized compounds are given in Table 1.

3.1. 7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl chloride (2)

This compound was prepared according to a literature method [15].

3.2. 6-(Aryl or heterocyclyl) carbamoyl-7-chlorothieno[2,3-f]-1,3-benzodioxoles 3a–c, 4a, b *and* 5

A mixture of **2** (2.75 g, 0.01 mol) and the respective amino compound (0.01 mol) in dry benzene (40 ml) was heated under reflux for 4 h and then allowed to cool. The precipitated solid was collected and recrystallized from a $C_2H_5OH/CHCl_3$ mixture to give **3a**–**c**, **4a**, **b** or **5** in the form of white crystals.

3.3. 7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl isothiocyanate (6)

To a suspension of **2** (8.25 g, 0.03 mol) in dry acetone (150 ml), potassium thiocyanate (2.91 g, 0.03 mol) was added. The reaction mixture was stirred at room temperature for 20 min. The precipitated product was collected by filtration and recrystallized from dry benzene to give yellow fine needles of **6**.

3.4. Ethyl 7-chlorothieno[2,3-f]-1,3-benzodioxole-6-carboxylate (7)

Compound **2** (11.0 g, 0.04 mol) in abs. C_2H_5OH (100 ml) was heated under reflux for 3 h and then left to cool. The crystalline product thus formed was filtered, washed with H_2O and recrystallized from C_2H_5OH as white needles of **7**.

3.5. 7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbohydrazide (8)

A mixture of **7** (5.7 g, 0.02 mol) and hydrazine hydrate 99% (4 ml, 0.04 mol) in C_2H_5OH (50 ml) was heated under reflux for 4 h. The white precipitate which formed was collected and recrystallized from dioxane to give **8** in the form of fine needles.

3.6. 7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonylazide (9)

3.6.1. Method A

To a stirred suspension of **8** (2.7 g, 0.01 mol) in glacial CH_3CO_2H (30 ml), $NaNO_2$ solution 10% (14 ml, 0.02 mol) was added dropwise during 10 min at room temperature. The reaction mixture was allowed to stand for 1 h and then diluted with H_2O (20 ml) whereby a white precipitate was formed. It was collected by filtration, air dried and applied in the next reactions without purification. The yield of this method is given in Table 1.

3.6.2. Method B

A mixture of **2** (2.75 g, 0.01 mol) and NaN_3 (0.65 gm, 0.01 mol) in dry acetone (40 ml) was stirred at room temperature for 2 h. The precipitate that separated was filtered off, washed with H_2O and dried in air, yield: 65%. This product was identical to that prepared by method A in all aspects.

3.7. Ethyl N-(7-chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl) thiocarbamate (10)

Compound **6** (1.43 g, 0.005 mol) in abs. C_2H_5OH (25 ml) was heated under reflux for 4 h, concentrated and left to cool. The crystalline product thus formed was collected and recrystallized from C_2H_5OH as yellow fine plates of **10**.

3.8. N-Aryl or heterocyclyl-N′-(7-chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl) thioureas 11a, b, 12a–c, 13a, b *and* 14

A mixture of **6** (1.43 g, 0.005 mol) and the respective amine (0.005 mol) in dry benzene (30 ml) was heated under reflux for 2 h. The precipitated product was collected by filtration and recrystallized from the proper solvent. Compounds **11a**, **b** and **12a–c** were recrystallized from DMF, **13a**, **b** and **14** from a $C_2H_5OH/CHCl_3$ mixture.

3.9. 2-(7-Chloroethieno[2,3-f]-1,3-benzodioxole-6-carbonyl) imino-5-phenylthiazolo[3,2-b]-1,2,4-thiadiazoline (15)

Equimolar quantities (0.01 mol) of **13b** and PCl_5 in $POCl_3$ (20 ml) were refluxed for 4 h at 140–150 °C. The excess amount of $POCl_3$ was removed under reduced pressure. The residue was titurated with H_2O, filtered and crystallized from C_2H_5OH to give **15** as pale white needles.

3.10. N-(7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl)-N′-ethoxycarbonylmethylthiourea (17)

A mixture of **6** (1.43 g, 0.05 mol) and ethyl glycinate hydrochloride (0.7 g, 0.005 mol) in dry pyridine (15 ml) was heated under reflux for 4 h. The product thus precipitated on cooling and dilution with H_2O was filtered off and crystallized from C_2H_5OH as white crystals of **17**.

3.11. 4-(7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl)-1-cyanoacetylthiosemicarbazide (19)

A mixture of **6** (2.85 g, 0.01 mol) and cyanoacethydrazide (1.0 g, 0.01 mol) in dry benzene or acetone (30 ml) was refluxed for 3 h. The product which formed on hot was collected by filtration and recrystallized from a $C_2H_5OH/CHCl_3$ mixture to give **19**.

3.12. 2-(7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl) amino-5-cyanomethyl-1,3,4-thiadiazole (20)

A suspension of compound **19** (0.1 g) in glacial CH_3CO_2H (30 ml) was refluxed for 5 h. On cooling, the precipitated solid was collected and recrystallized from dioxane as white crystals of **20**.

3.13. Reaction of 6 with 3-methyl-1-phenyl-2-pyrazolin-5-one; formation of compunds 21 *and* 22

To a suspension of **6** (2.85 g, 0.01 mol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (1.74 g, 0.01 mol) in dry benzene or toluene (40 ml), TEA (3 ml) was added. The resulting mixture was heated under reflux for 4 h and allowed to cool. The yellow precipitate that separated was collected and assigned as triethylammonium salt **21**.
Compound **21** (0.57 g, 0.01 mol) in concentrated HCl (5 N, 20 ml) was stirred at room temperature for 3 h. The solid product was collected by filtration, washed with H_2O, dried in air and crystallized from $C_2H_5OH/CHCl_3$, mixture to give compound **22** in the form of yellow needles.

3.14. 1-(7-Chlorothieno[2,3-f]-1,3-benzodioxole-6-carbonyl)-3,5-dimethyl-1 H-pyrazole (23)

A mixture of **8** (1.35 g, 0.05 mol) and acetylacetone (2 ml, 0.02 mol) was heated under reflux for 4 h. The product which formed on cooling was collected and recrystallized from C_2H_5OH to give **23** in the form of pale yellow crystals.

3.15. 2-(7-Chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)-1,3,4-oxadiazole-5(4 H)-thione (24)

A mixture of **8** (2.70 g, 0.01 mol) and CS_2 (2 ml) in pyridine (40 ml) was heated on a water bath for 8 h. The reaction mixture was diluted with H_2O (40 ml). The white precipitate which formed was collected, dissolved in NaOH (10%, 15 ml) and filtered. The clear filtrate was acidified with CH_3CO_2H. The precipitated solid was collected by filtration and crystallized from CH_3CO_2H as white crystals of **24**.

3.16. 2-(7-Chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)-5-phenacylthio-1,3,4-oxadiazole (25a)

A mixture of **24** (0.31 g, 0.001 mol), phenacyl bromide (0.2 g, 0.001 mol) and $CH_3CO_3Na \cdot 3\,H_2O$ (0.27 g, 0.002 mol) in ethanol (20 ml) was refluxed for 2 h. The precipitate that separated after cooling was collected and recrystallized from C_2H_5OH as white crystals of **25a**.

3.17. 2-(7-Chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)-5-ethoxycarbonylmethylthio-1,3,4-oxadiazole (**25b**)

The compound was synthesized in analogy to the method described above using ethyl chloroacetate instead of phenacyl bromide. It was recrystallized from C_2H_5OH to give **25b** in the form of white needles.

3.18. 3-(7-Chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)-s-triazolo[3,4-b][1,3,4]thiadiazolidine-6(5H)-one (**26**)

A mixture of **25b** (2.0 g, 0.05 mol) and hydrazine hydrate 99% (4 ml) in C_2H_5OH (30 ml) was heated under reflux for 4 h. The crystalline product which precipitated on hot was collected and recrystallized from dioxane to give **26** in the form of pale yellow crystals.

3.19. Ethyl N-(7-Chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)carbamate (**28**)

Compound **9** (0.28 g, 0.001 mol) in abs. C_2H_5OH (20 ml) was heated under reflux for 3 h. The crystalline solid that separated on cooling was collected and recrystallized from C_2H_5OH as buff prisms of **28**.

3.20. N-Aryl or heterocyclyl-N′-(7-chlorothieno[2,3-f]-1,3-benzodioxol-6-yl)ureas **29, 30a–c** *and* **31**

A mixture of **9** (0.28 g, 0.001 mol) and the respective amine (0.001 mol) in dry toluene (20 ml) was heated under reflux for 4 h. On cooling, the precipitated solid was collected by filtration and recrystallized from the proper solvent. Compound **29** was recrystallized from a $C_2H_5OH/CHCl_3$ mixture whilst compounds **30a–c** and **31** were recrystallized from dioxane.

3.21. 7-Chloro-6-p-tolylcarbamoylthieno[2,3-f]-1,3-benzodioxole (**32**)

This compound was prepared by reaction of **2** with *p*-toluidine according to a literature method [15].

3.22. 2-Methyl-[1,3]dioxolo[5,6][1]benzothieno[2,3-c] quinolin-6(5H)-one (**33**)

A mixture of **32** (1.5 g) and anh. $AlCl_3$ (6.0 g) in chlorobenzene (30 ml) was heated on a water-bath for 2 h. The mixture was poured onto ice-dil. HCl. The precipitated solid was filtered off, washed several times with petr. ether (40–60) and recrystallized from a $C_2H_5OH/CHCl_3$ mixture.

3.23. Biological screening

The screened compounds were dissolved in DMSO to get a solution of 1% concentration. Filter paper discs (Whatman No. 1 filter paper, 5 mm diameter) were saturated with this solution. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the tested bacteria or Czapek's Dox agar dishes seeded by the tested fungi. The inhibition zones were measured at the end of an incubation period of 48 h (at 37 °C for bacteria and at 28 °C for fungi) Tioconazol (Tyrosyd®) was used as a reference substance.

References

1 Elliottt, A. J.; in: Katritzky, A. R.; Rees, C. W. (eds.); Comprehensive Heterocyclic Chemistry, Vol. 6, Part 4B, Chapter 4.30, p. 781, Pergamon Press, Oxford 1984
2 Fujimoto, K.; Maruhashi, K.: Jap. Pat. 09,48,782: C.A. **126**, 238372t (1997)
3 Jurd, L.: J. Heterocycl. Chem. **33**, 1227 (1996)
4 Dorsch, D.; Mederski, W.; Werner, W.; Osswald, M.; Ralf, R. M.; Schmitges, C.-J.; Christadler, M.; Wilm, C.: Bioorg. Med. Chem. Lett. **7**, 275 (1997)
5 Devine, P. N.; Tschaen, D. M.: PCT Int. Appl. Wo 97,21,700; C. A. **127**, 121714k (1997)
6 Cheng, M.-M.; Lee, C.; Klutchko, S.; Winters, T.; Reynolds, E. E.; Welch, K. M.; Flynn, M. A.; Doherty, A. M.: Bioorg. Med. Chem. Lett. **6**, 2999 (1996)
7 Osswald, M.; Mederski, W.; Dorsch, D.; Schmitges, C.-J.; Wilm, C.; Christadler, M.: Ger. Offen. DE 19,612,101; C.A. **127**, 318978f (1997)
8 Desai, N. C.; Shukla, H. K.; Thaker, K. A.: J. Inst. Chem. **56**, 124 (1984)
9 Segawa, J.; Kitano, M.; Kazuno, K.; Tsuda, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Kise, M.: J. heterocycl. Chem. **29**, 1117 (1992)
10 Kaminsky, D.; Meltzer, R. I.: J. Med. Chem. **11**, 160 (1968)
11 Bakhite, E. A.; Abbady, M. S.; Radwan, Sh. M.: Collect. Czech. Chem. Commun. **58**, 1457 (1993)
12 Radwan, Sh. M.; Bakhite, E. A.; Kamel El-Dean, A. M.: Bull. Fac. Sci., Assiut Univ. **23**, 1 (1994)
13 Bakhite, E. A.; Radwan, Sh. M.; El-Saghier, A. M. M.: Indian J. Chem. **34B**, 97 (1995)
14 Atalla, A. A.; Bakhite, E. A.; Radwan, Sh. M.: Phosphorous, Sulfur Silicon **101**, 83 (1995)
15 Gakhar, H. K.; Kaur, R.; Gupta, S. B.: Monatsh. Chem. **126**, 1253 (1995)
16 Ramachandraiah, G.; Reddy, K. K.: Sulphur Lett. **6**, 1 (1987)
17 Gramachandraiah, G.; Reddy, K. K.: Indian J. Chem, **27B**, 185 (1988)
18 Elmoghayar, M. R. H.; Abdalla, S. O.; Nasr, M. Y. A.-S.: J. Heterocycl. Chem. **21**, 781 (1984)
19 Jayachandran, T.; Paramasivam, R.; Ramakrishnan, V. T.: Indian J. Chem. **25B**, 89 (1986)
20 Bauer, A. W.; Kirby, W. W. M.; Sherris, J. C.; Turck, M.: Am. J. Clin. Pathol. **45**, 493 (1966)
21 Kalyoncuoglu, N.; Rollas, S.; Sur-Altiner, D.; Yegenoglu, Y.; Ang, O.: Pharmazie **47**, 769 (1992)

Received September 25, 1998
Accepted December 8, 1998

Dr. Etify A. Bakhite
Chemistry Department
Faculty of Science
Assiut University
Assiut 71516
Egypt