26. Synthesis of Thiazole and Fused Thiazolo Derivatives[1])

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The syntheses of thiazole and fused thiazolo derivatives **2–4**, **6–8**, **10a–11b**, **13–16** from heterocyclic isothiocyanates **1**, **5**, **9**, and **12** bearing an ortho ester group and bifunctional reagents, such as substituted propargylamines, is described. Different regioselectivity of intramolecular nucleophilic attack of the thiourea S-atom on the C≡C bond, resulting in the formation of both thiazolo and thiazino derivatives, as well as NMR structure elucidation are discussed.

Introduction. – A variety of methods are available for the synthesis of thiazole derivatives [1], but there are only few syntheses leading to fused tricyclic thiazolo heterocycles [2]. Some fused thiazolo heterocycles possess biological or pharmacological activities [3] [4].

The syntheses of thiazole derivatives using a reaction between thiourea and a compound containing a primary halogen group adjacent to a C≡C bond has been already described [5]. High regioselectivity for this ring closure has been described with the formation of only a five-membered ring.

The cyclization reactions of thiourea derivatives prepared by the reaction of the secondary α,α-disubstituted propargylamines with isothiocyanates led to the formation of only tetrahydrothiazole derivatives [6]. This method has been also used for the syntheses of thiazolo-quinazole derivatives from methyl 2-(isothiocyanato)benzoate, and no formation of thiazino ring was observed [7]. Heterocyclic isothiocyanates bearing ester groups in *ortho*-positions are useful synthons for the syntheses of fused *N*-heterocycles by addition of substituted amines and related compounds [3] [8–11].

In the present paper, we describe the syntheses of isomeric thiazolo[3,2-*a*]pyridopyrimidine, thiazolo[2,3-*b*]- and thiazino[2,3-*b*]pteridine, and thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine derivatives.

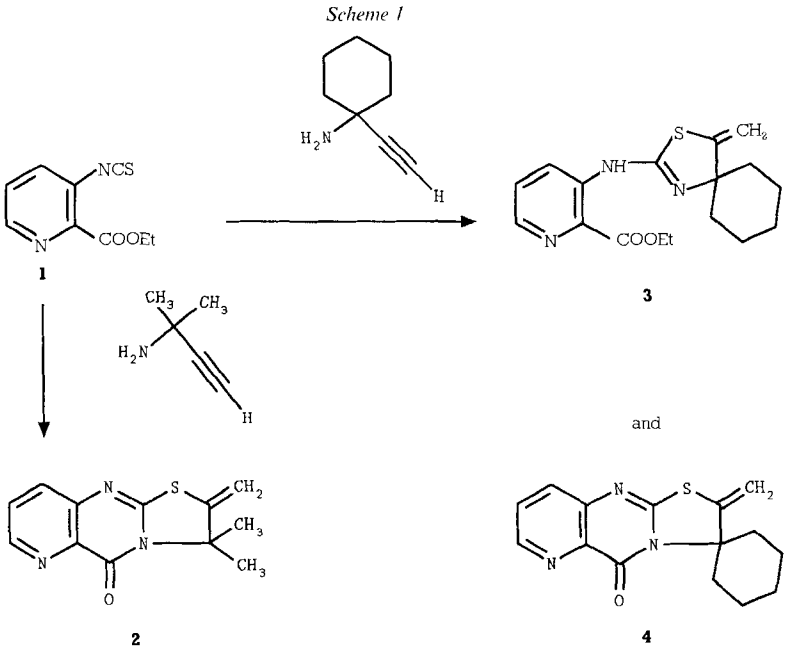
Results and Discussion. – The reaction between heterocyclic isothiocyanates and substituted propargylamines proceeds in three steps. The first step is the formation of a thiourea derivative, which could not be isolated. The second step is an intramolecular nucleophilic attack of the thiourea S-atom onto the C≡C bond.

[1]) Partly presented at ESOC 7, Namur, Belgium, 1991.

Regioselectivity in a ring closure by internal nucleophilic attack has been described [5] [12]. For nucleophilic attack of the S-atom at the C≡C bond, the bonding distances are close enough for both five- and six-membered ring formation [13], and according to *Baldwin*'s ring closure rules, both are favored [12]. We observed different regioselectivity of nucleophilic attack of the S-atom at the C≡C bond, and the formation of both thiazolo[2,3-*b*]- and thiazino[2,3-*b*]pteridine derivatives (*cf. Scheme 4*). In other reactions, thiazino derivatives were formed in a small amount, according to ^{1}H-NMR spectra. In some cases, we could not separate both products. The third step is further condensation of thiazolo and/or thiazino derivatives to fused systems.

Ethyl 3-isothiocyanatopyridine-2-carboxylate (**1**) [9] reacted with 1,1-dimethyl-2-propynylamine to 2,3-dihydro-3,3-dimethyl-2-methylidene-5-oxopyrido[3,2-*d*]thiazolo-[3,2-*a*]pyrimidine (**2**) and with eth-1-ynylcyclohexylamine to compounds **3** and **4** (*Scheme 1*). Both reactions formed five-membered rings, which could be isolated and detected

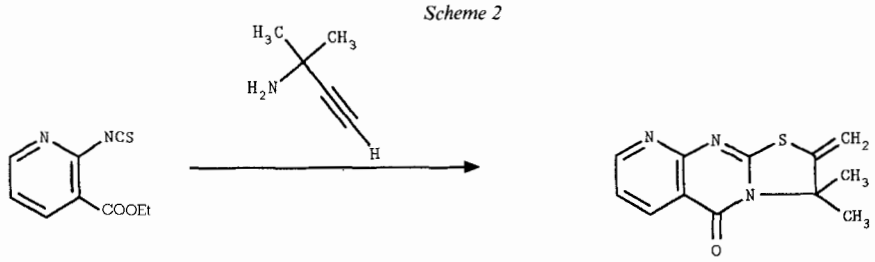
Scheme 1



with NMR spectroscopy. Two *dublets* with a ^2J values of *ca.* 2.5 Hz are characteristic for an exocyclic methylidene group. In the NMR spectrum of the evaporated reaction mixture, we observed also signals for the thiazino isomer which was not isolated (*ca.* 5%).

An analogous treatment of ethyl 2-isothiocyanato-3-pyridinecarboxylate (**5**) [9] with 1,1-dimethylpropargylamine gave 2,3-dihydro-3,3-dimethyl-2-methylidene-5-oxopyrido-[2,3-*d*]thiazolo[3,2-*a*]pyrimidine (**6**; *Scheme 2*) and in a very little amount the thiazino derivative (*ca.* 5%) which was observed in the ^{1}H-NMR spectrum of the crude reaction product and was not isolated and purified. For the thiazino ring, two *dublets* of low

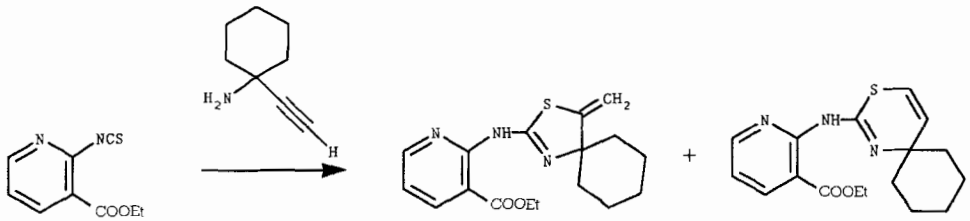
Scheme 2



5 **6**

intensity with a ^3J value of *ca.* 10 Hz at 5.65 and 6.09 ppm were observed. In the reaction of eth-1-ynylcyclohexylamine with isothicyanato-ester **5**, the expected fused product was not formed. In this case, we isolated only the thiazolo derivative **7** and the thiazino derivative **8** in ratio 1.78:1 (*Scheme 3*).

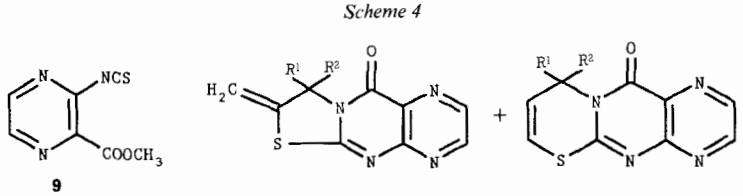
Scheme 3



5 **7** **8**

Methyl 3-isothiocyanatopyrazine-2-carboxylate (**9**) [10] reacted with substituted propargylamines with low regioselectivity in the second reaction step (*Scheme 4*) leading to a mixture of both five- and six-membered fused rings, *i.e.* thiazolo[2,3-*b*]pteridine derivatives **10a** and **10b** and thiazino[2,3-*b*]pteridine derivatives **11a** and **11b** which could not be separated chromatographically. The ratio of the products **10a**/**11a** is according to ^{1}H-NMR *ca.* 1:1.2, and for **10b**/**11b** the ratio is 3.6:1.

Scheme 4



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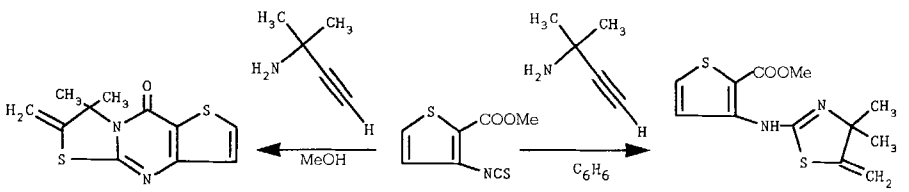
	R^1	R^2
10a	CH_3	CH_3
10b	$-(CH_2)_5-$	

	R^1	R^2
11a	CH_3	CH_3
11b	$-(CH_2)_5-$	

For the thiazino compounds, we observed two *dublets* with a ^3J value of *ca.* 10.6 Hz which is characteristic for olefinic protons (see *Exper. Part*).

When methyl 3-isothiocyanatothiophene-2-carboxylate (**12**) [3] was heated with 1,1-dimethylpropargylamine in MeOH, it underwent a transformation to give 6,7-dihydro-7,7-dimethyl-6-methylidene-9-oxothiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine (**13**), which is a less known ring system [4]. In benzene, the reaction product was methyl 3-[(4,5-dihydro-4,4-dimethyl-5-methylidenethiazol-2-yl)amino]thiophene-2-carboxylate (**14**; *Scheme 5*).

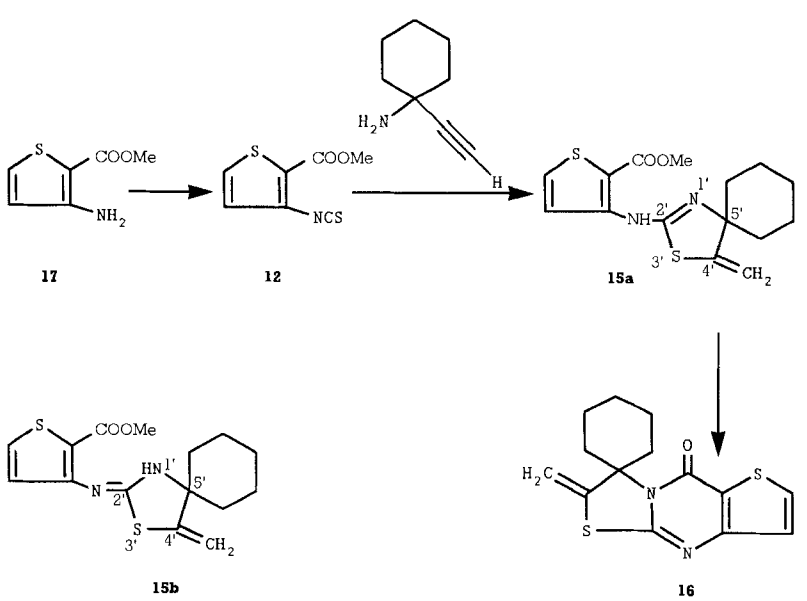
Scheme 5



13 **12** **14**

Isothiocyanate **12** reacted with eth-1-ynylcyclohexylamine at elevated temperature, and prolonged reaction in MeOH or benzene led to methyl 3-[(4-methylidene-3-thia-1-azaspiro[4.5]dec-1-en-2-yl)amino]thiophene-2-carboxylate (**15a**). Further reaction of **15a** with *t*-BuOK led to 6′,7′-dihydro-6′-methylidenespiro[cyclohexane-1,7′-thiazolo[3,2-*a*]-thieno[3,2-*d*]pyrimidin]-9′-one (**16**; *Scheme 6*).

Scheme 6



17 **12** **15a**

15b **16**

The prototropic tautomerism in heterocyclic compounds involves the shift of a proton between a ring N-atom and a substituent atom connected to the ring. The relative position of a functional group with respect to the hetero atoms often determines the tautomeric nature of such compounds [14]. Dihydrothiazoles, bearing protomeric amino group in a position corresponding to enanime function, are in tautomeric equilibrium with this functional group [2]. In the case of the dihydrothiazoles **3**, **7**, **14**, and **15**, a proton shift between two N-atoms forming an amidine-like substructure with an endocyclic or exocyclic C=N bond has to be discussed.

Previously, we used the selective heteronuclear $^{13}C\{^1H\}$-NOE technique for the analysis of the tautomerism in the pteridine system [10], and now we have applied this NMR technique for the determination of the tautomerism of compound **15** in a solution.

The assignment of the ^{13}C-NMR spectrum of **15** was achieved by comparison of the ^{13}C-chemical shifts of methyl 3-aminothiophene-2-carboxylate (**17**) [15]. Furthermore, an unambiguous assignment of the tertiary and quaternary C-atoms of **15** and **17** was supported by analysis of the coupling patterns in the gated-decoupled ^{13}C-NMR spectra (see *Exper. Part* for coupling constants, *cf.* [21]), selective heteronuclear $^{13}C\{^1H\}$ decoupling and NOE experiments, and finally by a long-range heteronuclear shift-correlation experiment (HC-COSY) of **15** (*Fig. 1*).

To decide whether the exchangeable proton of compound **15** is bonded to the exocyclic N-atom (tautomer **15a**) or to the ring N-atom of the dihydrothiazole ring (tautomer **15b**), we irradiated at the resonance frequency of N*H* (9.26 ppm) in the ^1H-NMR

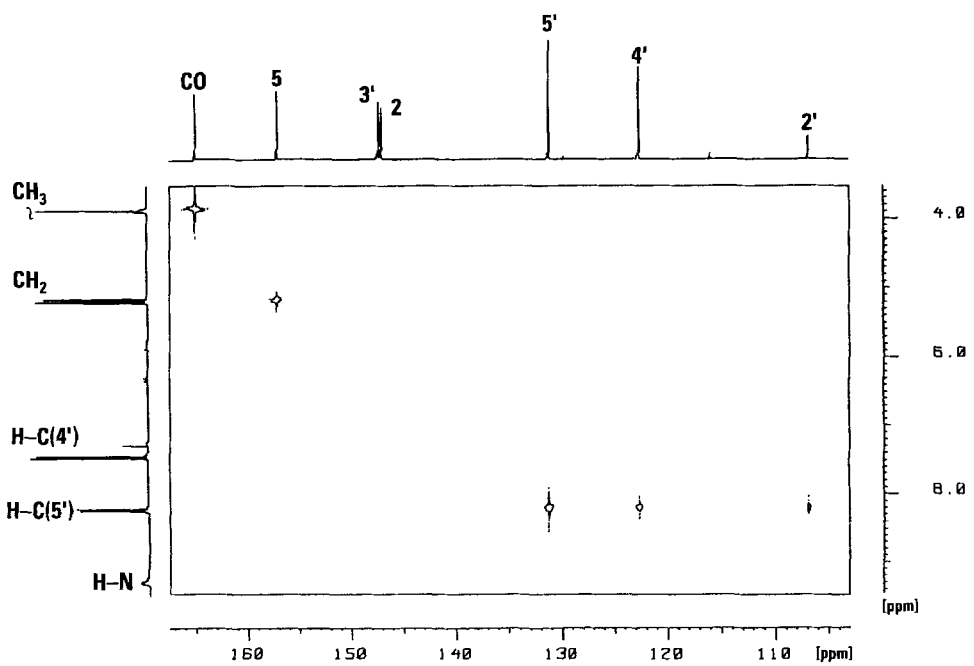


Fig. 1. *2D-^1H,^{13}C-NMR Spectrum of* **15a** (250.13/62.89 MHz, long-range shift correlation)

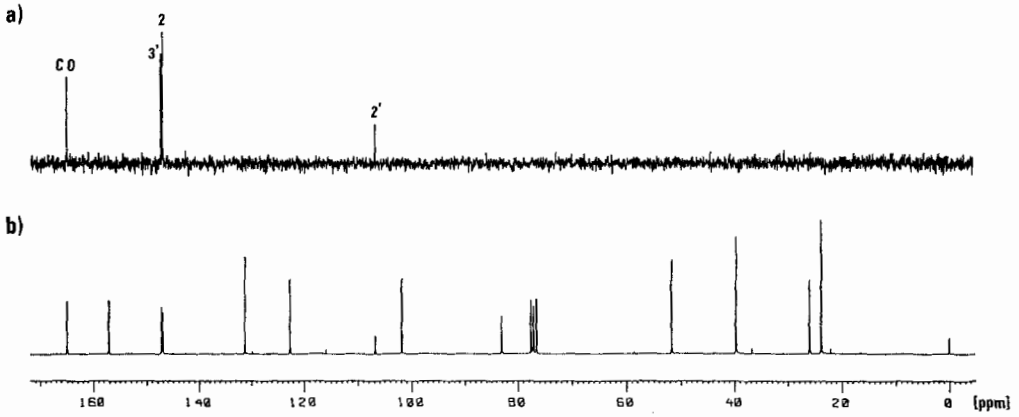


Fig. 2. *62.89-MHz ^{13}C-NMR Spectrum of* **15a** ($CDCl_3$). *a*) Proton-noise decoupled, *b*) NOE-difference spectrum after irradiation of H–N.

spectrum of the compound **15**, which resulted in signal enhancements of C(2′), C(3′), C(2), and $COOCH_3$ (*Fig. 2*).

An energy-optimized molecular model (ALCHEMY II) [16] of **15a** (*Fig. 3*) demonstrates that the range of distances between H–N and these C-atoms is significantly smaller than in the tautomeric form **15b** (**15a**: 1.946 Å (C(2)) to 2.644 Å ($COOCH_3$); **15b**:

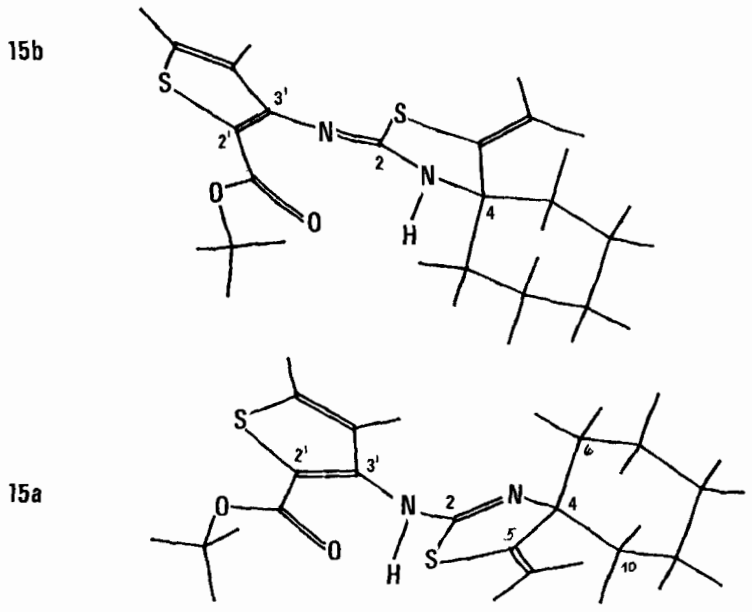


Fig. 3. *Molecular model of* **15a** *and* **15b** (drawing without H-atoms (= open valences) except of N–H for better overview)

1.986 Å (C(2)) to 4.359 Å (C(7))). Because of the relative short distance between H–N and C(4) in isomer **15b** (in our molecular model *ca.* 2.11 Å), the lack of a signal enhancement of C(4) may be interpreted as an argument against structure **15b**, which clearly has to be discarded.

The conclusion, that the observed NOEs do not arise from tautomer **15b** but from the tautomer **15a** is also supported by the fact that heteronuclear NOE's in ^{13}C-NMR spectra are difficult to determine for distances $\geq$ 2.9 Å because of the critical signal/noise ratio in such cases [17]. The small signals in the ^{13}C-NMR spectrum of **15a** (*Fig. 2*) are due to impurities and do not arise from tautomer **15b**. As we have found only one set of signals in the ^{13}C-NMR spectra of **4**, **7**, and **14** too, tautomeric equilibria seem not to be existent for the presented dihydrothiazoles with the tautomer containing an exocyclic C=N bond in a detectable concentration by NMR spectroscopy.

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Experimental Part

General. M.p.: *Reichert* hot-stage microscope, uncorrected. IR Spectra (in KBr, cm^{-1}): *Perkin-Elmer 325* and *Perkin-Elmer FTIR 1600* instruments. NMR Spectra in $CDCl_3$: ^{1}H- and ^{13}C-NMR: *Bruker WM-250* spectrometer, 5 mm ^{1}H/^{13}C dual probehead (^{1}H; 250.13 MHz, ^{13}C; 62.89 MHz) and *Varian VXR 300* spectrometer (^{1}H; 300 MHz); δ in ppm rel. to TMS; multiplicities and coupling constants in ^{13}C-NMR from gated-decoupled spectra (size 32 K; sweep width 7812.5 Hz (Hz/Pt = 0.477) and 7462.7 Hz (Hz/Pt = 0.455) for **17** and **15a**, resp. ^{1}H,^{13}C-COSY Spectrum: sequence: D1–90°(^{1}H)-D0-180°(^{13}C)-D0-D3-90°(1H), 90°(^{13}C)-D4-BB,FID; 90° ^{1}H pulse 12 µs, 180° ^{13}C pulse 14 µs, relaxation delay D1 = 3s, polarization time D3 = refocussing time D4 = 64.94 ms (optimized for J = 7.7 Hz), 90° spectral width 7462.7 Hz in F2, 1054.9 Hz in F1, data matrix 4096 × 512 (zero-filling in F1), 56 scans during 256 time increments, 2 dummy scans, *Lorentz* to *Gauss* multiplication in F1 (LB = –3, GB = 0.3), exponential multiplication in F2 (LB = 1). Selective heteronuclear ^{13}C{^{1}H}-NOE Difference Spectrum (*cf.* [18] [19]). 80 mg/0.5 ml $CDCl_3$. Size: 16 K, sweep width 11111 Hz, decoupling power for selective CW pre-irradiation 51 dB below 0.2 W, decoupling powder for broad band decoupling 0 dB below 0.2 W, decoupling time 3 s, switch delay for appropriate settings of decoupler frequency, power and decoupler status twice 0.05 s, recycling time 3.837 s, pulse length 4 µs (*ca.* 50° pulse), 8200 acquisitions each and off-resonance (200 scans, 8 dummy scans, 41 cycles), exponential multiplication of the difference FID prior to *Fourier* transformation (LB = 1). EI-MS: *Varian MAT 311* mass spectrometer. Elemental analyses: *Heraeus* C,H,N,O rapid analyzer and *Perkin-Elmer 2400* CHN analyzer.

*2,3-Dihydro-3,3-dimethyl-2-methylidenepyrido[3,2-*d*]thiazolo[3,2-*a*]pyrimidin-5-one* (**2**). To a soln. of *ethyl 3-isothiocyanatopyridine-2-carboxylate* (**1**) [8] (0.28 g, 1.3 mmol) in MeOH (7 ml), 1,1-dimethylprop-2-ynylamine (0.14 g, 1.3 mmol) was added, and the mixture was heated at reflux for 6 h, precipitated product was filtered off and purified using column chromatography (silica gel, Et_2O/MeOH 3:1): 0.08 g (23%) of **3**. M.p. 129–131°. IR: 2980, 2960, 1690, 1575, 1550, 1430. ^{1}H-NMR: 1.98 (*s*, 2CH_3); 5.31, 5.42 (2*d*, J = 2.7, CH_2=); 7.62 (*dd*, J(8,9) = 8.3, H–C(8)); 7.86 (*dd*, H–C(9)); 8.76 (*dd*, J(7,8) = 4.0, J(7,9) = 1.6, H–C(7)): ^{13}C-NMR: 158.7 (C(5)); 158.1 (C(10a)); 148.7 (C(7)); 145.1 (C(9a)); 144.6 (C(2)); 137.1 (C(5a)); 133.9 (C(9)); 128.5 (C(8)); 105.6 (CH_2=); 73.3 (C(3)); 26.53 (2 CH_3). MS: 245 (100, M^+). Anal. calc. for $C_{12}H_{11}N_3OS$ (245.31): C 58.76, H 4.52, N 17.13; found: C 59.08, H 4.25, N 16.72.

Reaction of **1** [8] *and Eth-1-ynylcyclohexylamine.* A soln. of **1** (0.5 g, 2.4 mmol) and eth-1-ynylcyclohexylamine (0.311 g, 2.53 mmol) in MeOH (7 ml) was heated under reflux for 8 h, evaporated under reduced pressure and separated by column chromatography (silica gel, CH_2Cl_2/acetone, 100:1 and 30:1, as solvents). The first

fraction gave, after evaporation, *ethyl 3-[(4-methylidene-3-thia-1-azaspiro[4.5]dec-1-en-2-yl)amino]pyridine-2-carboxylate* (**3**; 0.064 g, 8.1%). M.p. 106–110°. IR: 3241, 2927, 2854, 1684, 1639, 1587, 1516, 1456, 1389, 1313, 1255, 1206, 1154, 1091, 1033, 992, 856. ^{1}H-NMR: 1.2–1.87 (*m*, cyclohexylidene); 1.4 (*t*, J = 7.2, CH_3); 4.43 (*q*, J = 7.2, CH_2O); 5.09, 5.12 (2*d*, J = 1.9, CH_2=); 7.41 (*dd*, J(5,6) = 4.6, H–C(5)); 8.26 (*dd*, H–C(6)); 9.22 (*dd*, J(4,5) = 8.7, J(4,6) = 1.2, H–C(4)); 10.24 (br., NH). ^{13}C-NMR: 167.8 (*C*OOEt); 156.1 (C(6)); 147.7 (C(2′)); 141.5 (C(4)); 116.1 (C(5)); 101.9 (CH_2=); 62.2 (CH_2O); 39.6 (C(6,10)); 25.9 (C(8)); 23.7 (C(7,9)); 14.2 (CH_3). MS: 331 (100, M^+). Anal. calc. for $C_{17}H_{21}N_3O_2S$ (331.42): C 61.60, H 6.39, N 12.68; found: C 61.28, H 6.19, N 12.60.

The second fraction gave, after evaporation, *2′,3′-dihydro-2′-methylidenespiro[cyclohexane-1,3′-pyrido[3,2-a]thiazolo[3,2-d]pyrimidin]-5′-one* (**4**; 0.134 g, 25.5%). M.p. 144–146° (from EtOH). IR: 3360, 2998, 1695, 1573, 1550, 1462, 1423, 1361, 1319, 1298, 1220, 1205, 1127, 1010, 885, 820, 810, 695. ^{1}H-NMR: 1.5–2.02 (*m*, 8H, cyclohexylidene); 3.08–3.29 (*m*, 2H, cyclohexylidene); 5.32, 5.78 (2*d*, J = 2.6, CH_2=); 7.59 (*dd*, J(8′,9′) = 8.3, H–C(8′)); 7.83 (*dd*, H–C(9′)); 8.74 (*dd*, J(7′,8′) = 4.3, J(7′,9′) = 1.6, H–C(7′)). ^{13}C-NMR: 159.0 (*d*, J = 1.3, C(5′)); 158.7 (*s*, C(10′a)); 148.6 (*ddd*, J = 182.3, 7.9, 3.3, C(7′)); 144.5 (*dt*, J = 8.4, 1.7, C(9′a)); 144.0 (*m*, C(2′)); 137.6 (*ddd*, J = 11.7, 4.6, 1.3, C(5′a)); 133.8 (*dd*, J = 166.8, 6.3, C(9′)); 128.5 (*dd*, J = 165.6, 9.6, C(8′)); 108.8 (*dd*, J = 163.5, 161.4, CH_2=); 76.1 (br. *s*, C(3′)); 30.3 (C(1), C(6)); 23.3 (C(4)); 21.7 (C(3), C(5)). MS: calc. for $C_{15}H_{15}N_3OS$: 285.0936; found: 285.0935.

Under the same reaction conditions in benzene only compound **3** was formed in 62.8% yield.

2,3-Dihydro-3,3-dimethyl-2-methylidene-5-pyrido[2,3-d]thiazolo[3,2-a]pyrimidin-5-one (**6**). Prepared in the same manner as compound **2** in MeOH: 44.2% (from EtOH). M.p. 143–145°. IR: 3420, 3000, 1689, 1575, 1509, 1430, 1329, 1286, 1240, 1179, 1140, 1011, 895, 794. ^{1}H-NMR: 1.95 (*s*, 2CH_3); 5.31, 5.41 (2*d*, J = 1.8, CH_2=); 7.35 (*dd*, J(7,8) = 4.8, H–C(7)); 8.53 (*dd*, J(6,7) = 7.8, J(6,8) = 2.1, H–C(6)); 8.88 (*dd*, H–C(8)). ^{13}C-NMR: 161.3 C(5)); 160.4 (C(10a)); 157.9 (C(9a)); 156.1 (C(8)); 144.0 (C(2)); 136.3 (C(6)); 121.3 (C(7)); 115.3 (C(5a)); 105.6 (CH_2=); 73.2 (C(3)); 26.7 (2CH_3). MS: 245 (100, M^+). Anal. calc. for $C_{12}H_{11}N_3OS$ (245.31): C 58.76, H 4.52, H 17.13; found: C 58.78, H 4.62, N 17.09.

Reaction of Ethyl 2-Isothiocyanatopyridine-3-carboxylate (**5**) [11] *and Eth-1-ynylcyclohexylamine.* A soln. of **5** (0.3 g, 1.44 mmol) and eth-1-ynylcyclohexylamine (0.201 g, 1.63 mmol) in benzene or EtOH (15 ml) was heated under reflux for 4 h, evaporated under reduced pressure and separated by column chromatography (silica gel, $CHCl_3$/Acetone 50:1 and 30:1, as solvents). The first fraction gave, after evaporation, *ethyl 2-[(4-methylidene-3-thia-1-azaspiro[4.5]dec-1-en-2-yl)amino]pyridine-3-carboxylate* (**7**; 0.253 g, 52.8%). M.p. 145–146° (from EtOH). IR: 3210, 2940, 2930, 2860, 1698, 1628, 1605, 1582, 1510, 1460, 1450, 1395, 1370, 1310, 1290, 1260, 1145, 1090, 1072, 1025, 990, 842, 779. ^{1}H-NMR: 1.2–1.92 (*m*, cyclohexylidene); 1.38 (*t*, J = 7.1, CH_3); 4.37 (*q*, J = 7.1, CH_2O); 5.02, 5.16 (2*d*, J = 1.3, CH_2=); 6.84 (*dd*, J(5,6) = 4.8, H–C(5)); 8.21 (*dd*, J(4,5) = 7.8, J(4,6) = 1.6, H–C(4)); 8.34 (*dd*, J(5,6) = 4.8, H–C(6)); 10.7 (br. *s*, NH); ^{13}C-NMR: 166.6 (*m*, *C*OOEt); 157.1 (*ddd*, J = 179.5, 7.6, 3.6, C(6)); 148.7 (overlap in gated dec. spectrum, C(2′)); 140.2 (*ddd*, J = 165.2, 6.7, 1.8, C(4)); 115.6 (*dd*, J = 167.9, 7.6, C(5)); 108.1 (*m*, C(3)); 100.8 (*t*, J = 160.5, CH_2=); 75.8 (br., C(4′)); 61.7 (CH_2O); 39.7 (C(6′), C(10′)); 26.0 (C(8′)); 23.1 (C(7′), C(9′)); 14.2 (CH_3). MS: 331 (100, M^+). Anal. calc. for $C_{17}H_{21}N_3O_2S$ (331.42): C 61.60, H 6.39, N 12.68; found: C 61.77, H 6.53, N 12.77.

The second fraction gave, after evaporation, *ethyl 2-[(3-thia-1-azaspiro[5.5]undeca-1,4-dien-2-yl)amino]-pyridine-3-carboxylate* (**8**; 29.8%). M.p. 86–87°. IR: 3302, 2930, 2855, 1693, 1618, 1589, 1499, 1451, 1421, 1368, 1328, 1288, 1256, 1182, 1136, 1086, 991, 923, 906, 814. ^{1}H-NMR: 1.4 (*t*, J = 7.1, CH_3); 1.3–1.9 (*m*, cyclohexylidene); 4.38 (*q*, J = 7.1, CH_2O); 5.85, 6.19 (2*d*, J = 9.6, H–C(4′), H–C(5′)); 6.84 (*dd*, J(5,6) = 4.8, H–C(5)); 8.19 (*dd*, J(4,5) = 7.6, J(4,6) = 1.7, H–C(4)); 8.34 (*dd*, H–C(6)); 10.28 (br., NH). MS: 331 (73, M^+), 28,8 (100, $[M-43]^+$). Anal. calc. for $C_{17}H_{21}N_3O_2S$ (331.42): C 61.60, H 6.39, N 12.68; found: C 61.47, H 6.23, N 12.46.

Reaction of Methyl 3-Isothiocyanatopyrazine-2-carboxylate (**9**) [10] *and 1,1-Dimethylprop-2-ynylamine.* A soln. of **9** (0.42 g, 2.2 mmol) and 1,1-dimethylprop-2-ynylamine (0.26 g, 2.4 mmol) in MeOH (5 ml) was heated under reflux for 6 h. Precipitated product was filtered off and recrystallized from EtOH to give 0.33 g (62%) of *2,3-dihydro-8,8-dimethyl-7-methylidenethiazolo[2,3-b]pteridin-10-one* (**10a**) and *9,9-dimethylthiazino[2,3-b]-pteridin-11-one* (**11a**) in a ratio (according to NMR data) of 1:1.2. It was not possible to separate both products. M.p. 233–235°. IR: 3440, 2990, 1708, 1575, 1519, 1450, 1410, 1320, 1283, 1235, 1210, 1160, 1130, 1110, 910, 880, 825, 725. MS: 246 (100, M^+). Anal. calc. for $C_{11}H_{10}N_4OS$ (246.29): C 53.64, H 4.09, N 22.75; found: C 53.52, H 4.04, N 22.60.

10a: ^{1}H-NMR: 1.99 (*s*, 2CH_3); 5.34, 5.45 (2*d*, J = 2.9, CH_2=); 8.66, 8.86 (2*d*, J = 2.1, H–C(2), H–C(3)).

11a: ^{1}H-NMR: 1.94 (*s*, 2CH_3); 5.70, 6.09 (2*d*, J = 10.7, H–C(8), H–C(7)); 8.69, 8.86 (2*d*, J = 2.1, H–C(2), H–C(3)).

Reaction of **9** [10] *and Eth-1-ynylcyclohexylamine.* A soln. of **9** (0.45 g, 2.3 mmol) and eth-1-ynylcyclohexylamine (0.28 g, 2.3 mmol) in EtOH (5 ml) was heated under reflux for 6 h. Precipitated product was filtered off and

recrystallized from i-PrOH to give 0.13 g (32%) of *2′,3′-dihydro-7′-methylidenespiro[cyclohexane-1,8′-thiazolo[2,3-b]pteridin]-10′-one* (**10b**) and *spiro[cyclohexane-1,9′-thiazino[2,3-b]pteridin]-11′-one* (**11b**) in a ratio of 3.6:1 (NMR). It was not possible to separate the products. M.p. 217–220°. IR: 3440, 2939, 2870, 1700, 1582, 1550, 1540, 1460, 1405, 1325, 1269, 1249, 1210, 1190, 1115, 1040, 900, 830, 790, 725. ^{1}H-NMR: 1.47–2.08 (*m*, 8 H, cyclohexylidene); 3.0–3.22 (*m*, 2 H, cyclohexylidene); 5.36, 5.80 and 6.24, 6.42 (2 × 2*d*, first set of signals J = 2.8, CH_2=, second set of signals J = 10.6, H–C(7′), H–C(8′), **11b**); 8.69, 8.84 (2*d*, J = 1.2, pyrazine). MS: 286 (100, M^+). Anal. calc. for $C_{14}H_{14}N_4OS$ (286.36): C 58.72, H 4.93, N 19.57; found: C 58.95, H 4.99, N 19.68.

2,3-Dihydro-7,7-dimethyl-6-methylidenethiazolo[3,2-a]thieno[3,2-d]pyrimidine (**13**). From methyl *3-isothiocyanatothiophene-2-carboxylate* (**12**; 0.32 g, 1.61 mmol) and 1,1-dimethylprop-2-ynylamino (0.15 g, 1.61 mmol) in MeOH (8 ml) at reflux for 6 h. Precipitated product was filtered off and crystallized from EtOH: 0.24 g (60.6%) of **13**. M.p. 134–135°. IR: 3450, 3130, 2980, 1680, 1550, 1500, 1305. ^{1}H-NMR: 1.97 (*s*, 2CH_3); 5.28, 5.39, (2*d*, J = 1.7, CH_2=); 7.16 (*d*, J = 5.1, H–C(3)); 7.71 (*d*, J = 5.1, H–C(2)). MS: 250 (100, M^+). Anal. calc. for $C_{11}H_{10}N_2OS_2$ (250.34): C 52.78, H 4.03, N 11.19; found: C 52.65, H 4.03, N 11.12.

Methyl 3-[(4,5-Dihydro-4,4-dimethyl-5-methylidenethiazol-2-yl)amino]thiophene-2-carboxylate (**14**). A soln. of **12** (0.46 g, 2.3 mmol) and 1,1-dimethylprop-2-ynylamine (0.23 g, 2.8 mmol) in benzene (10 ml) was heated under reflux for 6 h, evaporated under reduced pressure, and purified by column chromatography (silica gel, $CHCl_3$/acetone 50:1): 0.42 g (64.5%) of **14**. M.p. 99–100°. IR: 3310, 2967, 2854, 1675, 1632, 1572, 1452, 1425, 1260, 1165, 1105, 1023, 971, 875, 780. ^{1}H-NMR: 1.46 (*s*, 2CH_3); 3.87 (*s*, CH_2O); 5.14, 5.16 (2*d*, J = 1.8, CH_2=); 7.41 (*d*, J = 5.5, H–C(4)); 8.11 (*d*, J = 5.5, H–C(5)); 9.2 (br., NH). ^{13}C-NMR: 165.0 (*C*OOMe); 156.6 (C(5′)); 148.3 (C(3)); 147.2 (C(2′)); 131.3 (C(5)); 122.6 (C(4)); 106.9 (C(2)); 102.4 (CH_2=); 80.0 (C(4′)); 51.7 (CH_3); 30.2 (2CH_3). MS: calc. for $C_{12}H_{14}N_2O_2S_2$: 282.0497; found: 282.0496.

Methyl 3-[(4-Methylidene-3-thia-1-azaspiro[4.5]dec-1-en-2-yl)amino]thiophene-2-carboxylate (**15a**). A soln. of **12** (0.51 g, 2.6 mmoles) and eth-1-ynylcyclohexylamine (0.32 g, 2.6 mmol) in EtOH or benzene (10 ml) was heated under reflux for 6 h. Precipitated product was filtered off and recrystallized from EtOH: 0.63 g (84.8%) of **15a**. M.p. 139–142°. IR: 3320, 2949, 2859, 1685, 1670, 1640, 1612, 1572, 1451, 1420, 1408, 1281, 1255, 1160, 1105, 999, 872, 780, 730. ^{1}H-NMR: 1.30–1.98 (*m*, cyclohexylidene); 3.88 (*s*, CH_3); 5.12, 5.19 (2*d*, J = 1.8, CH_2=); 7.42 (*d*, J = 5.6, H–C(4)); 8.20 (*d*, J = 5.6, H–C(5)); 9.28 (br., NH). ^{13}C-NMR: 165.0 (*m*, *C*OOMe); 157.1 (br. *s*, C(4′)); 147.3 (*dd*, J = 11.4, 2.3, C(3)); 147.0 (*s*, C(2′)); 131.3 (*dd*, J = 185.8, 7.3, C(5)); 122.6 (*dd*, J = 177.6, 4.6, C(4)); 106.8 (*dd*, J = 7.7, 5.5, C(2)); 101.9 (*dd*, J = 162.2, 159.9, CH_2=); 83.1 (br. *s*, C(5′)); 51.7 (CH_3); 39.7 (C(6′), C(10′)); 26.0 (C(8′)); 23.8 (C(7′), C(9′)). MS: 322 (100, M^+). Anal. calc. for $C_{15}H_{14}N_2O_2S_2$ (322.45): C 55.87, H 5.63, N 8.69; found: C 55.78, H 5.61, N 8.63.

6′,7′-Dihydro-6-methylidenespiro[cyclohexane-1,7′-thiazolo[3,2-a]thieno[3,2-d]pyrimidin]-9′-one (**16**). To a soln. of **15** (0.64 g, 2 mmol) in abs. toluene (10 ml), *t*-BuOK (0.09 g, 0.7 mmol) was added, the mixture stirred at reflux temp. for 6 h, and then washed with 10 ml of H_2O. The org. phase was dried (Na_2SO_4). After drying, the solvent was removed under reduced pressure and the product recrystallized from EtOH: 0.35 g (60.1%) of **16**. M.p. 98–100°. IR: 3085, 2929, 1658, 1544, 1500, 1452, 1270, 1222, 1125, 1015, 876, 782. ^{1}H-NMR: 1.42–2.0 (*m*, 8H, cyclohexylidene); 3.05–3.25 (*m*, 2H, cyclohexylidene); 5.29, 5.74 (2*d*, J = 1.8, CH_2=); 7.15 (*d*, J = 5.3, H–C(3′)); 7.71 (*d*, J = 5.3, H–C(2′)). MS: 290 (100, M^+). Anal. calc. for $C_{14}H_{14}N_2OS_2$ (290.41): C 57.90, H 4.86, N 9.65; found: C 58.16, H 4.95, N 9.69.

Methyl 3-Aminothiophene-2-carboxylate (**17**). Commercial product available from *Aldrich* was used without further purification. ^{1}H-NMR: 3.81 (*s*, CH_3); 5.53 (br. *s*, NH_2); 6.51 (*d*, J = 5.4, H–C(4)); 7.24 (*d*, J = 5.4, H–C(5)). ^{13}C-NMR: 164.8 (*m*, *C*OOMe); 154.0 (*dd*, J = 10.5, 3.8, C(3)); 131.4 (*dd*, J = 184.5, 5.7, C(5)); 119.7 (*dt*, J = 5.3, 4.3, C(4)); 100.9 (*m*, C(2)); 51.5 (*q*, J = 146.9, CH_3).

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