Heteroatom Chemistry
Volume 24, Number 2, 2013

Synthesis of New Thienopyridine Derivatives by a Reaction of 4-(Methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine with Amino Acids

Mátyás Milen,[1,2] Péter Ábrányi-Balogh,[1] András Dancsó,[2] László Drahos,[3] and György Keglevich[1]

[1]*Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

[2]*EGIS Pharmaceuticals PLC, Division for Chemical Research, H-1475 Budapest, P.O.B. 100, Hungary*

[3]*Hungarian Academy of Sciences, Chemical Research Center, H-1525 Budapest, Hungary*

Received 17 September 2012; revised 3 December 2012

ABSTRACT: *New thienopyridine derivatives were synthesized by the reaction of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-c]pyridine (***5***) with amino acids. The use of β-amino acids led to thienopyridopyrimidone derivatives (***9a–g***). Using α-amino acids, such as glycine and racemic alanine under the same reaction conditions, compounds with two thienopyridine units were obtained. The structure of the novel compounds was confirmed by IR, ^{13}C, and ^{1}H NMR spectroscopy, as well as mass spectrometry, along with single crystal X-ray analysis.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem 24:124–130, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21073

INTRODUCTION

The thienopyridine scaffold can be found in a few synthetic compounds having important biological and pharmacological activities. For example, ticlopidine (**1**), (*S*)-clopidogrel (**2**), and prasugrel (**3**) are adenosine diphosphate receptor antagonist (see Fig. 1). These compounds block the $P2Y_{12}$ receptors and thus inhibit platelet activation and aggregation [1–4]. Antiplatelet agents are useful in the prevention of stroke, myocardial infarction, and thrombosis [5–7]. Ticlopidine (**1**) and clopidogrel (**2**) have similar pharmacological activity, but they have different pharmacokinetics; clopidogrel (**2**) has fewer side effects than ticlopidine (**1**) [8]. (*S*)-Clopidogrel (Plavix) (**2**) was the world's second highest selling pharmaceutical in the mid-2000s, and the synthesis of this antiplatelet agent has been extensively investigated [9, 10].

In our earlier study, the [3+2] cycloadditions and Staudinger reaction were investigated to synthesize novel fused tricyclic, conformationally constrained thienopyridines [11]. As a continuation of our work, we now describe fused thienopyridine derivatives of other types. The starting material (**4**) was prepared by a simple procedure from commercially available 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine in a reaction with elemental sulfur [12].

Correspondence to: György Keglevich; e-mail: gkeglevich@mail.bme.hu.

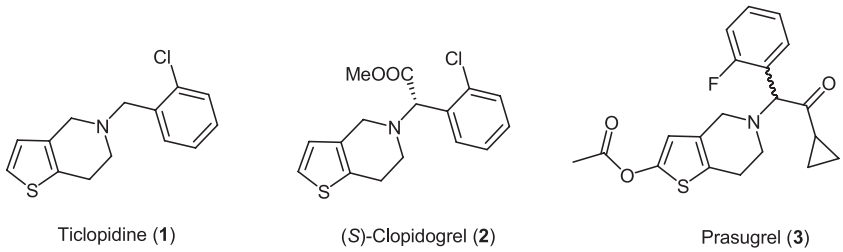
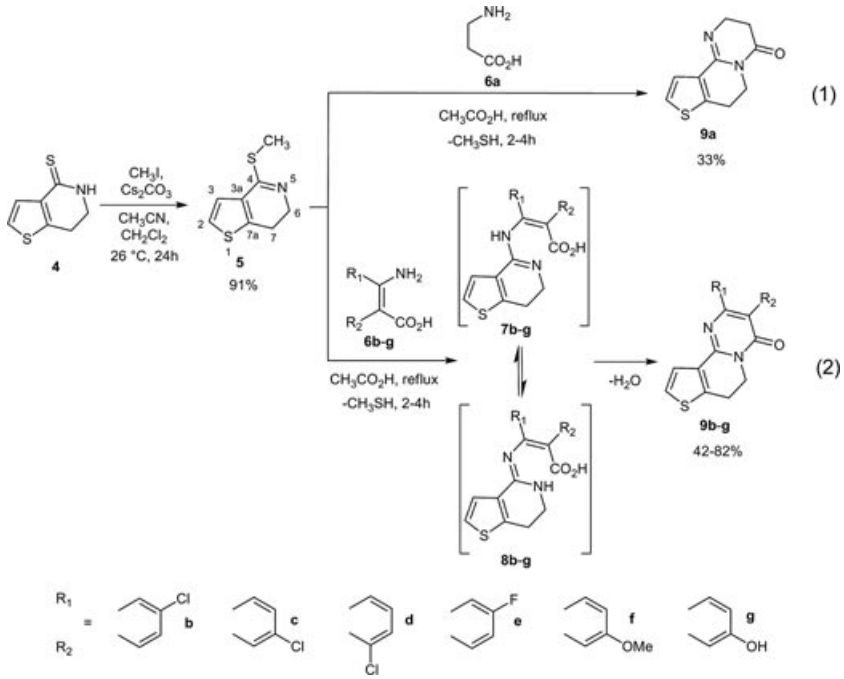


FIGURE 1 Ticlopidine (**1**), (*S*)-clopidogrel (**2**), and prasugrel (**3**).



SCHEME 1 The thienopyridine scaffold in synthetic drugs.

RESULTS AND DISCUSSION

The key intermediate, 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**5**), was obtained in a yield of 91% by *S*-methylation of the starting material (**4**) with 1.1 equiv of methyl iodide in acetonitrile/dichloromethane at 26°C for 24 h (Scheme 1). The alkylation was carried out in the presence of Cs_2CO_3 that is in most cases more favorable in the solid–liquid phase alkylations than the other alkali carbonates [13].

*The Reaction of 4-(Methylsulfanyl)-6,7-dihydrothieno[3,2-c]pyridine (**5**) with β-Amino Acids (**6a–g**)*

First, the 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**5**) was treated with β-alanine (**6a**) in glacial acetic acid at reflux temperature. The tri-heterocyclic product (**9a**) was obtained only in a 33% yield after purification by chromatography. The reaction sequence is shown in Scheme 1/(1). In accordance with earlier experiences [14], the alkylthio group in the iminothioether function could be substituted easily by amino compounds.

Next, the reaction was investigated under the same conditions, but with more special β-amino acids, such as substituted anthranilic acids (**6b–g**) (Scheme 1 (2)). The reaction of starting material **5** with 4-chloro-, 5-chloro-, 6-chloro-, and 4-fluoroanthranilic acids (**6b–e**) resulted in the formation of the appropriate tetracycles (**9b–e**) in moderate to reasonable yields (42–64%). When the reaction was carried out with 2-amino-5-methoxybenzoic acid (**6f**) and 2-amino-5-hydroxybenzoic acid (**6g**), the fused tetracyclic products **9f** and **9g** were obtained in a 76% and 82% yield, respectively. No reaction took place with reagents containing less nucleophilic amino groups, such as 2-amino-3,5-dichlorobenzoic acid, 2-amino-4-nitrobenzoic acid, and 4-amino-nicotinic acid.

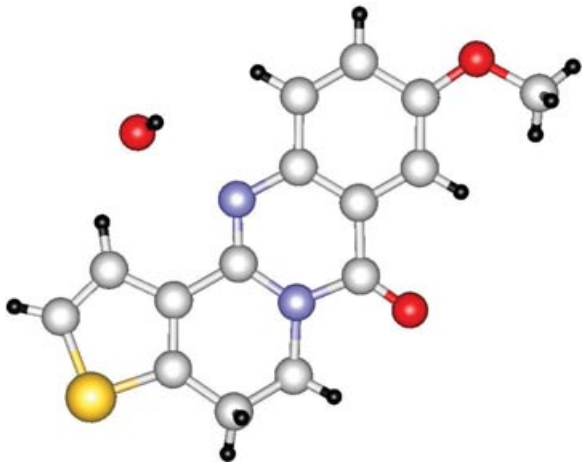


FIGURE 2 Perspective view of thienopyridoquinazolone derivative (**9f**) (the crystal contained 1 mol of water).

In the reaction of iminothioethers with β-amino acids or β-amino acid esters, a one-pot cyclocondensation took place after substitution [15].

The structure of products **9a–g** was proved by IR, ^{13}C, and ^{1}H NMR spectroscopy, as well as mass spectrometry. The new ring system was also justified by single crystal X-ray analysis. A perspective view of compound **9f** is shown in Fig. 2.

*The Reaction of 4-(Methylsulfanyl)-6,7-dihydrothieno[3,2-c]pyridine (**5**) with α-Amino Acids (**6h–j**)*

Then, the reaction of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**5**) was studied with glycine, racemic alanine, and 2-amino-2-methylpropionic acid using glacial acetic acid as the solvent. The condensation reaction of starting material **5** with glycine (**6h**) afforded (2*E*)-2-(6,-7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-ylidene)-5,6-dihydroimidazo[1,2-*a*]thieno[3,2-*c*]pyridine-3(2*H*)-one **11** in a yield of 77%. Presumably, this reaction takes place via intermediate **10**, which contains an active methylene group between the imine and the amide functions (Scheme 2). Gomez-Parra et al. observed the analogous transformation of 1-(ethylsulfanyl)-3,4-dihydroisoquinoline with glycine in boiling aqueous ethanol in the presence of equimolar sodium bicarbonate and prepared isoquinoline analogues of **11** [16].

When racemic alanine (**6i**) was used instead of glycine, 6,7-dihydro-5*H*-thieno[3,2-*c*]pyridine-4-one (**12**) was obtained in a yield of 56% as the main product. Compound **12** is known from the literature [17]. A smaller amount of thienopyridinone (**12**) was detected by LC-MS in all reactions. As another component, a "dimer" compound (**13**) was also observed in the reaction of **5** with alanine. The by-product (**13**) was obtained in a 24% yield, and it can be formed from intermediate **14** in a radical reaction (Scheme 3).

The reaction of starting material **5** and 2-amino-2-methylpropionic acid (2,2-dimethyl-glycine) gave only **12** as the product in a conversion of 96% after a 6 h reflux.

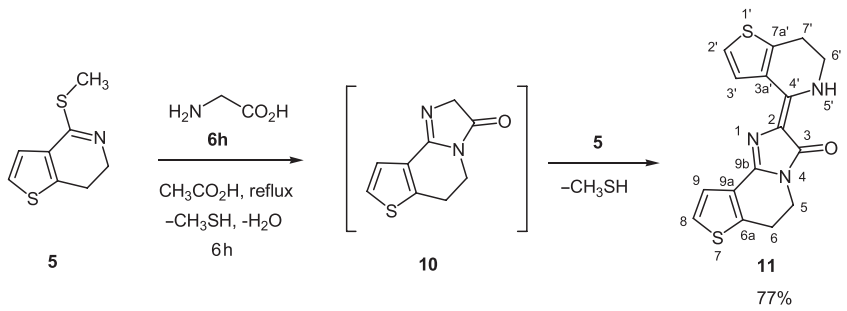
The structure of the new compounds (**11** and **13**) was proved by NMR spectroscopy and single crystal X-ray analysis. Perspective views of **11** and **13** are shown in Figs. 3 and 4, respectively. It is noted that heterocycle **13** has two stereogenic centers combined with a constitutional symmetry, and actually it is the *SR*-configuration that is the meso form.

In summary, novel fused thienopyridine derivatives (**9a–g**) were synthesized by the reaction of 4-(methylsulfanyl)-6,7-dihydrothieno [3,2-*c*]pyridine (**5**) and β-amino acids (**6a–g**). The reaction of compound **5** with glycine (**6h**) and alanine (**6i**) under the same conditions afforded products containing two thienopyridine units. These products (**11** and **13**) may be formed via active intermediates **10** and **14**, respectively.

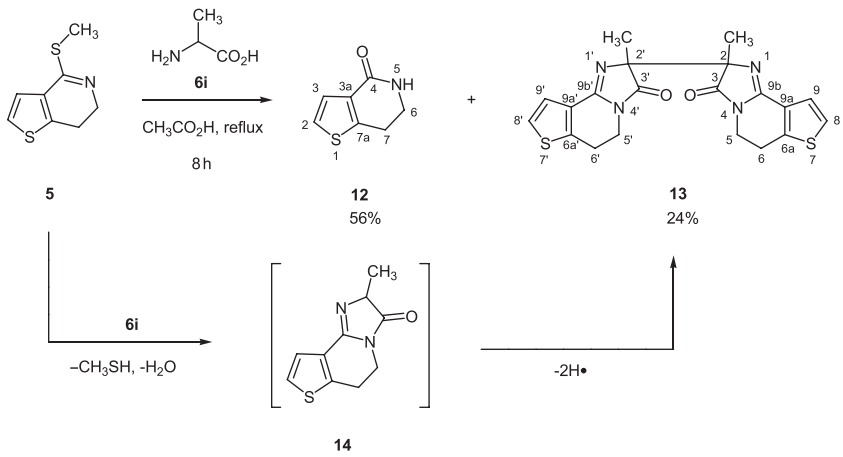
EXPERIMENTAL

General

All melting points were measured with a Kofler–Boëtius micro apparatus and were not corrected.



SCHEME 2



SCHEME 3

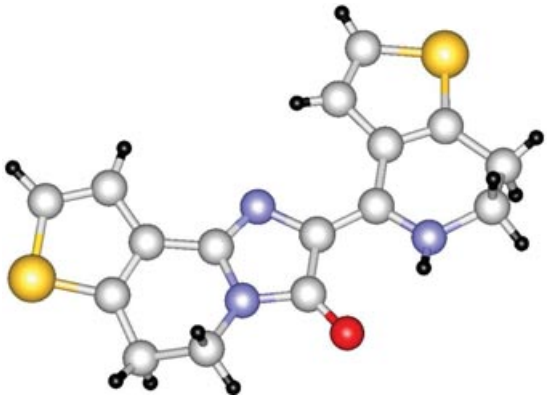


FIGURE 3 Perspective view of dihydroimidazothienopyridone derivative (**11**).

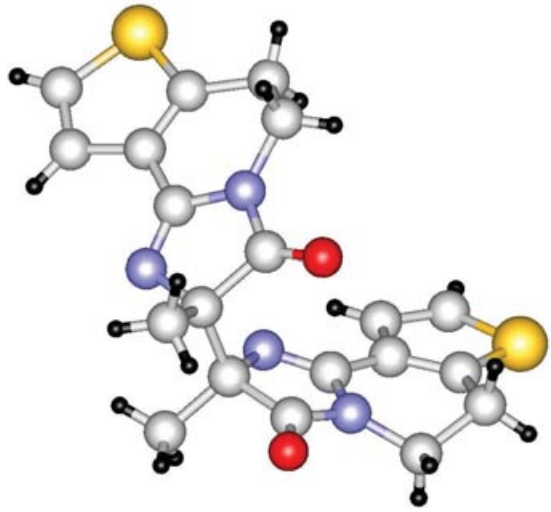


FIGURE 4 Perspective view of bisimidazothienopyridone derivative (**13**) (one of the two conformers).

^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity Inova 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively; Agilent Technologies Inc., Santa Clara, CA) or with a Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany). Deuterated dimethyl sulfoxide ([D_6]DMSO) or $CDCl_3$ was used as the solvent, and tetramethylsilane was used as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively.

The FT-IR spectra were recorded with a Bruker Alpha spectrometer using KBr pellets or neat. Single crystal X-ray measurements were carried out on a Rigaku R-Axis Spider instrument (Rigaku Americas, The Woodlands, TX). A sealed copper X-ray tube was used at 1.6 kW, $\lambda = 1.541870$ Å. Data collection was made at room temperature; all the calculations and the structure solutions were made by the Rigaku CrystalStructure and CrystalClear softwares. Elemental analyses were performed with a Vario EL III analyzer. The reactions were followed by analytical thin layer chromatography on silica gel 60 PF_{254} and LC-MS chromatography. Analytical samples of new compounds were obtained by recrystallization from the solvents given below.

The numbering of the basic ring systems is shown in Fig. 5.

Preparation of 4-methylsulfanyl)-6,7-dihydrothieno[3,2-c]pyridine(5)

To a solution of 5.4 g (32.0 mmol) 6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (**4**) and 12.4 g (38.0 mmol) Cs_2CO_3 in the solvents of 130 mL acetonitrile and 60 mL dichloromethane, 2.2 mL (35.0 mmol, 5.0 g) methyl iodide was added. The reaction mixture was stirred at 26°C for 24 h. After

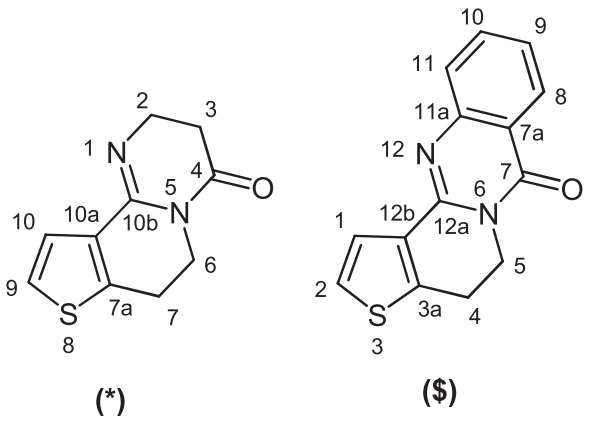


FIGURE 5 Numbering of the basic 2,3,6,7-tetrahydro-4*H*-thieno[3′,2′:3,4]pyrido[1,2-*a*]pyrimidin-4-one (*) and 4,5-dihydro-7*H*-thieno[3′,2′:3,4]pyrido[2,1-*b*]quinazolin-7-one ($) scaffolds.

that the inorganic salts were filtered off, and the filtrate was concentrated. Then the residue was taken up in dichloromethane (50 mL) and the mixture was washed with water twice (2×30 mL). Finally, the organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by bulb-to-bulb distillation.

Yield 5.4 g (91%); light yellow liquid; bp 80°C/0.41 mbar; IR (film): ν = 1581, 1236, 1166, 864 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 4.9 Hz, 1H), 7.06 (d, J = 5.1 Hz, 1H), 3.85 (t, J = 7.9 Hz, 2H), 2.86 (t, J = 7.7 Hz, 2H), 2.44 (s, 3H) {lit [18] τ ($CDCl_3$) 2.88 (1H, d, J 5.0 Hz, 2-H), 3.03 (1H, d, J 5.0 Hz, 3-H), 6.18 (2H, t, J 7.5 Hz, 6-H_2), 7.20 (2H, t, J 7.5 Hz, 7-H_2), and 7.58 (3H, s, Me)}; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (C-4), 141.8 (C-3a), 131.1 (C-7a), 123.3 (C-2), 122.2 (C-3), 49.0 (C-6), 22.8 (C-7), 11.7 (S-CH_3).

General Procedure for the Preparation of the Thienopyridine Derivatives

The suspension of an equimolar amount of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**5**) (0.30 g, 1.6 mmol) and amino acids [0.15 g of β-alanine (**6a**), 0.28 g of 4-chloroanthranilic acid (**6b**), 0.28 g of 5-chloroanthranilic acid (**6c**), 0.28 g of 6-chloroanthranilic acid (**6d**), 0.25 g of 4-fluoroanthranilic acid (**6e**), 0.27 g of 2-amino-5-methoxybenzoic acid (**6f**), 0.25 g of 2-amino-5-hydroxybenzoic acid (**6g**), 0.12 g of glycine (**6h**), 0.15 g of racemic alanine (**6i**), and 0.17 g of 2-amino-2-methylpropionic acid] was refluxed in glacial acetic acid (20 mL) until the starting material disappeared (2–8 h). After cooling, evaporation of the solvent gave a crude product, which was purified by flash-chromatography on silica (PF_{254}) using hexane-dichloromethane as the eluent.

The following products were thus prepared.

*2,3,6,7-Tetrahydro-4H-thieno[3′,2′:3,4]pyrido [1,2-a]pyrimidin-4-one (***9a***)**. Yield 0.11 g (33%); white crystals; mp 155–157°C (EtOH); IR (KBr): ν = 1686, 1645, 1416, 1380, 1320, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, J = 5.3 Hz, 1H), 7.14 (d, J = 5.3 Hz, 1H), 4.18 (t, J = 6.1 Hz, 2H), 3.75 (t, J = 7.3 Hz, 2H), 3.01 (t, J = 6.1 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (CO-4), 147.9 (C-10b), 142.6 (C-10a), 131.4 (C-7a), 125.3 (C-9), 123.9 (C-10), 43.0 (C-2), 39.3 (C-6), 30.6 (C-3), 24.2 (C-7); $C_{10}H_{10}N_2OS$ (206.27): calcd: C, 58.23; H, 4.89; N, 13.58, S, 15.54; found: C, 57.90; H, 4.83; N, 13.48; S, 15.35. HRMS calcd. for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 207.0592; found 207.0591.

*10-Chloro-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9b***)*$^{\$}$. Yield 0.30 g (64%); white crystals; mp 193–195°C (CH_3CN); IR (KBr): ν = 1671, 1590, 1416, 1314, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.36 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 4.51 (t, J = 6.7 Hz, 2H), 3.22 (t, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (CO-7), 148.8 (C-11a), 147.9 (C-12a), 143.5 (C-12b), 140.4 (CCl-10), 132.0 (C-3a), 128.4 (C-8), 126.8 (two signs C-9 and C-11), 125.9 (C-2), 124.5 (C-1), 119.2 (C-7a), 40.6 (C-5), 23.2 (C-4). $C_{14}H_9ClN_2OS$ (288.76): calcd: C, 58.23; H, 3.14; Cl, 12.28; N, 9.70, S, 11.10; found: C, 58.05; H, 3.19; Cl, 12.17; N, 9.66; S, 11.02. HRMS calcd. for $C_{14}H_{10}ClN_2OS$ $[M + H]^+$ 289.0202; found 289.0206.

*9-Chloro-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9c***)*$^{\$}$. Yield 0.26 g (54%); white crystals; mp 198–200°C (EtOH); IR (KBr): ν = 1658, 1579, 1558, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.65–7.63 (m, 2H), 7.24 (d, J = 5.2 Hz, 1H), 4.52 (t, J = 6.7 Hz, 2H), 3.22 (t, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (CO-7), 147.0 (C-12a), 146.4 (C-11a), 143.2 (C-12b), 134.6 (C-10), 132.0 (CCl-9), 131.9 (C-3a), 128.9 (C-8), 126.3 (C-11), 125.8 (C-2), 124.5 (C-1), 121.8 (C-7a), 40.7 (C-5), 23.2 (C-4). $C_{14}H_9ClN_2OS$ (288.76): calcd: C, 58.23; H, 3.14; Cl, 12.28; N, 9.70, S, 11.10; found: C, 58.05; H, 3.23; Cl, 12.05; N, 9.69; S, 11.02. HRMS calcd. for $C_{14}H_{10}ClN_2OS$ $[M + H]^+$ 289.0202; found 289.0208.

*8-Chloro-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9d***)*$^{\$}$. Yield 0.26 g (54%);

white crystals; mp 225–226°C (EtOH); IR (KBr): ν = 1679, 1670, 1455, 808, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 5.3 Hz, 1H), 7.59 dd (J_1 = 1.5 Hz, J_2 = 8.2 Hz, 1H), 7.57–7.53 (m, 1H), 7.41 (dd, J_1 = 1.5 Hz, J_2 = 7.7 Hz, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.48 (t, J = 6.7 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8 (CO-7), 150.3 (C-11a), 147.4 (C-12a), 143.6 (C-12b), 134.2 (CCl-8), 133.5 (C-10), 131.9 (C-3a), 129.0 (C-9), 126.7 (C-11), 125.8 (C-2), 124.5 (C-1), 118.0 (C-7a), 40.6 (C-5), 23.3 (C-4). $C_{14}H_9ClN_2OS$ (288.76): calcd: C, 58.23; H, 3.14; Cl, 12.28; N, 9.70, S, 11.10; found: C, 58.28; H, 3.23; Cl, 12.16; N, 9.72; S, 11.06. HRMS calcd. for $C_{14}H_{10}ClN_2OS$ $[M + H]^+$ 289.0202; found 289.0207.

*10-Fluoro-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9e***)*[$]. Yield 0.19 g (42%); white crystals; mp 177–178°C (CH_3CN); IR (KBr): ν = 1661, 1587, 1484, 1135, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.33 (dd, J_1 = 2.6 Hz, J_2 = 9.7 Hz, 1H), 7.24 (d, J = 5.3 Hz, 1H), 7.15–7.11 (m, 1H), 4.52 (t, J = 6.8 Hz, 2H), 3.22 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (d, J = 253.9 Hz, CF-10), 161.0 (CO-7), 150.0 (d, J = 13.2, C-11a), 147.9 (C-12a), 143.5 (C-12b), 132.1 (C-3a), 129.6 (d, J = 10.7 Hz, C-8), 126.0 (C-2), 124.5 (C-1), 117.6 (d, J = 2.1 Hz, C-7a), 115.0 (d, J = 23.4 Hz, C-9), 112.5 (d, J = 22.0 Hz, C-11), 40.5 (C-5), 23.3 (C-4). $C_{14}H_9FN_2OS$ (272.30): calcd: C, 61.75; H, 3.33; N, 10.29, S, 11.78; found: C, 61.81; H, 3.34; N, 10.33; S, 11.68. HRMS calcd. for $C_{14}H_{10}FN_2OS$ $[M + H]^+$ 273.0498; found 273.0500.

*9-Methoxy-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9f***)*[$]. Yield 0.35 g (76%); white crystals; mp 164–165°C (CH_3CN); IR (KBr): ν = 1656, 1488, 1361, 1025, 831, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 5.1 Hz, 1H), 7.66 (d, J = 2.9 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.32 (dd, J_1 = 3.1 Hz, J_2 = 9.0 Hz, 1H), 7.22 (d, J = 5.3 Hz, 1H), 4.54 (t, J = 6.7 Hz, 2H), 3.92 (s, 3H), 3.20 (t, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5 (CO-7), 158.1 (C-9), 145.0 (C-12a), 142.4 (C-12b), 141.9 (11-a), 132.4 (C-3a), 128.9 (C-11), 125.7 (C-2), 124.5 (C-10), 124.2 (C-1), 121.5 (C-7a), 106.5 (C-8), 55.8 (OCH_3), 40.7 (C-5), 23.3 (C-4). $C_{15}H_{12}N_2O_2S$ (284.34): calcd: C, 63.36; H, 4.25; N, 9.85; S, 11.28; found: C, 63.17; H, 4.22; N, 9.83; S, 11.19. HRMS calcd. for $C_{14}H_{13}N_2O_2S$ $[M + H]^+$ 285.0698; found 285.0697. X-ray structure: CCDC 900934.

*9-Hydroxy-4,5-dihydro-7H-thieno[3′,2′:3,4]pyrido [2,1-b]quinazole-7-one (***9g***)*[$]. Yield 0.36 g (82%); white crystals; mp 274–276°C (EtOH); IR (KBr): ν = 3261, 1636, 1585, 1308, 835 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ = 10.03 (bs, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 2.9 Hz, 1H), 7.26 (dd, J_1 = 2.9 Hz, J_2 = 8.8 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 3.22 (t, J = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 160.4 (CO-7), 156.0 (C-9), 144.4 (C-12a), 142.8 (C-12b), 140.6 (C-11a), 131.9 (C-3a), 128.8 (C-11), 125.2 (two signs C-2 and C-10), 124.0 (C-1), 121.6 (C-7a), 109.5 (C-8), 40.2 (C-5), 22.6 (C-4); $C_{14}H_{10}N_2O_2S$ (270.31): calcd: C, 62.21; H, 3.73; N, 10.36; S, 11.86; found: C, 62.05; H, 3.79; N, 10.25; S, 11.73. HRMS calcd. for $C_{14}H_{11}N_2O_2S$ $[M + H]^+$ 271.0541; found 271.0546.

*(2E)-2-(6,7-Dihydrothieno[3,2-c]pyridine-4(5H)-ylidene)-5,6-dihydroimidazo[1,2-a]thieno[3,2-c] pyridine-3(2H)-one (***11***)*. Yield 0.41 g (77%); yellow crystals; mp 249–250°C ($CHCl_3$-EtOH); IR (KBr): ν = 1616, 1479, 1310, 1293, 1216, 689 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ = 9.20 (bs, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.52 (d, J = 5.2 Hz, 1H), 7.49 (d, J = 5.3 Hz, 1H), 7.42 (d, J = 5.2 Hz, 1H), 3.87 (t, J = 6.8 Hz, 2H), 3.67–3.63 (m, 2H), 3.18 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ = 166.8 (CO-3), 145.8 (C-4′), 144.2 (C-9b), 140.4 (C-9a), 138.8 (C-3a′), 129.2 (C-2′), 128.6 (C-6a)[a], 128.3 (C-7a′)[b], 125.5 (C-8), 123.4 (C-9), 122.8 (C-2′), 113.9 (C-2), 39.6 (C-6′), 37.3 (C-5), 23.7 (C-6)[c], 23.3 (C-7′)[d], [a-b], [c-d] may be reversed; $C_{16}H_{13}N_3OS_2$ (327.43): calcd: C, 58.69; H, 4.00; N, 12.83; S, 19.59; found: C, 58.54; H, 4.02; N, 12.73; S, 19.41. HRMS calcd. for $C_{16}H_{14}N_3OS_2$ $[MH^+]$ 328.0578; found 328.0583. X-ray structure: CCDC 900932.

*6,7-Dihydrothieno[3,2-c]pyridine-4(5H)-one (***12***)*. Yield 0.14 g (56%); white crystals; mp 89–91°C (EtOAc-Et_2O); IR (KBr): ν = 3289, 1659, 1633, 1484, 1314 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 5.3 Hz, 1H), 7.11 (d, J = 5.3 Hz, 1H), 6.64 (b, 1H), 3.66–3.63 (m, 2H), 3.06 (t, J = 6.9 Hz, 2H) {lit [17] (300 MHz, $CDCl_3$) δ = 7.45 (d, 1H), 7.13 (d, 1H), 5.9–5.7 (br s, 1H), 3.7–3.6 (m, 2H), 3.1 (t, 2H)}; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0 (CO-4), 146.1 (C-3a), 132.1 (C-7a), 125.9 (C-2), 123.0 (C-3), 41.2 (C-6), 24.4 (C-7). HRMS calcd. for C_7H_8NOS $[M + H]^+$ 154.0327; found 154.0329.

*2,2′-Dimethyl-5,5′,6,6′-tetrahydro-2,2′-bisimidazo [1,2-a]thieno[3,2-c]pyridine-3,3′ (2H,2′H)-dione (***13***).* Yield 0.08 g (24%); light brown crystals; mp 200–202°C (decomp.), (MeOH); IR (KBr): ν = 1726, 1637, 1473, 1342, 1308, 967, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, J = 5.3 Hz, 2H), 7.20 (d, J = 5.3 Hz, 2H), 3.91–3.86 (m, 2H), 3.71–3.65 (m, 2H), 3.13 (t, J = 6.2 Hz, 4H), 1.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.7 (CO-3, CO-3′), 153.9 (C-9b, C-9b′), 144.6 (C-9a, C-9a′), 127.4 (C-6a, C-6a′), 124.7 (C-8, C-8′), 124.3 (C-9, C-9′), 75.2 (C-2, C-2′), 37.7 (C-5, C-5′), 23.6 (C-6, C-6′), 17.9 ($2\times CH_3$); HRMS calcd. for $C_{20}H_{19}N_4O_2S_2$ $[M + H]^+$ 411.0949; found 411.0952. X-ray structure: CCDC 900933.

SUPPORTING INFORMATION

Deposited X-ray structures can be found at the Cambridge Crystallographic Data Centre, http://www.ccdc.cam.ac.uk.

ACKNOWLEDGEMENT

The authors are grateful to Réka Puskás for the microanalyses.

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