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CONVENIENT HETEROCYCLIZATION REACTIONS WITH ETHYL 2-AMINO-4,5,6,7-TETRAHYDROBENZO[b] THIOPHENE-3-CARBOXYLATE: SYNTHESIS OF PYRAZOLE, ISOXAZOLE AND PYRIDAZINE

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The ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **2** reacts with ethyl acetoacetate to give the hydrazone derivative **4**. The reactivity of **4** towards a number of different reagents including active methylene compounds as well as the use of **4** to synthesize fused heterocyclic systems is described.

Keywords: Thiophene; pyrazole; isoxazole; pyridazine

INTRODUCTION

During recent years, we have maintained a comprehensive program aimed at investigating the reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate with active methylene compounds followed by heterocyclization of the resultant azo derivatives with simple available reagents. Such a synthetic route has proved to be an easy and facile approach for the synthesis of hithero unreported derivatives of polyfunctionally substituted thiophenes, 2,3-dihydrothiazoles, and thiazolidines.[1–3] The importance of such compounds is due to their diverse pharmacological activities including antibacterial[4], immunomodulatory[5], antiflammatory[6], antidiabatic[7,8], antiplatelet activating factor[9], and antivi-

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ral activities[10]. Thus in continuation of our previous work, we report herein the use of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate[11] **1** for the synthesis of a variety of azole, azine or azoloazine derivatives incorporating a tetrahydrobenzo [b]-thiophene moiety with potential biological activity.

RESULTS AND DISCUSSION

The reaction of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **1** with sodium nitrite in the presence of acetic and hydrochloric acids gave the diazonium salt **2**. Its reaction with ethyl acetoacetate **3** gave the hydrazone derivative **4**. The structure of **4** was based on analytical and spectral data. The ^{1}H NMR spectrum showed the presence of two triplets at δ 1.66, 1.69 ppm due to two CH_3ester groups, a singlet at δ 2.02 ppm of the CH_3 group, two quartets at δ 4.25, 4.28 ppm for two CH_2 ester groups and a singlet at δ 8.41 ppm (D_2O exchangeable) for the NH group. Moreover, the ^{13}C NMR spectrum showed δppm 18.9, 19.0, 20.2 ($3CH_3$), 29.3, 30.1 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 64.2, 65.8 (2 CH_2), 124.9, 126.7, 132.2, 133.0 (thiophene C), 169.4, 175.8, 181.3 (3 C=O). The reactivity of **4** towards a number of reagents was studied. Thus, the reaction of **4** with either hydrazine hydrate **5a** or phenyl hydrazine **5b** gave the corresponding pyrazole derivatives **6a** and **6b** respectively. The structures of the latter products were confirmed on the basis of analytical and spectral data.

On the other hand, the reaction of **4** with either urea **7a** or thiourea **7b** in sodium ethoxide solution gave the pyrimidine derivatives **8a** and **8b** respectively. The reaction of **4** with hydroxylamine hydrochloride gave the isoxazole derivative **9**, while the reaction of **4** with phenyl isothiocyanate **10** yielded the triazine derivative **12**. The structure of **12** was confirmed on the basis of analytical and spectral data (see experimental section). Formation of **12** took place through the intermediate formation of **11** followed by elimination of ethanol.

The reactivity of **4** towards cyanomethylene reagents was also studied. Thus, the reaction of **4** with either malononitrile **13a** or ethyl cyanoacetate **13b** gave the pyridazine derivatives **14a** and **14b** respectively. The structures of **14a** and **14b** were confirmed on the basis of analytical and spectral

data. The ^1H NMR spectrum which showed the presence of two triplets at δ 1.16, 1.18 ppm for two CH_3 ethyl ester groups, two quartets at δ 4.25, 4.28 ppm for two CH_2 ethyl ester groups and a singlet at δ 9.38 ppm (D_2O exchangeable) corresponding to the NH group. Moreover, the ^{13}C NMR spectrum exhibted the following peaks δppm 19.0, 22.0, 22.2 ($3CH_3$), 23.3, 23.9 (cyclohexane C-2, C-3), 29.3, 30.1 (cyclohexane C-1, C-4), 65.2, 66.1 ($2CH_2$), 125.9, 128.7, 134.2, 136.0, 145.3, 153.6, 160.8 165.7 (thiophene & pyridazine C), 174.3, 175.5, 180.8 (3C=O). Boiling of **14a** in dimethylformamide containing sodium hydroxide gave **14b**. Its formation can be explained in terms of elimination of ammonia.

TABLE I Analytical data of the newly synthesized products:

Compd	*m.p. °C*	*Mol. form.*	*% Analysis (Calcd/Found)*			
			C	*H*	*N*	*S*
4	103	$C_{17}H_{22}N_2O_5S$	55.7	6.0	7.6	8.7
			55.6	6.1	7.4	8.5
6a	78	$C_{15}H_{18}N_4O_3S$	53.8	5.4	16.7	9.5
			53.6	5.5	16.6	9.8
6b	81	$C_{21}H_{22}N_4O_3S$	61.4	5.4	13.6	7.8
			61.3	5.4	13.9	8.0
8a	177–9	$C_{16}H_{18}N_4O_4S$	53.0	5.0	15.4	8.8
			52.9	5.1	15.5	9.0
8b	164	$C_{16}H_{18}N_4O_3S_2$	50.7	4.7	14.8	16.9
			50.7	4.6	15.0	17.0
9	146	$C_{15}H_{17}N_3O_4S$	53.7	5.1	12.5	9.5
			53.5	5.0	12.6	9.8
12	88	$C_{22}H_{21}N_3O_4S_2$	58.0	4.6	9.2	14.0
			58.1	4.6	9.2	13.8
14a	>300	$C_{20}H_{22}N_4O_4S$	57.9	5.3	13.5	7.7
			58.0	5.2	13.6	7.9
14b	176	$C_{20}H_{21}N_3O_5S$	57.8	5.0	10.1	7.7
			57.7	5.1	10.2	7.8

Compd	*m.p. °C*	*Mol. form.*	*% Analysis*		*(Calcd/Found)*	
			C	*H*	*N*	*S*
16	150	$C_{27}H_{25}N_3O_5S$	64.4	5.0	8.3	6.3
			64.6	4.9	8.0	6.7
17	158	$C_{20}H_{21}N_3O_5S_2$	53.7	4.7	9.4	14.3
			53.7	4.5	9.2	14.6
21	92	$C_{29}H_{26}N_4O_5S$	64.2	4.8	10.3	5.9
			63.9	5.0	10.0	6.0
25	223–6	$C_{23}H_{23}N_5O_5S$	57.4	4.8	14.5	6.6
			57.3	5.1	14.4	6.8
26	87	$C_{29}H_{27}N_7O_5S$	59.5	4.6	16.7	5.5
			59.4	4.5	17.0	5.5
27	110	$C_{30}H_{27}N_5O_5S$	63.2	4.7	12.3	5.6
			63.1	5.0	12.1	5.5
28	142	$C_{20}H_{22}N_4O_4S$	57.9	5.3	13.5	7.7
			57.8	5.2	13.2	7.9
30a	131	$C_{20}H_{26}N_6O_4S$	53.8	5.9	18.8	7.1
			58.7	6.2	19.1	7.0
30b	128	$C_{26}H_{30}N_6O_4S$	59.7	5.8	16.0	6.1
			59.6	5.6	16.3	5.8
31	212–5	$C_{24}H_{23}N_5O_3S$	62.5	5.0	15.1	6.9
			62.5	4.6	15.2	7.0
32	122	$C_{20}H_{25}N_5O_5S$	53.7	5.6	15.6	7.1
			53.5	5.8	15.5	6.9
33	117	$C_{25}H_{21}N_5O_3S_2$	59.6	4.1	13.9	12.7
			59.7	4.2	14.0	12.6
34	234–7	$C_{27}H_{26}N_4O_4S$	64.5	5.2	11.5	6.4
			64.4	5.1	11.8	6.6
37	156	$C_{27}H_{21}N_5O_3S$	65.4	4.3	14.1	6.4
			65.6	4.0	13.9	6.0

TABLE II Spectral data of the synthesized compounds

Compd	*IR selected bands (cm^{-1})[a]*	*^1H NMR (δ ppm)*
4	3480–3360 (NH), 1690, 1685–1675 (3C=O), 1660 (C=N), 1635 (C=C).	1.66, 169 (2t, 6H, $2CH_3$), 2.02 (s, 3H, CH_3), 2.20–2.23 (m, 4H, $2CH_2$), 2.75- 2.78 (m, 4H, $2CH_2$), 4.24, 4.28 (2q, 4H, $2CH_2$), 8.41 (s, 1H, NH).
6a	3650–3480 (OH, NH), 1690 (C=O), 1655 (C=N), 1635 (C=C).	1.68 (t, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.02–2.12 (m, 4H, $2CH_2$), 2.70–2.75 (m, 4H, $2CH_2$), 4.26 (q, 2H, CH_2), 8.89 (s, 1H, NH), 10.21 (s, 1H, OH).
6b	3580–3360 (OH), 1700 (C=O), 1655 (C=N), 1640 (C=C).	1.16 (t, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.11–2.23 (m, 4H, $2CH_2$), 2.75–2.77 (m, 4H, $2CH_2$), 4.26 (q, 2H, CH_2), 7.32–7.45 (m, 5H, C_6H_5), 10.22 (s, 1H, OH).
8a	3580–3365 (2OH), 1700 (C=O), 1655 (C=N), 1635 (C=C).	1.16 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.21–2.23 (m, 4H, $2CH_2$), 2.70–2.75 (m, 4H, $2CH_2$), 4.26 q, 2H, CH_2), 10.21, 10.23 (2s, 2H, 2OH).
8b	3469–3320 (OH, SH), 1700 (C=O), 1660 (C=N), 1635 (C=C).	1.17 (t, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.11–2.13 (m, 4H, $2CH_2$), 4.21 (q, 2H, CH_2), 8.35 (s, 1H, SH), 10.28 (s, 1H, OH).
9	3580–3370 (OH), 1690 (C=O), 1660 (C=N), 1640 (C=C).	1.17 (t, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.21–2.23 (m, 4H, $2CH_2$), 2.78–2.80 (m, 4H, $2CH_2$), 4.21 (q, 2H, CH_2), 10.20 (s, 1H, OH).
12	1710, 1690–1680 (3C=O), 1660 (C=N), 1640 (C=C).	1.16 (t, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.21–2.23 (m, 4H, $2CH_2$), 2.77–2.79 (m, 4H, $2CH_2$), 4.25 (q, 2H, CH_2), 7.32–7.46 (m, 5H, C_6H_5).
14a	3480–3360 (NH), 2220 (CN), 1690, 1680, (2 C=O), 1660 (C=N), 1635 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.09 (s, 3H, CH_3), 2.19–2.21 (m, 4H, $2CH_2$), 2.75- 2.78 (m, 4H, $2CH_2$), 4.20–4.28 (2q, 4H, $2CH_2$), 9.38 (s, 1H, NH).
14b	2225 (CN), 1690, 1685- 1675 (3C=O), 1660 (C=N), 1640 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.06 (s, 3H, CH_3), 2.19–2.21 (m, 4H, $2CH_2$), 2.77- 2.80 (m, 4H, $2CH_2$), 4.21, 4.26 (2q, 4H, $2CH_2$).
16	2220 (CN), 1700, 1680- 1670 (3C=O), 1660 (C=N), 1640 (C=C).	1.16, 1.17 (2t, 6H, $2CH_3$), 2.22–2.23 (m, 4H, $2CH_2$), 2.62–2.73 (m, 4H, $2CH_2$), 4.22, 4.24 (2q, 4H, $2CH_2$), 6.73, 6.92 (2d, 2H, CH=CH), 7.31–7.36 (m, 5H, C6H5).
17	3400–3420 (NH_2), 1690, 1680, 1670 (3C=O), 1660 (C=N), 1640 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.20–2.23 (m, 4H, $2CH_2$), 2.67–2.70 (m, 4H, $2CH_2$), 4.20, 4.24 (2q, 4H, $2CH_2$), 4.65 (s, 2H, NH_2), 6.89 (s, 1H, thiophene H-2).
21	3450–3310 (NH_2), 2220 (CN), 1690, 1680–1670 (3C=O)1660 (C=N), 1635 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.12–2.14 (m, 4H, $2CH_2$), 2.62–2.70 (m, 4H, $2CH_2$), 4.20, 4.23 (2q, 4H, $2CH_2$), 4.87 (s, 2H, NH_2), 7 32–7.38 (m, 6H, C_6H_5, benzene CH).

Compd	*IR selected bands (cm^{-1})*[a]	*^1H NMR (δ ppm)*
25	3460–3360 (NH_2), 2220 (CN), 1695, 1685–1670 (3C=O), 1655 (C=N), 1640 (C=C).	1.15, 1.16 (2t, 6H, $2CH_3$), 2.12–2.14 (m, 4H, $2CH_2$), 2.26–2.28 (m, 4H, $2CH_2$), 4.21, 4.25 (2q, 4H, $2CH_2$), 4.45 (s, 2H, CH_2), 5.34 (s, 2H, NH_2), 6.98 (s, 1H, pyridine H-5).
26	3450–3320 (NH_2, NH), 2220 (CN), 1700, 1685- 1680 (3C=O), 1660 (C=N), 1640 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.21–2.23 (m, 4H, $2CH_2$), 2.69–2.71 (m, 4H, $2CH_2$), 4.26, 4.28 (2q, 4H, $2CH_2$), 5.23 (s, 2H, NH_2), 6.97 (s, 1H, pyridine H-5), 7.32- 7.36 (m, 5H, C_6H_5), 9.38 (s, 1H, NH).
28	3450–3420 (NH), 2225, 2220 (2CN), 2690, 1680 (2C=O), 1660 (C=N), 1645 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.09 (s, 3H, CH_3), 2.21–2.24 (m, 4H, $2CH_2$), 2.65-2.69 (m, 4H, $2CH_2$), 4.21, 4.25 (2q, 4H, $2CH_2$), 9.21 (s, 1H, NH).
30a	3460–3370 ($2NH_2$, NH), 1685, 1670 (2C=O), 1650 (C=N), 1635 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.03 (s, 3H, CH_3), 2.22–2.24 (m, 4H, $2CH_2$), 6.67- 2.72 (m, 4H, $2CH_2$), 4.21, 4.32 (2q, 4H, $2CH_2$), 4.64, 5.21 (2s, 4H, $2NH_2$), 9.30 (s, 1H, NH).
30b	3465–3320 (NH_2, 2NH), 1690, 1675 (2C=O), 1660 (C=N), 1645 (C=C).	1.16, 1.18 (2t, 6H, $2CH_3$), 2.04 (s, 3H, CH_3), 2.21–2.24 (m, 4H, $2CH_2$), 2.69- 2.71 (m, 4H, $2CH_2$), 4.22, 4.31 (2q, 4H, $2CH_2$), 4.84 (s, 2H, NH_2), 7.32–7.40 (m, 5H, C_6H_5), 9..30, 9.32 (2s, 2H, 2NH).
31	3460–3320 (2NH), 2225, 2220 (CN), 1685, 1670 (2C=O), 1660 (C=N), 1640 (C=C).	1.16 (t, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.12–2.16 (m, 4H, $2CH_3$), 2.67–2.69 (m, 4H, $2CH_2$), 4.24 (q, 2H, CH_2), 7.32–7.41 (m, 5H, C_6H_5), 8.98, 9.25 (2s, 2H, 2NH).
32	3460–3310 (2NH, NH2), 1685, 1680 (2C=O), 1660 (C=N), 1635 (C=C).	1.15, 1.17 (2t, 6H, $2CH_3$), 2.04 (s, 3H, CH_3), 2.27–2.25 (m, 4H, $2CH_2$), 2.65- 2.75 (m, 4H, $2CH_3$), 4.24, 4.32 (2q, 4H, $2CH_2$), 5.35 (s, 2H, NH_2), 9.36, 9.38 (2s, 2H, 2NH).
33	2225, 2220 (CN), 1685, 1675 (2C=O), 1655 (C=N), 1635 (C=C).	1.17 (t, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.22–2.25 (, 4H, $2CH_2$), 2.69–2.78 (m, 4H, $2CH_3$), 4.24 (q, 2H, CH_2), 7.32–7.39 (m, 5H, C_6H_5).
34	3440–3320 (NH), 2225, 2220 (2CN), 1685, 1670 (2C=O), 1655 (C=N), 1645 (C=C).	1.17, 1.18 (2t, 6H, $2CH_3$), 2.23–2.25 (m, 4H, $2CH_2$), 2.69–2.72 (m, 4H, $2CH_2$), 4.24, 4.34 (2q, 4H, $2CH_2$), 6.65, 6.72 (2d, 2H, CH=CH), 7.32, 7.45 (m, 5H, C_6H_5), 9.25 (s, 1H, NH).
37	3585–3320 (OH), 2225, 2220–2215 (3CN), 1685 (C=O), 1660 (C=N), 1645 (C=C).	1.16 (t, 3H, CH_3), 2.21–2.24 (m, 4H, $2CH_2$), 2.65–2.73 (m, 4H, $2CH_2$), 4.24 (q, 2H, CH_2), 6.20 (s, 1H, CH), 7.32–7.45 (m, 6H, C_6H_5, benzene CH), 10.25 (s, 1H, OH).

a. CH stretching (aromatic, CH_3, CH_2) appear at expected υ values.

TABLE III ^{13}C NMR data of some selected compounds

Compd. No.	*^{13}C NMR: ([$^2H_6$] DMSO): δ/ppm*
4	18.9, 19.0, 20.2 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 64.2, 65.8 (2 CH_2), 124.9, 126.7, 132.2, 133.0 (thiophene C), 169.4, 175.8, 181.3 (3 C=O).
6a	19.0, 20.2 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.2 (CH_2), 125.9, 128.7, 134.2, 136.0, 165.7 (thiophene C, pyrazole C), 175.6 (C=O).
8a	19.0, 21.2 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.2 (CH_2), 125.9, 128.7, 134.2, 136.0 (thiophene C), 159.5, 157.5, 122.4, 165.7 (pyramidine C), 175.6 (C=O).
9	19.0, 20.2 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.2 (CH_2), 124.9, 129.2, 134.2, 136.0, (thiophene C), 125.9, 136.6, 166.8 (isoxazole C), 180.6 (C=O).
14a	19.0, 22.0, 22.2 ($3CH_3$), 29.3, 30.1 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.2, 66.1 ($2CH_2$), 125.9, 128.7, 134.2, 136.0, 145.3, 153.6, 160.8 165.7 (thiophene & pyridazine C), 174.3, 175.5, 180.8 (3C=O).
17	19.9, 21.2 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 64.2, 65.1 ($2CH_2$), 126.9, 128.9, 136.2, 138.0(two thiophene C), 144.3, 151.6, 165.7 (pyridazine C), 174.3, 176.5, 180.8 (3C=O).
21	19.7, 20.3 ($3CH_3$), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.0, 65.9 ($2CH_2$), 120.4 (CN), 125.6, 128.9, 136.0, 138.2, 148.6, 150.4, (thiophene, benzene C), 144.3, 151.6, 165.7 (pyridazine C), 177.3, 179.5, 180.8 (3C=O).
37	20.3 (CH_3), 30.1, 29.3 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 65.0 (CH_2), 118.7, 119.9, 120.4 (3CN), 125.3, 127.9, 136.0, 136.2, 142.6 (benzene C), 177.3 (CO)

The reactivity of the ortho CH_3 group to cyano group which is present in **14b** was studied. Thus, the reaction of **14b** with benzaldehyde **15** in a solution of dimethylformamide containing piperidine gave the benzal derivative **16**. Moreover, the reaction of **14b** with elemental sulfur in a solution of dimethylformamide containing triethylamine gave the thieno[4,3-d]pyridazine derivative **17**.[12,13]

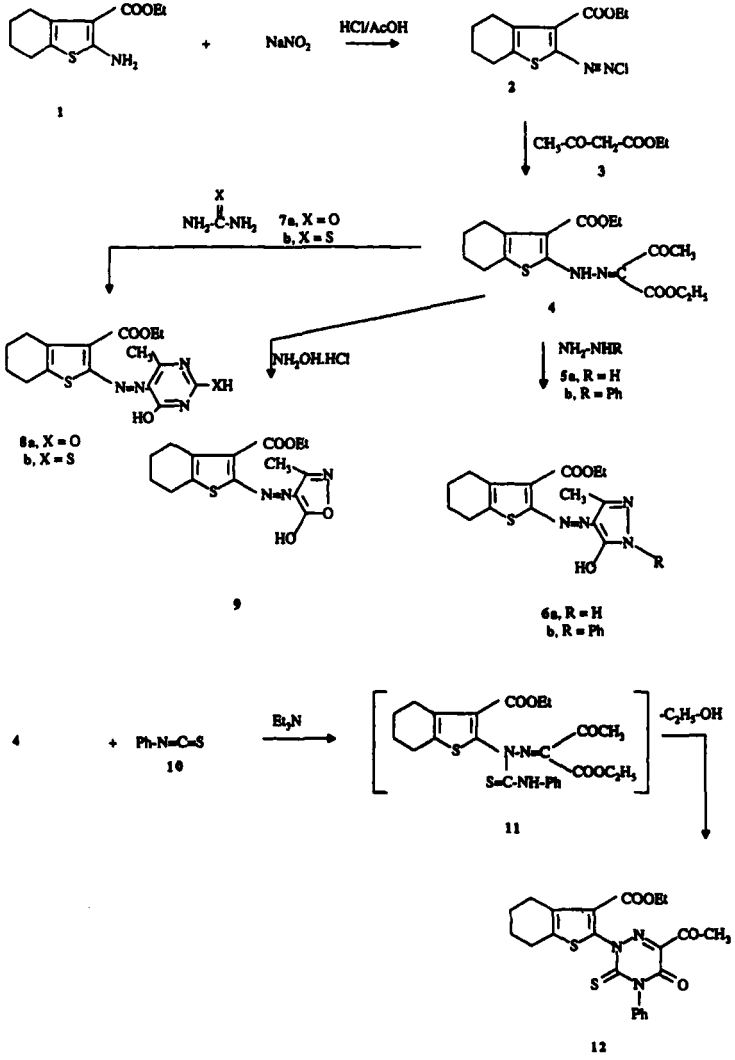

CHART 1

The reaction of **14b** with benzalmalononitrile **18** led to formation of the phthalazine derivative **21**. Formation of **21** took place through the intermediate formation of **19** and **20** followed by elimination of hydrogen cyanide. The structure of **21** was confirmed on the basis of analytical and spectral data. Thus, the IR spectrum showed the presence of the NH_2 stretching absorption at 3450–3310 cm^{-1}, one CN group stretching frequency at 2220 $cm^{-1}$and three CO groups absorption at 1690, 1680–1670 cm^{-1}. The ^1H NMR showed the presence of two triplets at δ 1.16, 1.18 ppm due to two CH_3 groups of the two ethyl ester groups, a multiplet at δ 2.12–2.14 and 2.62–2.70 ppm for the four CH_2 groups of the tetramethylene moiety attached to the thiophene ring, two quartets at δ 4.20–4.23 ppm for two CH_2 ester groups, a singlet at δ 4.87 ppm (D_2O exchangeable) corresponding to NH_2 group and a multiplet at δ 7.32–7.38 ppm for phenyl group.

The reaction of **14b** with malononitrile **13a** gave a single product with molecular formula $C_{23}H_{23}N_5O_5S$. Four possible isomeric structures **22–25** were considered for such formula. The possibility of **22** and **23** were ruled out on the basis of the IR spectrum of the reaction product, which showed the presence of only one CN group stretching frequency at 2220 cm^{-1}. On the other hand, structure **24** was eliminated on the basis of the ^1H NMR spectrum which showed one singlet at δ 5.34 ppm (D_2O exchangeable) due to the presence of only one NH_2 group together with the presence of a singlet at δ 4.45 ppm due to the presence of CH_2 group. Thus, the obtained data are in agreement with structure **25**.

The reactivity of the CH_2 group which is present in **25** was studied. Thus, compound **25** reacted with benzenediazonium chloride to give the corresponding phenylhydrazone derivative **26**. On the other hand, compound **25** reacted with benzaldehyde to give the benzylidene derivative **27**.

The reaction of **4** with malononitrile in a benzene/acetic acid solution containing ammonium acetate gave the Knoevenagel condensation product **28** not the pyridazine derivative **29**. The structure of **28** was established on the basis of analytical and spectral data. Thus, the IR spectrum showed the presence of the NH stretching mode at 3450–3420 cm^{-1}, two CN groups stretchings at 2225, 2220 $cm^{-1}$and two CO groups stretchings at 1690, 1680 cm^{-1}. Moreover, the ^1H NMR spectrum showed the presence of two triplets at δ 1.16, 1.18 ppm for two CH_3 ester groups, a singlet at δ 2.09 ppm for CH_3 group, two quartets for two CH_2 ester groups at δ 4.21, 4.25 ppm and a singlet at δ 9.21 ppm (D_2O exchangeable) for NH group. The reaction of **28** with either hydrazine hydrate **5a** or phenyl hydrazine

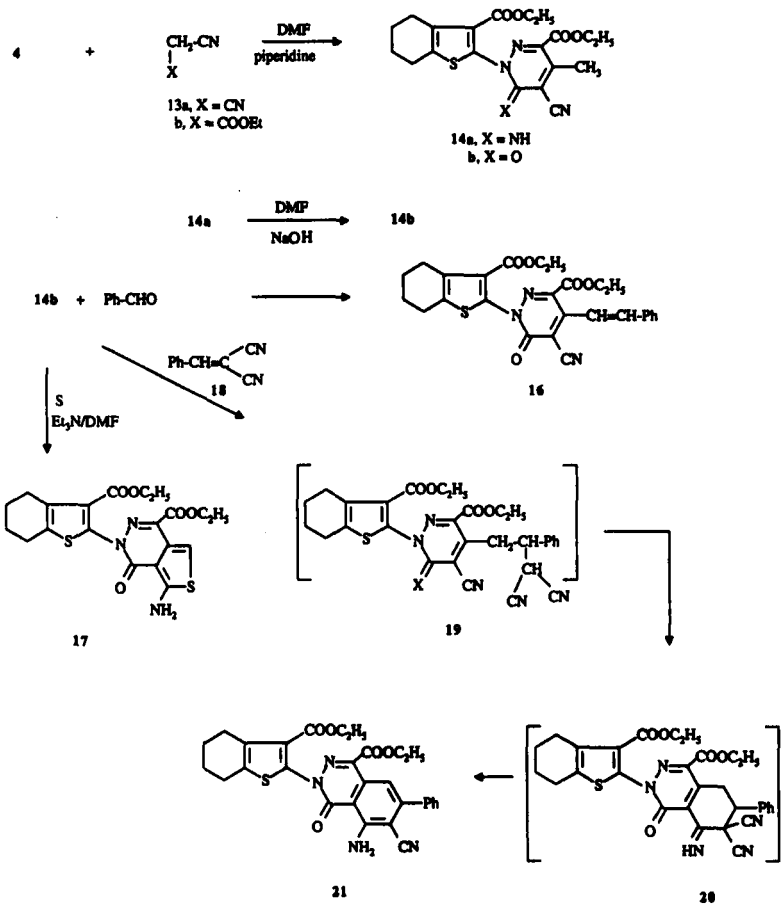

CHART 2

5b gave the pyrazole derivatives **30a** and **30b** respectively. The structures of **30a** and **30b** were based on the obtained analytical and spectral data (see the experimental section).

Heating of **28** with aniline in an oil bath (at 140°C) gave the anilide derivative **31**. The reaction of **28** with hydroxylamine hydrochloride in 1,4-dioxane containing sodium acetate gave the isoxazole derivative **32**. On The other hand, the reaction of **28** with phenylisothiocyanate in boiling 1,4-dioxane containing triethylamine gave the triazine derivative **33**.

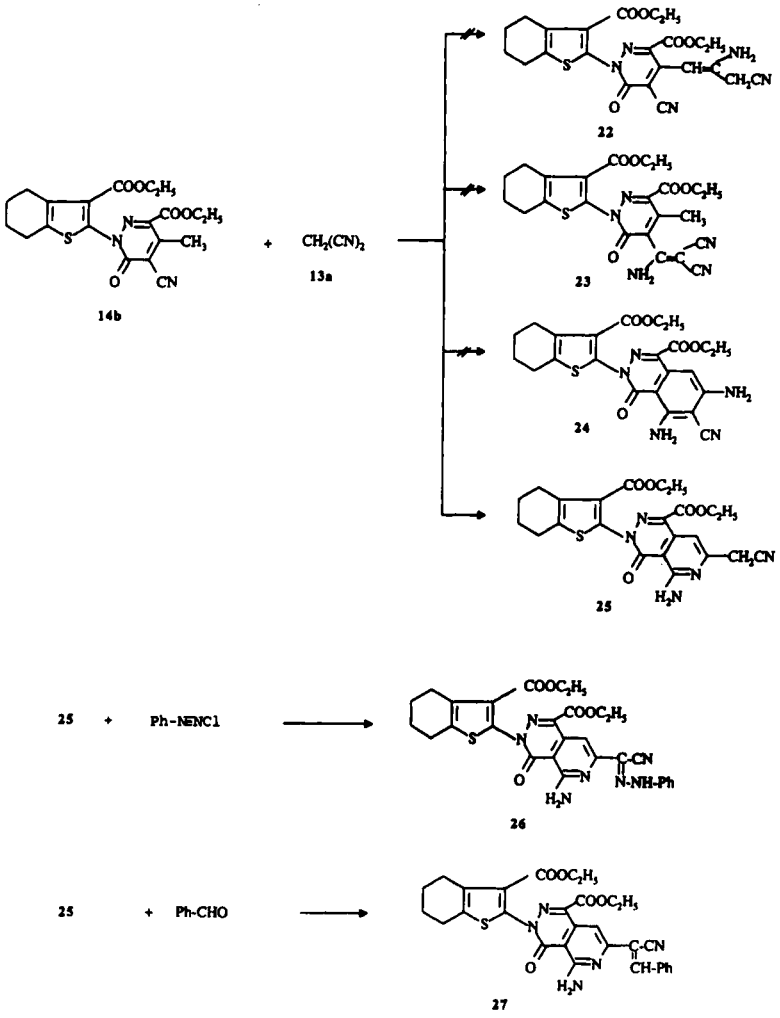

CHART 3

Moreover, the reaction of **28** with benzaldehyde gave the benzal derivative **34**. The structure of **34** was confirmed on the basis of analytical and spectral data (see Table II).

On the other hand, the reaction of **28** with benzalmalononitrile **18** gave the substituted phenol derivative **37**. Formation of **37** took place via the interme-

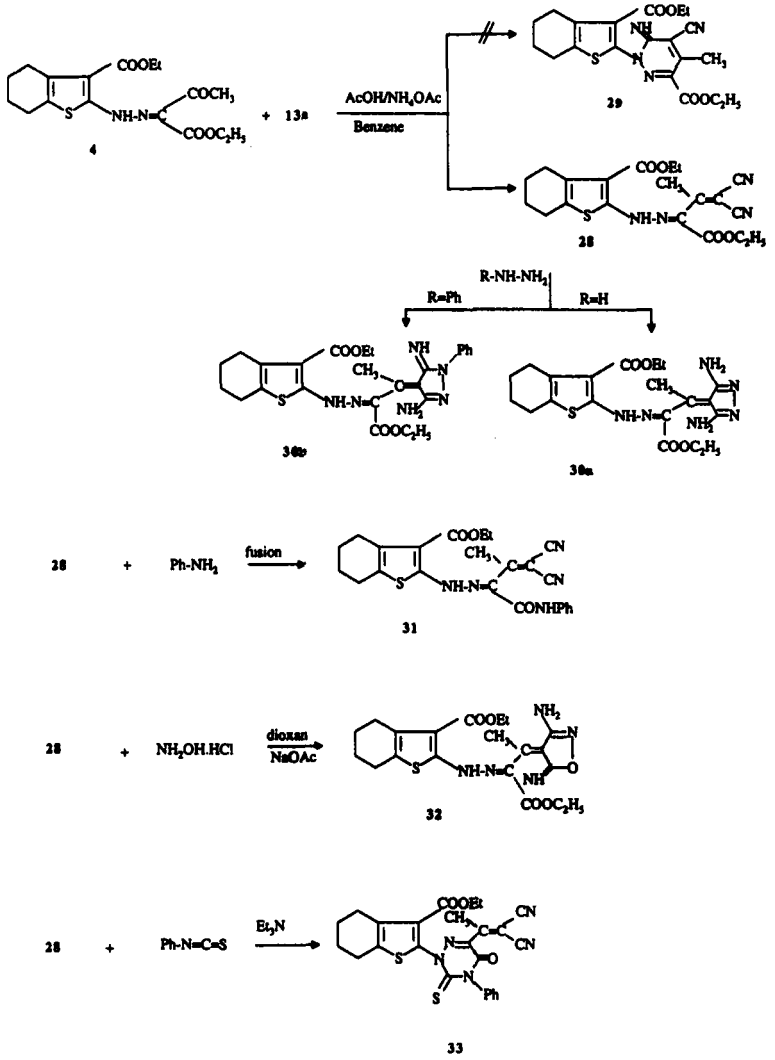

CHART 4

diate formation of **35** and **36** through Michael addition with concomitant, together with loss of ethanol and hydrogen cyanide. Structure of **37** was confirmed on the basis of analytical and spectral data (see Tables II & III).

EXPERIMENTAL SECTION

The melting points are not corrected. The IR spectra were obtained (KBr) on a Pye Unicam SP-1000 spectrophotometer. The ^1H NMR spectra were measured on a Varian EM 390–90 Mhz in CD_3SOCD_3 as solvent, using TMS as internal standard, and chemical shifts were expressed in δ values. Elemental analyses were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

Ethyl 2-hydrazono-(ethyl 3-oxobutanoato-2yl)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (4)

To a cold solution (0–5 °C) of **3** (0.01 mol), 1.3 g) in ethanol (50 ml), 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **2** [prepared by adding sodium nitrite (0.02 mol) solution to a cold solution (0–5 °C) of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **1** (0.01 mol) in acetic/hydrochloric acid with continuous stirring] was added with stirring. The solid product formed upon standing for 1h at room temperature was collected by filtration and crystallized from ethanol to give red orange crystals, yield 81 % (2.8 g).

Ethyl 2-azo-(5-hydroxy-3-methylpyrazolo)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (6a); Ethyl 2-azo-(5-hydroxy-3-methyl-1-phenylpyrazolo)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (6b); Ethyl 2-hydrazono-(ethyl 3,5-diamino-pyrazolo-4-yl-2,3-dioxobutanoato)-4,5,6,7-tetrahydrobenzo-[b] thiophene-3-carboxylate (30a); Ethyl 2-hydrazono-(ethyl 3-amino-pyrazolo-4-yl-2,3-dioxo-5-imino-1-phenylbutanoato)-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxylate (30b)

General procedure

To a solution of **4** (0.01 mol) or **28** (0.01 mol) in ethanol (10 ml) either of hydrazine hydrate or phenyl hydrazine (0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 5h then the solid product formed upon pouring into ice/water containing few drops of hydrochloric acid was collected by filtration. Compound **6a**: yellow crystals from 1,4-dioxane, yield 80 % (2.7 g). Compound **6b**: yellow crystals, from

1,4-dioxane, yield 74 % (3.0 %). Compound **30a**: orange crystals, from ethanol, yield 68 % (3.0 g). Compound **30b**: orange crystals, from 1,4 dioxane, yield 65 % (3.4 g).

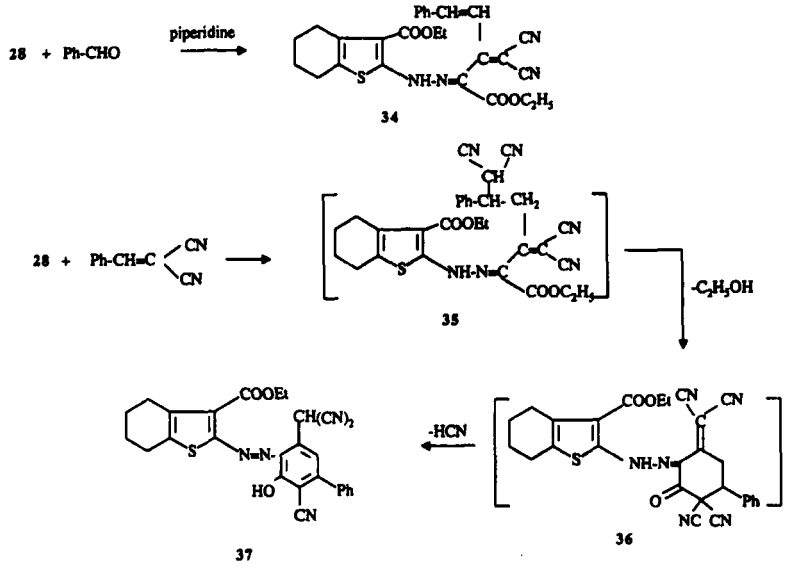

CHART 5

Ethyl 2-azo-(2,4-dihydroxy-6-methylpyrimido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (8a); Ethyl 2-azo-(4-hydroxy-2-mercapto-6-methylpyrimido)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (8b)

To a suspension of **4** (0.01 mol) in sodium ethoxide (0.01 mol) [prepared by adding sodium metal (0.01 mol) to ethanol absolute (20 ml)] either urea or thiourea is added. The reaction mixture was heated in a boiling water bath for 3 h then poured into ice/water. The solid product formed upon addition of hydrochloric acid (till pH 6) was collected by filtration. Compound **8a**: pale yellow crystals from dimethylformamide, yield 77 % (2.8 g). Compound **8b**: pale yellow crystals, from acetic acid, yield 71 % (2.7 g).

Ethyl 2-azo-(5-hydroxy-3-methylisoxazol)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (9); Ethyl 2-hydrazono-(ethyl 2-yl-3-(3-amino-5-iminoisoxazolo-4-yl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxylate (32)

To a solution of **4** or **28** (0.01 mol) in absolute ethanol (20 ml) containing sodium acetate (0.01 mol), hydroxylamine hydrochloride (0.01 mol) is added. The reaction mixture was heated under reflux for 7h then poured into ice/water, the solid product formed upon standing for 4h was collected by filtration. Compound **9**: White crystals, from ethanol, yield 68 % (2.1 g). Compound **32**: yellow crystals from ethanol, yield 77 % (3.4 g).

Ethyl 2-(6-acetyl-5-oxo-4-phenyl-2-thioxo-1,2,4-triazino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylate (12); Ethyl 2-(5-cyano-3-ethoxycarbonyl-4-methyl-6-iminopyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (14a) and Ethyl 2-(5-cyano-3-ethoxycarbonyl-4-methyl-6-oxopyridazino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (14b)

General procedure

To a solution of **4** (0.01 mol) in dimethylformamide (30 ml) containing triethylamine (0.5 ml) either of phenylisothiocyanate (0.01 mol) or malononitrile (0.01 mol) or ethyl cyanoacetate (0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 h then poured into ice water containing few drops of hydrochloric acid. The formed solid product was collected by filtration. Compound **12**: Orange crystals, from dimethylformamide, yield 70 % (3.2 g). Compound **14a**: red crystals, from ethanol, yield 74 % (3.1 g). Compound **14b**: Pale brown crystals, from acetic acid, yield 68 % (2.8 g)

Conversion of 14a into 14b

To a solution of **14a** (0.01 mol) in dimethylformamide (50 ml), sodium hydroxide (0.01 mol) was added. The reaction mixture was heated under reflux for 3h then poured into ice/water containing few drops of hydrochloric acid (till pH 6–7). The formed solid product was collected by filtration to give **14b** (identical m.p., mixed m.p. and finger print IR spectrum).

Ethyl 2-(4-benzalmethino-5-cyano-3-ethoxycarbonyl-6-oxopyridazo)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (16); Ethyl 2-(7-amino-5-α-benzalacetonitrilo-3-ethoxycarbonyl-8-oxopyrido[4,3-d] pyridazo)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (27); Ethyl 2-hydrazono-(α-cyano-β-2-phenylvinyl-ethoxycarbonylcrotono-nitrilo-ylideno)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylate (34)

General procedure

To a solution of either **14b** or **25** or **28** (0.01 mol), in dimethylformamide (30 ml) containing triethylamine (1 ml) benzaldehyde (0.01 mol) is added. The reaction mixture, in each case is heated under reflux for 5 h then poured into ice/water containing few drops of hydrochloric acid. The solid product formed, in each case, was collected by filtration. Compound **16**: Yellow crystals, from acetic acid, yield 73 % (3.7 g). Compound **27**: Yellow crystals, from dimethylformamide, yield 71 % (4.1 g). Compound **34**: Orange crystals, from acetic acid, yield 74 % (3.7 g).

Ethyl 2-(6-amino-3-ethoxycarbonyl-7-oxothieno[4,3-d]pyridazo)-4,5,6,7-tetrahydrobenzo[b]thio-phene-3-carboxylate (17); Ethyl 2-(5-α- acetanilido-7-amino-3-ethoxycarbonyl-8-oxopyrido[4,3-d] pyridazo)-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxylate (25)

To a solution of **14b** in dioxane containing triethylamine either malononitrile or elemental sulfure was added. The reaction mixture in each case was heated under reflux for 5 h and the solid product formed, in each case, upon pouring into ice water containing few drops of hydrochloric acid, was collected by filtration. Compound **17**: Orange crystals, from dimethylformamide, yield 72 % (3.2 g). Compound **25**: Pale brown crystals, from acetic acid, yield 75 % (3.6 g).

Ethyl 2-(7-amino-6-cyano-3-ethoxycarbonyl-5-phenyl-8-oxobenzo[d] pyridazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (21); Ethyl 2-azo(2-cyano-5-dicyanomethino-3-phenylphenol-6-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene (37)

To a solution of either **14b** (0.01 mol) or **28** (0.01 mol) in dimethylformamide (30 ml) containing triethylamine (0.5 ml) benzalmalononitrile

(0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then evaporated in vacuo. The remaining product was triturated with diethylether and the formed solid product was collected by filtration. Compound **21**: Pale yellow crystals, from 1,4-dioxane, yield 92 % (5.0 g). Compound **37**: Red crystals, from ethanol, yield 77 % (3.8 g).

Ethyl 2-hydrazono-α-cyano-β-methyl-γ-ethoxycarbonylcrotononitrilo)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (28)

To a solution of 4 (0.01 mol) in benzene/acetic acid mixture (50 ml, 5:2) containing ammonium acetate (0.01 mol), malononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 6h then evaporated in vacuo. The solid product formed upon trituration with diethyl ether was collected by filtration and crystallized from dimethylformamide to give orange crystals, yield 78 % (3.2 g).

Ethyl 2-(6-α-cyanocrotononitrilo-β-yl-5-oxo-4-phenyl-3-thioxo-1,2,3,4-triazino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (33)

To a solution of **28** (0.01 mol) in dioxan (30 ml) containing triethylamine (0.5 ml), phenylisothiocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 8h then evaporated in vacuo. The remaining product was triturated with diethyl ether and the formed solid product was collected by filtration and crystallized from 1,4-dioxane to give yellow crystals, yield 72 % (3.6 g).

Biological activity

The diverse biological activities of azole and azine derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Their bactericidal and antifungal activities[13,14] were studied. A disc of blotting paper is impregnated with a known volume and appropriate concentration of a compound to be tested, which is then placed on a sensitivity testing agar plate which was inoculated with the test organism. The compound diffuses from the disc into the medium. The culture was examined for areas of no growth around the disc (zones of inhibition) after overnight incubation. Growth of bacterial strains sensitive to a com-

pound is inhibited at certain distances from the center of the disc whereas resistant strains glow up to the edge of the disc.

TABLE IV In Vitro bactericidal and fungicidal activity of some of the newly synthesized compounds

Compd. No.	*Bacillus cerceus (Gram positive)*	*Staph. aureus (Gram positive)*	*E. Coli (Gram negative)*	*K. Pneumonia (Gram negative)*
4	+++	++	+	++
6a	++	++	++	++
6b	+++	+++	++	+
8a	++	+++	+	++
8b	+++	++	+	+
9	++	+	+	++
12	+	++	+++	+
14a	+++	+	+	+++
14b	+	++	++	
16	+++	+++	+	++
17	++	+	+++	++
21	++	+++	+	+
25	+++	+	+++	+++
26	+	++	+	+
27	++	+++	++	+++
28	+	+	+	+
30a	++	+	+++	+++
30b	+	+++	+	+
31	++	++	+++	+
32	+++	+	+	+++
33	+++	+	+++	+
34	+++	+	++	+
37	+++	++	+++	++

Slight inhibition = +, Modrate inhibition = ++, Strong inhibition = +++ Rating percent control: No inhibition = 0; Slight inhibition = 10, 20, 30; Modrate inhibition = 40, 50, 60; Strong inhibition = 70, 80, 90; complete inhibition = 100.

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