γ-Oxo Carboxylic Acids in Heterocyclic Synthesis, III. Synthesis of Biologically Active 4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,5-tetrahydropyridazin-3-ones

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Heterocyclic Synthesis

α-Benzylamino-β-(5,5-dioxodibenzothiophen-2-carbonyl)propionic acid (**1**) has been synthesized by treating the corresponding β-aroylacrylic acid with benzylamine in dry benzene. On treatment with hydrazine hydrate the keto acid **1** furnishes the corresponding pyridazinone derivative **2**. The behaviour of **2** towards carbon electrophiles, namely, ethyl chloroacetate, acrylonitrile, formaldehyde and secondary amines (under Mannich reaction conditions), aromatic aldehydes and carbon nucleophiles, namely, $POCl_3/PCl_3$ and P_2S_5 has been investigated. The 3-chloropyridazine derivative **13** reacts with hydrazine hydrate to give the 3-hydrazino derivative **14**. On treatment with ethyl acetoacetate and/or acetylacetone the hydrazine **14** undergoes cyclization to afford pyrazolone derivative **16** and 3-(3,5-dimethylpyrazol-1-yl)pyridazine derivative **17**, respectively. On reaction with acetylhydrazine in boiling butanol and/or sodium azide in DMF the 3-chloropyridazine derivative **13** affords the triazolo[4,3-b]pyridazine **18** and the tetrazolo[1,5-b]pyridazine **19**, respectively. The anti-microbial activity of the synthesized derivatives has been investigated.

A review (in two parts) on the pharmacological activity of pyridazine derivatives has been published [1, 2]. They include analgesic, antiinflammatory, antisecretory, antiulcer agents, antidepressants, neuroleptics, anxiolytics, sedative-hypnotics, tranquillizers, *anti*-convulsants, GABA antagonists, blood platelet aggregation inhibitors and antithrombotics, antitumor agents, immunosuppressant agents, cardiotonics, coronary vasodilatators, antiarrhythmics, cardioselective β-blockers, antihypertensive, antihypotensive and hypocholesterolaemic agents.

α,β-Unsaturated γ-oxo acids are of limited use since the unsaturated acids are difficult to obtain. Most frequently used are mucic acid and its derivatives, which produce 4,5-dihalopyridazines from 2,3-dichloro-4-oxobut-2-enoic acid [3] or 2,3-dibromo-4-oxobut-2-enoic acid [4]. Several pyridazinones have been obtained by pyrolytic decomposition of semicarbazones of 4-oxo acids [5] or hydrazones of unsaturated 4-oxo acids [6]. Prompted by these observations and in continuation of our studies on the utilization of α,β-unsaturated γ-oxo acids in the synthesis of diazine heterocycles [7–9], we thought it worthwile to synthesize a new series of pyridazine derivatives, with the objective of obtaining new biologically active compounds.

The various steps involved in the synthesis of the title compound **2** and its reaction with a variety of reagents are shown in Schemes 1 and 2.

The required α-benzylamino-β-(5,5-dioxodibenzothiophen-2-carbonyl)propionic acid (**1**) was synthesized from the corresponding β-(5,5-dioxodibenzothiophen-2-carbonyl)acrylic acid and benzylamine in dry benzene under Michael reaction conditions. The condensation of **1** with hydrazine hydrate in boiling ethanol furnished the corresponding 4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,5-tetrahydropyridazin-3-one (**2**).

Reactivity of **2**, which bears bulkyheteryl moieties at position 4 and 6 and the effects of steric hinderance of these groups have been studied with different carbon electrophiles and nitrogen nucleophiles. Thus, pyridazinone **2** reacted with ethyl chloroacetate in boiling dry acetone and dry K_2CO_3 to afford 4-benzylamino-3-*o*-carboethoxymethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**3**). Alkaline hydrolysis of the

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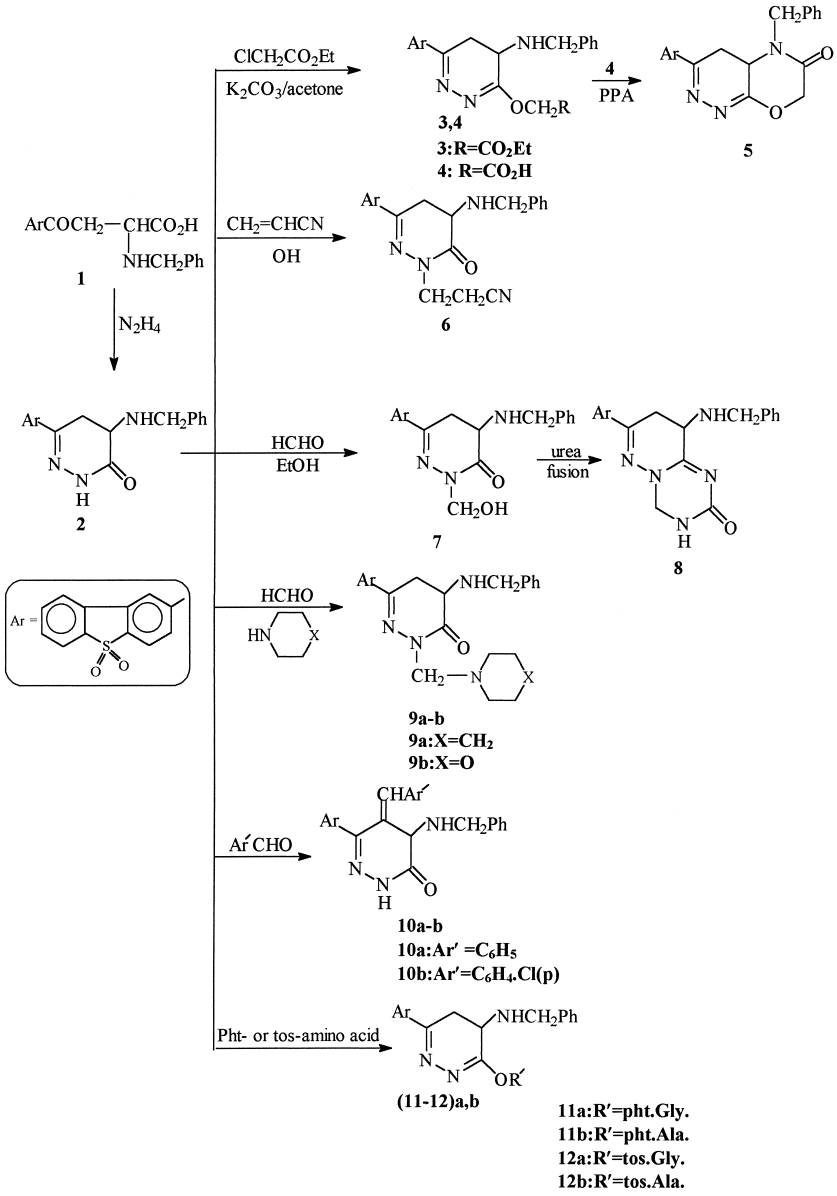
ester **3** followed by acidification yielded the 4-benzylamino-3-*o*-carboxymethyl-6-(5,5-dioxo-dibenzothiophen-2-yl)-4,5-dihydropyridazine (**4**) which upon subsequent dehydration with polyphosphoric acid furnished the 1-benzyl-7-(5,5-dioxodibenzothiophen-2-yl)-2-oxomorpholino-[3,4-b]-2,3,8,8a-tetrahydropyridazine (**5**). The reactivity of **2** towards some reagents which are known to attack the nitrogen atom at position 2 of pyridazin-3-(2H)-one was studied. Thus, on treatment of **2** with acrylonitrile in boiling ethanol containing catalytic amounts of aqueous sodium hydroxide solution, a Michael-type addition occurred at the activated double bond and afforded the 4-benzylamino-2-cyanoethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazin-3-one (**6**).

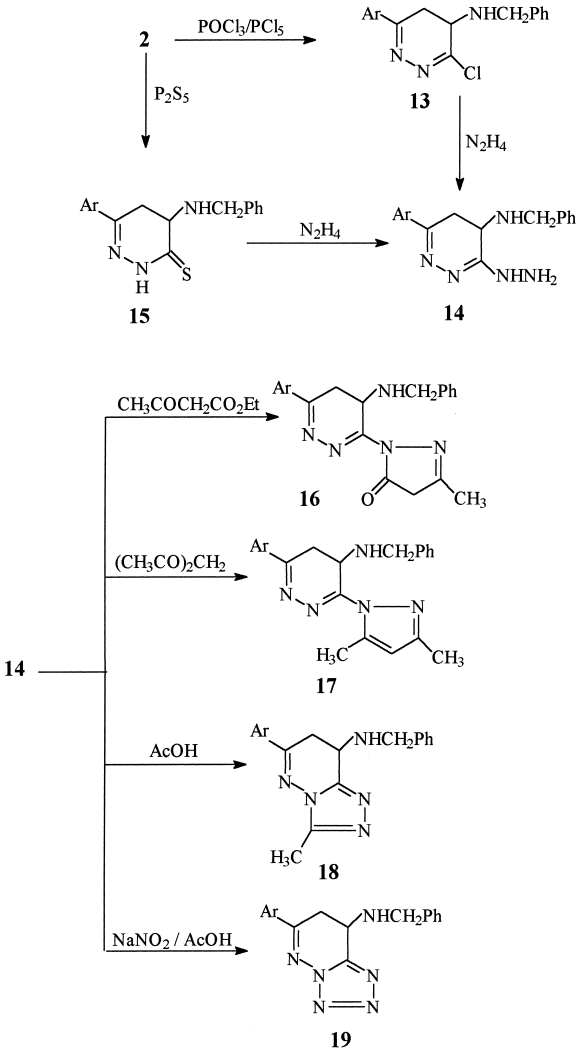
On the other hand, compound **2** reacted readily with formaldehyde in boiling ethanol to give the



Scheme 1.

2-hydroxymethyl derivative **7** which on cyclocondensation with urea yielded 9-benzylamino-7-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,8,9-pentahydropyridazino[1,6-a]-1,3,5-triazin-2-one (**8**). When **2** was allowed to react with formaldehyde and secondary amines, namely, piperidine and/or morpholine in ethanol, we obtained the Mannich bases **9a,b**, respectively. The same bases were obtained when the corresponding hydroxymethyl derivative **7** was treated with piperidine and/or morpholine. Base catalysed condensation of **2** with aromatic aldehydes, namely, benzaldehyde and/or *p*-chlorobenzaldehyde afforded the corresponding 5-arylidene-4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4-trihydropyridazin-3-one (**10a,b**). Sometimes the incorporation of amino acid residues in various sulfur- and nitrogen-containing heterocycles enhances the biological profile manyfold over that of its parent nucleus [10–12]. Due to the interest in this class of compounds we have previously reported the synthesis and biological evaluation of 2-*N*-(pht- or tos-aminoacyl)mercapto- or amino-pyrimidine derivatives [13]. In continuation, we considered to synthesize novel congeners bearing pyridazine and amino acid moieties in a single molecular framwork likely to constitute potent antimicrobial agents. Thus, compound **2** reacted with phthalyl and/or tosyl derivatives of the amino acids glycine and/or DL-alanine to furnish 4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-3-*o*-(pht- or tos-amino acid)-4,5-dihydropyridazine derivatives (**11, 12**)$_{a,b}$, respectively.

In an attempt to prepare biologically active compounds from pyridazine derivatives, the utilization of hydrazinopyridazine derivatives [14] has been also investigated. Thus, on treatment with $POCl_3$–PCl_5 4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,5-tetrahydropyridazin-3-one (**2**) gave 3-chloropyridazine derivative **13** which was subsequently converted into the 3-hydrazinopyridazine derivative **14** by treatment with hydrazine hydrate in refluxing ethanol. Interestingly, the structure of compound **14** was established chemically by independent synthesis *via* the reaction of **2** with phosphorus pentasulphide in boiling xylene. Upon subsequent reaction with hydrazine hydrate The 3-mercaptopyridazine derivative **15** yielded the 3-hydrazino derivative **14**. Reaction of **14** with ethyl acetoacetate in boiling ethanol produced 4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-3-[1*N*-(3-methylpyrazolin-5-one)]-4,5-dihydropyridazine (**16**). With acetylacetone **14** cyclized to



Scheme 2.

4-benzylamino-3-(3,5-dimethylpyrazol-1-yl)-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**17**). On the other hand, refluxing of **14** with acetic acid produced the corresponding 8-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-1,2,4-triazolo[4,3-b]-7,8-dihydropyridazine (**18**). Compound **18** was also obtained by an independent synthesis *via* the condensation of **13** with acetylhydrazine in boiling *n*-butanol. Further, the reaction of **14** with a mixture of sodium nitrite and conc. HCl afforded the 8-benzylamino-6-(5,5-di-

oxodibenzothiophen-2-yl)-1,2,3,4-tetrazolo[1,5-b]-

Table 1: Activity (A) and minimum inhibitory concentration (MIC) calculated as mmol/ml for compound **2b–7b**.

Comp.	*Bacillus subtilis*		*Bacillus cereus*		*Escherichia coli*		*Aspergillus niger*		*Penicillium notatum*	
	A[a]	MIC[b]	A	MIC	A	MIC	A	MIC	A	MIC
2	+++	1.2×10^{-3}	++	6.0×10^{-4}	++	3.0×10^{-4}	++	6.0×10^{-4}	++	3.0×10^{-4}
6	+	2.7×10^{-4}	++	5.3×10^{-4}	++	2.7×10^{-4}	++	5.3×10^{-4}	++	5.3×10^{-4}
7	++	2.8×10^{-4}	++	1.1×10^{-3}	++	5.6×10^{-4}	++	5.6×10^{-4}	++	1.1×10^{-3}
9b	+	2.4×10^{-4}	+++	9.7×10^{-4}	++	4.8×10^{-4}	++	2.4×10^{-4}	+++	9.7×10^{-4}
11a	++	4.1×10^{-4}	++	4.1×10^{-4}	++	2.1×10^{-4}	++	4.1×10^{-4}	++	4.1×10^{-4}
17	+++	1.0×10^{-3}	++	2.5×10^{-4}	++	5.1×10^{-4}	++	5.1×10^{-4}	++	2.5×10^{-4}
19	++	5.7×10^{-4}	++	5.7×10^{-4}	++	2.8×10^{-4}	++	2.8×10^{-4}	++	5.7×10^{-4}

[a] The width of the zone of inhibition indicates the potency of antimicrobial activity.
(–) no antimicrobial activity; (+) weak activity with the diameter of the zone equal to 0.7 cm;
(++) moderate activity with the diameter of the zone equal to 1.3 cm; (+++) marked activity with the diameter of the zone equal to 1.7 cm; [b] origin of cultures.
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The results of the control samples were not included in the Table; they show negative responses.

7,8-dihydropyridazine (**19**). Compound **19** was also obtained *via* reaction of **13** with sodium azide.

The structures of the above compounds were confirmed from their physical and analytical data (Table 2) and from their spectral data (Table 3).

Screening for Antimicrobial Activity

The antimicrobial activities of our compounds were determined in vitro by the filter paper disc method [14]. All compounds were tested for activity against Gram-positive, Gram-negative bacteria, and selected fungi.

The culture medium was normal nutrient agar (NA) supplemented with 1 g of yeast per ml. According to the solubility of the tested compounds, different polar and nonpolar solvents were used, and a good solubility was shown in 10% acetone (v/v) for all test compounds. Based on the previous preliminary test, closely spaced test concentrations (500, 250, 125 μg/ml) were selected. A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarized in Table 1. Only **2**, **9b** and **17** were found to possess marked activity at a minimal inhibitory concentration (MIC) of (500 μg/ml) against *Bacillus subtilis*, *Bacillus cereus* and *Penicillium notatum*; these compounds also showed weak activity at (MIC) of (250 μg/ml) against *Escherichia coli* and *Aspergillus niger*. All other compounds showed very weak activity against the different strains of bacteria and fungi.

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Pye-Unicam Sp-1200 spectrophotometer and ^{1}H-NMR spectra in DMSO on a JOEl Fx 90 Q9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ, ppm). Mass spectra were recorded on an HP Model MS 5988 spectrometer and microanalytical data were obtained from the Microanalytical Center at Cairo University.

α-Benzylamino-β-(5,5-dioxodibenzothiophen-2-carbonyl)propionic acid (**1**)

A mixture of β-aroylacrylic acid (15 g, 0.047 mol) and benzylamine (7.49 g, 0.07 mol) in dry benzene (150 ml) was heated under reflux for 3 h. The resulting solid formed after concentration and cooling was crystallized from an appropriate solvent to give compound **1**.

4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,5-tetrahydropyridazin-3-one (**2**)

A boiling solution of the keto acid **1** (14.8 g, 0.035 mol) in ethanol (150 ml) was treated with hydrazine hydrate (1.85 g, 0.037 mol). The reaction mixture was refluxed 6 h and the product separated after concentration was crystallized from a suitable solvent giving the corresponding pyridazinone **2**.

Table 2: Analytical data.

Comp.	M.p.[a] [°C]	Yield [%]	Mol. formula [mol. wt.]	Calcd. (found) [%] C	H	N
1	268 –70	75	$C_{23}H_{19}NO_5S$ (421)	65.55 (65.45	4.51 4.30	3.32 3.42)
2	216–8	83	$C_{23}H_{19}N_3O_3$ S (417)	66.18 (66.52	4.55 4.71	10.07 10.32)
3	212–4	85	$C_{27}H_{25}N_3O_5S$ (503)	64.41 (64.23	4.97 5.24	8.34 8.55)
4	236–8	75	$C_{25}H_{21}N_3$ O_5S (475)	63.15 (63.34	4.42 4.62	8.84 9.05)
5	182–3	63	$C_{25}H_{19}N_3O_4S$ (457)	65.64 (65.44	4.15 4.53	9.19 9.32)
6	210–2	70	$C_{26}H_{22}N_4O_3S$ (470)	66.38 (66.60	4.68 4.92	11.91 11.71)
7	200–2	81	$C_{24}H_{21}N_3O_4S$ (447)	64.42 (64.64	4.69 4.85	9.39 9.66)
8	164–6	75	$C_{25}H_{21}N_5O_3S$ (471)	63.69 (63.92	4.45 4.34	14.86 14.70)
9a	232–4	71	$C_{29}H_{30}N_4O_3S$ (514)	67.70 (67.53	5.83 5.72	10.89 10.82)
9b	191–3	67	$C_{28}H_{28}N_4O_4S$ (516)	65.11 (65.36	5.42 5.54	10.85 10.71)
10a	131–2	69	$C_{30}H_{23}N_3O_3S$ (505)	71.28 (71.53	4.55 4.80	8.31 8.51)
10b	150–2	71	$C_{30}H_{22}$ ClN_3O_3S (539.5)	66.72 (66.92	4.07 4.30	7.78 7.60)
11a	213–5	72	$C_{33}H_{24}N_4O_6S$ (604)	65.56 (65.81	3.97 4.20	9.27 9.52)
11b	220–2	80	$C_{34}H_{26}N_4O_6S$ (618)	66.01 (66.28	4.20 4.44	9.06 9.35)
12a	191–3	81	$C_{32}H_{28}N_4O_6S_2$ (628)	61.14 (61.34	4.45 4.73	8.91 9.04)
12b	223–5	78	$C_{33}H_{30}N_4O_6S_2$ (642)	61.68 (61.82	4.67 4.93	8.72 8.91)
13	192–4	82	$C_{23}H_{18}$ ClN_3O_2S (435.5)	63.37 (63.64	4.13 4.38	9.64 9.80)
14	228–30	92	$C_{23}H_{21}N_5O_2S$ (431)	64.03 (64.21	4.87 4.70	16.24 16.42)
15	160 –2	72	$C_{23}H_{19}N_3O_2S_2$ (433)	63.74 (63.83	4.38 4.62	9.69 9.91)
16	240–2	84	$C_{27}H_{23}N_5O_3S$ (497)	65.19 (65.42	4.62 4.94	14.08 14.45)
17	226–8	83	$C_{28}H_{25}N_5O_2S$ (495)	67.87 (67.70	5.05 5.34	14.14 14.37)
18	238–40	81	$C_{25}H_{21}N_5O_2S$ (455)	65.93 (65.82	4.61 4.90	15.38 15.64)
19	203–5	77	$C_{23}H_{18}N_6O_2S$ (442)	62.44 (62.53	4.07 3.98	19.00 19.12)

[a] All compounds were recrystallized from ethanol except for **1**, **3**, **14** and **18** which were recrystallized from benzene.

4-Benzylamino-3-o-carboethoxymethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**3**)

A mixture of pyridazinone **2** (1.8 g, 0.004 mol), anhydrous K_2CO_3 (2.20 g, 0.016 mol), ethyl chloroacetate (1.96 g, 0.016 mol) and dry acetone (50 ml) was refluxed for 35 h. The excess acetone was removed by distillation and the reaction mixture then poured into water and the organic material was extracted with ether. After evapouration of the dried ethereal solution, the solid that separated was crystallized from a suitable solvent to afford the corresponding ester **3**.

Table 3: Spectral data of compounds **1–19**.

Comp.	IR (KBr) [cm^{-1}]	^{1}H-NMR (DMSO) δ/ppm[a]	MS (70 eV) *m/z* [%]
1	3470–3200 (OH and NH), 1715 (carboxylic CO), 1675 (ketonic CO), 1625 (C=C), 1330 and 1160 (S=O)	2.6–3.3 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 4.1 (q, 1H, methine), 5.7 (br s, 1H, acyclic NH), 6.8–7.6 (m, 12H, ArH), 11.5 (s, 1H, OH)	421(M^+, 4.18), 216 (100)
2	3450–3170 (OH and NH), 1675–1660 (amidic CO), 1620 (C=C), 1595 (C=N), 1340 and 1150 (S=O)	2.7–3.4 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.8 (q, 1H, methine), 5.5 (br s, 1H, acyclic NH), 6.7–7.8 (m, 12H, ArH), 8.9 (br s, 1H, cyclic NH)	417 (M^+, 3.41), 91 (100)
3	3300–3200 (NH), 1735 (CO ester), 1628 (C=C), 1605 (C=N), 1350 and 1140 (S=O)	1.2 (t, J = 7.1 Hz, 3H, ester CH_3), 2.7–3.4 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.7 (q, J = 7.1 Hz, 2H, ester CH_2), 4.0 (q, 1H, methine), 4.6 (s,2H, OCH_2), 5.9 (br s, 1H, acyclic NH), 6.8–7.9 (m, 12 H, ArH)	503 (M^+, 4.66), 77 (100)
5	1680 (amidic CO), 1618 (C=C), 1607 (C=N), 1350 and 1140 (S=O)	2.6–3.4 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.8 (q, 1H, methine), 4.9 (s, 2H, OCH_2CO), 6.8 –7.9 (m, 12H, ArH)	457 (M^+, 0.82), 216 (100)
6	3330–3190 (NH), 2240 (C≡N),1670 (amidic CO), 1626 (C=C), 1610 (C=N), 1370 and 1145 (S=O)	2.1 (t, J = 7.2 Hz, 2H, NCH_2), 2.7–3.4 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.6 (t, J = 7.2 Hz, 2H, CH_2CN), 4.0 (q, 1H, methine), 5.7 (br s, 1H, acyclic NH), 6.7–7.8 (m, 12H, ArH)	472(M^++2,3.19), 470 (M^+, 5.32), 51 (100)
7	3440–3210 (OH and NH), 1668 (amidic CO), 1625 (C=C), 1608 (C=N), 1355 and 1140 (S=O)	2.7–3.7 (m, with interference , 6H, non-equivalent CH_2, CH_2Ph and NCH_2), 4.0 (q, 1H, methine), 5.8 (br s, 1H, acyclic NH), 6.8–7.8 (m, 12H, ArH), 11.5 (s, 1H, OH)	447 (M^+, 0.42), 216 (100)
8	3300–3170 (NH), 1675 (amidic CO), 1624 (C=C), 1590 (C=N), 1360 and 1130 (S=O)	2.6–3.5 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.9 (q, 1H, methine), 4.9 (s, 2H, NCH_2N), 5.8 (br s, 1H, acyclic NH), 6.7–7.8 (m, 12H, ArH), 8.8 (br s, 1H, cyclic NH)	471 (M^+, 2.84), 91 (100)
10a	3450–3150 (OH and NH), 1670 (amidic CO), 1630 (C=C), 1585 (C=N), 1370 and 1180 (S=O)	3.1 (s, 2H, CH_2Ph), 4.0 (s, 1H, methine), 5.5 (br s, 1H, acyclic NH), 6.4 (s, 1H, ylidenic H), 6.8–7.9 (m, 17 H, ArH), 8.9 (br s, 1H, cyclic NH)	505 (M^+, 5.88), 77 (100)
11b	3340–3170 (NH), 2950–2840 (aliphatic CH), 1780–1735 (imidic CO), 1725 (CO ester), 1619 (C=C), 1580 (C=N), 1450 and 1120 (S=O)	1.6 (d, 3H, CH_3), 2.5–3.3 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.9 (q, 1H, methine), 4.5 (q, 1H, NCHCO), 5.6 (br s, 1H, acyclic NH), 6.8–7.9 (m, 16 H, ArH)	618 (M^+, 3.41), 185 (100)
14	3310–3170 ($NHNH_2$ and NH), 1625 (C=C), 1610 (C=N), 1380 and 1130 (S=O)	2.6–3.4 (m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 3.9 (q, 1H, methine), 5.5 (br s, 1H, acyclic NH), 6.2 (br s, 2H, NH_2) 6.9–7.9 (m, 12 H, ArH), 9.2 (br s, 1H, $NHNH_2$)	431 (M^+ , 1.84), 79 (100)
16	3320–3180 (NH), 2960–2830 (aliphatic CH), 1675 (amidic CO), 1630 (C=C), 1605 (C=N), 1350 and 1100 (S=O)	2.5–3.5 (m, with interference, 7H, non-equivalent CH_2, CH_2Ph and CH_3), 4.0–4.5 (m, with interference, 3H, methine and pyrazolone protons), 5.6 (br s, 1H, acyclic NH), 6.8–7.9 (m, 12H, ArH)	497 (M^+, 2.64), 77 (100)
17	3310–3140 (NH), 1625 (C=O), 1590 (C=N), 1410 and 1165 (S=O)	2.3 (s, 6H, 2×CH_3), 2.6–3.4 (m, with interference , 4H, non-equivalent CH_2 and CH_2Ph), 3.9 (q, 1H, methine), 5.7 (br s , 1H, acyclic NH), 6.8–7.9 (m, 12H, ArH)	495 (M^+ , 1.61), 69 (100)
18	3360–3205 (NH), 1618 (C=C), 1594 (C=N), 1370 and 1133 (S=O)	2.5–3.3 (m, with interference, 7H, CH_3, non-equivalent CH_2 and CH_2Ph), 4.0 (q, 1H, methine), 5.5 (br s , 1H, acyclic NH), 6.8–7.8 (m, 12H, ArH)	455 (M^+, 3.23), 57 (100)
19	3200–3150 (NH), 1620 (C=C), 1595 (C=N), 1420 and 1170 (S=O), 1090–1050 (tetrazole ring)[8].	2.5–3.3(m, with interference, 4H, non-equivalent CH_2 and CH_2Ph), 4.1 (q, 1H, methine), 5.4 (br s, 1H, acyclic NH), 6.8–7.8 (m, 12H, ArH)	442 (M^+, 0.96), 109 (100)

[a] All NH signals were exchangeable with D_2O oxide.

4-Benzylamino-3-o-carboxymethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**4**)

The ester **3** (1.4 g, 0.0028 mol) was added to a solution containing NaOH (0.44 g, 0.011 mol) dissolved in a mixture of ethanol (20 ml) and water (30 ml). The mixture was refluxed for 5 h. The alkaline solution was acidified with ice-cold diluted HCl and extracted with ether. The solid separated after evapouration of the dried ethereal layer was crystallized from a proper solvent to yield the corresponding acid **4**.

1-Benzyl-7-(5,5-dioxodibenzothiophen-2-yl)-2-oxomorpholino[3,4-b]-2,3,8,8a-tetrahydropyridazine (**5**)

A mixture of acid **4** (0.71 g, 0.0015 mol) and 20 g of polyphosphoric acid was kept at 120 °C with stirring for 1 h, the mixture was cooled, 100 g of ice was added and the isolated product was crystallized from a proper solvent to furnish **5**.

4-Benzylamino-2-cyanoethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazin-3-one (**6**)

A mixture of pyridazinone **2** (0.58 g, 0.0014 mol) and acrylonitrile (0.08 g, 0.0015 mol) in ethanol (25 ml) was treated with a few drops of 10% NaOH solution and the mixture was heated under reflux for 4 h. The colourless solid which formed after concentration and cooling was crystallized from a proper solvent to furnish **6**.

4-Benzylamino-2-hydroxymethyl-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazin-3-one (**7**)

A solution of pyridazinone **2** (1.58 g, 0.0038 mol) in methanol (25 ml) was treated with formaldehyde (1.14 g, 0.038 mol), and the reaction mixture was refluxed for 6 h. The colourless solid which precipitated after cooling, filtered off, dried and crystallized from a suitable solvent to afford **7**.

9-Benzylamino-7-(5,5-dioxodibenzothiophen-2-yl)-2,3,4,8,9-pentahydropyridazino[1,6-a]-1,3,5-triazin-2-one (**8**)

A mixture of 2-hydroxymethyl pyridazinone **7** (0.54 g, 0.0012 mol) and urea (0.09 g, 0.0015 mol) was heated in an oil-bath at 180 °C for 3 h, cooled and triturated with ethanol. The solid obtained was crystallized from a suitable solvent to give **8**.

4-Benzylamino-2-(piperidyl- or morpholinomethyl)-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazin-3-ones (**9a,b**)

A mixture of pyridazinone **2** (0.75 g, 0.0018 mol), formaldehyde (0.81 g, 0.027 mol) and secondary amines, namely, piperidine and/or morpholine (0.17 g, 0.002 mol) in ethanol (30 ml) was left overnight at room temperature and then heated under reflux for 3 h. The solid which formed after removal of most of the solvent was crystallized from a suitable solvent to afford **9a,b** as colourless crystals (see Table 2).

Independent synthesis of Mannich bases (**9a,b**)

A mixture of 2-hydroxymethylpyridazinone **7** (0.5 g, 0.001 mol) and secondary amines, namely, piperidine and/or morpholine (0.1 g, 0.0012 mol) in ethanol (25 ml) was heated under reflux for 3 h. The solid that separated after concentration and cooling was crystallized from a proper solvent to yield a product identified to be **9a,b** by mp and mmp determination.

5-Arylidene-4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-2,3,4-trihydropyridazin-3-one (**10a,b**)

A mixture of the pyridazinone **2** (0.75 g, 0.0018 mol) and aromatic aldehydes (0.0019 mol), namely, benzaldehyde (0.2 g) and/or *p*-chlorobenzaldehyde (0.27 g) in ethanol (20 ml) was treated with 4% ethanolic sodium hydroxide solution (20 ml) and the whole mixture was refluxed for 3 h. The solid product which formed after cooling and acidification was filtered off and crystallized from a suitable solvent to furnish **10a,b**.

4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-3-o-(pht- or tos-amino acid)-4,5-dihydropyridazine derivatives (**11,12**)$_{a,b}$

An *N*-phthalyl or *N*-tosylamino acids, namely, glycine and DL-alanine (0.001 mol) and pyridazinone **2** (0.5 g,0.001 mol) were dissolved in tetrahydrofuran (50 ml). The reaction mixture was cooled to 0 °C, then dicyclohexylcarbodiimide (0.021 g) was added and the mixture stirred for 2 h at 0 °C, left for 24 h at 0 °C and for another 24 h at r.t. The dicyclohexylurea was filtered off, the filterate evaporated *in vacuo* and the residue recrystallized from a suitable solvent to furnish (**11, 12**)$_{a,b}$, respectively.

4-Benzylamino-3-chloro-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**13**)

A mixture of pyridazinone **2** (3.5 g, 0.0084 mol), $POCl_3$ (41.3 g, 0.27 mol) and PCl_5 (2.5 g, 0.012 mol) was refluxed on a steam bath for 4 h. The reaction mixture was poured gradually on crushed ice and the solid that separated was filtered off and crystallized from a suitable solvent to afford **13**.

4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-3-hydrazino-4,5-dihydropyridazine (**14**)

A mixture of compound **13** (2.2 g, 0.005 mol) and hydrazine hydrate (0.35 g, 0.007 mol) in ethanol (50 ml) was heated under reflux for 6 h. The reaction mixture was concentrated to one third its orignial volume and allowed to cool. The resulting solid which deposited was filtered off and crystallized from a suitable solvent to give **14**.

Independent synthesis of **14**

(i) 4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazin-3(2H)-thione (**15**)

A mixture of pyridazinone **2** (0.8 g, 0.0019 mol) in (25 ml) of xylene and (2.0 g, 0.009 mol) of P_2S_5 was heated under reflux for 3 h, filtered while hot and left to cool. The product separated was crystallized from a suitable solvent to yield the corresponding thione derivative **15**.

(ii): The thione derivative **15** (0.5 g, 0.0012 mol) and hydrazine hydrate (0.1 g, 0.002 mol) in benzene (25 ml) was heated under reflux for 3 h. The solid obtained after concentration and cooling was crystallized from a proper solvent to yield a product identified to be **14** by mp and mmp determination.

4-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-3-[1N-(3-methylpyrazolin-5-one)]-4,5-dihydropyridazine (**16**)

A mixture of **14** (0.52 g, 0.0012 mol) and ethyl acetoacetate (0.2 g, 0.0015 mol) in ethanol (25 ml) was refluxed for 6 h. The solid that separated, after concentration and cooling, was crystallized from a suitable solvent to give **16**.

4-Benzylamino-3-(3,5-dimethylpyrazol-1-yl)-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine (**17**)

A mixture of **14** (0.52 g, 0.0012 mol) and 2,4-pentanedione (0.15 g, 0.0015 mol) in ethanol (25 ml) was heated at reflux for 4 h. The solid that separated upon cooling was filtered off and crystallized from a suitable solvent to furnish **17**.

8-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-1,2,4-triazolo[4,3-b]-7,8-dihydropyridazine (**18**)

The hydrazinopyridazine **14** (0.52 g, 0.0012 mol) in AcOH (25 ml) was heated under reflux for 8 h. The solid separated after concentration and cooling was crystallized from a proper solvent to give **18**.

Independent synthesis of **18**

A mixture of 3-chloropyridazine **13** (0.52 g, 0.0012 mol) and acetylhydrazine (0.09 g, 0.0012 mol) in *n*-butanol (30 ml) was heated under reflux for 48 h. The solid product that separated after concentration and cooling was crystallized from a proper solvent to yield a product identified to be **18** by mp and mmp determination.

8-Benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)-1,2,3,4-tetrazolo[1,5-b]-7,8-dihydropyridazine (**19**)

To a solution of hydrazinopyridazine **14** (0.52 g, 0.0012 mol) dissolved in 10% aq. HCl (10 ml) was added a solution of sodium nitrite (0.1 g, 0.0014 mol) dissolved in water (2 ml) dropwise under cooling and the mixture was allowed to stand for 45 min. The mixture was basified with solid $NaHCO_3$, extracted into $CHCl_3$ and the organic layer was dried (Na_2SO_4). Solvent was removed in vacuo and the residue was crystallized from a proper solvent to give **19**.

Independent synthesis of **19**

A mixture of chloropyridazine **13** (0.52 g, 0.0012 mol) and NaN_3 (0.1 g, 0.0015 mol) in DMF (25 ml) was refluxed for 6 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from a proper solvent to give a product identified to be **19** by mp and mmp determination.

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