AN EFFICIENT SYNTHESIS FOR PYRIMIDO[4',5':4,5]-THIENO[2,3-*c*]PYRIDAZINE DERIVATIVES *VIA* INTRAMOLECULAR AZA-WITTIG REACTION-HETEROCYCLIZATION STRATEGY

José M. Quintela*, Rafael Alvarez-Sarandés, M. Carmen Veiga, and Carlos Peinador

Departamento de Química Fundamental e Industrial, Facultad de Ciencias, Universidad de La Coruña, Campus de A Zapateira, E-15071, La Coruña, Spain

Abstract- A ready one-pot preparation for substituted pyrimidothienopyridazines is reported. Aza-Wittig reaction of iminophosphorane (**3**), derived from ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**2**), with isocyanates, followed by heterocyclization on addition of amines provided a novel synthetic route to the functionalized pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines (**6**). The guanidine-type intermediate compounds (**5**) derived from addition of amines to the carbodiimides (**4**) could be isolated and characterized, thus confirming the suggest reaction pathway.

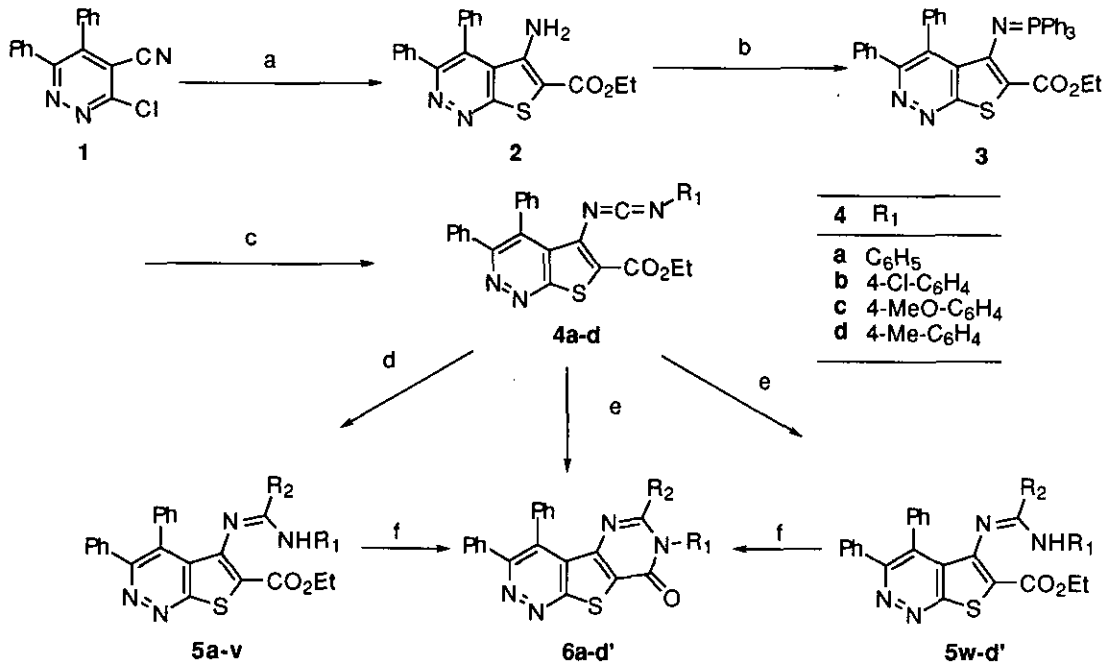
Over the past decade, great progress has been made in the field of heterocyclic compounds by the aza-Wittig methodology.[1] Both inter- and intramolecular versions of the aza-Wittig reaction have assumed increasing importance for the specific construction of many heterocyclic compounds, in particular nitrogen heterocyclic compounds.[1,2] In this context, iminophosphorane-mediated synthesis of heterocyclic ring systems has developed remarkably in recent years, which is obviously linked to the rapid progress in the preparation of functionalized iminophosphoranes.[3]

The iminophosphoranes of heterocyclic and heteroaromatic β-enamino esters have proved to be very versatile synthons for the construction of manifold heterocondensed systems.[1c] Fused nitrogen heterocycles have been prepared *via* such iminophosphorane intermediates recently.[1,4] We become interested in the preparation of *N*-heteroaryliminophosphoranes because these species are promising building blocks for the synthesis of nitrogen heterocycles such as pyrimidothienopyridazine derivatives *via* the intermolecular aza-Wittig reaction and heterocyclization.

Heterocyclic annulated pyridazines continue to attract considerable attention which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives.[5] On the other hand, fused pyrimidines are found in a broad variety of pharmaceuticals, agrochemicals, and veterinary products.[6] Many potential drugs have been modelled on them, particularly in cancer and viral chemotherapy.[7] Recently, our researches have been devoted to the synthesis of condensed tricyclic systems of po-

tential biological activity with a thiophene ring as the central nucleus.[8] Synthesis of fused bi- and polycyclic compounds by annulation of a pyrimidine ring to an existing ring is numerous and was the subject of a recent review.[9] Recently, Wamhoff *et al.*[10] have developed a novel and general type of pyrimidine annulation to an existing heterocyclic ring by employing heterocyclic 2-triphenylphosphoranylidenamino esters and isocyanates. Whereas pyridine-annulated sulfur-containing heterocycles have been studied extensively,[11] comparatively little is known about aza-analogous systems in which an *S*-heterocycle is fused to a pyridazine nucleus. This assessment prompted us to prepare some derivatives of the pyrimidothienopyridazine system as aza-isosteres with potential biological activity of pharmaceutically relevant pyridothienopyrimidine derivatives.[12]

Scheme 1



Reagents: a: $HSCH_2CO_2Et$, K_2CO_3, EtOH/THF, reflux, 1 h, 92%. b: PPh_3, NEt_3, C_2Cl_6, toluene, 90 °C, 48 h., sealed tube, 76%. c: R_1NCO, THF, rt, 0.5-7 h, (R_1= MePh: reflux, 4 h), 49-70%. d: amine, THF, 0-4 °C, 10 h., 53-75%. e: amine, THF, rt, 10 h., 57-90%. f: K_2CO_3, acetone, reflux, 0.25 h., 85-95%.

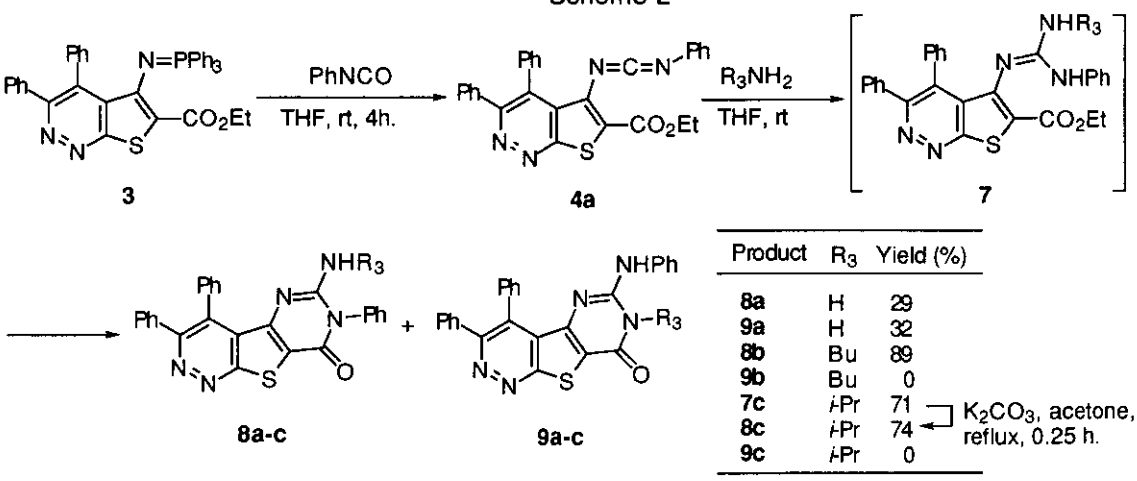
5,6	R_1	R_2	5,6	R_1	R_2	5,6	R_1	R_2
a	C_6H_5	Diethylamino	**k**	4-Cl-C_6H_4	Morpholino	**u**	4-Me-C_6H_4	Morpholino
b	C_6H_5	Piperidino	**l**	4-Cl-C_6H_4	Thiomorpholino	**v**	4-Me-C_6H_4	Thiomorpholino
c	C_6H_5	4-Methylpiperazino	**m**	4-Cl-C_6H_4	Pyrrolidino	**w**	C_6H_5	Thiomorpholino
d	C_6H_5	Morpholino	**n**	4-MeO-C_6H_4	Diethylamino	**x**	4-NO_2-C_6H_4	4-Methylpiperazino
e	C_6H_5	Pyrrolidino	**o**	4-MeO-C_6H_4	Piperidino	**y**	4-NO_2-C_6H_4	Morpholino
f	4-NO_2-C_6H_4	Diethylamino	**p**	4-MeO-C_6H_4	4-Methylpiperazino	**z**	4-NO_2-C_6H_4	Thiomorpholino
g	4-NO_2-C_6H_4	Piperidino	**q**	4-MeO-C_6H_4	Pyrrolidino	**a'**	4-NO_2-C_6H_4	Pyrrolidino
h	4-Cl-C_6H_4	Diethylamino	**r**	4-Me-C_6H_4	Diethylamino	**b'**	4-MeO-C_6H_4	Morpholino
i	4-Cl-C_6H_4	Piperidino	**s**	4-Me-C_6H_4	Piperidino	**c'**	4-MeO-C_6H_4	Thiomorpholino
j	4-Cl-C_6H_4	4-Methylpiperazino	**t**	4-Me-C_6H_4	4-Methylpiperazino	**d'**	4-Me-C_6H_4	Pyrrolidino

In connection with these facts and in continuation of our efforts directed towards the synthesis of tricyclic systems containing a pyridazine subunit,[13] this paper reports detailed results on the annulation of the pyrimidine ring to a preformed thienopyridazine system employing *N*-heteroaryl iminophosphoranes as a conveniently accessible precursor. Pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines were obtained in a one-pot reaction of the corresponding iminophosphorane of heteroaromatic *β*–enamino ester (**3**) with isocyanates, followed by heterocyclization on addition of amines.

The starting compound for the aza-Wittig reaction heterocyclization sequence was prepared from the readily available ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**2**).[14] The key iminophosphorane (**3**) was obtained, in 76% yield, by a modified Kirsanov reaction of the *β*–enamino ester (**2**) with *in situ* generated dichlorotriphenylphosphorane using a hexachloroethane-triphenylphosphine-triethylamine reagent system (Scheme 1).[4c] The molecular structure of the iminophosphorane (**3**) was supported by the spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectrum) and elemental analysis.

An aza-Wittig-type reaction of iminophosphorane (**3**) with several aryl isocyanates in dry tetrahydrofuran (TLC monitored) followed by heterocyclization with secondary amines at room temperature directly affords substituted pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines (**6a-v**) in moderate to good yields (60-90%). As shown in Scheme 1, the guanidine-type intermediate derivatives (**5w-d'**) could be isolated in the above mentioned reaction conditions. Likewise, reaction of iminophosphorane (**3**) with aryl isocyanates and secondary amines at 0-4 °C resulted in the formation of triphenylphosphine oxide and the corresponding guanidine-type intermediate derivatives (**5a-v**). It is clear that compounds (**5**) are the key intermediates for the processes. In the presence of anhydrous potassium carbonate, the separated **5** underwent intramolecular heterocyclization across the electrophilic ester functionality to give the fused pyrimidines (**6a-v**) in very good yields (85-95%).

Scheme 2



Product	R_3	Yield (%)
8a	H	29
9a	H	32
8b	Bu	89
9b	Bu	0
7c	*i*-Pr	71
8c	*i*-Pr	74
9c	*i*-Pr	0

K_2CO_3, acetone, reflux, 0.25 h.

Structural elucidation of the guanidine compounds (**5**) and fused pyrimidines (**6**) was accomplished from their analytical and spectral data. The mass spectra showed the expected molecular ion peak and the IR spectra of compounds (**5**) exhibited a strong absorption band at ν = 3310-3360 cm^{-1} due to the NH

group, while the ^{13}C NMR spectra showed signals between δ = 13.4-14.3 and 60.4-61.6 ppm due to the ethoxy group; also, in the ^{1}H NMR spectra, the NH proton appear in the region 5.45-6.96 as a singlet, in addition to the set of signals due to the ethoxy group. After heterocyclization, the spectra of compounds (**6**) did not include those types of signals. The most salient features of the IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are given in Experimental.

Isolation and characterization of the guanidine derivatives indicates that the reaction involves formation of the corresponding carbodiimide (**4**) as highly reactive intermediate. Those carbodiimide derivatives (**4a-d**) have been isolated by treatment of iminophosphorane (**3**) with aryl isocyanates in dry THF at room temperature. Addition of a secondary amine to the highly reactive carbodiimide cumulenic system followed by intramolecular heteroconjugate addition annulation gives the final fused heterocyclic compounds (**6**).

Results for the cyclization of **3** with ammonia and primary amines are summarized in Scheme 2. Two isomeric pyrimidothienopyridazines (**8** and **9**) may be produced in the reaction of **3** with ammonia or primary amines *via* a guanidine-type intermediate (**7**) (compound (**7**) was isolated when R_3 = *i*-Pr). In fact, the reaction with ammonia gave **8** and **9** but the reaction with butylamine and isopropylamine afforded only **8**, compound (**9**) not being formed. The selectivity in the latter results can be ascribed mainly to the large difference in cyclization rates due to the steric hindrance around the Ph and R_3 groups. Compounds (**7c**, **8a-c** and **9a**) were characterized from the IR spectroscopic data and mass spectrometric data. The ^{1}H NMR spectrum of compound (**8a**) showed a broad singlet at δ = 6.03 due to the NH_2 group, while the ^{1}H NMR spectrum of **9a** exhibited two singlet signals at δ = 8.76 and δ = 11.36 due to the NHPh and NHCO groups. In addition, the NHR_3 proton in compounds (**8b** and **8c**) resonates as a triplet or as a doublet respectively, confirming the proposed structures.

In summary, this synthetic approach may be useful in view of the pharmacological interest in this compound class and affords a new, general route to pyrimidothienopyridazines bearing various substituents in the pyrimidine ring. The present procedure generates under exceptionally mild conditions a guanidine-type functionality which cyclizes very readily to the fused pyrimidine. In a search of the literature it is surprising that pyrimidothienopyridazines have been practically ignored and, to our knowledge, this is the first example of annulation of a pyrimidine ring to an existing thienopyridazine system based on the intramolecular aza-Wittig and heterocyclization strategy. Advantages of the present method are: easy availability of starting materials, good yield in the iminophosphorane preparation as well as in the cyclization step, and experimental simplicities of the one-pot procedure.

EXPERIMENTAL

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 783 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on a VG QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

Ethyl 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (2):

To a solution of **1**[14] (9.14 g, 31.36 mmol) and ethyl 2-mercaptoacetate (4.11 g, 37.64 mmol) in EtOH/THF (5:1) (600 mL) Na_2CO_3 (3.99 g, 37.64 mmol) was added. The reaction mixture was refluxed for 2.5 h. After cooling, the solid formed was filtered off and recrystallized from EtOH to yield **2** (10.82 g, 92%); mp 188-190°C; (lit.,[15] 180-182°C).

Ethyl 3,4-diphenyl-5-[triphenylphosphoranylideneamino]thieno[2,3-*c*]pyridazine-6-carboxylate (3):

To a mixture of **2** (1.00 g, 2.66 mmol), triphenylphosphine (1.05 g, 4 mmol) and hexachloroethane (0.95 g, 4 mmol) in dry toluene (12 mL), triethylamine (0.93 mL, 6.6 mmol) was added dropwise. The reaction mixture was heated at 90°C in a sealed tube for 48 h. After cooling, the precipitate obtained was filtered off and recrystallized from EtOH/CH_2Cl_2 to give **3** (1.29 g, 76%); mp 255-257°C. IR (KBr): 1690 (CO), 1490, 1190, 1110. ^{1}H NMR δ ($CDCl_3$): 0.96 (t, 3H, J= 7.0 Hz, CH_3), 3.64 (q, 2H, J= 7.0 Hz, OCH_3), 7.01-7.45 (m, 25H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3), 59.8 (OCH_2), 108.4, 126.9, 127.3, 127.5, 127.6, 128.0, 128.2, 130.6, 130.4, 131.0, 131.6, 132.1, 132.3, 132.7, 134.4, 135.1, 138.0, 149.4, 156.2, 162.4, 163.9. MS (FAB, *m/z*, %): 636 [$(MH)^+$, 100], 279 (80). *Anal.* Calcd for $C_{39}H_{30}N_3O_2PS$: C, 73.68; H, 4.76; N, 6.61. Found C, 73.65; H, 4.76; N, 6.57.

General procedure for the synthesis of carbodiimides (4a-d).

To a solution of **3** (0.15 g, 0.24 mmol) in dry THF (2.5 mL) an appropriate isocyanate (0.28 mmol) was added. After the mixture had been stirred at rt for 0.5-7 h (4-methoxyphenylisocyanate: reflux for 4 h) and the iminophosphorane (**3**) had disappeared (TLC monitored), the solvent was evaporated under reduced pressure, ether (5 mL) was added and then the resultant solution was stirred at rt for 0.5 h and the solid formed was filtered off and recrystallized from acetone.

Ethyl 3,4-diphenyl-5-phenyliminomethyleneaminothieno[2,3-*c*]pyridazine-6-carboxylate (**4a**) (62%); mp 169-171°C. IR (KBr): 2120 (NCN), 1710 (CO), 1440, 1245, 1180, 760, 700. ^{1}H NMR δ ($CDCl_3$): 1.41 (t, 3H, J=7.1 Hz, CH_3), 4.42 (q, 2H, J=7.1 Hz, OCH_2), 6.95-7.38 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3), 62.3 (CH_2), 124.6, 125.7, 127.6, 127.9, 128.2, 128.5, 129.2, 130.3, 130.4, 132.8, 133.1, 134.8, 135.2, 136.6, 156.2, 158.5, 161.7. MS (EI, *m/z*, %): 476 (M^+, 82), 475 (27), 447 (73), 328 (18), 299 (25), 272 (18), 227 (25), 77 (100). *Anal.* Calcd for $C_{28}H_{20}N_4O_2S$: C, 70.57; H, 4.23; N, 11.76. Found C, 70.31; H, 4.48; N, 11.95.

Ethyl 5-(4-chlorophenyliminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**4b**) (61%); mp 186-188°C. IR (KBr): 2180 (NCN), 1690 (CO), 1490, 1330, 1100, 830, 760, 700. ^{1}H NMR δ ($CDCl_3$): 1.42 (t, 3H, J=7.1 Hz, CH_3), 4.43 (q, 2H, J=7.1 Hz, OCH_2), 6.93 (d, 2H, J=8.3 Hz, C_6H_4), 7.20-7.38 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3), 62.3 (CH_2), 124.4, 125.8, 127.6, 127.8, 128.2, 128.5, 129.2, 130.3, 130.4, 124.4, 131.0, 132.7, 134.6, 135.3, 136.5, 156.2, 160.6, 161.7. MS (EI, *m/z*, %): 512 (M^++2, 38), 510 (M^+, 93), 481 (100), 328 (20), 299 (51), 227 (38), 110 (64), 77 (61). *Anal.* Calcd for $C_{28}H_{19}N_4O_2ClS$: C, 65.81; H, 3.75; N, 10.96. Found C, 66.05; H, 3.87; N, 10.68.

Ethyl 5-(4-methoxyphenyliminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**4c**) (67%); mp 133-135°C. IR (KBr): 2180 (NCN), 1715 (CO), 1500, 1250, 1030, 830, 760, 700. ^{1}H NMR

δ ($CDCl_3$): 1.41 (t, 3H, *J*=7.0 Hz, CH_3), 3.78 (s, 3H, OCH_3), 4.42 (q, 2H, *J*=7.0 Hz, OCH_2), 6.78, 6.94 (AA'BB' system, 4H, *J*=9.0 Hz, C_6H_4), 7.26-7.37 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_3), 55.5 (OCH_3), 62.2 (CH_2), 114.4, 125.7, 127.6, 127.8, 128.1, 128.5, 129.0, 130.4, 132.5, 136.8, 139.9, 147.5, 152.3, 156.2, 160.6, 161.7. MS (EI, *m/z*, %): 506 (M^+, 61), 477 (65), 328 (19), 299 (28), 149 (44), 135 (63), 77 (100). *Anal.* Calcd for $C_{29}H_{22}N_4O_3S$: C, 68.76; H, 4.38; N, 9.47. Found C, 68.42; H, 4.57; N, 9.56.

Ethyl 3,4-diphenyl-5-(*p*-tolyliminomethyleneamino)thieno[2,3-*c*]pyridazine-6-carboxylate (**4d**) (70%); mp 157-159°C. IR (KBr): 2180 (NCN), 1715 (CO), 1500, 1250, 1200, 820, 760, 700. ^1H NMR δ ($CDCl_3$): 1.41 (t, 3H, *J*=7.1 Hz, CH_3), 2.31 (s, 3H, $PhCH_3$), 4.42 (q, 2H, *J*=7.1 Hz, OCH_2), 6.87, 7.06 (AA'BB' system, 4H, *J*=8.5 Hz, C_6H_4), 7.08-7.38 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_3), 21.0 ($PhCH_3$), 62.2 (OCH_2), 124.4, 127.6, 127.9, 128.1, 128.5, 129.8, 130.3, 132.8, 133.6, 134.8, 135.5, 136.6, 152.1, 154.2, 160.7, 161.8. MS (EI, *m/z*, %): 490 (M^+, 100), 461 (98), 299 (35), 227 (24), 91 (77), 77 (55). *Anal.* Calcd for $C_{29}H_{22}N_4O_2S$: C, 71.00; H, 4.52; N, 11.42. Found C, 71.24; H, 4.59; N, 11.19.

General procedure for the synthesis of ethyl carboxylates (5a-v).

To a solution of **3** (0.15 g, 0.24 mmol) in dry THF (2.5 mL) an appropriate isocyanate (0.28 mmol) was added. After the mixture had been stirred at rt for 0.5-7 h (4-methoxyphenylisocyanate: reflux for 4 h) and the iminophosphorane (**3**) had disappeared (TLC monitored), the mixture was ice-cooled and then treated with an appropriate amine (0.28 mmol). The resultant solution was stirred at 0-4°C for 10 h, and then worked up in one of the following ways: (A) the solid formed was filtered off, washed with ether (5 mL) and recrystallized from acetone/CH_2Cl_2. (B) The solvent was evaporated under reduced pressure, ether (5 mL) was added and then the resultant solution was stirred at rt for 0.5 h and the solid formed was filtered off and recrystallized from acetone/CH_2Cl_2.

Ethyl 5-diethylaminophenylaminomethyleneamino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5a**) (64%); mp 241-243°C. IR (KBr): 3220 (NH), 1705 (CO), 1580, 1490, 1240, 1020. ^1H NMR δ ($CDCl_3$): 0.95 (t, 6H, *J*=7.0 Hz, $NCH_2C\underline{H}_3$), 1.32 (t, 3H, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 3.07 (br s, 4H, $NC\underline{H}_2CH_3$), 4.27 (q, 2H, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 5.31 (s, 1H, NH), 6.60-7.28 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 12.9 ($NCH_2\underline{C}H_3$), 14.3 ($OCH_2\underline{C}H_3$), 41.9 ($N\underline{C}H_2CH_3$), 60.9 ($O\underline{C}H_2CH_3$), 114.7, 118.9, 122.2, 127.2, 127.6, 128.6, 128.9, 130.4, 134.2, 135.1, 137.2, 140.5, 148.6, 150.8, 155.6, 162.1, 162.6. MS (EI, *m/z*, %): 549 (M^+, 16), 476 (100). *Anal.* Calcd for $C_{32}H_{31}N_5O_2S$: C, 69.92; H, 5.68; N, 12.74. Found C, 69.72; H, 5.60; N, 12.68.

Ethyl 3,4-diphenyl-5-phenylaminopiperidinomethyleneaminothieno[2,3-*c*]pyridazine-6-carboxylate (**5b**) (73%); mp 262-264°C. IR (KBr): 3320 (NH), 1710 (CO), 1600, 1230. ^1H NMR δ ($CDCl_3$): 1.30 (t, 3H, *J*=7.0 Hz, $OCH_2C\underline{H}_3$), 1.44-1.67 (m, 6H, CH_2), 2.86 (br s, 4H, CH_2NCH_2), 4.27 (q, 2H, *J*=7.0 Hz, $OC\underline{H}_2CH_3$), 5.26 (s, 1H, NH), 6.82-7.35 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_3), 24.3 ($NCH_2CH_2\underline{C}H_2$), 25.0 ($NCH_2\underline{C}H_2$), 47.4 ($NCH_2$), 61.2 ($OCH_2$), 118.3, 122.0, 127.4, 127.6, 128.8, 129.0, 129.2, 130.6, 134.4, 135.2, 136.9, 140.6, 141.0, 150.3, 155.8, 162.2, 162.6. MS (EI, *m/z*, %): 561 (M^+, 20), 488 (100), 447 (24), 187 (28), 77 (40). *Anal.* Calcd for $C_{33}H_{31}N_5O_2S$: C, 70.56; H, 5.56; N, 12.47. Found C, 70.41; H, 5.28; N, 12.65.

Ethyl 5-(4-methylpiperazinophenylaminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5c**) (53%); mp 232-234°C. IR (KBr): 3320 (NH), 1710 (CO), 1600, 1410, 1230. ^{1}H NMR δ(CDCl$_3$): 1.32 (t, 3H, *J*=7.0 Hz, OCH$_2$C<u>H</u>$_3$), 1.74-2.20 [m, 4H, C<u>H</u>$_2$N(CH$_3$)C<u>H</u>$_2$], 2.24 (s, 3H, NCH$_3$), 2.91 (br s, 4H, CH$_2$NCH$_2$), 4.28 (q, 2H, *J*=7.0 Hz, OC<u>H</u>$_2$CH$_3$), 5.70 (s, 1H, NH), 6.86-7.37 (m, 15H, C$_6$H$_5$). ^{13}C NMR δ(CDCl$_3$): 14.3 (OCH$_2$<u>C</u>H$_3$), 46.1 (NCH$_3$), 46.2, 54.3 (NCH$_2$), 61.4 (OCH$_2$), 118.7, 122.4, 127.6, 128.0, 129.0, 130.4, 134.4, 136.9, 140.3, 150.0, 155.8, 162.5, 162.7. MS (EI, *m/z*, %): 576 (M$^+$, 10), 494 (25). *Anal.* Calcd for C$_{33}$H$_{32}$N$_6$O$_2$S: C, 68.73; H, 5.93; N, 14.57. Found C, 68.48; H, 5.78; N, 14.50.

Ethyl 5-morpholinophenylaminomethyleneamino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5d**) (81%); mp 260-262°C. IR (KBr): 3320 (NH), 1710 (CO), 1620, 1600, 1230, 980. ^{1}H NMR δ(CDCl$_3$): 1.29 (t, 3H, *J*=7.0 Hz, OCH$_2$C<u>H</u>$_3$), 2.87 (br s, 4H, CH$_2$NCH$_2$), 3.28-3.53 (m, 4H, CH$_2$OCH$_2$), 4.26 (q, 2H, *J*=7.0 Hz, OC<u>H</u>$_2$CH$_3$), 5.86 (s, 1H, NH), 6.89-7.39 (m, 15H, C$_6$H$_5$). ^{13}C NMR δ(CDCl$_3$): 14.2 (CH$_3$), 46.8 (NCH$_2$), 61.3 (OCH$_2$), 66.1 (CO$_2$<u>C</u>H$_2$), 118.9, 122.6, 127.5, 127.6, 127.8, 129.0, 130.4, 135.0, 136.7, 140.2, 150.3, 155.4, 161.0, 162.5. MS (EI, *m/z*, %): 563 (M$^+$, 18), 517 (40), 490 (46). *Anal.* Calcd for C$_{32}$H$_{29}$N$_5$O$_3$S: C, 68.19; H, 5.18; N, 12.42. Found C, 67.99; H, 5.10; N, 12.44.

Ethyl 5-(4-nitrophenylaminopiperidinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5g**) (69%); mp 256-258°C. IR (KBr): 3320 (NH), 1710 (CO), 1600, 1340, 1110, 960. ^{1}H NMR δ (CDCl$_3$): 1.16 (t, 3H, *J*=7.0 Hz, OCH$_2$C<u>H</u>$_3$), 1.40-1.47 (m, 6H, CH$_2$), 2.90 (br s, 4H, CH$_2$NCH$_2$), 4.09-4.27 (m, 2H, OCH$_2$), 6.84 (s, 1H, NH), 7.03-7.35 (m, 12H, C$_6$H$_5$+C$_6$H$_4$), 8.05 (d, 2H, *J*= 8.8 Hz, C$_6$H$_4$). ^{13}C NMR δ(CDCl$_3$): 14.0 (CH$_3$), 24.2 (NCH$_2$CH$_2$<u>C</u>H$_2$), 24.9 (NCH$_2$<u>C</u>H$_2$), 47.6 (NCH$_2$), 61.2 (OCH$_2$), 115.6, 117.3, 124.9, 127.4, 127.8, 129.3, 130.0, 130.4, 134.3, 135.2, 136.4, 141.2, 147.3, 147.5, 149.1, 155.7, 161.5, 162.1. MS (EI, *m/z*, %): 606 (M$^+$, 16), 560 (11), 533 (29), 521 (61), 492 (70), 299 (27), 84 (100). *Anal.* Calcd for C$_{33}$H$_{30}$N$_6$O$_4$S: C, 65.33; H, 4.98; N, 13.85. Found C, 65.09; H, 4.85; N, 14.01.

Ethyl 5-(4-chlorophenylaminopiperidinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5i**) (75%); mp 255-257°C. IR (KBr): 3350 (NH), 1720 (CO), 1680, 1620, 1490, 1440, 1230. ^{1}H NMR δ(CDCl$_3$): 1.06-1.25 (m, 3H, CH$_2$), 1.27-1.44 (m, 6H, CH$_3$+CH$_2$), 2.60-2.90 (m, 4H, CH$_2$), 4.28 (q, 2H, *J*=7.0 Hz, OC<u>H</u>$_2$CH$_3$), 5.67 (s, 1H, NH), 6.81 (d, 2H, *J*= 8.8 Hz, C$_6$H$_4$), 7.10-7-48 (m, 12H, C$_6$H$_5$+C$_6$H$_4$). MS (FAB, *m/z*, %): 598 [(MH)$^+$+2, 36], 596 [(MH)$^+$, 76], 550 (77), 522 (42), 221 (100). *Anal.* Calcd for C$_{33}$H$_{30}$N$_5$O$_2$ClS: C, 66.49; H, 5.07; N, 11.75. Found C, 66.40; H, 5.01; N, 11.70.

Ethyl 5-(4-methoxyphenylaminopiperidinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5o**) (70%); mp 220-222°C. IR (KBr): 3330 (NH), 1710 (CO), 1610, 1440, 1230. ^{1}H NMR δ(CDCl$_3$): 1.23-1.46 (m, 9H), 2.84 (br s, 4H, CH$_2$NCH$_2$), 3.74 (s, 3H, OCH$_3$), 4.29 (q, 2H, *J*=7.0 Hz, OCH$_2$), 5.46 (s, 1H, NH), 6.71, 6.82 (AA'BB' system, 4H, *J*= 8.8 Hz, C$_6$H$_4$), 7.00-7.31 (m, 10H, C$_6$H$_5$). ^{13}C NMR δ(CDCl$_3$): 14.3 (OCH$_2$<u>C</u>H$_3$), 24.4 (NCH$_2$CH$_2$<u>C</u>H$_2$), 25.1 (NCH$_2$<u>C</u>H$_2$), 47.4 (NCH$_2$), 55.5 (OCH$_3$), 61.2 (OCH$_3$), 114.0, 121.0, 127.3, 127.6, 130.4, 133.8, 134.3, 135.2, 137.0, 144.2, 147.1, 151.3, 155.2, 155.7, 162.5. MS (EI, *m/z*, %): 591 (M$^+$, 12), 545 (29), 518 (55). *Anal.* Calcd for C$_{34}$H$_{33}$N$_5$O$_3$S: C, 69.01; H, 5.62; N, 11.83. Found C, 68.78; H, 5.86; N, 11.92.

Ethyl 3,4-diphenyl-5-[piperidino-(*p*-tolylamino)methyleneamino]thieno[2,3-*c*]pyridazine-6-carboxylate (**5s**) (69%); mp 235-237°C. IR (KBr): 3325 (NH), 1710 (CO), 1605, 1440, 1230. ^{1}H NMR δ ($CDCl_3$): 1.33 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 1.23-1.56 (m, 6H, CH_2), 2,24 (s, 3H, $PhCH_3$), 2.83 (br s, 4H, CH_2NCH_2), 4.29 (q, 2H, *J*=7.0 Hz, OCH_2), 5.48 (s, 1H, NH), 6.74, 6.97 (AA'BB' system, 4H, *J*= 8.3 Hz, C_6H_4), 7.13-7.63 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.3 ($OCH_2\underline{C}H_3$), 20.6 ($PhCH_3$), 24.4 ($NCH_2CH_2\underline{C}H_2$), 25.1 ($NCH_2\underline{C}H_2$), 47.4 ($NCH_2$), 61.3 ($OCH_2$), 118.6, 127.4, 127.6, 129.4, 130.4, 131.7, 134.4, 135.2, 137.0, 138.0, 148.2, 150.5, 155.8, 162.6. MS (EI, *m/z*, %): 575 (M^+, 17). *Anal.* Calcd for $C_{34}H_{33}N_5O_2S$: C, 70.93; H, 5.78; N, 12.16. Found C, 70.99; H, 5.72; N, 12.11.

General procedure for the synthesis of ethyl carboxylates (5w-d' and 7c) and pyrimido-[4',5':4,5]thieno[2,3-*c*]pyridazines (6a-v, 8a-c and 9a).

To a solution of **3** (0.15 g, 0.24 mmol) in dry THF (2.5 mL) an appropriate isocyanate (0.28 mmol) was added. After the mixture had been stirred at rt for 0.5-7 h (4-methoxyphenyl isocyanate: reflux for 4 h), the iminophosphorane (**3**) had disappeared (TLC monitored) and it was therefore treated with an appropriate amine (0.28 mmol). The resultant solution was stirred at rt for 10 h, and then worked up in one of the following ways: (A) the solid formed was filtered off, washed with ether (5 mL) and recrystallized from acetone/CH_2Cl_2. (B) The solvent was evaporated under reduced pressure, ether (5 mL) was added and then the resultant solution was stirred at rt for 0.5 h and the solid formed was filtered off and recrystallized from acetone/CH_2Cl_2.

Ethyl 3,4-diphenyl-5-phenylaminothiomorpholinomethyleneaminothieno[2,3-*c*]pyridazine-6-carboxylate (**5w**) (81%); mp >300°C. IR (KBr): 3340 (NH), 1720 (CO), 1600, 1500, 1240. ^{1}H NMR δ ($CDCl_3$): 1.27 (t, 3H, *J*= 7.0 Hz, CH_3), 2.24-2.42 (m, 4H, CH_2SCH_2), 3.14-3.38 (m, 4H, CH_2NCH_2), 4.23 (q, 2H, *J*=7.0 Hz, OCH_2), 5.86 (s, 1H, NH), 6.86-7.40 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.2 (CH_3), 26.4 (SCH_2), 49.0 (NCH_2), 61.2 (OCH_2), 116.4, 119.0, 122.5, 127.6, 127.8, 127.9, 129.0, 130.4, 134.4, 135.0, 136.7, 140.2, 147.8, 150.3, 155.7, 162.0, 162.3. MS (FAB, *m/z*, %): 580 [$(MH)^+$, 86], 534 (100), 460 (25), 371 (22). *Anal.* Calcd for $C_{32}H_{29}N_5O_2S_2$: C, 66.30; H, 5.04; N, 12.08. Found C, 66.25; H, 4.92; N, 12.10.

Ethyl 5-(4-methylpiperazino-4-nitrophenylaminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5x**) (74%); mp 265-267°C. IR (KBr): 3220 (NH), 1720 (CO), 1600, 1340, 980. ^{1}H NMR δ ($CDCl_3$): 1.24 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 2.15-2.38 [m, 7H, $CH_2N(CH_3)CH_2$], 2.84-3.09 (m, 4H, CH_2NCH_2), 4.18 (q, 2H, *J*=7.0 Hz, OCH_2), 6.60 (s, 1H, NH), 7.10-8.04 (m, 10H, C_6H_5), 7.00, 8.08 (AA'BB' system, 4H, *J*= 9.1 Hz, C_6H_4). MS (FAB, *m/z*, %): 622 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{33}H_{31}N_7O_4S$: C, 63.75; H, 5.03; N, 15.77. Found C, 63.70; H, 5.20; N, 15.78.

Ethyl 5-(morpholino-4-nitrophenylaminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5y**) (81%); mp 284-286°C. IR (KBr): 3320 (NH), 1720 (CO), 1600, 1500, 1340, 1240, 1120. ^{1}H NMR δ ($CDCl_3$): 1.16 (t, 3H, *J*= 7.0 Hz, CH_3), 2.80-2.98 (m, 4H, CH_2NCH_2), 3.52 (br s, 4H, CH_2OCH_2), 4.10-4.30 (m, 2H, OCH_2), 6.96 (s, 1H, NH), 7.08-8.04 (m, 12H, C_6H_5+C_6H_4), 8.08 (d, 2H, *J*= 9.1 Hz, C_6H_4). MS (FAB, *m/z*, %): 609 [$(MH)^+$, 100), 535 (32), 522 (31), 494 (21), 181 (51). *Anal.* Calcd for $C_{32}H_{28}N_6O_5S$: C, 63.15; H, 4.64; N, 13.81. Found C, 63.10; H, 4.69; N, 13.72.

Ethyl 5-(4-nitrophenylaminothiomorpholinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5z**) (69%); mp 266-268°C. IR (KBr): 3320 (NH), 1710 (CO), 1590, 1340, 1240. ^{1}H NMR δ ($CDCl_3$): 1.20 (t, 3H, *J*= 7.0 Hz, CH_3), 2.29-2.49 (m, 4H, CH_2SCH_2), 3.19-3.40 (m, 4H, CH_2NCH_2), 4.17 (q, 2H, *J*= 7.0 Hz, OCH_2), 6.70 (s, 1H, NH), 6.99, 8.07 (AA'BB' system, 4H, *J*= 9.2 Hz, C_6H_4), 7.02-7.45 (m, 10H, C_6H_5). MS (FAB, *m/z*, %): 625 [$(MH)^+$, 17], 551 (3), 288 (53), 181 (100). *Anal.* Calcd for $C_{32}H_{28}N_6O_4S_2$: C, 61.52; H, 4.52; N, 13.45. Found C, 61.42; H, 4.45; N, 13.40.

Ethyl 5-(4-nitrophenylaminopyrrolidinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5a'**) (77%); mp 258-260°C. IR (KBr): 3310 (NH), 1720 (CO), 1600, 1500, 1330. ^{1}H NMR δ ($CDCl_3$): 1.13 (t, 3H, *J*= 7.0 Hz, CH_3), 1.65-1.87 (m, 4H, CH_2CH_2), 2.89-3.07 (m, 4H, CH_2NCH_2), 4.08 (q, 2H, *J*= 7.0 Hz, OCH_2), 6.83 (s, 1H, NH), 6.99, 8.05 (AA'BB' system, 4H, *J*= 9.1 Hz, C_6H_4), 7.08-7.31 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 13.9 (CH_3), 25.1 (CH_2CH_2), 47.8 (CH_2NCH_2), 60.9 (OCH_2), 115.2, 118.3, 124.7, 127.3, 127.6, 127.9, 129.5, 129.9, 130.6, 134.3, 135.2, 136.1, 141.1, 147.1, 147.6, 148.1, 155.2, 161.3, 161.9. MS (FAB, *m/z*, %): 593 [$(MH)^+$, 39], 316 (60), 288 (100). *Anal.* Calcd for $C_{32}H_{28}N_6O_4S$: C, 64.85; H, 4.76; N, 14.18. Found C, 64.70; H, 4.79; N, 14.10.

Ethyl 5-(4-methoxyphenylaminomorpholinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5b'**) (60%); mp 242-244°C. IR (KBr): 3340 (NH), 1720 (CO), 1620, 1520, 1240, 990. ^{1}H NMR δ ($CDCl_3$): 1.31 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 2.83 (br s, 4H, CH_2NCH_2), 3.34-3.59 (m, 4H, CH_2OCH_2), 3.75 (s, 3H, OCH_3), 4.27 (q, 2H, *J*= 7.0 Hz, OCH_2), 5.72 (s, 1H, NH), 6.73, 6.92 (AA'BB' system, 4H, *J*= 9.0 Hz, C_6H_4), 6.96-7.42 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 13.4 (CH_3), 46.0 (NCH_2), 54.7 (OCH_3), 60.4 (OCH_2), 65.3 (CH_2OCH_2), 113.3, 116.0, 121.0, 126.0, 126.7, 127.0, 128.5, 129.6, 132.7, 133.7, 134.3, 135.9, 147.1, 150.6, 154.8, 161.2, 161.4. MS (FAB, *m/z*, %): 594 [$(MH)^+$, 89], 219 (100). *Anal.* Calcd for $C_{33}H_{31}N_5O_4S$: C, 66.76; H, 5.26; N, 11.80. Found C, 66.54; H, 5.28; N, 11.70 .

Ethyl 5-(4-methoxyphenylaminothiomorpholinomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5c'**) (67%); mp 236-238°C. IR (KBr): 3340 (NH), 1715 (CO), 1620, 1520, 1240. ^{1}H NMR δ ($CDCl_3$): 1.29 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 2.20-2.47 (m, 4H, CH_2SCH_2), 3.10-3.37 (m, 4H, CH_2NCH_2), 3.74 (s, 3H, OCH_3), 4.25 (q, 2H, *J*= 7.0 Hz, OCH_2), 5.65 (s, 1H, NH), 6.72, 6.85 (AA'BB' system, 4H, *J*= 8.9 Hz, C_6H_4), 7.12-7.43 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_3), 26.4 (SCH_2), 49.0 (NCH_2), 55.5 (OCH_3), 61.2 (OCH_2), 144.2, 116.0, 121.8, 127.4, 127.6, 127.8, 127.9, 130.4, 133.3, 134.3, 135.0, 136.8, 148.0, 151.4, 155.6, 162.1, 162.2. MS (EI, *m/z*, %): 609 (M^+, 10), 536 (19), 477 (22), 328 (13), 300 (17), 272 (18), 103 (61), 57 (100). *Anal.* Calcd for $C_{33}H_{31}N_5O_3S$: C, 65.00; H, 5.12; N, 11.48. Found C, 65.17; H, 5.27; N, 11.31.

Ethyl 5-(pyrrolidino-*p*-tolylaminomethyleneamino)-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**5d'**) (73%); mp 236-238°C. IR (KBr): 3360 (NH), 1720 (CO), 1600, 1450, 1250, 700. ^{1}H NMR δ ($CDCl_3$): 1.30 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 1.65-1.86 (m, 4H, CH_2CH_2), 2.23 (s, 3H, $PhCH_3$), 2.92 (br s, 4H, CH_2NCH_2), 4.26 (q, 2H, *J*= 7.0 Hz, OCH_2), 5.45 (s, 1H, NH), 6.73, 6.94 (AA'BB' system, 4H, *J*= 8.2 Hz, C_6H_4), 7.14-7.33 (m, 10H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 14.2 ($OCH_2\underline{C}H_3$),

20.6 ($PhCH_3$), 25.1 ($NCH_2\underline{C}H_2$), 47.5 (NCH_2), 61.0 (OCH_2), 120.9, 126.9, 127.4, 127.6, 127.7, 129.2, 130.5, 132.5, 134.4, 135.0, 135.3, 148.6, 149.0, 155.4, 162.0, 162.6. MS (EI, *m/z*, %): 561 (M^+, 12), 488 (29), 328 (8), 300 (9), 187 (30), 57 (100). *Anal.* Calcd for $C_{33}H_{31}N_5O_2S$: C, 70.56; H, 5.56; N, 12.47. Found C, 70.43; H, 5.42; N, 12.71.

Ethyl 5-*i*-propylaminophenylaminomethyleneamino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxylate (**7c**) (71%); mp 210-212°C. IR (KBr): 3405 (NH), 3300 (NH), 1700 (CO), 1640, 1500. ^1H NMR δ ($CDCl_3$): 0.95 [br s, 2H, $CH(C\underline{H}_3)_2$], 1.32 (t, 3H, *J*= 7.0 Hz, $OCH_2C\underline{H}_3$), 3.13-3.40 (m, 1H, CH), 3.84 (d, 1H, *J*= 7.7 Hz, $N\underline{H}CH$), 4.32 (q, 2H, *J*= 7.0 Hz, OCH_2), 5.92 (s, 1H, NHPh), 7.00-7.61 (m, 15H, C_6H_5). MS (FAB, *m/z*, %): 536 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{31}H_{29}N_5O_2S$: C, 69.51; H, 5.46; N, 13.07. Found C, 69.29; H, 5.62; N, 13.26.

6-Diethylamino-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6a**) (71%); mp > 300°C. IR (KBr): 1680 (CO), 1540, 1340, 1280, 725. ^1H NMR δ ($CDCl_3$): 0.50 (t, 6H, *J*= 7.0 Hz, CH_3), 2.74 (q, 4H, *J*= 7.0 Hz, NCH_2), 7.26-7.52 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 12.2 (CH_3), 45.17 (NCH_2), 119.3, 127.9, 127.8, 127.9, 128.0, 128.5, 128.6, 128.7, 129.2, 130.3, 130.4, 133.6, 135.7, 136.7, 137.4, 149.6, 156.3, 156.4, 159.9, 164.6. MS (EI, *m/z*, %): 503 (M^+, 41), 474 (100), 398 (19), 384 (10), 355 (6), 328 (10), 300 (6), 272 (7), 148 (18), 77 (35). *Anal.* Calcd for $C_{30}H_{25}N_5OS$: C, 71.55; H, 5.00; N, 13.91. Found C, 71.39; H, 5.12; N, 14.05.

8-Oxo-3,4,7-triphenyl-6-piperidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6b**) (60%); mp 283-285°C. IR (KBr): 1680 (CO), 1540, 1250. ^1H NMR δ ($CDCl_3$): 0.95-1.10 (m, 4H, CH_2), 1.21-1.52 (m, 2H, CH_2), 2.79-2.98 (m, 4H, CH_2NCH_2), 7.26-7.51 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 23.8 ($NCH_2CH_2\underline{C}H_2$), 24.7 ($NCH_2\underline{C}H_2$), 49.5 ($NCH_2$), 119.7, 127.5, 127.7, 127.9, 128.0, 128.2, 128.9, 129.8, 130.3, 130.4, 133.4, 135.6, 136.6, 137.1, 149.4, 156.2, 156.4, 159.5, 164.5. MS (FAB, *m/z*, %): 531 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{31}H_{25}N_5OS$: C, 72.21; H, 4.89; N, 13.58. Found C, 72.20; H, 4.72; N, 13.68.

6-(4-Methylpiperazino)-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6c**) (60%); mp 294-296°C. IR (KBr): 1680 (CO), 1520, 1300, 1140. ^1H NMR δ ($CDCl_3$): 2.00-2.18 [m, 4H, $C\underline{H}_2N(CH_3)C\underline{H}_2$], 2.15 (s, 3H, NCH_3), 2.67-2.89 (m, 4H, CH_2NCH_2), 7.25-7.50 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 45.6 (NCH_3), 48.1, 53.7 (NCH_2), 120.4, 127.6, 127.8, 128.1, 128.7, 129.2, 130.3, 130.4, 133.6, 135.6, 136.5, 149.0, 155.5, 156.3, 159.0, 163.0. MS (EI, *m/z*, %): 530 (M^+, 23), 460 (31), 83 (100), 70 (19). *Anal.* Calcd for $C_{31}H_{26}N_6OS$: C, 70.17; H, 4.94; N, 15.84. Found C, 70.10; H, 4.85; N, 15.98.

6-Morpholino-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3*c*]pyridazine (**6d**) (82%); mp > 300°C. IR (KBr): 1680 (CO), 1530, 1110. ^1H NMR δ ($CDCl_3$): 2.71 (br s, 4H, CH_2NCH_2), 3.24 (br s, 4H, CH_2OCH_2), 7.32-7.51 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 48.7 (NCH_2), 65.7 (OCH_2), 120.5, 127.6, 127.8, 128.1, 128.8, 129.2, 130.3, 130.4, 133.6, 135.6, 136.3, 136.4, 149.1, 155.6, 156.4, 159.2, 164.5. MS (EI, *m/z*, %): 517 (M^+, 100), 472 (64), 384 (44), 355 (8), 328 (26), 300 (16), 272 (13), 162 (39), 77 (94). *Anal.* Calcd for $C_{30}H_{23}N_5O_2S$: C, 69.61; H, 4.48; N, 13.53. Found C, 69.71; H, 4.44; N, 13.64.

8-Oxo-3,4,7-triphenyl-6-pyrrolidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6e**) (80%); mp >300°C. IR (KBr): 1680 (CO), 1520, 1350. ^{1}H NMR δ(CDCl$_3$): 1.46-1.75 (m, 4H, NCH$_2$CH$_2$), 2.46-2.67 (m, 4H, NCH$_2$), 7.27-7.53 (m, 15H, C$_6$H$_5$). ^{13}C NMR δ(CDCl$_3$): 25.1 (NCH$_2$CH$_2$), 50.0 (NCH$_2$), 116.3, 127.5, 127.7, 127.8, 128.0, 128.7, 129.1, 129.2, 130.4, 130.5, 133.7, 135.7, 136.8, 150.7, 153.5, 156.1, 159.7, 164.9. MS (EI, *m/z*, %): 501 (M$^+$, 42), 472 (25), 370 (21), 328 (14), 300 (11), 272 (11), 146 (61), 77 (100). *Anal.* Calcd for C$_{30}$H$_{23}$N$_5$OS: C, 71.83; H, 4.62; N, 13.96. Found C, 71.90; H, 4.70; N, 13.88.

6-Diethylamino-7-(4-nitrophenyl)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6f**) (84%); mp >300°C. IR (KBr): 1680 (CO), 1520, 1340. ^{1}H NMR δ(CDCl$_3$): 0.58 (t, 6H, *J*= 7.0 Hz, CH$_3$), 2.75 (q, 4H, *J*= 7.0 Hz, NCH$_2$), 7.23-7.37 (m, 10H, C$_6$H$_5$), 7.54, 8.32 (AA'BB' system, 4H, *J* = 8.9 Hz, C$_6$H$_4$). ^{13}C NMR δ(CDCl$_3$): 12.2 (CH$_3$), 45.2 (NCH$_2$), 119.5, 124.4, 127.4, 127.7, 127.8, 128.1, 128.2, 130.0, 130.3, 130.5, 133.5, 135.9, 136.5, 142.9, 147.1, 149.8, 155.5, 156.8, 159.0, 164.3. MS (EI, *m/z*, %): 548 (M$^+$, 37), 519 (100), 398 (27), 384 (9), 355 (10), 328 (18), 300 (20), 272 (34), 118 (71), 77 (77). *Anal.* Calcd for C$_{30}$H$_{24}$N$_6$O$_3$S: C, 65.68; H, 4.41; N, 15.32. Found C, 65.79; H, 4.50; N, 15.35

7-(4-Nitrophenyl)-8-oxo-3,4-diphenyl-6-piperidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6g**) (68%); mp >300°C. IR (KBr): 1690 (CO), 1525, 1340, 1250. ^{1}H NMR δ(CDCl$_3$): 1.02-1.27 (m, 4H, CH$_2$), 1.25-1.49 (m, 2H, CH$_2$), 2.59-2.87 (m, 4H, CH$_2$NCH$_2$), 7.26-7.41 (m, 10H, C$_6$H$_5$), 7.59, 8.34 (AA'BB' system, 4H, *J*= 8.9 Hz, C$_6$H$_4$). ^{13}C NMR δ(CDCl$_3$): 23.7 (NCH$_2$CH$_2$CH$_2$), 24.7 (NCH$_2$CH$_2$), 49.8 (NCH$_2$), 119.0, 124.2, 127.6, 127.8, 127.9, 128.8, 129.4, 130.3, 130.4, 133.4, 135.8, 136.5, 142.7, 146.9, 149.7, 155.7, 156.5, 158.8, 164.4. MS (EI, *m/z*, %): 560 (M$^+$, 53), 531 (19), 410 (14), 384 (13), 355 (11), 328 (28), 300 (28), 272 (29), 205 (100), 130 (35), 77 (57). *Anal.* Calcd for C$_{31}$H$_{24}$N$_6$O$_3$S: C, 66.41; H, 4.31; N, 14.99. Found C, 66.60; H, 4.26; N, 15.02.

7-(4-Chlorophenyl)-6-diethylamino-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6h**) (67%); mp >300°C. IR (KBr): 1680 (CO), 1540, 1100. ^{1}H NMR δ(CDCl$_3$): 0.55 (t, 6H, *J*= 7.0 Hz, CH$_3$), 2.74 (q, 4H, *J*= 7.0 Hz, NCH$_2$), 7.23-7.48 (m, 14H, C$_6$H$_5$+C$_6$H$_4$). ^{13}C NMR δ (CDCl$_3$): 12.2 (CH$_3$), 45,1 (NCH$_2$), 119.3, 127.6, 127.8, 128.9, 129.0, 129.4, 129.9, 130.2, 130.4, 133.6, 134.4, 135.7, 136.6, 149.6, 151.6, 156.0, 156.5, 159.6, 164.5. MS (EI, *m/z*, %): 539 (M$^+$+2, 19), 537 (M$^+$, 45), 508 (32), 398 (24), 384 (15), 355 (6), 328 (11), 300 (7), 272 (10), 111 (25). *Anal.* Calcd for C$_{30}$H$_{24}$N$_5$OClS: C, 66.97; H, 4.50; N, 13.02. Found C, 66.85; H, 4.51; N, 13.10.

7-(4-Chlorophenyl)-8-oxo-3,4-diphenyl-6-piperidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6i**) (85%); mp >300°C. IR (KBr): 1680 (CO), 1550, 1250, 1090. ^{1}H NMR δ(CDCl$_3$): 1.01-1.29 (m, 4H, CH$_2$), 1.24-1.57 (m, 2H, CH$_2$), 2.60-2.86 (m, 4H, CH$_2$NCH$_2$), 7.27-7.46 (m, 14H, C$_6$H$_5$+C$_6$H$_4$). ^{13}C NMR δ (CDCl$_3$): 23.8 (NCH$_2$CH$_2$CH$_2$), 24.8 (NCH$_2$CH$_2$), 45.7 (NCH$_2$), 119.5, 127.6, 127.7, 127.8, 128.0, 129.1, 129.5, 130.3, 130.4, 133.4, 134.1, 135.5, 135.7, 136.5, 149.5, 156.2, 156.3, 159.2, 164.4. MS (EI, *m/z*, %): 551 (M$^+$+2, 11), 549 (M$^+$, 27), 520 (12), 384 (10), 355 (5), 328 (12), 300 (12), 272 (13), 194 (100), 111 (29). *Anal.* Calcd for C$_{31}$H$_{24}$N$_5$OClS: C, 67.69; H, 4.40; N, 12.73. Found C, 67.47; H, 4.35; N, 12.79.

7-(4-Chlorophenyl)-6-(4-methylpiperazino)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno-[2,3-*c*]pyridazine (**6j**) (85%); mp >300°C. IR (KBr): 1680 (CO), 1540, 1300, 1000. ^{1}H NMR δ ($CDCl_3$): 1.89-2.18 [m, 4H, $C\underline{H}_2N(CH_3)C\underline{H}_2$], 2.14 (s, 3H, NCH_3), 2.64-2.91 (m, 4H, CH_2NCH_2), 7.24-7.58 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 45.7 (NCH_3), 48.3, 53.8 (NCH_2), 120.2, 127.6, 127.7, 128.1, 129.3, 129.4, 130.2, 130.4, 133.4, 134.5, 134.9, 135.6, 136.4, 149.2, 155.6, 156.4, 159.0, 164.3. MS (FAB, *m/z*, %): 565 [$(MH)^+$, 48]. *Anal.* Calcd for $C_{31}H_{25}N_6OClS$: C, 65.89; H, 4.46; N, 14.87. Found C, 65.72; H, 4.58; N, 14.72.

7-(4-Chlorophenyl)-6-morpholino-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6k**) (88%); mp >300°C. IR (KBr): 1680 (CO), 1530, 1250, 1090. ^{1}H NMR δ ($CDCl_3$): 2.63-2.87 (m, 4H, CH_2NCH_2), 3.18-3.41 (m, 4H, CH_2OCH_2), 7.25-7.50 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 48.7 (CH_2NCH_2), 65.7 (CH_2OCH_2), 120.4, 127.7, 127.8, 128.2, 129.4, 130.2, 130.4, 133.6, 134.7, 135.6, 136.4, 149.1, 155.4, 156.5, 158.9, 164.3. MS (EI, *m/z*, %): 553 (M^++2, 39), 551 (M^+, 90), 506 (70), 426 (45), 384 (85), 355 (17), 328 (40), 300 (29), 272 (27), 196 (51), 111 (100), 77 (60). *Anal.* Calcd for $C_{31}H_{22}N_5O_2ClS$: C, 65.27; H, 4.02; N, 12.69. Found C, 65.39; H, 4.10; N, 12.60.

7-(4-Chlorophenyl)-8-oxo-3,4-diphenyl-6-thiomorpholino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6l**) (71%); mp >300°C. IR (KBr): 1680 (CO), 1540, 1250, 1010. ^{1}H NMR δ ($CDCl_3$): 2.04-2.31 (m, 4H, CH_2SCH_2), 3.04-3.34 (m, 4H, CH_2NCH_2), 7.27-7.51 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 26.2 (SCH_2), 51.2 (NCH_2), 120.8, 127.4, 127.7, 127.9, 128.1, 128.2, 129.5, 123.3, 123.4, 133.6, 134.7, 135.1, 135.6, 136.4, 149.0, 155.8, 156.5, 159.1, 164.4. MS (EI, *m/z*, %): 569 (M^++2, 17), 567 (M^+, 37), 494 (100), 384 (39), 355 (8), 328 (6), 300 (6), 272 (13), 111 (23). *Anal.* Calcd for $C_{30}H_{22}N_5OClS_2$: C, 63.43; H, 3.90; N, 12.33. Found C, 63.58; H, 3.79; N, 12.56.

7-(4-Chlorophenyl)-8-oxo-3,4-diphenyl-6-pyrrolidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6m**) (83%); mp 284-286°C. IR (KBr): 1670 (CO), 1520, 1350, 1090. ^{1}H NMR δ ($CDCl_3$): 1.50-1.69 (m, 4H, $NCH_2C\underline{H}_2$), 2.51-2.78 (m, 4H, NCH_2), 7.26-7.45 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 25.1 ($NCH_2\underline{C}H_2$), 50.2 (NCH_2), 116.1, 127.5, 127.7, 128.0, 129.4, 130.4, 133.5, 134.6, 135.2, 135.8, 136.6, 150.7, 153.3, 156.2, 159.4, 164.8. MS (EI, *m/z*, %): 537 (M^++2, 35), 353 (M^+, 81), 506 (43), 398 (10), 370 (56), 353 (11), 328 (34), 300 (27), 272 (27), 180 (100), 111 (98), 70 (75). *Anal.* Calcd for $C_{30}H_{22}N_5OClS$: C, 67.22; H, 4.14; N, 13.06; Found C, 67.18: H, 4.38; N, 13.24.

6-Diethylamino-7-(4-methoxyphenyl)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6n**) (69%); mp > 300°C. IR (KBr): 1670 (CO), 1500, 1540, 1240. ^{1}H NMR δ ($CDCl_3$): 0.54 (t, 6H, *J*= 7.0 Hz, CH_3), 2.75 (q, 4H, *J*= 7.0 Hz, NCH_2), 3.84 (s, 3H, OCH_3), 7.06 (d, 2H, *J* = 8.9 Hz, C_6H_4), 7.18-7.38 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 12.3 (CH_3), 45.1 (NCH_2), 55.4 (OCH_3), 119.2, 114.3, 127.5, 127.7, 127.8, 127.9, 129.4, 129.8, 130.2, 130.4, 133.6, 135.6, 136.7, 149.5, 156.3, 156.5, 159.2, 160.1, 164.6. MS (EI, *m/z*, %): 533 (M^+, 19), 504 (19), 372 (12), 355 (3), 328 (2), 300 (3), 272 (5), 135 (100), 77 (17). *Anal.* Calcd for $C_{31}H_{27}N_5O_2S$: C, 69.77; H, 5.10; N, 13.12; Found C, 69.70; H, 5.06; N, 13.01.

7-(4-Methoxyphenyl)-8-oxo-3,4-diphenyl-6-piperidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6o**) (66%); mp > 300°C. IR (KBr): 1670 (CO), 1600, 1540, 1510, 1250, 1020. ^{1}H NMR δ ($CDCl_3$): 1.01-1.22 (m, 4H, CH_2), 1.32-1.49 (m, 2H, CH_2), 2.60-2.78 (m, 4H, CH_2NCH_2), 3.84 (s, 3H, OCH_3), 6.97 (d, 2H, *J*= 8.9 Hz, C_6H_4), 7.22-7.41 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 23.9 ($NCH_2CH_2\underline{C}H_2$), 24.8 ($NCH_2\underline{C}H_2$), 49.6 ($NCH_2$), 55.5 ($OCH_3$), 119.7, 114.2, 127.6, 127.8, 128.0, 129.1, 129.6, 130.3, 130.4, 133.5, 135.7, 136.7, 149.4, 156.2, 156.8, 159.1, 159.9, 164.6. MS (EI, *m/z*, %): 545 (M^+, 17), 516 (8), 384 (5), 272 (5), 190 (100). *Anal.* Calcd for $C_{32}H_{27}N_5O_2S$: C, 70.44; H, 4.99; N, 12.83. Found C, 70.28; H, 5.21; N, 12.69.

7-(4-Methoxyphenyl)-6-(4-methylpiperazino)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno-[2,3-*c*]pyridazine (**6p**) (75%); mp 292-294°C. (KBr): 1680 (CO), 1530, 1300, 1250, 760, 700. ^{1}H NMR δ ($CDCl_3$): 1.89-2.09 [m, 4H, $C\underline{H}_2N(CH_3)C\underline{H}_2$], 2.13 (s, 3H, NCH_3), 2.65-2.91 (m, 4H, CH_2NCH_2), 3.84 (s, 3H, OCH_3), 6.98 (d, 2H, *J*=8.9 Hz, C_6H_4), 7.21-7.41 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 45.7 (NCH_3), 48.2, 53.9 (NCH_2), 55.4 (OCH_3), 120.3, 114.3, 127.6, 127.7, 128.0, 128.9, 129.0, 130.3, 130.4, 133.5, 135.6, 136.5, 149.1, 156.1, 156.2, 159.2, 159.5, 164.5. MS (FAB, *m/z*, %): 561 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{32}H_{29}N_6O_2S$: C, 68.43; H, 5.20; N, 14.96. Found C, 68.59; H, 5.35; N, 15.12.

7-(4-Methoxyphenyl)-8-oxo-3,4-diphenyl-6-pyrrolidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6q**) (88%); mp >300°C. IR (KBr): 1680 (CO), 1520, 1250. ^{1}H NMR δ ($CDCl_3$): 1.48-1.61 (m, 4H, $NCH_2C\underline{H}_2$), 2.51-2.68 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 6.97 (d, 2H, *J*= 8.8 Hz, C_6H_4), 7.19-7.41 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 25.1 ($NCH_2\underline{C}H_2$), 50.1 (NCH_2), 55.5 (OCH_3), 116.2, 114.3, 127.5, 127.7, 128.0, 129.2, 130.1, 130.4, 135.7, 135.7, 136.7, 150.6, 153.7, 156.1, 159.4. MS (FAB, *m/z*, %): 532 [$(MH)^+$, 39]. *Anal.* Calcd for $C_{31}H_{25}N_5O_2S$: C, 70.04; H, 4.74; N, 13.17. Found C, 70.08; H, 4.78; N, 13.18.

6-Diethylamino-8-oxo-3,4-diphenyl-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6r**) (70%); mp 294-296°C. IR (KBr): 1680 (CO), 1540, 1270. ^{1}H NMR δ ($CDCl_3$): 0.52 (t, 6H, *J*= 6.9 Hz, CH_3), 2.39 (s, 3H, $PhCH_3$), 2.75 (q, 4H, *J*= 6.9 Hz, NCH_2), 7.14-7.37 (m, 14H, C_6H_5 +C_6H_4). ^{13}C NMR δ ($CDCl_3$): 12.3 (CH_3), 21.2 (CH_3), 45.2 (NCH_2), 119.3, 127.6, 127.8, 127.9, 128.0, 128.2, 129.1, 129.8, 130.3, 130.4, 130.7, 133.7, 134.7, 135.7, 136.8, 138.5, 149.6, 156.4, 160.0, 164.7. MS (EI, *m/z*, %): 517 (M^+, 50), 488 (100), 398 (17), 384 (16), 355 (6), 328 (12), 300 (13), 272 (10), 162 (25), 119 (53). *Anal.* Calcd for $C_{31}H_{27}N_5OS$: C, 71.93; H, 5.26; N, 13.53. Found C, 72.09; H, 5.36; N, 13.39.

8-Oxo-3,4-diphenyl-6-piperidino-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6s**) (72%); mp > 300°C. IR (KBr): 1680 (CO), 1530, 1250. ^{1}H NMR δ ($CDCl_3$): 1.00-1.27 (m, 4H, CH_2), 1.22-1.56 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.60-2.85 (m, 4H, CH_2NCH_2), 7.18-7.40 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 21.1 (CH_3), 23.8 ($NCH_2CH_2\underline{C}H_2$), 24.8 ($NCH_2\underline{C}H_2$), 49.5 ($NCH_2$), 119.7, 127.5, 127.7, 128.0, 129.6, 130.3, 130.4, 133.5, 134.4, 135.6, 136.5, 138.3, 149.4, 156.2, 156.6, 159.6, 159.7, 164.6. MS (EI, *m/z*, %): 529 (M^+, 23), 500 (10), 272 (3), 174 (100). *Anal.* Calcd for $C_{32}H_{27}N_5OS$: C, 72.57; H, 5.14; N, 13.22. Found C, 72.42; H, 5.26; N, 13.41.

6-(4-Methylpiperazino)-8-oxo-3,4-diphenyl-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6t**) (80%); mp 299-301°C. IR (KBr): 1680 (CO), 1530, 1300. ^{1}H NMR δ ($CDCl_3$): 1.89-2.10 [m, 4H, $C\underline{H_2}N(CH_3)C\underline{H_2}$], 2.14 (s, 3H, NCH_3), 2.41 (s, 3H, $PhCH_3$), 2.67-2.89 (m, 4H, CH_2NCH_2), 7.23-7.36 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 21.1 (CH_3), 45.7 (NCH_3), 48.2, 55.9 (NCH_2), 120.1, 127.6, 127.8, 128.0, 129.7, 130.2, 130.4, 133.5, 133.8, 135.6, 136.5, 138.6, 149.1, 155.9, 156.2, 159.4, 164.4. MS (FAB, *m/z*, %): 545 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{32}H_{28}N_6OS$: C, 70.57; H, 5.18; N, 15.43. Found C, 70.62; H, 4.99; N, 15.65.

6-Morpholino-8-oxo-3,4-diphenyl-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6u**) (81%); mp > 300°C. IR (KBr): 1680 (CO), 1530, 1510, 1250. ^{1}H NMR δ ($CDCl_3$): 2.41 (s, 3H, CH_3), 2.61-2.84 (m, 4H, CH_2NCH_2), 3.16-3.29 (m, 4H, CH_2OCH_2), 7.19-7.41 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 21.2 (CH_3), 48.6 (NCH_2), 65.7 (OCH_2), 120.5, 127.6, 127.7, 127.8, 128.1, 129.8, 130.2, 130.4, 133.6, 135.6, 136.5, 138.8, 149.0, 155.7, 156.3, 159.3, 164.4. MS (EI, *m/z*, %): 531 (M^+, 100), 486 (75), 426 (24), 384 (48), 355 (9), 328 (21), 300 (15), 272 (13), 176 (53), 91 (80). *Anal.* Calcd for $C_{31}H_{25}N_5O_2S$: C, 70.04; H, 4.74; N, 13.17. Found C, 69.82; H, 4.98; N, 13.11.

8-Oxo-3,4-diphenyl-6-thiomorpholino-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6v**) (62%); mp > 300°C. IR (KBr): 1680 (CO), 1530, 1250. ^{1}H NMR δ ($CDCl_3$): 2.01-2.28 (m, 4H, CH_2SCH_2), 2.41 (s, 3H, CH_3), 3.01-3.23 (m, 4H, CH_2NCH_2), 7.16-7.40 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 21.2 (CH_3), 26.1 (SCH_2), 51.0 (NCH_2), 120.7, 127.4, 127.6, 127.8, 128.1, 129.9, 130.3, 130.4, 133.6, 134.0, 135.5, 136.5, 138.8, 149.9, 156.2, 156.3, 159.4, 164.4. MS (EI, *m/z*, %): 547 (M^+, 47), 474 (100), 384 (28), 355 (4), 328 (4), 300 (4), 272 (7), 146 (24), 91 (31). *Anal.* Calcd for $C_{31}H_{25}N_5OS_2$: C, 67.98; H, 4.60; N, 12.79; Found C, 67.77; H, 4.55; N, 12.89.

6-Amino-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**8a**) (29%); mp > 300°C. IR (KBr): 3500 (NH_2), 1680 (CO), 1640, 1550, 1510. ^{1}H NMR δ (DMSO-d_6): 6,03 (br s, 2H, NH_2), 7.29-7.58 (m, 15H, C_6H_5). MS (EI, *m/z*, %): 447 (M^+, 14), 446 (10), 272 (5), 119 (24), 77 (100). *Anal.* Calcd for $C_{26}H_{17}N_5OS$: C, 69.78; H, 3.83; N, 15.65. Found C, 69.70; H, 3.92; N, 15.78.

6-Butylamino-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**8b**) (89%); mp 275-277°C. IR (KBr): 3480 (NH), 1680 (CO), 1570, 1300. ^{1}H NMR δ ($CDCl_3$): 0.78 (m, 3H, CH_3), 1.01-1.29 (m, 4H, CH_2CH_2), 2.61-2.79 (m, 2H, NCH_2), 4.03 (t, 1H, *J*= 5.4 Hz, NH), 7.20-7.65 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 13.7 (CH_3), 19.7 (CH_2), 31.1 (CH_2), 41.5 (NCH_2), 127.4, 127.8, 127.9, 128.0, 128.4, 130.3, 130.5, 130.8, 133.6, 133.8, 152.1, 156.1, 135.5, 137.0, 152.2, 156.5, 159.8, 165.0. MS (EI, *m/z*, %): 503 (M^+, 38), 474 (12), 461 (12), 446 (40), 378 (8), 300 (12), 272 (16), 77 (100). *Anal.* Calcd for $C_{30}H_{25}N_5OS$: C, 71.55; H, 5.00; N, 13.91. Found C, 71.46; H, 4.82; N, 13.99.

6-*i*-Propylamino-8-oxo-3,4,7-triphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**8c**) (74%); mp 302-304°C. IR (KBr): 3420 (NH), 1690 (CO), 1550, 1110. ^{1}H NMR δ ($CDCl_3$): 0.78 (d, 6H, *J*= 6.5 Hz, CH_3), 3.33 (m, 1H, CH), 3.82 (d, 1H, *J*= 7.6 Hz, NH), 7.28-7.65 (m, 15H, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 22.4 (CH_3), 43.7 (CH), 127.4, 127.8, 128.0, 128.4, 130.3, 130.5, 130.8, 133.8, 135.7, 136.8, 150.9, 151.4, 156.1, 158.7, 164.7. MS (EI, *m/z*, %): 489 (M^+, 100), 446 (75), 370 (15),

328 (23), 300 (16), 272 (16), 119 (32), 77 (91). *Anal.* Calcd for $C_{29}H_{23}N_5OS$: C, 71.14; H, 4.73; N, 14.30. Found C, 71.03; H, 4.99; N, 14.35.

8-Oxo-3,4-diphenyl-7-phenylamino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine **(9a)** (32%); mp >300°C. IR (KBr): 3300 (NH), 1710 (CO), 1690, 1590, 1560, 1330. ^{1}H NMR δ (DMSO-d$_6$): 6.77-7-56 (m, 15H, C_6H_5), 8.76 (s, 1H, NHPh), 11,36 (s, 1H, NHCO). MS (EI, *m/z*, %): 447 (M^+, 8), 446 (4), 272 (7), 239 (16), 119 (27), 91 (49), 77 (100). *Anal.* Calcd for $C_{26}H_{17}N_5OS$: C, 69.78; H, 3.83; N, 15.65. Found C, 69.70; H, 3.95; N, 15.66.

General procedure for the synthesis of pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines (6w-d').

A catalytic amount of K_2CO_3 was added to a solution of **5** (0.09 g) in acetone (5 mL). The solution was refluxed for 15 min. The solid formed was filtered off and recrystallized from acetone/CH_2Cl_2.

8-Oxo-3,4,7-triphenyl-6-thiomorpholino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine **(6w)** (85%); mp > 300°C. IR (KBr): 1680 (CO), 1540, 1510, 1300, 1240. ^{1}H NMR δ (CDCl$_3$): 2.02-2.31 (m, 4H, CH_2SCH_2), 2.97-3.12 (m, 4H, CH_2NCH_2), 7.27-7.55 (m, 15H, C_6H_5). ^{13}C NMR δ (CDCl$_3$): 26.1 (SCH_2), 51.0 (NCH_2), 120.9, 127.6, 127.8, 128.0, 128.2, 128.7, 129.3, 130.3, 130.4, 133.6, 135.6, 136.5, 136.7, 139.1, 149.0, 156.1, 156.3, 159.3, 164.4. MS (EI, *m/z*, %): 533 (M^+, 35), 460 (100), 384 (26), 355 (4), 328 (5), 300 (4), 272 (8), 230 (14), 77 (53). *Anal.* Calcd for $C_{30}H_{23}N_5OS_2$: C, 67.52; H, 4.34; N, 13.12. Found C, 67.31; H, 4.38; N, 13.25.

6-(4-Methylpiperazino)-7-(4-nitrophenyl)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine **(6x)** (85%); mp > 300°C. IR (KBr): 1680 (CO), 1520, 1350, 1000. ^{1}H NMR δ (CDCl$_3$): 1.89-2.16 [m, 4H, $C\underline{H}_2N(CH_3)C\underline{H}_2$], 2.14 (s, 3H, NCH_3), 2.63-2.83 (m, 4H, CH_2NCH_2), 7.28-7.33 (m, 10H, C_6H_5), 7,59, 8,35 (AA'BB' system, 4H, *J*= 8.3 Hz, C_6H_4). ^{13}C NMR δ (CDCl$_3$): 45.7 (NCH_3), 48.5, 53.7 (NCH_2), 120.4, 124.4, 127.4, 127.7, 127.9, 128.0, 128.3, 129.4, 130.2, 130.4, 133.4, 135.8, 136.4, 142.1, 147.2, 149.4, 155.1, 156.5, 158.6, 164.4. MS (FAB, *m/z*, %): 576 [$(MH)^+$, 100]. *Anal.* Calcd for $C_{31}H_{25}N_7O_3S$: C, 64.68; H, 4.37; N, 17.03; Found C, 64.89; H, 4.28; N, 17.05.

6-Morpholino-7-(4-nitrophenyl)-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine **(6y)** (87%); mp > 300°C. IR (KBr): 1680 (CO), 1530, 1340, 1110. ^{1}H NMR δ (CDCl$_3$): 2.64-2.85 (m, 4H, CH_2NCH_2), 3.18-3.38 (m, 4H, CH_2OCH_2), 7.23-7.41 (m, 10H, C_6H_5), 7.60, 8.36 (AA'BB' system, 4H, *J*= 8.9 Hz, C_6H_4). ^{13}C NMR δ (CDCl$_3$): 48.8 (NCH_2), 65.6 (OCH_2), 120.5, 124.4, 127.0, 127.8, 127.9, 128.0, 128.3, 129.4, 130.2, 130.4, 133.4, 135.8, 136.3, 141.9, 147.2, 149.3, 154.9, 156.7, 158.5, 164.2. MS (EI, *m/z*, %): 562 (M^+, 100), 517 (55), 505 (50), 426 (40), 384 (71), 355 (17), 328 (44), 300 (32), 272 (31), 77 (90), 57 (99). *Anal.* Calcd for $C_{30}H_{22}N_6O_4S$: C, 65.92; H, 4.06; N, 15.37. Found C, 66.10; H, 4.30; N, 15.26.

7-(4-Nitrophenyl)-8-oxo-3,4-diphenyl-6-thiomorpholino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine **(6z)** (85%); mp > 300°C. IR (KBr): 1680 (CO), 1520, 1350, 1250. ^{1}H NMR δ (CDCl$_3$): 2.03-2.24 (m, 4H, CH_2SCH_2), 3.01-3.24 (m, 4H, CH_2NCH_2), 7.26-7.39 (m, 10H, C_6H_5), 7.58, 8.38 (AA'BB' system, 4H, *J*= 8.9 Hz, C_6H_4). ^{13}C NMR δ (CDCl$_3$): 26.1 (SCH_2), 51.1 (NCH_2), 121.0, 124.5, 127.8, 127.3, 127.9, 128.2, 128.3, 129.5, 130.3, 130.4, 133.5, 135.7, 136.3, 142.2, 147.2,

149.2, 155.2, 156.7, 158.6, 164.6. MS (EI, *m/z*, %): 578 (M^+, 44), 505 (100), 442 (6), 384 (30), 355 (5), 328 (8), 272 (13). *Anal.* Calcd for $C_{30}H_{22}N_6O_3S_2$: C, 62.27; H, 3.83; N, 14.52. Found C, 62.08; H, 3.95; N, 14.53.

7-(4-Nitrophenyl)-8-oxo-3,4-diphenyl-6-pyrrolidino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6a'**) (93%); mp 299-301°C. IR (KBr): 1680 (CO), 1530, 1350. ^{1}H NMR δ ($CDCl_3$): 1.51-1.69 (m, 4H, $NCH_2C\underline{H}_2$), 2.49-2.76 (m, 4H, NCH_2), 7.27-7.41 (m, 10H, C_6H_5+C_6H_4), 7.53,8-53 (AA'BB' system, 4H, *J*= 8.8 Hz, C_6H_4). ^{13}C NMR δ ($CDCl_3$): 25.2 ($NCH_2\underline{C}H_2$), 50.3 (NCH_2), 116.3, 124.4, 127.3, 127.4, 127.6, 127.8, 128.2, 130.2, 130.4, 130.5, 133.6, 135.8, 136.6, 142.6, 147.3, 150.9, 153.0, 156.4, 158.9, 164.7. MS (EI, *m/z*, %): 546 (M^+, 23), 517 (6), 370 (12), 328 (14), 300 (16), 272 (20), 130 (51), 70 (100). *Anal.* Calcd for $C_{30}H_{22}N_6O_3S$: C, 65.92; H, 4.06; N, 15.37. Found C, 66.08; H, 4.10; N, 15.60.

7-(4-Methoxyphenyl)-6-morpholino-8-oxo-3,4-diphenyl-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**6b'**) (92%); mp 300-302°C. IR (KBr): 1680 (CO), 1530, 1500, 1250, 1110, 1010. ^{1}H NMR δ ($CDCl_3$): 2.63-2.89 (m, 4H, CH_2NCH_2), 3.15-3.33 (m, 4H, CH_2OCH_2), 3.84 (s, 3H, OCH_3), 6.98 (d, 2H, *J*= 8.7.0 Hz, C_6H_4), 7.22-7.39 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 48.7 (NCH_2), 55.5 (OCH_2), 65.8 (OCH_3), 120.8, 114.4, 127.6, 127.8, 128.1, 128.7, 129.0, 130.3, 130.4, 133.7, 135.6, 136.5, 149.0, 155.9, 156.3, 159.4, 164.5. MS (EI, *m/z*, %): 547 (M^+, 100), 502 (83), 426 (28), 384 (52), 355 (17), 328 (28), 300 (29), 272 (28), 192 (86), 121 (92). *Anal.* Calcd for $C_{31}H_{25}N_5O_3S$: C, 67.99; H, 4.60; N, 12.79; Found C, 67.81; H, 4.75; N, 12.64.

7-(4-Methoxyphenyl)-8-oxo-3,4-diphenyl-6-thiomorpholino-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-c]-pyridazine (**6c'**) (93%); mp >300°C. IR (KBr): 1670 (CO), 1510, 1250, 1210. ^{1}H NMR δ ($CDCl_3$): 2.03-2.31 (m, 4H, CH_2SCH_2), 3.01-3.19 (m, 4H, CH_2NCH_2), 3.86 (s, 3H, CH_3), 7.00 (d, 2H, *J*= 8.9 Hz, C_6H_4), 7.21-7.41 (m, 12H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 26.2 (SCH_2), 51.0 (NCH_2), 55.5 (CH_3), 121.0, 114.5, 127.7, 127.8, 128.0, 128.3, 129.1, 129.2, 130.3, 130.4, 133.6, 135.6, 136.5, 148.9, 156.4, 159.4, 159.6, 164.4. MS (EI, *m/z*, %): 563 (M^+, 52), 490 (100), 384 (31), 355 (6), 328 (5), 300 (5), 272 (9), 162 (24), 77 (27). *Anal.* Calcd for $C_{31}H_{25}N_5O_2S_2$: C, 66.05; H, 4.47; N, 12.42. Found C, 66.24; H, 4.31; N, 12.57.

8-Oxo-3,4-diphenyl-6-pyrrolidino-7-(*p*-tolyl)-7,8-dihydropyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**6d'**) (91%); mp 290-292°C. IR (KBr): 1670 (CO), 1520, 1340, 750. ^{1}H NMR δ ($CDCl_3$): 1.46-1.76 (m, 4H, $NCH_2C\underline{H}_2$), 2.41 (s, 3H, CH_3), 2.49-2.87 (m, 4H, NCH_2), 7.15-7.42 (m, 14H, C_6H_5+C_6H_4). ^{13}C NMR δ ($CDCl_3$): 21.2 (CH_3), 25.1 ($NCH_2\underline{C}H_2$), 50.0 (NCH_2), 116.1, 127.5, 127.7, 127.9, 128.7, 129.7, 130.4, 133.6, 134.0, 135.7, 136.7, 138.7, 150.6, 153.6, 156.1, 159.7, 164.9. MS (EI, *m/z*, %): 515 (M^+, 63), 486 (38), 370 (31), 328 (15), 300 (12), 272 (12), 160 (97), 91 (100). *Anal.* Calcd for $C_{31}H_{25}N_5OS$: C, 72.21; H, 4.89; N, 13.58. Found C, 72.03; H, 4.85; N, 13.50.

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