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Synthesis of Dihydrothienopyridine Derivatives Fused with Triazole Rings

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ABSTRACT: *New dihydro[3,2-c][1,2,4]triazolo[4,3-a]pyridines were synthesized by the reaction of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-c]pyridine with acid hydrazides. One bis(dihydrothienotriazolopyridine) was also prepared. In a few cases, the corresponding intermediate could be detected by LC-MS. The bromophenyl derivative was involved in Suzuki and Sonogashira cross-coupling reactions.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 24:226–233, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21087

INTRODUCTION

The thienopyridine ring system can be found in biologically and pharmacologically active compounds, such as ticlopidine (**1**), (*S*)-clopidogrel (**2**), and prasugrel (**3**) (Fig. 1). These thienopyridine derivatives block the $P2Y_{12}$ component of the adenosine diphosphate receptor and thus inhibit platelet activation and aggregation [1–4]. Antiplatelet agents are used for treatment of ischemic strokes, heart attacks, artherosclerosis, and prevention of thrombosis [5–7]. (*S*)-Clopidogrel (trade name Plavix) (**2**) was the world's second top-selling drug in 2005, and the synthesis of this agent has been extensively investigated [8, 9].

In our previous study, the [3+2] and [2+2] cycloadditions [10], as well as cyclocondensation reactions [11], were investigated to synthesize novel fused conformationally constrained thienopyridines.

The 1,2,4-triazole derivatives form an important class within heterocyclic compounds, and, therefore, many analogues were synthesized and reported [12–14]. A number of representatives are used in agriculture as insecticides with low mammalian toxicity [15]. Other compounds containing 1,2,4-triazole core exhibit various medicinal and pharmaceutical properties [16–24]. Moreover, 1,2,4-triazole derivatives play an important role in synthetic organic chemistry. *N*-Heterocyclic carbenes, which can be prepared from 1,2,4-triazolium salts, have been used as ligands in several catalytic reactions [25]. A few alkyl- or aryl-1,2,4-triazolium salts form a new generation of ionic liquids with a high degree of flexibility [26, 27].

As a continuation of our work, we now describe new, fused tricyclic heterocycles containing two biologically significant cores, such as the thienopyridine and the triazole units. To the best of our knowledge, only one compound containing a dihydro[3,2-*c*][1,2,4]triazolo[4,3-*a*]pyridine ring was described in the literature, but there are no data on the synthesis of this species represented by formula **4** (Fig. 2) [28].

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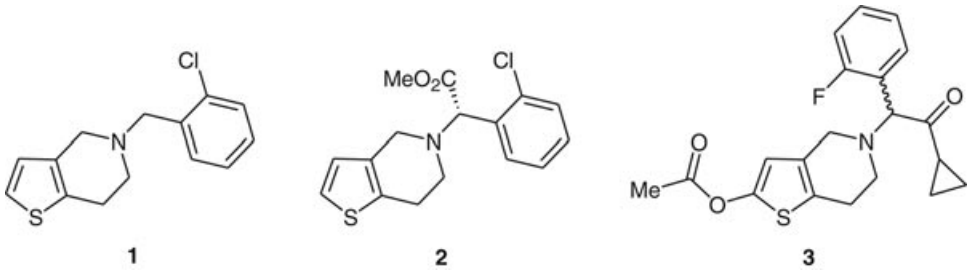


FIGURE 1 Ticlopidine (**1**), (*S*)-clopidogrel (**2**) and prasugrel (**3**).

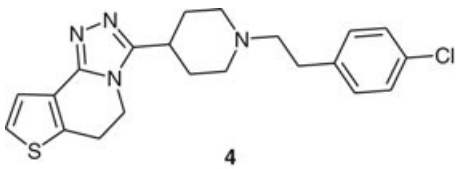


FIGURE 2 The only dihydrotriazolopyridine analogue described [28].

RESULTS AND DISCUSSION

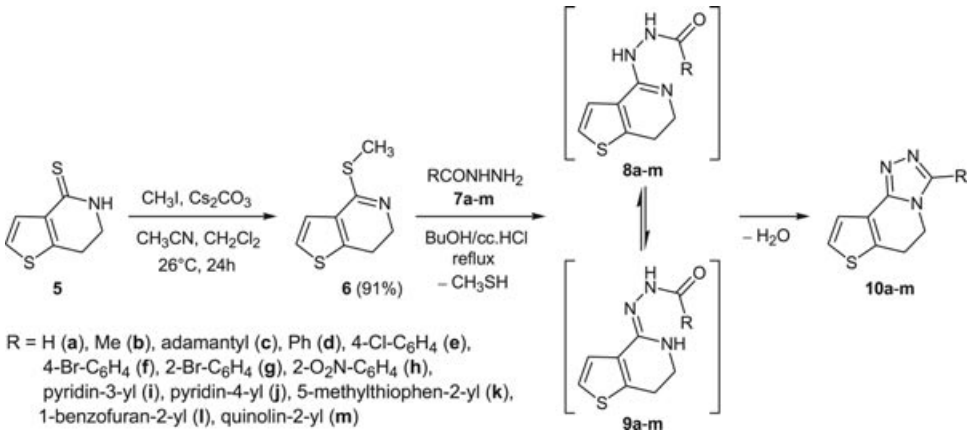
*Synthesis of 5,6-Dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine Derivatives (***10 a–m***) by the Cyclocondensation Reaction*

The starting material (**5**) was prepared by a simple procedure based on a microwave-assisted thionation reaction from commercially available 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine [29]. The 6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (**5**) seemed to be a useful intermediate for the preparation of new 1,2,4-triazole derivatives [30–32]. However, no reaction was observed between compound **5** and acetic hydrazide (**7b**) in boiling butanol. Therefore to convert the thione (**5**) to a more reactive species, it was *S*-alkylated with methyl iodide to form 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**6**) [11] (Scheme 1). The methylation was carried out in acetonitrile/dichloromethane at 26°C in the presence of Cs_2CO_3.

The reaction of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine (**6**) with various acid hydrazides (**7a–m**) in the presence of catalytic amount of concentrated HCl in boiling butanol took place smoothly and resulted in the formation of dihydrotriazolopyridine derivatives (**10a–m**) in moderate to good yields (32%–94%) (Scheme 1; Table 1).

TABLE 1 Details for the Synthesis of Dihydrotriazolopyridines **10a–m**

Entry	*Product*	*Time (h)*	*Yield (%)*
1	**10a**	1	74
2	**10b**	1	61
3	**10c**	1	32
4	**10d**	2	54
5	**10e**	1	79
6	**10f**	2	82
7	**10g**	5	55
8	**10h**	0.5	69
9	**10i**	1	94
10	**10j**	1	88
11	**10k**	1	68
12	**10l**	1	72
13	**10m**	1	65



SCHEME 1

We observed that the size and the electronic effect of the R group have an equal influence on the reaction. As compared to H, the yields decreased in the case of methyl and adamantyl substituents in the order of 74%, 61%, and 32%, respectively. In these cases, the reaction time was 1 h (Table 1, entries 1–3). The ring closure of intermediates **8c/9c** was influenced by the steric hindrance due to the adamantyl group. In the instance, when R = Ph, the reaction took place in 2 h and the yield was 54% (Table 1, entry 4). However, the 4-chlorophenyl substituent enhanced the ring closure reaction due to the electron-withdrawing effect of the chlorine substituent. In this case, the reaction time was 1 h and the product was obtained in 79% yield (Table 1, entry 5). In the case of the 4-bromobenzoic hydrazide, the reaction time was 2 h and the yield of product **10f** remained the same (Table 1, entry 6). This could be explained by the lower extent of the electron-withdrawing effect of the bromine atom. A bromine substituent in the ortho position caused a prolonged reaction time as a consequence of the steric hindrance (Table 1, entry 7). The 2-nitrophenyl group with a strong electron withdrawing effect resulted in a short reaction time of 30 min. Product **10h** was obtained in a yield of 69% (Table 1, entry 8). The best results were obtained with nicotinic and isonicotinic hydrazides, when the yields were 94% and 88%, respectively (Table 1, entries 9 and 10). With other heterocyclic hydrazides, the products were obtained in yields of 65%–72% (Table 1, entries 11–13).

All reactions were monitored by LC-MS and continued until the starting material disappeared. It is worth mentioning that we were able to detect intermediate **8**/**9** by LC-MS in three instances. Thus, **8f**/**9f** ($[M + H]^+ = 351$), **8g**/**9g** ($[M + H]^+ = 351$), and **8h**/**9h** ($[M + H]^+ = 317$) could be detected.

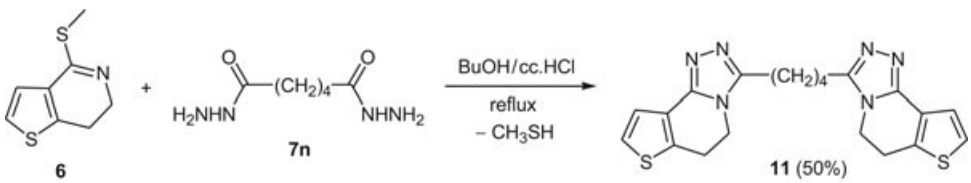
In the reaction of adipic acid dihydrazide (**7n**) with two molecules of dihydrothienopyridine (**6**) under the same conditions, the corresponding bis product (**11**) was formed in a yield of 50%. Compound **11** contains two dihydrotriazolopyridine scaffolds connected with a chain of four methylene groups (Scheme 2). In many cases, dimeric molecules show an increased biological activity, as compared to their monomers [33].

*Synthesis of Additional 5,6-Dihydrothieno[3,2-c][1,2,4]triazolo[4,3-a]pyridine Derivatives (**12a,b,13**) by Cross-Coupling Reactions*

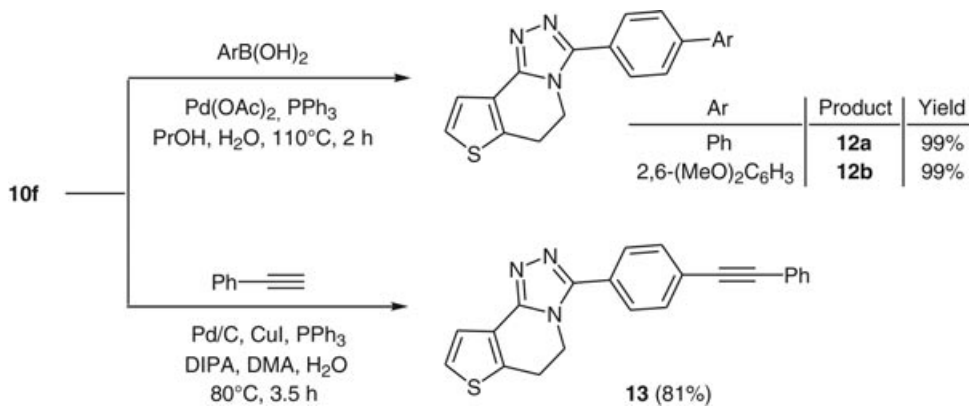
Finally, we studied the cross-coupling reactions, such as the Suzuki and the Sonogashira reaction of 3-(4-bromophenyl)-5,6-dihydrothieno[3,2-*c*][1,2,4]triazolo[4,3-*a*]pyridine (**10f**). The Suzuki reaction was carried out with two arylboronic acids in the presence of $Pd(OAc)_2$ and triphenylphosphine in PrOH–H_2O at reflux [34]. The corresponding products (**12a** and **12b**) obtained in the reaction with phenylboronic acid and 2,6-dimethoxyphenylboronic acid were isolated in a yield of 99% (Scheme 3). The Sonogashira coupling reaction of 3-(4-bromophenyl)-5,6-dihydrothieno[3,2-*c*][1,2,4]triazolo[4,3-*a*]pyridine (**10f**) with phenylacetylene in the presence of CuI, $PdCl_2(PPh_3)_2$, and piperidine [35] was unsuccessful. However, product **13** was obtained, when Pd/C, CuI, PPh_3, diisopropylamine (DIPA) were used in dimethylacetamide (DMA)–H_2O solution (Scheme 3) [36]. The yield was 81%.

The structures of products **10a–m**, **11**, **12a**, **12b**, and **13** were confirmed by ^{13}C and ^1H NMR, as well as IR spectroscopy.

In summary, 17 new tricyclic 5,6-dihydrothieno[3,2-*c*][1,2,4]triazolo[4,3-*a*]pyridine derivatives were synthesized, which are biologically and pharmacologically interesting fused scaffolds. Among them, 14 triheterocyclic compounds (**10a–m**) were obtained by the reaction of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (**6**) with acid hydrazides (**7a–m**). In three cases, the reaction intermediate (**8**/**9**) was observed by LC-MS. A bis-product (**11**) was also made available. Three additional derivatives (**12a**, **12b**, and **13**) were prepared by the cross-coupling reaction of 3-(4-bromophenyl)-5,6-dihydrothieno[3,2-*c*][1,2,4]triazolo[4,3-*a*]pyridine (**10f**).



SCHEME 2



SCHEME 3

EXPERIMENTAL

General

^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity Inova 500 spectrometer (Agilent Technologies Inc., Santa Clara, CA) (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or with a Bruker Avance III spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively). DMSO-d_6 or $CDCl_3$ was used as the solvent, and tetramethylsilane was used as the internal standard. The FT-IR spectra of KBr pellets or neat samples were recorded with a Bruker alpha spectrometer. All melting points were measured with a Kofler–Boëtius microapparatus and were not corrected.

The reactions were monitored by analytical thin-layer chromatography on silica gel 60 PF_{254} and liquid chromatography–mass spectrometry chromatography. Analytical samples of new compounds were obtained by crystallization.

Commercially available reagents were purchased from Sigma–Aldrich and used without further purification. Carboxylic acid hydrazides (**7a**–**n**) are commercially available. They may be easily synthesized from the appropriate esters by treatment with hydrazine hydrate in ethanol according to the analogous procedure described [37].

General Procedure for the Preparation of the 5,6-Dihydrothieno[3,2-c][1,2,4]triazolo-[4,3-a]pyridine Derivatives

5.3 Mmol of the appropriate acylhydrazide [0.32 g of formic hydrazide (**7a**), 0.39 g of acetic hydrazide (**7b**), 1.0 g of adamantine-1-carbohydrazide (**7c**), 0.72 g of benzoic hydrazide (**7d**), 0.90 g of 4-chlorobenzoic hydrazide (**7e**), 1.14 g of 4-bromobenzoic hydrazide (**7f**), 1.14 g of 2-bromobenzoic hydrazide (**7g**), 0.96 g of 2-nitrobenzoic hydrazide (**7h**), 0.72 g of nicotinic hydrazide (**7i**), 0.72 g of isonicotinic hydrazide (**7j**), 0.82 g of 5-methylthiophene-2-carboxylic acid hydrazide (**7k**), 0.93 g of benzofuran-2-carboxylic acid hydrazide (**7l**), and 0.99 g of quinoline-2-carbohydrazide (**7m**)] were added to a stirred solution of 0.40 g (2.1 mmol) of 4-(methylsulfanyl)-6,7-dihydrothieno[3,2-*c*]pyridine-4(5*H*)-thione (**5**) and 0.13 mL of cc. HCl in 50 mL of butanol. The solution was stirred at 120°C for 0.5–5 h until the starting material disappeared. The reaction mixture was concentrated in vacuo. The crude product was partitioned between 100 mL of dichloromethane and 50 mL of 5% HCl solution. The organic layer was washed with 25 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (PF_{254}) using dichloromethane as the eluent.

*5,6-Dihydrothieno[3,2-c][1,2,4]triazolo[4,3-a]-pyridine (**10a**).* Yield 0.28 g (74%); white crystals; mp 201–204°C (EtOH); ^{1}H NMR (500 MHz, DMSO): δ = 9.45 (s, 1H), 7.72 (d, J = 5.3 Hz, 1H), 7.69 (d, J = 5.3 Hz, 1H), 4.53 (t, J = 7.3 Hz, 2H), 3.43 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 146.3 (C=N), 143.6 (C=), 142.7 (HC=N), 127.4 (HC=), 123.2 (HC=), 120.9 (C=), 43.1 (CH_2), 23.0 (CH_2); IR (KBr): ν = 2489, 1785, 1622, 1566, 1229, 936 cm^{-1}; HRMS calcd. for $C_8H_8N_3S$ $[M + H]^+$ 178.0433; found 178.0434.

*3-Methyl-5,6-dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine (**10b**).* Yield 0.25 g (61%); white crystals; mp 196–198°C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 4.12 (t, J = 7.1 Hz, 2H), 3.27 (t, J = 7.1 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6 (C=N), 148.6 (C=N), 135.6 (C=), 126.3 (C=), 124.9 (HC=), 123.3 (HC=), 40.9

(CH_2), 23.9 (CH_2), 10.4 (CH_3); IR (KBr): ν = 3052, 1482, 1430, 944, 763, 725 cm^{-1}; HRMS calcd. for $C_9H_{10}N_3S$ $[M + H]^+$ 192.0590; found 192.0591.

*3-Tricyclo[3.3.1.1^{3,7}]dec-1-yl-5,6-dihydrothieno-[3,2-c][1,2,4]triazolo[4,3-a]pyridine (***10c***).* Yield 0.21 g (32%); white crystals; mp 273–275°C (decomp.) (MeCN); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, J = 5.0 Hz, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.40 (t, J = 6.8 Hz, 2H), 3.23 (t, J = 6.9 Hz, 2H), 2.20–2.16 (m, 6H), 2.16–2.10 (m, 3H), 1.86–1.78 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8 (C=N), 149.8 (C=N), 135.3 (C=), 126.9 (C=), 124.6 (HC=), 123.9 (HC=), 44.1 (CH_2), 39.8 (CH_2), 36.6 (CH_2), 34.6 (C), 28.1 (CH), 24.5 (CH_2); IR (KBr): ν = 2899, 1589, 1478, 944, 701 cm^{-1}; HRMS calcd. for $C_{18}H_{22}N_3S$ $[M + H]^+$ 312.1529; found 312.1524.

*3-Phenyl-5,6-dihydrothieno[3,2-c][1,2,4]triazolo-[4,3-a]pyridine (***10d***).* Yield 0.29 g (54%); white crystals; mp 177–180°C (MeCN); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 2H), 7.63 (d, J = 5.1 Hz, 1H), 7.53–7.49 (m, 3H), 7.29–7.28 (m, 1H), 4.33 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8 (C=N), 149.4 (C=N), 136.1 (C=), 130.0 (HC=), 128.9 (HC=), 128.5 (HC=), 127.1 (C=), 126.5 (C=), 125.0 (HC=), 123.6 (HC=), 42.4 (CH_2), 24.3 (CH_2); IR (KBr): ν = 1588, 1508, 1478, 709, 700, 687 cm^{-1}; HRMS calcd. for $C_{14}H_{12}N_3S$ $[M + H]^+$ 254.0746; found 254.0744.

*3-(4-Chlorophenyl)-5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine (***10e***).* Yield 0.48 g (79%); pale yellow crystals; mp 208–210°C (EtOH); ^1H NMR (500 MHz, DMSO): δ = 7.82–7.79 (m, 2H), 7.66–7.63 (m, 2H), 7.60 (d, J = 5.1 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 4.39 (t, J = 7.1 Hz, 2H), 3.30 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 151.5 (C=N), 149.2 (C=N), 137.7 (C=), 134.8 (ClC=), 130.2 (HC=), 129.1 (HC=), 126.2 (two signals: 126.21, 126.15) (C=, HC=), 125.7 (C=), 122.8 (HC=), 42.3 (CH_2), 23.6 (CH_2); IR (KBr): ν = 1589, 1475, 1463, 1096, 840, 701 cm^{-1}; HRMS calcd. for $C_{14}H_{11}ClN_3S$ $[M+H]^+$ 288.0357; found 288.0361.

*3-(4-Bromophenyl)-5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine (***10f***).* Yield 0.57 g (82%); white crystals; mp 216–219°C (BuOH); ^1H NMR (500 MHz, DMSO): δ = 7.89–7.86 (m, 2H), 7.80–7.78 (m, 2H), 7.71 (d, J = 5.1 Hz, 1H), 7.67 (d, J = 5.3 Hz, 1H), 4.49 (t, J = 7.2 Hz, 2H), 3.41 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 151.3 (C=N), 147.7 (C=N), 141.9 (C=), 132.4 (HC=), 131.0 (HC=), 127.3 (HC=), 125.3 (C=), 123.6 (BrC=), 123.1 (HC=), 122.4 (C=), 43.0 (CH_2), 23.3 (CH_2); IR (KBr): ν = 3382, 2375, 1605, 1011, 859, 728 cm^{-1}; HRMS calcd. for $C_{14}H_{11}BrN_3S$ $[M + H]^+$ 331.9852; found 331.9846.

*3-(2-Bromophenyl)-5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine (***10g***).* Yield 0.39 g (55%); brown oil; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.70 (m, 1H), 7.66 (d, J = 5.1 Hz, 1H), 7.58–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.43–7.39 (m, 1H), 7.30 (d, J = 5.3 Hz, 1H), 4.11 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1 (C=N), 149.2 (C=N), 136.6 (C=), 133.0 (HC=), 132.9 (HC=), 131.9 (HC=), 128.8 (C=), 127.8 (HC=) 126.2 (C=), 125.1 (HC=), 123.6 (two signals: 123.62, 123.59) (HC=, BrC=), 42.4 (CH_2), 24.1 (CH_2); IR (film): ν = 3384, 3074, 1476, 1438, 765 cm^{-1}; HRMS calcd. for $C_{14}H_{11}BrN_3S$ $[M + H]^+$ 331.9852; found 331.9845.

*3-(2-Nitrophenyl)-5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine (***10h***).* Yield 0.43 g (69%); yellow crystals; mp 208–211°C (MeCN); ^1H NMR (500 MHz, DMSO): δ = 8.39–8.36 (m, 1H), 8.12–8.10 (m, 1H), 7.92–7.89 (m, 1H), 7.88 (d, J = 4.8 Hz, 1H), 7.84–7.80 (m, 1H), 7.71 (d, J = 5.3 Hz, 1H), 3.76–3.71 (m, 2H), 3.26–3.22 (m, 2H); ^{13}C NMR (125 MHz, DMSO): δ = 165.1 (C=N), 154.5 (C=), 150.6 (O_2NC=), 147.6 (C=N), 133.4 (HC=), 132.3 (HC=), 131.0 (HC=), 128.5 (C=), 126.7 (HC=), 124.2 (HC=), 124.1 (HC=), 121.8 (C=), 40.2 (CH_2), 22.8 (CH_2); IR (KBr): ν = 3075, 2879, 1705, 1635, 1528, 1344 cm^{-1}; HRMS calcd. for $C_{14}H_{13}N_4O_3S$ $[M + H]^+$ 317.0703; found 317.0702.

*3-Pyridin-3-yl-5,6-dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine (***10i***).* Yield 0.50 g (94%); white crystals; mp 162–164°C (EtOH); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.94–8.90 (m, 1H), 8.77–8.74 (m, 1H), 8.11–8.07 (m, 1H), 7.63 (d, J = 5.2 Hz, 1H), 7.50–7.46 (m, 1H), 7.32 (d, J = 5.2 Hz, 1H), 4.38 (t, J = 7.0 Hz, 2H), 3.32 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0 (HC=N), 150.2 (C=N), 149.8 (C=N), 148.7 (HC=), 136.3 (C=), 136.1 (HC=), 126.2 (C=), 125.2 (HC=), 123.8 (HC=), 123.6 (HC=), 123.5 (C=), 42.5 (CH_2), 24.2 (CH_2); IR (KBr): ν = 1583, 1572, 1475, 722 cm^{-1}; HRMS calcd. for $C_{13}H_{11}N_4S$ $[M + H]^+$ 255.0699; found 255.0700.

*3-Pyridin-4-yl-5,6-dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine (***10j***).* Yield 0.47 g (88%); white crystals; mp 214–216°C (MeCN); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.80–8.77 (m, 2H), 7.65–7.63 (m, 2H), 7.61 (d, J = 5.2 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 4.42 (t, J = 7.1 Hz, 2H), 3.33 (t, J = 7.0 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (two signals: 150.52, 150.47) (C=N, HC=N), 150.1 (C=N), 136.4 (C=), 134.6 (C=), 126.0 (C=), 125.3 (HC=), 123.6 (HC=), 122.2 (HC =), 42.6 (CH_2), 24.2 (CH_2); IR (KBr): ν = 3067, 1603, 1585, 1473, 1460, 708 cm^{-1}; HRMS calcd. for $C_{13}H_{11}N_4S$ $[M+H]^+$ 255.0699; found 255.0703.

*3-(5-Methylthiophen-2-yl)-5,6-dihydrothieno[3,2-c][1,2,4]triazolo[4,3-a]pyridine (**10k**).* Yield 0.39 g (68%); white crystals; mp 164–166°C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, J = 4.6 Hz, 1H), 7.26 (d, J = 4.0 Hz, 1H), 7.26–7.22 (m, 1H), 6.84–7.79 (m, 1H), 4.39 (t, J = 6.6 Hz, 2H), 3.29 (t, J = 6.6 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.1 (C=N), 148.1 (C=N), 143.2 (C=), 135.8 (C=), 127.8 (HC=), 126.3 (C=), 126.0 (HC=), 125.6 (C=), 124.9 (HC=), 123.7 (HC=), 42.0 (CH_2), 24.1 (CH_2), 15.2 (CH_3); IR (KBr): ν = 1588, 1571, 1508, 930, 791, 700 cm^{-1}; HRMS calcd. for $C_{13}H_{12}N_3S_2$ $[M + H]^+$ 274.0467; found 274.0467.

*3-(1-Benzofuran-2-yl)-5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine (**10l**).* Yield 0.45 g (72%); white crystals; mp 240–242°C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.66 (m, 1H), 7.63 (d, J = 5.2 Hz, 1H), 7.58–7.50 (m, 1H), 7.48 (d, J = 0.8 Hz, 1H), 7.40–7.36 (m, 1H), 7.33–7.30 (m, 1H), 7.28 (d, J = 5.2 Hz, 1H), 4.73 (t, J = 7.0 Hz, 2H), 3.37 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (HC=), 149.5 (C=N), 145.3 (C=), 144.2 (C=), 136.6 (C=), 127.6 (HC=), 125.8 (C=), 125.7 (HC=), 125.0 (HC=), 123.8 (HC=), 123.7 (HC=), 121.9 (HC=), 111.4 (C=), 107.7 (C=), 42.9 (CH_2), 24.1 (CH_2); IR (KBr): ν = 1420, 1252, 931, 691 cm^{-1}; HRMS calcd. for $C_{16}H_{12}N_3OS$ $[M+H]^+$ 294.0696; found 294.0700.

*3-(Quinolin-2-yl)-5,6-dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine (**10m**).* Yield 0.42 g (65%); white crystals; mp 231–232°C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.13–8.09 (m, 1H), 7.88–7.84 (m, 1H), 7.77–7.72 (m, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.61–7.56 (m, 1H), 7.30 (d, J = 5.2 Hz, 1H), 5.23 (t, J = 7.2 Hz, 2H), 3.37 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8 (C=N), 150.7 (C=N), 148.1 (C=N), 147.2 (C=), 137.4 (C=), 136.8 (HC=), 129.9 (HC=), 129.4 (HC=), 127.8 (HC=), 127.2 (C=), 126.1 (C=), 124.8 (HC=), 123.8 (HC=), 120.7 (HC=), 44.0 (CH_2), 24.3 (CH_2); IR (KBr): ν = 1599, 1582, 1421, 841, 761 cm^{-1}; HRMS calcd. for $C_{17}H_{13}N_4S$ $[M + H]^+$ 305.0855; found 305.0854.

*3,3'-Butane-1,4-diylbis(5,6-dihydrothieno[3,2-c]-[1,2,4]triazolo[4,3-a]pyridine) (**11**).* Compound **11** was prepared in a similar manner as described in the preparation of **10a**–**m**. In this reaction, 1.25 equiv (0.46 g, 2.64 mmol) of adipic acid dihydrazide (**7n**) was used. Yield 0.22 g (50%); white crystals; mp >335°C (DMF); ^{1}H NMR (400 MHz, DMSO): δ = 7.54 (d, J = 5.2 Hz, 2H), 7.39 (d, J = 5.2 Hz, 2H), 4.19 (t, J = 7.1 Hz, 4 H), 3.26 (t, J = 6.9 Hz, 4H), 2.83–2.78 (m, 4H), 1.83–1.78 (m, 4H); ^{13}C NMR (100 MHz, DMSO): δ = 152.8 (C=N), 148.0 (C=N), 141.5 (C=), 137.0 (C=), 125.9 (HC=), 122.6 (HC=), 40.6 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 23.4 (CH_2); IR (KBr): ν = 2323, 1610, 1566, 1426, 855, 726 cm^{-1}; HRMS calcd. for $C_{20}H_{21}N_6S_2$ $[M + H]^+$ 409.1264; found 409.1265.

General Procedure for the Suzuki Reaction

The solution of 0.10 g (0.30 mmol) of **10f** and 0.33 mmol of the appropriate boronic acid (40 mg of phenylboronic acid and 60 mg of 2,6-dimethoxyphenylboronic acid) in 20 mL of propane-1-ol was purged with argon for 15 min. 1 mg of $Pd(OAc)_2$ (1.5%), 3.5 mg of PPh_3 (4.5%), 38 mg (0.36 mmol) of Na_2CO_3, and 3 mL of water were added, and the solution was stirred at 110°C for 2 h until the starting material disappeared. The reaction mixture was concentrated in vacuo. The crude product was partitioned between 20 mL of dichloromethane and 15 mL of water. The organic layer was washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo.

*3-Biphenyl-4-yl-5,6-dihydrothieno[3,2-c][1,2,4]-triazolo[4,3-a]pyridine (**12a**).* Yield 98 mg (99%); white crystals; mp 259–261°C (MeCN); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77–7.75 (m, 2H), 7.74–7.72 (m, 2H), 7.64 (d, J = 5.3 Hz, 1H), 7.64–7.61 (m, 2H), 7.49–7.45 (m, 2H), 7.41–7.37 (m, 1H), 7.28 (d, J = 5.1 Hz, 1H), 4.38 (t, J = 7.1 Hz, 2H), 3.28 (t, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.6 (C=N), 149.5 (C=N), 142.8 (C=), 140.0 (C=), 136.1 (C=), 128.9 (two signals: 128.91, 128.87) (2×HC=), 127.9 (HC=), 127.5 (HC=), 127.1 (HC=), 126.5 (C=), 125.9 (C=), 125.0 (HC=), 123.7 (HC=), 42.4 (CH_2), 24.3 (CH_2); IR (KBr): ν = 1467, 843, 768, 700, 695 cm^{-1}; HRMS calcd. for $C_{20}H_{16}N_3S$ $[M+H]^+$ 330.1059; found 330.1054.

*3-(2',6'-Dimethoxybiphenyl-4-yl)-5,6-dihydrothieno[3,2-c][1,2,4]triazolo[4,3-a]pyridine (**12b**).* Yield 116 mg (99%); white crystals; mp 241–243°C (MeCN); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.71 (m, 2H), 7.66 (d, J = 5.2 Hz, 1H), 7.53–7.49

(m, 2H), 7.31 (t, $J = 8.4$ Hz, 1H), 7.29 (d, $J = 4.7$ Hz, 1H), 6.67 (d, $J = 8.4$ Hz, 2H), 4.43 (t, $J = 7.0$ Hz, 2H), 3.75 (s, 6H), 3.27 (t, $J = 7.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.5$ (HC═), 153.0 (C═N), 149.3 (C═N), 136.2 (C═), 136.1 (C═), 131.6 (HC═), 129.2 (C═), 127.7 (HC═), 126.6 (C═), 125.1 (HC═), 125.0 (C═), 123.7 (HC═), 118.4 (C═), 104.2 (HC═), 55.9 (CH_3), 42.4 (CH_2), 24.4 (CH_2); IR (KBr): $\nu = 1584$, 1242, 1104, 845, 732 cm^{-1}; HRMS calcd. for $C_{22}H_{20}N_3O_2S$ $[M + H]^+$ 390.1271; found 390.1265.

*3-[4-(Phenylethynyl)phenyl]-5,6-dihydrothieno-[3,2-c][1,2,4]triazolo[4,3-a]pyridine (**13**).* To the mixture of 15 mg of Pd/C (5%), 6 mg of CuI (10%), 8 mg of PPh_3 (10%) in 5 mL of *N*,*N*-dimethylacetamide, 0.25 mL of water, 0.1 g (0.3 mmol) of **10f**, 0.063 mL (0.45 mmol) of diisopropylamine, and 0.044 mL (0.4 mmol) of phenylacetylene were added. The solution was stirred at 80°C until the starting material disappeared (3.5 h). The reaction mixture was cooled down, diluted with 10 mL of water, and washed with 20 mL of $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (PF_{254}) using dichloromethane–hexane as the eluent.

Yield 86 mg (81%); white crystals; mp 248–250°C (MeCN); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.71$–7.68 (m, 2H), 7.68–7.65 (m, 2H), 7.64 (d, $J = 5.1$ Hz, 1H), 7.57–7.54 (m, 2H), 7.38–7.35 (m, 3H), 7.29 (d, $J = 5.3$ Hz, 1H), 4.36 (t, $J = 7.1$ Hz, 2H), 3.28 (t, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.3$ (C═N), 149.6 (C═N), 136.2 (C═), 132.0 (HC═), 131.7 (HC═), 128.6 (HC═), 128.4 (two signals: 128.40, 128.36) (2×HC═), 126.6 (C═), 126.4 (C═), 125.1 (two signals: 125.13, 125.09) (C═, HC═), 123.7 (HC═), 122.8 (C═), 91.5 (C≡), 88.6 (C≡), 42.5 (CH_2), 24.3 (CH_2); IR (KBr): $\nu = 3077$, 2887, 1571, 1463, 944, 835, 755, 689, 520 cm^{-1}; HRMS calcd. for $C_{22}H_{16}N_3S$ $[M + H]^+$ 354.1059; found 354.1057.

REFERENCES

[1] CAPRIE Streeting Committee. Lancet 1996, 348, 1329–1339.
[2] Sabatine, M. S. Eur Heart J Suppl 2006, 8, G31–G34.
[3] Aalla, S.; Gilla, G.; Metil, D. S.; Anumula, R. R.; Vummenthala, P. R.; Padi, P. R. Org Process Res Dev 2012, 16, 240–243.
[4] Aradi, D.; Rideg, O.; Vorobcsuk, A.; Magyarlaki, T.; Kónyi, A.; Pintér, T.; Horváth, I. G.; Komócsi, A. Eur J Clin Invest 2012, 42, 384–392.
[5] Meijden, M. W.; Leeman, M.; Gelens, E., Noorduin, W. L.; Meekes, H.; Enckevort, W. J. P.; Kaptein, B.; Vlieg, E.; Kellogg, R. M. Org Process Res Dev 2009, 13, 1195–1198.
[6] Aw, D.; Sharma, J. C. Postgrad Med J 2012, 88, 34–37.
[7] Meves, S. H.; Overbeck, U.; Endres, H. G.; Krogias, C.; Neubauer, H. Thromb Haemost 2012, 107, 69–79.
[8] Kalinski, C.; Lemonie, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. Synthesis 2008, 24, 4007–4011.
[9] Aillaud, I.; Haurena, C.; Gall, E. L.; Martens, T.; Ricci, G. Molecules 2010, 15, 8144–8155.
[10] Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Keglevich, Gy. Synthesis 2012, 44, 3447–3452.
[11] Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Drahos, L.; Keglevich, Gy. Heteroatom Chem 2013, 24, 124–130.
[12] Balasubramanian, M.; Keay, J. G.; Csriven, E. F. V.; Shobana, N. Heterocycles 1994, 37, 1951–1975.
[13] Moulin, A.; Bibian, M.; Blayo, A. L.; El Habnouni, S.; Martinez, J.; Fehrentz, J. A. Chem Rev 2010, 110, 1809–1827.
[14] Holm, S. C.; Straub, B. F. Org Prep Proc Int 2011, 43, 319–347.
[15] Hull, J. W.; Romer, D. R.; Podhorez, D. E.; Ash, M. L.; Brady, C. H. Beilstein J Org Chem 2007, 3, 23, and references contained therein.
[16] Lu, W. C.; Cao, X. F.; Hu, M.; Li, F.; Yu, G. A.; Liu, S. H. Chem Biodivers 2011, 8, 1497–1511.
[17] Li, Y.; Dong, F.; Liu, X.; Xu, J.; Kong, Z.; Chen, X.; Zheng, Y. Env Sci Technol 2012, 46, 2675–2683.
[18] Pascual, J. Exp Opin Pharmacother 2004, 5, 669–677.
[19] Johnston, M. M.; Rapoport, A. M. Drugs 2010, 70, 1505–1518.
[20] Martin, V. M. J Antimicrob Chemother 1999, 44, 429–437.
[21] Huijgens, P. C.; Simoons-Smit, A. M.; van Loene, A. C.; Prooy, E.; van Tinteren, H.; Ossenkoppele, G. J.; Jonkhoff, A. R. J Clin Pathol 1999, 52, 376–380.
[22] Duplantier, A. J.; Bachert, E. L.; Cheng, J. B.; Cohan, J. B.; Jenkinson, T. H.; Kraus, K. G.; McKechney, M. W.; Pillar, J. D.; Watson, J. W. J Med Chem 2007, 50, 344–349.
[23] Groessl, M.; Reisner, E.; Hartinger, C. G., Eichinger, R.; Semenova, O.; Timerbaev, A. R.; Jakupec, M. A.; Arion, V. B.; Keppler, B. K. J Med Chem 2007, 50, 2158–2193.
[24] Sugane, T.; Tobe, T.; Hamaguchi, W.; Shimada, I.; Maeno, K.; Miyata, J.; Suzuki, T.; Kimizuka, T.; Kohara, A.; Morita, T.; Doihara, H.; Saita, K.; Aota, M.; Furutani, M.; Shimada, Y.; Hamada, N.; Sakamoto, S.; Tsukamoto, S.-i. J Med Chem 2011, 54, 387–391.
[25] Potts, K. T. Chem Rev 1961, 61, 87–127.
[26] Mirzaei, Y. R.; Twamley, B.; Shreeve, J. M. J Org Chem 2002, 67, 9340–9345.
[27] Meyer, D.; Strassner, T. J Org Chem 2011, 76, 305–308.
[28] Tanaka, H.; Kuroita, T., Ishibuchi, S.; Uschio, H.; Futamura, T.; Ohashi, Y.; Yano, K. WO 9703986 A1, 1997.
[29] Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Keglevich, Gy. J Sulfur Chem 2012, 33, 33–41.
[30] Abrahám, G.; Sólyom, S., Csuzdi, E.; Berzsenyi, P. Ling, I.; Tarnawa, I.; Hámori, T.; Pallagi, I.; Horváth, K.; Andrási, F.; Kapus, G.; Hársing, L. G.; Király, I.; Patthy, M.; Horváth, G. Bioorg Med Chem 2000, 8, 2127–2144.

[31] Beal, D. M.; Bryans, J. S.; Johnson, P. S.; Newman, J.; Pasquinet, C.; Peakman, T. M.; Ryckmans, T.; Underwood, T. J. Wheeler, S. Tetrahedron Lett 2011, 52, 5913–5917.
[32] Filippakopoulos, P.; Picaud, S.; Fedorov, O.; Knapp, S.; Keller, M.; Wrobel, M.; Bracher, F.; Morgenstern, O. Bioorg Med Chem 2012, 20, 1878–1886.
[33] Portoghese, P. S.; Ronsisvalle, G.; Larson, D. L.; Yim, C. B.; Sayre, L. M.; Takemori, A. E. Life Sci 1982, 31, 1283–1286.
[34] Huff, B. E.; Koenig, T. M.; Mitchell, D.; Staszek, M. A. Org Synth 1998, 75, 53–60.
[35] Hamze, A.; Provot, O.; Alami, M.; Brion, J. D. Org Lett 2005, 7, 5625–5628.
[36] Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. J Org Chem 2003, 68, 3327–3329.
[37] Fahmy, M. M.; Mohamed, R. R.; Mohamed, N. A. Molecules 2012, 47, 7927–7940.