Monatshefte für Chemie 127, 1037–1043 (1996)

Monatshefte für Chemie
Chemical Monthly

Synthesis of New Pyridazino[4′,3′:4,5]-thieno[3,2-*d*]-1,2,3-triazine and Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine Derivatives

J. M. Quintela*, M. C. Veiga, R. Alvarez-Sarandés, L. González, and **C. Peinador**

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

Summary. 8,9-Diphenylpyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazin-4(3*H*)-one (**2**), 3-substituted 8,9-diphenylpyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazin-4(3*H*)-ones (**3a–c**), 3,4-diphenylpyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazin-8(7*H*)-one (**4**), 8-chloro-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (**5**), 8-substituted 3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazines (**6a–h**) and 7-substituted 3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-8(7*H*)-ones (**7a–c**) were synthesized from 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide (**1**).

Keywords. Thieno[2,3-*c*]pyridazine-6-carboxamide; Pyridazino[4′,3′:4,5]thieno[3,2-*d*]1,2,3-triazines; Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazines; Pyridazines; 1,2,3-Triazines.

Synthese neuer Pyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazin- und Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-Derivate

Zusammenfassung. Folgende Verbindungen wurden ausgehend von 5-Amino-3,4-diphenylthieno[2,3-*c*]pyridazin-6-carboxamid (**1**) synthetisiert: 8,9-Diphenylpyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazin-4(3*H*)-on (**2**), 3-substituierte 8,9-Diphenylpyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazin-4(3*H*)-one (**3a–c**), 3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-8[7*H*]-on (**4**), 8-Chlor-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin (**5**), 8-substituierte 3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (**6a–h**) und 7-substituierte 3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-8(7*H*)-one (**7a–c**).

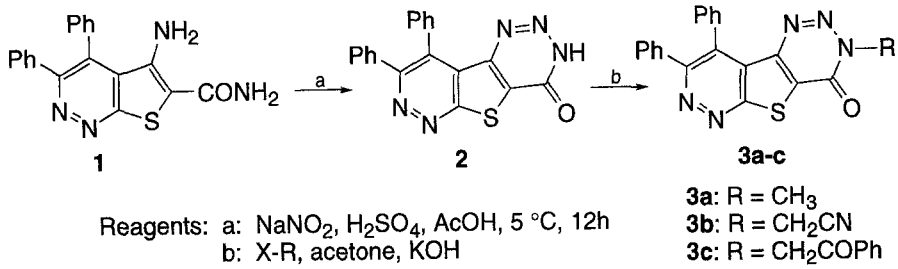
Introduction

Many heterocyclic annelated pyridazines have attracted considerable attention because of their various pharmacological activities [1]. On the other hand, some 1,2,3-triazine systems condensed with carbocycles or heterocycles are known to exhibit antiallergic activity [2], and triazolopyridazine derivatives are used in bronchi sickness therapy [3]. The search for biologically active substances led us to the investigation of condensed S,N-heterocycles. In previous papers [4], we have reported the synthesis of condensed tricyclic systems of potential biological activity

with a thiophene ring as the central nucleus. In connection with these facts, we report in this paper the utility of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide (**1**) as a synthon for the preparation of new pyridazino[4′,3′:4,5]thieno[3,2-*d*]-1,2,3-triazines and pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazines with potential biological activity.

Results and Discussion

The precursor 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide(**1**) was synthesized directly from 4-cyano-5,6-diphenylpyridazine-3(2*H*)-thione and 2-chloroacetamide using an excess of potassium carbonate in refluxing ethanol [4d]. Nitrosation of **1** with sodium nitrite in acetic acid at 5 °C gave triazin-4(3*H*)-one (**2**) which was obtained in analytically pure form directly from the reaction mixture in 65% yield. Methylation of **2** with methyl iodide afforded the 3-methylated product (**3a**). Using the same procedure, **2** was converted into 3-substituted pyridazinothienotriazin-4(3*H*)-ones (**3b** and **3c**) by treatment with electrophilic reagents such as chloroacetonitrile and 2-bromoacetophenone, respectively (Scheme 1).

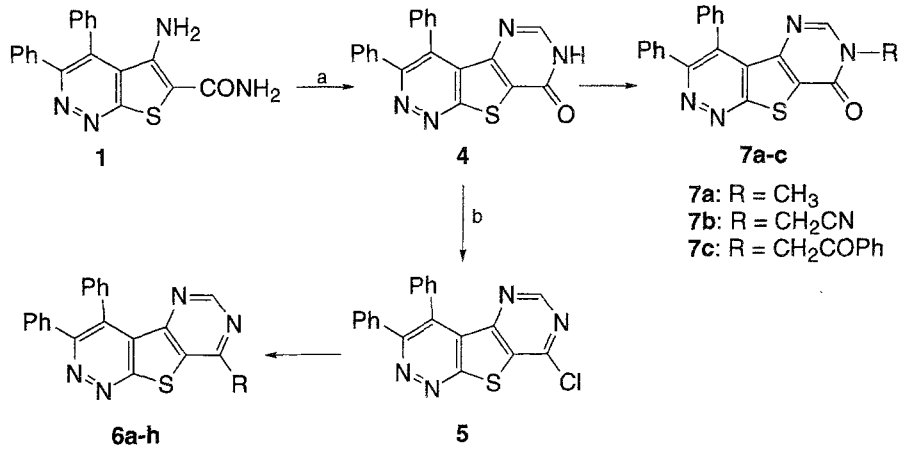


Scheme 1

Compounds **2** and **3a–c** were characterized by microanalyses and spectroscopic data. The mass spectra showed the expected molecular ion peaks, and the IR spectra exhibited the characteristic bands of the amide group. Moreover, the ^{1}H NMR spectrum of compound **2** showed a characteristic peak at 12.24 ppm (exchangeable with deuterium oxide) which can be attributed to the N-bound proton at position 3.

Only few papers [5] dealing with the pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine system have been published so far. The pyrimidine ring was attached to the thiophene ring by refluxing **1** with formic acid to give pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-8(7*H*)-one (**4**). Upon treatment with phosphorus oxychloride, **4** afforded the 8-chloroderivative (**5**) which exhibited a remarkable reactivity of its 8-chloro substituent towards nucleophilic agents, thus affording the new 8-substituted pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine derivatives **6a–h** (Scheme 2).

Furthermore, treatment of **4** with electrophilic reagents such as methyl iodide, chloroacetonitrile, and 2-bromoacetophenone furnished 7-substituted pyrimidothienopyridazine derivatives **7a–c**. The structure of compounds **5**, **6**, and **7** were consistent with their elemental analyses and spectral data. Compounds **6a–h** showed a characteristic singlet between $\delta = 8.43$ ppm and $\delta = 8.75$ ppm for H-6 in the ^{1}H NMR spectra. The formation of the desired pyrimidothienopyridazine



Reagents: a: HCO_2H, reflux, 14h, b: PCl_5, $POCl_3$, reflux, 7 h

6	R	6	R
a	Piperidino	**e**	Morpholino
b	4-Methylpiperidino	**f**	Thiomorpholino
c	*N*-(4′-Acetylphenyl)piperazino	**g**	SC_6H_5
d	4-Methylpiperazino	**h**	OCH_2CH_3

Scheme 2

derivatives **6a–h** was also confirmed by their ^{13}C NMR spectra which showed a signal at $\delta = 154.3–154.8$ ppm corresponding to the carbon atom at position 6 of the newly formed pyrimidine ring. The most salient features of the ^1H NMR and ^{13}C NMR spectra are summarized in the experimental section.

Experimental

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained at 70 eV using a VG QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ sheets used for analytical thin layer chromatography and the Silica gel 60 (230–400 mesh) employed for medium pressure liquid chromatography (MPLC) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

8,9-Diphenylpyridazino[4′,3′:4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**2**)

To an ice-cooled solution of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide (**1**, 0.60 g, 1.72 mmol) in acetic acid (10 ml), a solution of sodium nitrite (0.16 g, 2.24 mmol) in sulfuric acid (1 ml) was added. The mixture was stirred for 12 h. The solution was poured into water and the solid material was filtered off and recrystallized from $EtOH/CH_2Cl_2$ to yield 0.40 g (65%) of **2**.

M.p.: 218 °C (decomp); $C_{19}H_{11}N_5OS$ (357.39); calc.: C 63.86; H 3.10; N 19.60; found: C 63.75; H 3.22; N 19.48; ^1H NMR ($CDCl_3$): $\delta = 7.33–7.43$ (m, 10H, C_6H_5), 12.24 (br s, H, NH) ppm; ^{13}C NMR

(*DMSO*-d_6): δ = 127.1; 127.8, 127.9, 128.4, 128.8, 130.2, 130.3, 132.4, 132.8 (C_6H_5), 136.0, 136.4, 147.1, 153.7, 157.4, 162.8 ppm; MS (EI): *m/z* (%) = 357 (M^+, 65), 328 (72), 300 (100), 285 (30), 273 (12): IR (KBr): ν = 3210 (NH), 1690 (CO), 1505, 1490, 1440, 1380 cm^{-1}.

*3-Substituted 8,9-Diphenylpyridazino[4',3':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-ones (**3a–c**); General Procedure*

A solution of **2** (0.20 g, 0.60 mmol), 15% KOH (1 ml, 3.2 mmol), and the appropriate electrophilic reagent (1.25 mmol) in acetone (10 ml) was stirred for 12 h at room temperature (**3a** and **3c**) or at reflux temperature (**3b**). The solvent was removed under reduced pressure, water (20 ml) was added, and the mixture was neutralized with 2 *N* HCl. The solid was recrystallized from acetone.

3-Methyl-8,9-diphenylpyridazino[4',3':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**3a**)

Yield: 50%; m.p.: >300 °C; $C_{20}H_{13}N_5OS$ (371.42); calc.: C 64.68, H 3.53, N 18.86; found: C 64.79, H 3.47, N 18.91; ^1H NMR ($CDCl_3$); δ = 4.10 (s, 3H, CH_3), 7.27–7.45 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): δ = 37.8 (CH_3), 126.9, 128.1, 128.2, 128.7, 129.3, 130.1, 130.5, 132.2, 132.4 (C_6H_5), 135.9, 136.2, 147.0, 153.3, 157.7, 163.5 ppm; MS (EI); *m/z* (%) = 371 (M^+, 82), 328 (100), 300 (60), 285 (26), 272 (11); IR (KBr): ν = 1660 (CO), 1480, 1440 cm^{-1}.

3-Cyanomethyl-8,9-diphenylpyridazino[4',3':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**3b**)

Yield: 60%; m.p.: 234–236 °C; $C_{21}H_{12}N_6OS$ (396.43); calc: C 63.63, H 3.05, N 21.20; found: C 63.50, H 3.15, N 21.09; ^1H NMR (*DMSO*-d_6) δ = 5.65 (s, 2H, CH_2), 7.33–7.39 (m, 10H, C_6H_5) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 37.9 (CH_2), 114.6 (CN), 126.9, 127.9, 128.5, 128.8, 128.9, 130.1, 130.3, 132.4, 132.6 (C_6H_5), 136.0, 136.2, 146.5, 152.3, 157.5, 162.8 ppm; MS (EI): *m/z* (%) = 396 (M^+, 11), 369 (7), 328 (17), 300 (16), 285 (9); IR (KBr): ν = 1680 (CO), 1480, 1440 cm^{-1}.

3-Phenacyl-8,9-diphenylpyridazino[4',3':4,5]thieno[3,2-d]-1,2,3-triazin-4(3H)-one (**3c**)

Yield: 51%; m.p.: 229–231 °C; $C_{27}H_{17}N_5O_2S$ (475.52); calc.: C 68.20, H 3.60, N 14.73; found: C 68.29, H 3.71, N 14.62; ^1H NMR ($CDCl_3$) δ = 5.93 (s, 2H, CH_2), 7.30–8.04 (m, 15H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): δ = 55.7 (CH_2), 126.9, 128.1, 128.6, 129.0, 129.2, 130.1, 130.5, 132.4, 132.5, 134.0, 134.4 (C_6H_5), 136.0, 136.3, 146.8, 153.1, 157.7, 163.5 ppm; MS (EI): *m/z* (%) = 475 (M^+, 80), 446 (13), 392 (32), 342 (66), 328 (35), 285 (53); IR (KBr): ν = 1680 (CO), 1480, 1440 cm^{-1}.

3,4-Diphenylpyrimido[4',5':4,5]thieno[3,2-c]pyridazin-8(7H)-one (**4**)

A solution of **1** (0.20 g, 0.57 mmol) in formic acid (3 ml) was refluxed for 14 h. The solvent was then removed under reduced pressure, and water (10 ml) was added to the residue. The solid was filtered off and recrystallized from ethanol/acetone to yield 0.18 g (90%) of **4**.

M.p.: >300 °C; $C_{20}H_{12}N_4OS$ (356.40); calc.: C 67.40, H 3.39, N 15.72; found: C 67.21, H 3.18, N 15.59; ^1H NMR (*DMSO*-d_6): δ = 7.21–7.41 (m, 10H, C_6H_5), 8.11 (s, 1H, H-6), 13.09 (br, s, H. NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 127.5, 127.6, 127.8, 128.1, 128.4, 130.3, 130.4, 132.8 (C_6H_5), 135.9, 136.8, 147.5 (C-6), 150.7, 156.8, 157.7, 163.1 ppm; MS (EI): *m/z* (%) = 356 (M^+, 42), 327 (8), 299 (5), 272 (11); IR (KBr): ν = 3030, 1680 (CO), 1675, 1580, 1500, 1420 cm^{-1}.

8-Chloro-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**5**)

A stirred solution of **4** (0.60 g, 1.68 mmol) and phosphorous pentachloride (0.52 g, 2.52 mmol) in phosphorous oxychloride (10 ml) was refluxed for 7 h. Then, the reaction mixture was evaporated under reduced pressure, ice (100 g) was added, and the solution was neutralized with $NaHCO_3$ and extracted

with dichloromethane (3 × 30 ml). The solvent was removed under reduced pressure and the resulting solid was purified by MPLC using CH_2Cl_2 as eluent to yield 0.36 g (58%) of **5**.

M.p.: 204–206 °C; $C_{20}H_{11}N_4CIS$ (374.85); calc.: C 64.08, H 2.96, N 14.95; found: C 63.87, H 3.03, N 14.76; ^{1}H NMR ($CDCl_3$): $\delta = 7.25–7.45$ (m, 10H, C_6H_5), 8.90 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 126.9$, 128.0, 128.5, 129.1, 130.1, 130.4, 132.2 (C_6H_5), 136.1, 136.9, 154.6 (C-6), 155.9, 156.2, 157.9, 163.3 ppm; MS (EI): *m/z* (%) = 376 ($M^+ + 2$, 37), 374 (M^+, 100), 345 (17), 309 (14), 283 (17), 238 (14); IR (KBr): $\nu = 1540$, 1490, 1440, 1420, 1320 cm^{-1}.

8-Substituted 3,4-Diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazines (**6a–g**); *General Procedure*

A solution of 8-chloro-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (**5**, 0.10 g, 0.27 mmol) and the appropriate amine (0.32 mmol) in ethanol/*THF* (10 ml, 1:4 v/v) was refluxed for 1 h. The solid was filtered off and recrystallized from ethanol/acetone.

3,4-Diphenyl-8-piperidinopyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (**6a**)

Yield: 60%; m.p.: 157–159 °C; $C_{25}H_{21}N_5S$ (423.53); calc.: C 70.90, H 5.00, N 16.53; found: C 71.15, H 4.87, N 16.68, ^{1}H NMR ($CDCl_3$): $\delta = 1.79$ (s, 6H, CH_2), 3.97 (s, 4H, NCH_2), 7.27–7.38 (m, 10H, $2C_6H_5$), 8.44 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.6$ (CH_2), 26.1 (CH_2), 47.8 (NCH_2), 116.7 (C-8a), 127.6 (C-4a), 127.9, 128.2, 128.4, 130.4, 130.5, 133.2, 135.8 (C_6H_5), 136.8, 154.6 (C-6), 154.8, 158.4 ppm; MS (EI): *m/z* (%) = 423 (M^+, 51), 422 (83), 394 (15), 368 (10), 339 (8), 283 (12); IR (KBr): $\nu = 2940$, 1500, 1440, 1360 cm^{-1}.

8-(4-Methylpiperidino)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (**6b**)

Yield: 71%; m.p.: 148–150 °C; $C_{26}H_{23}N_5S$ (437.56); calc.: C 71.37, H 5.30, N 16.00; found: C 71.43, H 5.13, N 15.87; ^{1}H NMR ($CDCl_3$): $\delta = 1.01$ (d, 3H, $J = 6.2$ Hz, CH_3), 1.25–1.43 (m, 2H, CH_2-$CH(CH_3)$), 1.72–190 (m, 3H, CH_2–*CH*), 3.11–3.24 (t, 2H, $J = 12.0$ Hz, NCH_2), 4.78 (d, 2H, $J = 13.5$ Hz, NCH_2), 7.23–7.41 (m, 10H, C_6H_5), 8.43 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.7$ (CH_3), 34.2 (CH_2), 47.0 (NCH_2), 116.7 (C-8a), 127.3 (C-4a), 127.6, 127.8, 128.1, 128.4, 130.4, 133.1, 135.8 (C_6H_5), 136.8, 154.6 (C-6), 154.8, 157.2, 158.3, 162.8 ppm; MS (EI): *m/z* (%) = 437 (M^+, 38), 394 (6), 368 (8), 354 (5), 341 (8), 326 (8), 302 (9); IR (KBr): $\nu = 2920$, 1550, 1500, 1490, 1360, 1300, 1250 cm^{-1}.

8-(N-(4′-Acetylphenyl)piperazino)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (**6c**)

Yield: 34%; m.p.: >280 °C; $C_{32}H_{26}N_6OS$ (542.66); calc.: C 70.83, H 4.83, N 15.49; found: C 71.06, H 4.67, N 15.53; ^{1}H NMR ($CDCl_3$): $\delta = 2.56$ (s, 3H, $COCH_3$), 3.62 (t, 4H, $J = 4.9$ Hz, NCH_2), 4.23 (t, 4H, $J = 4.9$ Hz, NCH_2), 6.94, 7.94 (AA′BB′ system, 4H, $J = 8.9$ Hz, C_6H_4), 7.24–7.42 (m, 10H, C_6H_5), 8.51 (s,1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 26.2$ (CH_3), 45.7 (NCH_2), 47.1 (NCH_2), 116.9 (C-8a), 127.0 (C-4a), 113.5, 127.7, 127.9, 128.3, 128.6, 130.4, 133.0, 136.2 ($C_6H_5 + C_6H_4$), 136.6, 153.4, 154.6 (C-6), 155.3, 157.5, 158.6, 162.5, 196.5 (CO) ppm; MS (EI): *m/z* (%) = 542 (M^+, 2), 368 (7), 210 (3), 206 (3); IR (KBr): $\nu = 1670$ (CO), 1600, 1520, 1440, 1390, 1240 cm^{-1}.

8-(4-Methylpiperazino)-3,4-diphenylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine (**6d**)

Yield: 60%; m.p.: 207–209 °C; $C_{25}H_{22}N_6S$ (438.55); calc.: C 68.47, H 5.05, N 19.16; found: C 68.65, H 5.14, N 19.34; ^{1}H NMR ($CDCl_3$): $\delta = 2.39$ (s, 3H, CH_3), 2.62 (t, 4H, $J = 4.9$ Hz, NCH_2), 4.04 (t, 4H, $J = 4.9$ Hz, NCH_2), 7.23–7.41 (m, 10H, C_6H_5), 8.46 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 46.0$ (NCH_3), 46.2, 54.8 (NCH_2), 116.8 (C-8a), 127.2 (C-4a), 127.7, 127.9, 128.2, 128.5, 130.4, 133.1, 135.9 (C_6H_5), 136.7, 154.5 (C-6), 155.1, 157.4, 158.6, 162.8 ppm; MS (EI): *m/z* (%) = 438 (M^+, 2), 381 (3), 368 (9); IR (KBr): $\nu = 2800$, 1540, 1445, 1360 cm^{-1}.

8-Morpholino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6e**)

Yield: 80%; m.p.: 224–226 °C; $C_{24}H_{19}N_5OS$ (425.51(; calc.: C 67.75, H 4.50, N 16.46; found: C 67.89, H 4.35, N 16.57; ^{1}H NMR ($CDCl_3$): $\delta = 3.89$ (t, 4H, $J = 4.5$ Hz, NCH_2), 4.02 (t, 4H, $J = 4.5$ Hz, OCH_2), 7.23–7.39 (m, 10H, $2C_6H_5$), 8.48 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 46.5$ (NCH_2), 66.6 (OCH_2), 116.7 (C-8a), 126.9 (C-4a), 127.6, 127.8, 128.1, 128.4, 130.4, 132.9, 135.8 (C_6H_5), 136.5, 154.3 (C-6), 155.1, 157.3, 158.6, 162.6 ppm; MS (EI): m/z (%) = 425 (M^+, 37), 424 (59), 368 (21), 283 (9); IR (KBr): $\nu = 2960$; 1550, 1490, 1445, 1430 cm^{-1}.

3,4-Diphenyl-8-thiomorpholinopyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6f**)

Yield: 70%; m.p.: 192–194 °C; $C_{24}H_{19}N_5S_2$ (441.57); calc.: C 65.28, H 4.34, N 15.86; found: C 65.43, H 4.45, N 15.93; ^{1}H NMR ($CDCl_3$): $\delta = 2.83$ (t, 4H, $J = 5.0$ Hz, SCH_2), 4.34 (t, 4H, $J = 5.0$ Hz, NCH_2), 7.27–7.39 (m, 10H, $2C_6H_5$), 8.48 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 27.2$ (SCH_2), 49.4 (NCH_2), 116.7 (C-8a), 127.1 (C-4a), 127.6, 127.9, 128.2, 128.5, 130.4, 132.9, 136.0 (C_6H_5), 136.6, 154.5 (C-6), 155.2, 157.4, 158.2, 162.6 ppm; MS (EI): m/z (%) = 441 (M^+, 27), 368 (76) 283 (13); IR (KBr): $\nu = 1545$, 1490, 1440, 1250 cm^{-1}.

3,4-Diphenyl-8-thiophenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6g**)

Yield: 50%; m.p.: 208–210 °C; $C_{26}H_{16}N_4S_2$ (448.56); calc.: C 69.62, H 3.59, N 12.49; found: C 69.43, H 3.47, N 12.33; ^{1}H NMR ($CDCl_3$): $\delta = 7.27$–7.71 (m, 15H, $3C_6H_5$), 8.75 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 126.1$, 127.9, 128.3, 128.8, 129.6, 130.2, 130.4, 132.5, 135.6 (C_6H_5), 135.3, 136.6, 153.4, 154.4 (C-6), 157.6, 163.4, 165.1 ppm; MS (EI): m/z (%) = 448 (M^+, 100), 415 (6), 371 (8), 344 (9); IR (KBr): $\nu = 1500$, 1440, 1420, 1280 cm^{-1}.

8-Ethoxy-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6h**)

To a solution of sodium ethoxide (0.05 g of sodium, 2 mmol) in ethanol (25 ml), **5** (0.20 g, 0.54 mmol) was added. The mixture was refluxed for 3 h. The solid was filtered off and recrystallized from ethanol to give 0.14 g (65%) of **6h**.

M.p.: 198–200 °C; $C_{22}H_{16}N_4OS$ (384.45); calc.: C 68.73, H 4.19, N 14.57; found: C 68.56, H 4.08, N 14.78; ^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (t, 3H, $J = 7.1$ Hz, CH_3), 4.69 (q, 2H, $J = 7.1$ Hz, OCH_2), 7.27–7.42 (m, 10H, $2C_6H_5$), 8.63 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.3$ (CH_3), 63.8 (OCH_2), 122.0 (C-8a), 127.3 (C-4a), 127.8, 127.9, 128.3, 128.7, 130.5, 130.8, 132.8, 136.1 (C_6H_5), 136.6, 154.8 (C-6), 155.2, 157.2, 164.1, 164.7 ppm; MS (EI): m/z (%) = 384 (M^+, 100), 369 (34), 355 (32), 339 (12); IR (KBr): $\nu = 1565$, 1525, 1440 cm^{-1}.

7-Substituted 3,4-Diphenylpyrimido[4',5':4,5]thieno[3,2-c]pyridazin-8(7H)-ones (**7a–c**); *General Procedure*

A solution of **4** (0.20 g, 0.56 mmol), 15% KOH (1 ml, 3.2 mmol), and the appropriate electrophilic reagent (1.25 mmol) in *THF* (15 ml) was stirred at room temperature for 48 h (**7a**) or at reflux temperature (20 h for **7b**, 6 h for **7c**). The solid formed was filtered off and recrystallized or purified by MPLC.

7-Methyl-3,4-diphenylpyrimidino[4',5':4,5]thieno[3,2-c]pyridazin-8(7H)-one (**7a**)

Recrystallized from acetone/dichloromethane; yield (91%); m.p.: >300 °C; $C_{21}H_{14}N_4OS$ (370.43); calc.: C 68.09, H 3.81, N 15.13; found: C 67.98, H 3.92; N 15.07; ^{1}H NMR ($CDCl_3$): $\delta = 3.64$ (s, 3H, CH_3), 7.26–7.30 (m, 10H, C_6H_5), 7.94 (s, 1H, H-6) ppm; MS (EI): m/z (%) = 370 (M^+, 90), 369 (100), 355 (5), 300 (6), 272 (20); IR (KBr): $\nu = 1660$ (CO), 1570, 1480, 1440, 1430 cm^{-1}.

7-Cyanomethyl-3,4-diphenylpyrimidino[4',5':4,5]thieno[3,2-c]pyridazin-8(7H)-one (**7b**)

Purified by MPLC using EtOH/dichloromethane (1:50) as eluent; yield (23%); m.p.: >300 °C; $C_{22}H_{13}N_5OS$ (395.44); calc.: C 66.82; H 3.31; N 17.71; found: C 66.95; H 3.25; N 17.67; ^{1}H NMR (*DMSO*-d_6): $\delta = 5.74$ (s, 2H, CH_2), 7.30–7.35 (m, 10H, C_6H_5), 8.38 (s, 1H, H-6) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 34.7$ (CH_2), 114.9 (CN), 126.4, 127.5, 127.8, 128.2, 128.5, 130.2, 130.3, 132.6 (C_6H_5), 135.9, 136.6, 149.0 (C-6), 150.1, 156.4, 156.8, 163.2; MS (EI): m/z (%) = 395 (M^+, 45), 394 (33), 355 (100), 310 (6), 296 (7); IR (KBr): $\nu = 1690$ (CO), 1590, 1480, 1450 cm^{-1}.

7-Phenacyl-3,4-diphenylpyrimidino[4',5':4,5]thieno[3,2-c]pyridazin-8(7H)-one (**7c**)

Recrystallized from acetone/dichloromethane; yield (60%); m.p.: 294–296 °C; $C_{28}H_{18}N_4O_2S$ (474.54); calc.: C 70.87; H 3.82; N 11.81; found: C 70.95; H 3.76; N 11.07; ^{1}H NMR ($CDCl_3$): $\delta = 5.47$ (s, 2H, CH_2), 7.22–8.04 (m, 15H, C_6H_5), 8.00 (s, 1H, H-6) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 51.2$ (CH_2), 127.7, 128.0, 128.2, 128.3, 128.6, 129.1, 130.5, 132.7, 134.0, 134.7 (C_6H_5), 136.0, 136.5, 148.1 (C-6), 156.9, 157.3, 164.1, 190.7 (CO) ppm; MS (EI): m/z (%) = 474 (M^+, 31), 473 (16), 355 (18); IR (KBr): $\nu = 1680$ (CO), 1590, 1480, 1440 cm^{-1}.

Acknowledgements

Financial support (Project No. 103038B95) from the *Xunta de Galicia* is gratefully acknowledged. The NMR, mass spectroscopic, and elemental analyses were kindly provided by *Servicios Generales de Apoyo a la Investigación* of the University of La Coruña.

References

[1] (a) Heinisch G, Kopelent H (1990) In: Ellis GP, West GB (eds) Progress in medicinal chemistry, vol 27. Elsevier, Amsterdam, p 1; (b) Heinisch G, Kopelent H (1990) In: Ellis GP, West GB (eds) Progress in medicinal chemistry, vol 29. Elsevier, Amsterdam, p 141; (c) Tišler M, Stanovnik B (1990) In: Katritzky AR (ed) Advances in heterocyclic chemistry, vol 49. Academic Press, San Diego, p 385

[2] (a) Youssefyeh RD, Brown RE, Wilson J, Shah U, Jones H, Loev B, Khaudwala A, Leibowitz RD, Sonnini-Goldman P (1984) J Med Chem **27**: 1639; (b) Khandwala A, Van Inwegen R, Couts S, Dally-Meade V, Youssefyeh RD (1983) Int Immunopharm **5**: 491; (c) Ferrand G, Dumas H, Depin JC, Chouvernac G (1987) Eur J Med Chem **22**: 337; (d) Cheng CC, Robins RK, Cheng KC, Lin DC (1968) J Pharm Sci **57**: 1044; (e) O'Reilly JM, Newlands ES, Glaser MG, Brampton M, Rice-Edwards JM, Illingworth RD, Richards PG, Kennard C, Colquhoun IR, Lewis P, Stevens MFG (1993) Eur J Cancer **29**: 940

[3] Negwer M (1987) Organic-chemical drugs and their synonyms, 4th edn. Akademie-Verlag, Berlin

[4] (a) Peinador C, Veiga C, Ojea V, Quintela JM (1995) Heterocycles **41**: 37; (b) Peinador C, Ojea V, Quintela JM (1992) J Heterocycl Chem **29**: 1693; (c) Peinador C, Moreira MJ, Quintela JM (1994) Tetrahedron **50**: 6705; (d) Quintela JM, Veiga MC, Alvarez-Sarandés R, Peinador C Monatsh Chem (in press)

[5] (a) Czech K, Haider N, Heinisch G (1991) Monatsh Chem **122**: 413; (b) Deeb A, Essawy AN, Yasine F, Fikry (1991) Z Naturforsch **46B**: 835

Received February 22, 1996. Accepted March 16, 1996