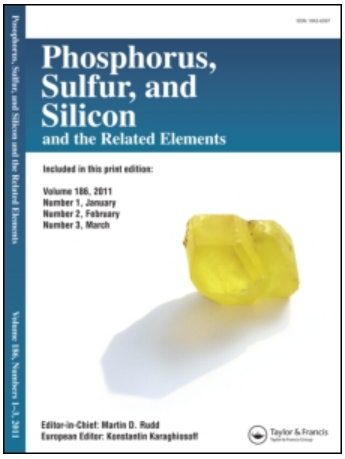


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of 5-Thioxo-hexahydrobenzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines and Related Compounds Based on Cyclocondensations of 2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene

Wolf-Diethard Pfeiffer[a]; Horst Dollinger[b]; Peter Langer[cd]
[a] Institut für Biochemie, Universität Greifswald, Greifswald, Germany [b] Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Riss, Germany [c] Institut für Chemie, Universität Rostock, Rostock, Germany [d] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock, Germany

To cite this Article Pfeiffer, Wolf-Diethard , Dollinger, Horst and Langer, Peter(2009) 'Synthesis of 5-Thioxo-hexahydrobenzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines and Related Compounds Based on Cyclocondensations of 2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 3, 626 — 637
To link to this Article: DOI: 10.1080/10426500802243216
URL: http://dx.doi.org/10.1080/10426500802243216

Phosphorus, Sulfur, and Silicon, 184:626–637, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802243216

Taylor & Francis
Taylor & Francis Group

Synthesis of 5-Thioxo-hexahydrobenzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines and Related Compounds Based on Cyclocondensations of 2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene

Wolf-Diethard Pfeiffer,[1] Horst Dollinger,[2] and Peter Langer[3,4]
[1]Institut für Biochemie, Universität Greifswald, Greifswald, Germany
[2]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach / Riss, Germany
[3]Institut für Chemie, Universität Rostock, Rostock, Germany
[4]Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock, Germany

5-Thioxo-4,6,8,9,10,11-hexahydro-benzo[b]thiopheno[2,3-d]-1,2,4-triazolo[1,5-c]pyrimidines and related compounds were prepared based on cyclizations of 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene with aminoketones and carboxylic hydrazides.

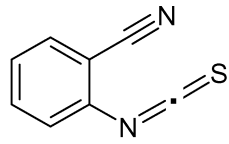
Keywords Cyclizations; heterocycles; isothiocyanates; nitriles

INTRODUCTION

2-Isothiocyanatobenzonitrile represents a preparatively useful difunctional benzene derivative that combines a nitrile and an isothiocyanate functionality. The reaction of this compound with O- and N-nucleophiles, such as butan-1-ol,[1] anilines,[2] and acetamidines,[3] was reported. Radical-type cyclizations have also been studied.[4] The cyclization of 2-isothiocyanatobenzonitrile with amines[5a] and hydrazine[6] gave 4-imino-1,2,3,4-tetrahydroquinazoline-2-thiones. We reported cyclization reactions of 2-isothiocyanatobenzonitrile with arylacetonitriles,[7] carboxylic hydrazides,[8] α-aminoesters,[9] and α-aminoketones.[10] Herein,

Received 26 March 2008; accepted 21 May 2008.
Financial support from Boehringer Ingelheim Pharma GmbH & Co. KG, from the DFG, and from the state of Mecklenburg-Vorpommern is gratefully acknowledged.
Address correspondence to Peter Langer, Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany. E-mail: peter.langer@uni-rostock.de

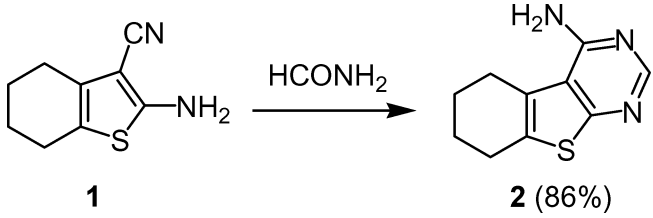
we report what is, to the best of our knowledge, the first application of this chemistry to a heterocyclic substrate. 2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene, a heterocyclic analog of 2-isothiocyanatobenzonitrile,[5b] was prepared by an improved procedure and used for novel cyclization reactions. These reactions allow the synthesis of 5-thioxohexahydro-benzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines and related compounds. It is also worth noting that related 1,2,4-triazolo[1,5-*c*]quinazolines are of considerable pharmacological relevance (antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neurostimulating, and benzodiazepine binding activity)[11–13] and benzimidazo[2,1-*b*]quinazoline-12(5*H*)-ones are potent immunosuppressors.[14]



2-Isothiocyanato-benzonitrile

RESULTS AND DISCUSSION

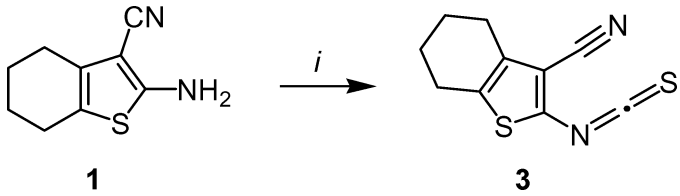
The reaction of 2-amino-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carbonitrile (**1**), available by a known procedure (Gewald synthesis),[15] with formamide afforded 4-amino-tetrahydrobenzo[*b*]thiopheno-2,3-*d*]pyrimidine (**2**) in 86% yield (Scheme 1).



1 **2** (86%)

SCHEME 1 Synthesis of **2**. Conditions: *i*: reflux, neat.

2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thiophene (**3**), obtained by a modified protocol,[16] was prepared by calcium carbonate mediated reaction of **1** with thiophosgene (Scheme 2). During the optimization of this reaction, the use of ultrasound irradiation proved to be important. In addition, the temperature and the purification



1 3

SCHEME 2 Synthesis of **3**. Conditions: *i*: $CSCl_2$, $CaCO_3$, CH_2Cl_2, 20°C, 4 h, ultrasound.

(extraction with hot petroleum ether) were important parameters. Several byproducts were formed (by reaction of **3** with unreacted **1**) when the temperature was allowed to rise above 20°C.

The reaction of **3** with formic hydrazide (**4a**) and acetic hydrazide (**4b**) afforded the 5-thioxo-4,6,8,9,10,11-hexahydro-benzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines **5a** and **5b**, respectively (Scheme 3, Table I). The formation of **5a,b** proceeds by attack of the amino group onto the isothiocyanate, cyclization by attack of the nitrogen atom onto the nitrile and subsequent attack of the imino group onto the amide. The cyclization of **3** with phenacyl bromide (**4c**) and 4-bromophenacyl bromide (**4d**) afforded the 5-thioxo-4,6,8,9,10,11-hexahydro-benzo[*b*]thiopheno[2,3-*d*]-imidazo[1,2-*c*]pyrimidines **5c** and **5d**, respectively.

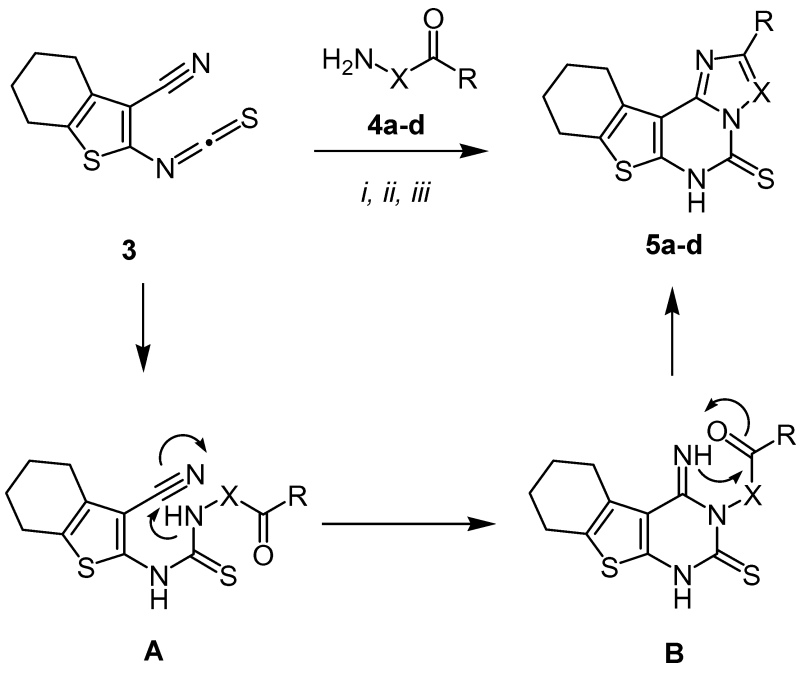
The reaction of **5a–d** with methyl iodide and benzyl bromide afforded the sulfides **6a–e** (Scheme 4, Table II). The reaction of **6a, 6b,** and **6d** with piperidine gave the 5-piperidino-hexahydro-benzo[*b*]-thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines **7a** and **7b** and the 5-piperidino-hexahydro-benzo[*b*]thiopheno[2,3-*d*]-imidazolo[1,2-*c*]-pyrimidine **7c**, respectively.

In conclusion, we have reported the synthesis of 5-thioxo-4, 6, 8, 9, 10, 11-hexahydro-benzo[*b*] thiopheno [2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines and related compounds based on cyclocondensations of 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with aminoketones and carboxylic hydrazides.

EXPERIMENTAL

General Comments

All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization



SCHEME 3 Synthesis of **5a–d**: *i*, method A (**5a**): EtOH, reflux, 12 h; method B (**5b**): N(*n*Pr)$_3$, EtOH, reflux, 14 h; method C (**5c,d**): 1) Na_2CO_3, H_2O, 20°C, 20 min; 2) CH_2Cl_2, reflux, 15 min; 3) EtOH, reflux, 24 h.

TABLE I Synthesis of 5a–d

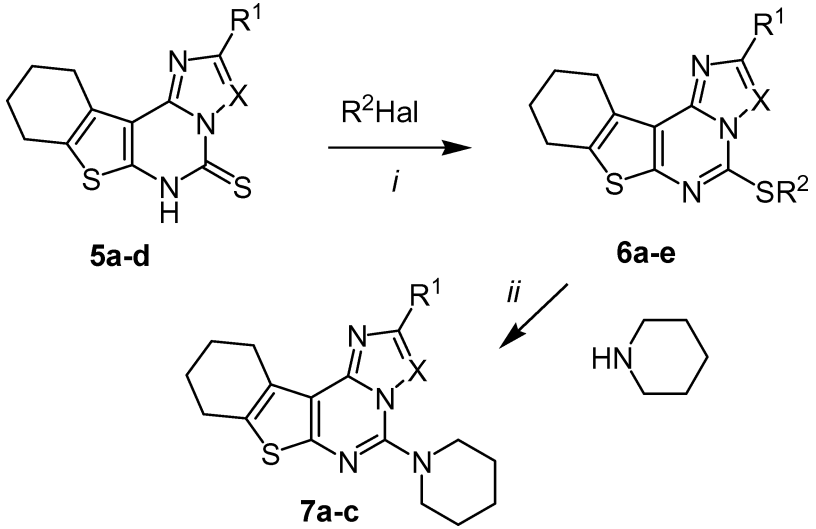
5	X	R	% (5)[a]
a	N	H	76
b	N	Me	78
c	CH	Ph	81
d	CH	4-BrC_6H_4	84

[a]Isolated yields.

(CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

5,6,7,8-Tetrahydrobenzo[*b*]thiopheno[2,3-*d*]pyrimidine-4-ylamine (2)

A mixture of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**1**) (1.78 g, 10.0 mmol) and formamide (3.60 g, 80.0 mmol)



SCHEME 4 Synthesis of **6a–e** and **7a–c.** *i*: method A (**6a,b,d,e**): NaOH, H_2O, MeI, 60°C; method B (**6c**): MeOH, NaOMe, BnBr, 2 h reflux; *ii*, neat, reflux, 16–18 h.

TABLE II Synthesis of 6a–e and 7a–c

5	6	7	X	R^1	R^2	% (**6**) [a]	% (**7**)[a]
a	**a**	**a**	N	H	Me	71	89
b	**b**	**b**	N	Me	Me	73	81
b	**c**		N	Me	Bn	86	—[b]
c	**d**	**c**	CH	Ph	Me	82	81
D	**e**		CH	4-BrC_6H_4	Me	87	—[b]

[a]Isolated yields; [b]experiment not carried out.

was refluxed for 20 min. On cooling, a precipitate crystallized, which was filtered off. Yield: 1.76 g (86%), orange prisms (EtOH), mp. 188°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 580$ (m), 688 (m), 1099 (m), 1168 (s), 1336 (m), 1446 (m), 1519 (m), 1599 (m), 2934 (m).^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.74–1.76 (t, 4H, 2 × CH_2), 2.59 (m, 4H, 2 × CH_2), 8.36 (s, 1H, Hetar), 11.89 (s, 2H, NH_2).^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 21.6$, 22.5, 23.3, 23.4, 113.8, 127.6, 130.6, 145.0, 158.9. MS (EI, 70 eV): $m/z = 206$ (M^+, 47), 178 (48), 149 (100), 77 (3), 28 (3). Anal.: calcd. for $C_{10}H_{11}N_3S$ (205.28): C, 58.51; H, 5.40; N, 20.47. Found: C, 58.62; H, 5.45; N, 20.51.

2-Isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3)

A suspension of **1** (36.7 g, 0.20 mol) in dichloromethane (300 mL) was slowly (within 20 min) added to a dichloromethane suspension (850 mL) of finely pulverized calcium carbonate (50.0 g, 0.50 mol) and of thiophosgene (28.7 g, 0.25 mol) at 20°C with vigorous stirring. After stirring for 4 h at 20°C with ultrasound irradiation, the solid was filtered off and washed with anhydrous dichloromethane (50 mL). The solvent and unreacted thiophosgene were distilled off using a rotary evaporator at 20°C. The crude product was dissolved in hot petroleum ether, and the red insoluble residue was filtered off. The solvent was removed in vacuo. Yield: 40.1 g (91%), light-brown crystals (petroleum ether), mp 68–70°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 1565$ (s, C=C), 2225 (m, CN), 2000 (m, NCS), 2950 (s, CH), 2870 (s, CH). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.71–1.95$ (m, 4H, CH_2), 2.49–2.76 (m, 4H, CH_2). Anal. calcd. for $C_{18}H_{12}N_5Cl$ (220.32): C, 54.52; H, 3.66; N, 12.72. Found: C, 54.61; H, 3.72; N, 12.78.

5-Thioxo-4,6,8,9,10,11-hexahydro-benzo[*b*]thiopheno[2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (5a)

An ethanol solution (30 mL) of **4a** (0.60 g, 10.0 mmol) was added to an ethanol solution (20 mL) of **3** (2.20 g, 10.0 mmol), and the mixture was refluxed for 12 h. The solvent was concentrated in vacuo to ca. 15 mL. After cooling, a precipitate formed, which was filtered off. Yield: 1.99 g (76%), yellow prisms (EtOH), mp. 246°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 869$ (m), 1049 (m), 1172 (m), 1224 (m), 1310 (s), 1526 (s), 1607 (s), 2936 (m). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.78–1.85$ (m, 4H, $2 \times CH_2$), 2.77 (t, 2H, CH_2), 2.94 (t, 2H, CH_2), 8.55 (s, 1H, Hetar). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 21.1$, 21.2, 22.1, 23.7, 24.1, 24.2, 24.3, 108.0, 117.5, 124.8. MS (EI, 70 eV): $m/z = 262$ (M^+, 100), 234 (35), 110 (3.65), 91 (3), 58 (4), 44 (7), 28 (48). Anal.: calcd. for $C_{11}H_{10}N_4S_2$ (262.36): C, 50.36; H, 3.84; N, 21.36. Found: C, 50.41; H, 3.81; N, 21.41.

2-Methyl-5-thioxo-5,6,8,9,10,11-hexahydrobenzo[*b*]thiopheno[2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (5b)

A mixture of **4b** (0.64 g, 10.0 mmol), **3** (2.20 g, 10.0 mmol), and tri(*n*-propyl)amine (0.5 mL) in ethanol (220 mL) was refluxed for 14 h. The solvent (200 mL) was evaporated in vacuo. After cooling, AcOH (1.5 mL) and water (20 mL) were added to give a precipitate, which was

filtered off. Yield: 2.15 g (78%), yellow needles (EtOH), mp. 276°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 872$ (m), 1222 (s), 1308 (s), 1380 (m), 1440 (m), 1539 (s), 1610 (s), 2934 (s). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.59–1.63$ (m, 4H, 2 × CH_2), 2.66 (s, 3H, Me), 2.79–2.82 (t, 2H, CH_2), 3.06–3.09 (t, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.2$, 21.5, 22.9, 24.1, 24.6, 128.5, 147.3. MS (EI, 70 eV): $m/z = 276$ (M^+, 100), 248 (26), 141 (21), 91 (12), 70 (10), 32 (12), 28 (57). Anal.: calcd. for $C_{12}H_{12}N_4S_2$ (276.38): C, 52.15; H, 4.38 N, 20.27. Found: C, 52.20; H, 4.41; N 20.35.

2-Phenyl-5-thioxo-5,6,8,9,10,11-hexahydrobenzo[*b*]thiopheno[2,3-*d*]imidazo[1,2-*c*]pyrimidine (5c)

To a CH_2Cl_2 solution (50 mL) of **3** (2.20 g, 10.0 mmol) was added an aqueous solution (50 mL) of 2-amino-1-phenylethan-1-one hydrochloride (1.72 g, 10.0 mmol) and an aqueous solution (15 mL) of sodium carbonate (2.00 g) with stirring. The solution was stirred for 15 min at room temperature. The mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the CH_2Cl_2 solution was refluxed for 15 min. The mixture was concentrated at reduced pressure. A precipitate formed, which was filtered off. The product was suspended in EtOH (250 mL), and the mixture was refluxed for 24 h. The product, which crystallized upon cooling, was filtered off. The filtrate was concentrated at reduced pressure to give an additional amount of product. Yield: 2.73 g (81%), yellow needles (EtOH), mp. 281°C. IR (KBr, cm^{-1}): $\tilde{\nu}$ =729 (m), 862 (m), 1199 (m), 1262 (s), 1313 (s), 1531 (s), 1612 (s), 2936 (m). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.87–2.88$ (m, 8H, 4 × CH_2), 7,33–8.13 (m, 5H, ArH), 8.53 (s, 1H, Hetar). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 21.2$, 22.2, 23.7, 24.5, 110.4, 125.3, 127.5. 128.0, 128.7, 130.0, 132.4. MS (EI, 70 eV): $m/z =$ 337 (M^+, 100), 277 (10), 168 (7), 117 (29), 115 (15), 101 (17), 91 (21), 45 (42), 32 (16). Anal.: calcd. for $C_{18}H_{15}N_3S$ (337.07): C, 64.06; H, 4.48; N, 12.45. Found: C, 64.12; H 51; N, 12.45.

2-(Bromophenyl)-5-thioxo-4,5,8,9,10,11-hexahydrobenzo[*b*]thiopheno-[2,3-*d*]imidazo[1,2-*c*]pyrimidine (5d)

The reaction was carried out following the procedure as given for **5c**. Starting with **3** (2.20 g, 10.0 mmol) and 2-amino-1-(4-bromophenyl)ethan-1-one hydrochloride (2.51 g, 10.0 mmol), **5d** was isolated (3.50 g, 84%) as yellow prisms (EtOH), mp. 295°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 862$ (m), 1009 (m), 1197 (s), 1316 (s), 1400 (m), 1477 (m), 1534 (s), 1578 (s), 2933 (m).^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.95$ (m,

6H, 2 × CH_2), 2.80–2.85 (t, 2H, CH_2), 3.25 (t, 2H, CH_2), 7.25–8.09 (m, 5H, ArH, Hetar). MS (EI, 70 eV): $m/z = 416$ (M^+, 33), 335 (2), 154 (5), 43 (5), 40 (13), 32 (80), 28 (100). Anal.: calcd. for $C_{18}H_{14}N_3S_2Br$ (416.36). C, 51.02; H, 3.34; N, 10.09. Found: C, 51.05; H, 3.41; N, 10.21.

5-Methylsulfanyl-8,9,10,11-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (6a)

Compound **5a** (2.62 g, 10.0 mmol) was dissolved in an aqueous solution of sodium hydroxide (0.02 M, 120 mL). The mixture was heated to 60°C, and methyl iodide (1.99 g, 14.0 mmol) was added dropwise over a period of 5 min. The precipitate formed on cooling was filtered off and washed with water. Yield: 1.96 g (71%), yellow prisms (EtOH), 258°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 1177$ (m), 1263 (m), 1351 (m), 1458 (m), 1532 (m), 1609 (s), 1625 (m), 2935 (m). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.96$–1.22 (m, 4H, 2 × CH_2), 1.60–1.65 (t, 2H, CH_2), 1.95–1.98 (t, 2H, CH_2), 2.79 (s, 3H, Me), 8.37 (s, 1H, 2-H, Hetar). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 13.0$, 14.0, 21.5, 22.4, 24.5, 65.5, 116.2, 127.9, 127.9, 132.9, 135.2, 153.9. MS (EI, 70 eV): $m/z = 276$ (M^+, 100), 246 (64), 218 (36), 77 (4), 32 (12), 28 (50). Anal.: calcd. for $C_{12}H_{12}N_4S_2$ (276.38). C, 52.25; H, 4.38; N, 20.27. Found: C, 52.25; H, 4.41; N, 20.35.

2-Methyl-5-methylsulfanyl-8,9,10,11-tetrahydrobenzo[*b*]thiopheno-[2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (6b)

From**5b** (2.76 g, 10.0 mmol), an aqueous solution of sodium hydroxide (0.02 M, 120 mL) and methyl iodide (1.99 g, 14.0 mmol), **6b** was isolated (2.12 g, 73%) as yellow needles (EtOH), mp. 184–185°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 856$ (m), 1305 (s), 1450 (s), 1495 (m), 1511 (s), 2931 (m). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$–2.01 (m, 4H, 2 × CH_2), 2.67 (s, 3H, Me), 2.77 (s, 3H, Me), 2.87–2.89 (t, 2H, CH_2), 3.12–3.14 (t, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.7$, 15.0, 22.4, 23.3, 25.5, 116.7, 128.8, 135.5, 147.4, 149.9, 154.9, 164.4. MS (EI, 70 eV): $m/z = 290$ (M^+, 100), 230 (36), 189 (16), 70 (4), 28 (27). Anal.: calcd. for $C_{13}H_{14}N_4S_2$ (290.41): C, 53.77; H, 4.86; N, 19.29. Found: C, 53.81; H, 4.92; N, 19.25.

2-Methyl-5-benzylsulfanyl-8,9,10,11-tetrahydrobenzo[*b*]thiopheno-[2,3-*d*]-1,2,4-triazolo[1,5-*c*]quinazoline (6c)

Compound **5b** (2.76 g, 10.0 mmol) and NaOMe (0.54 g, 10.0 mmol) were dissolved in absolute methanol (200 mL), and the mixture was heated

under reflux for 1 h. Benzylbromide (2.05 g, 12.0 mmol) was added to the solution and the solution was heated under reflux for further 2 h. On cooling, a crystalline precipitate separated, which was filtered off and washed with water. Yield: 3.15 g (86%), yellow needles (EtOH), mp. 141°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 699$ (m), 855 (m), 1043 (m), 1304 (s), 1457 (s), 1498 (s), 1611 (s), 2931 (s). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.92–1.96$ (m, 4H, 2 × CH_2), 2.64 (s, 3H, Me), 2.87–2.89 (t, 2H, CH_2), 3.09–3.11 (t, 2H, CH_2), 4.62 (s, 2H, CH_2, Bn), 7.24–7.49 (m, 5H, ArH). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 14.1$, 21.6, 22.4, 24.6, 24.7, 33.9, 116.0, 127.4, 128.0, 128.4, 129.0, 135.2, 136.4, 146.1, 148.1, 153.1, 163.5. MS (EI, 70 eV): $m/z = 366$ (M^+, 70), 334 (100), 162 (6), 91 (60). Anal.: calcd. for $C_{19}H_{18}N_4S_2$ (366.51): C, 62.26; H, 4.95; N, 15.29. Found: C, 62.37; H, 4.81; N, 15.35.

2-Phenyl-5-methylsulfanyl-8,9,10,11-tetrahydrobenzo[*b*]thiopheno-[2,3-*d*]imidazo[1,2-*c*]pyrimidine (6d)

Starting with **5c** (3.37 g, 10.0 mmol) and methyl iodide (1.99 g, 14.0 mmol, **6d** was isolated (2.88 g, 82%) as colorless prisms (EtOH), mp. 196°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 711$ (s), 1162 (m), 1220 (m), 1368 (m), 1471 (s), 1607 (m), 2932 (m). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.95–1.97$ (m, 4H, 2 × CH_2), 2.74 (s, 3H, Me), 2,84–2.86 (t, 2H, CH_2), 3.26–3.27 (t, 2H, CH_2), 7.31–8.04 (m, 6H, ArH, 1 Hetar). ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 13.0$, 21.4, 22.2, 24.2, 24.7, 105.0, 125.6, 127.5, 128.0, 128.3, 132.6, 133.4, 144.1. MS (EI, 70 eV): $m/z = 351$ (M^+, 15), 346 (15), 198 (100), 145 (15), 129 (11), 102 (12), 90 (28), 64 (10). Anal.: calcd. for $C_{19}H_{17}N_3S$ (351.19): C, 64.92; H, 4.87; N, 11.95. Found: C, 64.93; H, 4.91; N, 11.97.

2-(4-Bromophenyl)-5-methylsulfanyl-8,9,10,11-tetrahydrobenzo-[*b*]thiopheno[2,3-*d*]imidazo[1,2-*c*]pyrimidine (6e)

Starting with **5d** (4.16 g, 10.0 mmol) and methyl iodide (1.99 g, 14.0 mmol), **6e** was isolated (3.76 g, 87%) as yellow prisms (EtOH), mp. 209°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 732$ (s), 1162 (m), 1220 (m), 1368 (m), 1472 (s), 1604 (s), 2932 (m). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.96$ (m, 4H, 2 × CH_2), 2.81 (s, 3H, Me), 2.85–2.87 (t, 2H, CH_2), 3.26–3.27 (t, 2H, CH_2), 7.55–7.91 (m, 5H, ArH, Hetar). MS (EI, 70 eV): $m/z = 430$ (M^+, 20), 415 (3), 194 (2), 117 (3), 32 (23), 28 (100). Anal.: calcd. for $C_{19}H_{16}Br\ N_3S_2$ (430.39): C, 53.02; H, 3.75; N, 9.76. Found: C, 53.01; H, 3.76; N, 9.81.

5-Piperidino-8,9,10,11-tetrahydrobenzo[*b*]thiopheno][2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (7a)

A mixture of **6a** (2.76 g, 10.0 mmol) was dissolved in piperidine (10 mL), and the mixture was heated under reflux for 18 h. After cooling to room temperature, the precipitate was filtered and washed with methanol. Yield: 2.79 g (89%), colorless rods (EtOH), mp. 163°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 963$ (m), 1173 (s), 1443 (s), 1528 (s), 1617 (s), 2932 (m). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.70$–1.95 (m, 10H, 5 × CH_2), 2.80–2.83 (t, 2H, CH_2), 3.09–3.10 (t, 2H, CH_2), 3.86–3.89 (m, 4H, 2 × CH_2), 8.26 (s, 1H, Hetar). MS (EI, 70 eV): $m/z = 313$ (M^+, 100), 285 (16), 202 (10), 128 (6), 84 (19), 55 (11), 41 (18), 28 (74). Anal calcd. for $C_{16}H_{19}N_5S$ (313.42): C, 61.31; H, 6.11; N, 22.34. Found: C, 61.42; H, 6.23; N, 22.41.

2-Methyl-5-piperidino-8,9,10,11-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]1,2,4-triazolo[1,5-*c*]pyrimidine (7b)

A mixture of **6b** (2.90 g, 10.0 mmol) was dissolved in piperidine (10 mL), and the mixture was heated under reflux for 16 h. After cooling to room temperature, the precipitate was filtered and washed with methanol. Yield: 1.65 g (81%), colorless prisms (EtOH), mp. 134–135°C. IR (KBr, cm^{-1}): $\tilde{\nu} = 1190$ (m), 1243 (m), 1304 (s), 1380 (s), 1443 (s), 1517 (s), 1619 (s), 2852 (m), 2935 (s). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.63$–1.94 (m, 10H, 5 × CH_2), 2.62 (s, 3H, Me), 2.81–2.83 (t, 2H, CH_2), 3.08–3.09 (t, 2H, CH_2), 3.82–3.85 (t, 4H, 2 × CH_2). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta =$ 14.8, 22.3, 23.3, 24.6, 25.2, 25.5, 25.6, 49.1, 114.3, 128.4, 132.0, 145.4, 151.5, 155.4, 162.6. MS (EI, 70 eV): $m/z = 327$ (M^+, 100), 285 (7), 155 (8), 84 (8), 32 (12), 28 (54). Anal calcd. for $C_{17}H_{21}N_5S$ (327.45): C, 62.36; H, 6.46; N, 21.39. Found: C, 62.41; H, 6.51; N, 21.43

2-Phenyl-5-piperidino-8,9,10,11-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]imidazo[1,2-*c*]pyrimidine (7c)

A mixture of **6d** (3.51 g, 10.0 mmol) was dissolved in piperidine (10 mL), and the mixture was heated under reflux for 18 h. After cooling to room temperature, the precipitate was filtered off and washed with methanol. Yield: 3.14 g (81%), mp. 168–170°C, colorless rods (EtOH). IR (KBr, cm^{-1}): $\tilde{\nu} = 710$ (m), 850 (m), 1027 (m), 1162 (s), 1218 (s), 1368 (s), 1471 (s), 1510 (m), 1611 (s), 2932 (s). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.96$–1.98 (m, 8H, 5 × CH_2), 2.82–2.88 (m, 6H, 2 × CH_2), 3.27–3.28 (m, 4H, 2 × NCH_2), 7.33–8.04 (m, 6H, ArH, Hetar). ^{13}C NMR

(50 MHz, DMSO-d_6): $\delta = 14.2, 22.7, 23.5, 24.7, 25.6, 25.9, 26.0, 45.3, 50.1, 104.8, 117.9, 126.4, 128.2, 128.9, 129.6, 133.7, 134.2, 144.7, 145.0, 145.1, 146.9, 150.5$. MS (EI, 70 eV): $m/z = 388$ (M^+, 57), 351 (100), 335 (28), 318 (11), 303 (10), 277 (11), 118 (6), 91 (3), 28 (3). Anal calcd. for $C_{23}H_{24}N_4S$ (388.53): C, 71.10; H, 6.23; N, 14.42. Found: C, 71.12; H, 6.12; N, 14.41.

REFERENCES

[1] (a) T. Besson, J. Guillard, C. W. Rees, and M. Therisod, *J. Chem. Soc., Chem. Commun.*, 881 (1997); (b) T. Besson, M.-J. Dozias, J. Guillard, P. Jacquault, M.-D. Legoy, and C. W. Rees, *Tetrahedron*, **54,** 6475 (1998).

[2] G. Calestani, L. Capella, R. Leardini, M. Minozzi, D. Nanni, R. Papa, and G. Zanardi, *Tetrahedron*, **57,** 7221 (2001).

[3] D. W. Ludocici, M. J. Kukla, P. G. Grous, S. Krishnan, K. Andries, M.-P. de Bethune, H. Azijn, R. Pauwels, E. De Clercq, E. Arnold, and P. A. J. Janssen, *Bioorg. Med. Chem. Lett.*, **17,** 2225 (2001).

[4] R. Leardini, D. Nanni, P. Pareschi, A. Tundo, and G. Zanardi, *J. Org. Chem.*, **62,** 8394 (1997).

[5] (a) P. Pazdera, D. Ondracek, and E. Novacek, *Chem. Papers*, **43**, 771 (1989); (b) P. Pazdera, M. Rezka, and E. Novacek, *Chem. Papers*, **44,** 63 (1990).

[6] W.-D. Pfeiffer, A. Hetzheim, P. Pazdera, A. Bodtke, and J. Mücke, *J. Het. Chem.*, **36,** 1327 (1999).

[7] U. Albrecht, H. Reinke, and P. Langer, *Synthesis*, 3067 (2006).

[8] J. Blank, M. Kandt, W.-D. Pfeiffer, A. Hetzheim, and P. Langer, *Eur. J. Org. Chem.*, 182 (2003).

[9] A. Bodtke, H. Reinke, D. Michalik, and P. Langer, *Tetrahedron*, **62,** 7653 (2006).

[10] P. Langer and A. Bodtke, *Tetrahedron Lett.*, 5965 (2003).

[11] (a) J. E. Francis, W. D. Cash, S. Psychoyos, G. Ghai, P. Wenk, R. C. Friedmann, C. Atkins, V. Warren, P. Furness, J. L. Hyun, G. A. Stone, M. Desai, and M. Williams, *J. Med. Chem.*, **31,** 1014 (1988); (b) M. R. Pavia, S. J. Lobbestael, C. P. Taylor, F. M. Hershenson, and D. L. Miskell, D. L., *J. Med. Chem.*, **33,** 854 (1990); (c) J. E. Francis, W. D. Cash, W. D. Barbaz, P. S. Bernard, R. A. Lovell, G. C. Mazzenga, R. C. Friedmann, J. L. Hyun, A. F. Braunwalder, P. S. Loo, and D. A. Bennett, *J. Med. Chem.*, **34,** 281 (1991).

[12] (a) C. Cianci, T. D. Y. Chung, N. Menwell, H. Putz, M. Hagen, R. J. Colonno, and M. Krystal, *Antiviral Chem. Chemother.*, **7,** 353 (1996); (b) M. M. Gineinah, A. M. Ismaiel, and M. M. El-Kerdawy, *J. Het. Chem.*, **27,** 723 (1990); (c) K. C. Liu and M. K. Hu, *Arch. Pharm. (Weinheim)*, **319,** 188 (1986); (d) K. Kottke, H. Kuehmstedt, I. Graefe, H. Wehlau, and D. Knocke, DD 253623 (1988), *Chem. Abstr.*, **109,** 17046 (1988); (e) F. Kathawala and G. E. Hardtmann, *Ger. Offen.* 2,146,076 (1972), *Chem. Abstr.*, **77,** 48501 (1972); (f) F. Kathawala and G. E. Hardtmann, *Ger. Offen.* 2,261,095 (1971), *Chem. Abstr.*, **79,** 66385 (1973).

[13] (a) J.-W. Chern, P.-L. Tao, K.-C. Wang, A. Gutcait, S.-W. Liu, M.-H. Yen, S.-L. Chien, and J.-K. Rong, *J. Med. Chem.*, **41,** 3128 (1998); (b) W. Arnold, B. Buettelmann, M.-P. Heitz, and R. Wyler, *Heterocycles*, **43,** 2607 (1996); (c) J.-W. Chern, P.-L. Tao, M.-H. Yen, G.-Y. Lu, C.-Y. Shiau, Y.-J. Lai, S.-L. Chien, and C.-H. Chan, *J. Med. Chem.*, **36,** 2196 (1993); (d) P. Molina, M. Alajarin, and A. Vidal, A. *Tetrahedron Lett.*, 3849 (1988); (e) T. Nishio, M. Fujisawa, and Y. Omote, *J. Chem. Soc., Perkin*

Trans. 1, 2523 (1987); (f) S. Leistner, G. Wagner, and T. Strohscheidt, *Pharmazie*, **35,** 293 (1980).

[14] R. D. Carpenter, K. S. Lam, and M. J. Kurth, *J. Org. Chem.*, **72,** 284 (2007), and references cited therein.

[15] (a) K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, **99,** 94 (1966); (b) Y. Hu, Z.-C. Chen, Z.-G. Le, and Q.-G. Zheng, *Synthetic Comm.*, **34,** 3801 (2004); (c) R. M. Angell, F. L. Atkinson, M. J. Brown, T. T. Chuang, J. A. Christopher, M. Cichy-Knight, A. K. Dunn, K. E. Hightower, S. Malkakorpi, J. R. Musgrave, and M. Neu, *Bioorg. Med. Chem. Lett.*, **17,** 1296 (2007).