Synthesis of some 2-imidoylimino-2,3-dihydro-thiazolo[4,5-*d*]pyrimidines

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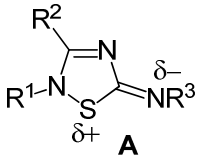
Abstract

The paper is concerned with chemistry of thiazolo[4,5-*d*]pyrimidine derivatives bearing a 1,3-diazapropenylidene fragment at position 2 and an oxygen or a mobile chlorine atom at position 7. These compounds are obtained in three steps: (i) cycloaddition of malononitrile to available 1,2,4-thiadiazol-5(2*H*)-imines to form *N*-(4-amino-5-cyanothiazol-2(3*H*)-ylidene)amidines; (ii) their acylation or condensation with DMF dimethyl acetal followed by; (iii) pyrimidine ring closure.

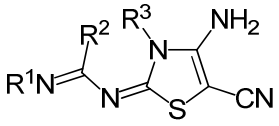
Keywords: 1,2,4-Thiadizol-5(2*H*)-imines, *N*-(4-amino-5-cyanothiazol-2(3*H*)-ylidene)amidines, thiazolo[4,5-*d*]pyrimidines, cycloaddition, substitution, cyclization

Introduction

Goerdeler and co-workers developed a convenient approach to synthesis of 1,2,4-thiadiazol-5(2*H*)-imines **A,** whose central feature is ability to take part in ring cleavage [3+2]-cycloadditions, where the structural element N=C-S serves as a quasi-1,3-dipolar reactant.[1]



A



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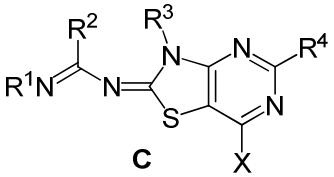
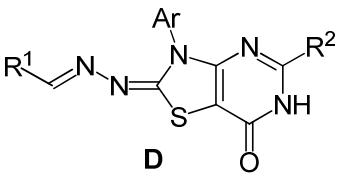


C

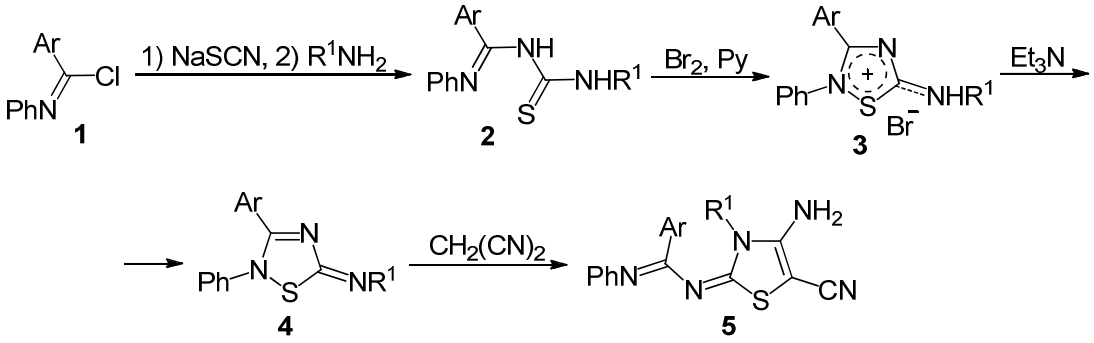


D

In the 2000s we found that compounds **A** interact with malononitrile to give adducts **B**, which were involved in further heterocyclizations.[2] The present paper is devoted to chemistry of a series of thiazolo[4,5-*d*]pyrimidines **C** bearing at position 2 a 1,3-diazapropenylidene fragment. We focused our attention on these species because the related 1,2-diazapropenylidene compounds **D** were found to show remarkable anti-inflammatory and antibacterial activities.[3]

Results and Discussion

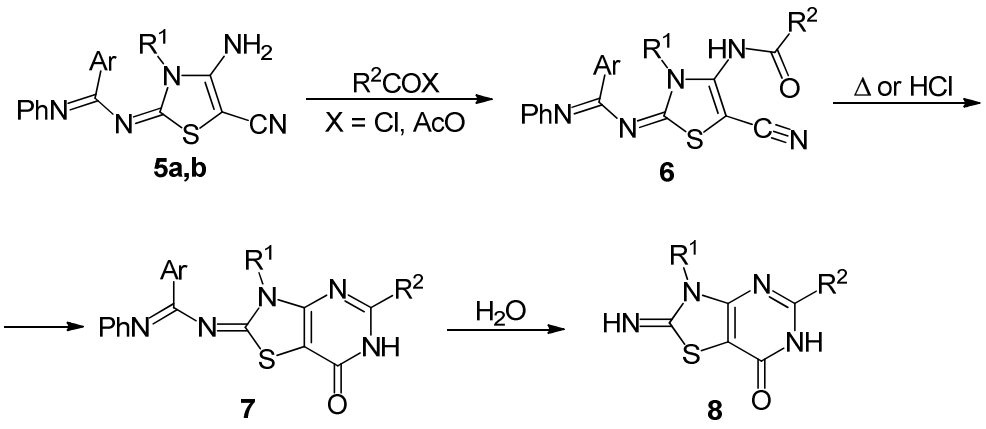
First and foremost, we synthesized some new key thiazole derivatives **5** starting from imidoyl chlorides **1** through carbamothioyl amidines **2**, 1,2,4-thiadiazolium salts **3**, and 1,2,4-thiadiazol-5(2*H*)-imines **4** (Scheme 1). Compounds **5** form as the result of the cycloaddition of malononitrile to bases **4** followed by a ring transformation with the participation of an active methylene group.[4] In this synthesis the free isolated bases **4a,b** were used but unstable **4c** was applied *in situ*.



1-5	Ar	R^1
a	Ph	Ph
b	4-MeC_6H_4	4-$MeOC_6H_4$
c	Ph	Bn

Scheme 1

Acylation of compounds **5** with acetic anhydride as well as benzoyl and *p*-nitrobenzoyl chlorides was performed in boiling pyridine (Scheme 2). In so doing the acetylation product **6a** was isolated in 74% yield but **6b** and **6c** were not because they underwent the pyrimidine ring closure to give thiazolo[4,5-*d*]pyrimidine derivatives **7b,c**. Interestingly, compound **7a** can also be obtained, albeit in low yield, if one heats **5a** in net acetic anhydride without adding pyridine. Another way to **7a** is treatment of **6a** with gaseous hydrogen chloride. Structures of compounds **7** were confirmed by ^{1}H NMR and IR spectroscopy and they are consistent with the well-known cyclization products of *o*-acylaminonitriles.[5]

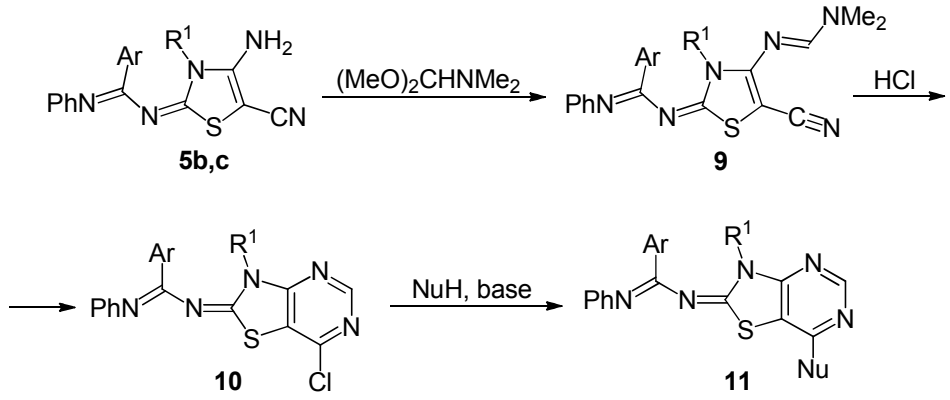


6-8	Ar	R^1	R^2
a	Ph	Ph	Me
b	Ph	Ph	4-$O_2NC_6H_4$
c	4-MeC_6H_4	4-$MeOC_6H_4$	Ph

Scheme 2

Compounds **7** were subject to the hydrolytic cleavage in acidic medium. Despite full conversion of the starting materials, products **8a,c** were isolated in a very low yield, which does not allow to judge the main result of the hydrolysis. However, it can serve as chemical verification of structure **7**; besides, **8a** was previously obtained by another method.[6]

A further strategy of the synthesis of thiazolo[4,5-*d*]pyrimidine derivatives based on compounds **5** is shown on Scheme 3. Condensation of **5** with DMF dimethyl acetal gives products **9** and their subsequent treatment with gaseous hydrogen chloride results in quantitative yield in compounds **10**.



11	Ar	R^1	Nu
a	4-MeC_6H_4	4-$MeOC_6H_4$	$O(CH_2CH_2)_2N$
b	4-MeC_6H_4	4-$MeOC_6H_4$	PhS
c	Ph	Bn	MeO

Scheme 3

This method of the pyrimidine ring formation by an intramolecular reaction of an amidine and a cyano groups was put into practice recently.[7] It enabled us to get compounds **10** containing an aromatic pyrimidine ring with a reactive chlorine atom, which can be easily replaced by nucleophiles to produce corresponding *N*-, *O*-, and *S*-substituted thiazolo[4,5-*d*]pyrimidines **11**.

Noteworthy, ^{1}H NMR spectroscopy of compounds **7, 10, 11** shown that in a solution they exist as mixtures of stereoisomers (signals of **7a,b, 11a, 11c** are broadened, **7c**, **10b, 11b** – duplicated). These stereoisomers can result from restricted *syn-anti* isomerization at nitrogen atoms as well as rotation around a single C–N bond in the side 1,3-diazapropenylidene fragment. In temperature dependent ^{1}H NMR the coalescence of signals was observed at 70-90 ºC (Supplementary Material).

Experimental Section

General. Melting points were determined on a capillary tube apparatus (bellow 250 ºC) and on a Fisher-Johns apparatus (above 250 ºC). IR spectra were taken on a Specord 71 IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian VXR 300, Varian Unity Plus 400, and a Bruker Avance DRX 500 spectrometer, TMS was used as the internal standard. Because of poor solubility of most compounds **7** and **11** in mentioned solvents, their ^{13}C NMR spectra were not obtained. Mass spectra were recorded on a Bruker Autoflex MALDI-TOF instrument. Combustion elemental analyses were performed by hand. All chemicals were supplied by Enamine (Kiev, Ukraine) and used without further purification.

***N*-Phenylbenzimidoyl chloride 1a** was prepared from *N*-phenylbenzamide and phosphorus pentachloride as described in ref. 8, bp 123-124 °C (0.02 mmHg) (lit. 175-176 °C (12 mmHg)).[8]
4-Methyl-*N*-phenylbenzimidoyl chloride 1b was prepared from 4-methyl-*N*-phenylbenzamide and phosphorus pentachloride as described in ref. 9, bp 132-134 °C (0.03 mmHg) (lit. 200 °C (16 mmHg)).[9]
***N*^{2}-Phenyl-*N*^{1}-(phenylcarbamothioyl)benzimidamide (2a) (typical procedure).** To a stirred solution of NaSCN (6.08 g, 75 mmol) in acetonitrile (100 mL), imidoyl chloride **1a** (16.18 g, 75 mmol) was added portionwise over 0.5 h at 15-20 °C. The mixture was stirred for a further 1 h and then a solution of aniline (6.83 mL, 75 mmol) in acetonitrile (20 mL) was added dropwise for 1 h at 10-12 °C. The resulting mixture was stirred for 2 h at 15-20 °C, diluted with water (50 mL), stirred for 0.5 h, and filtered to separate the product (22.70 g, 91%). Colorless crystals, mp 129-130 °C (from EtOH) (lit. 158 °C[10], 143-144 °C[11]). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, J_{HH} 8.0 Hz, 2Har.), 7.01 (t, J_{HH} 7.0 Hz, 1Har.), 7.17 (t, J_{HH} 7.5 Hz, 2Har.), 7.24-7.35 (m, 5Har.), 7.38-7.44 (m, 3Har.), 7.75 (d, J_{HH} 8.0 Hz, 2Har.), 8.15 (s, NH), 14.09 (s, NH).
***N*^{1}-(4-Methoxyphenylcarbamothioyl)-4-methyl-*N*^{2}-phenylbenzimidamide (2b).** This compound was prepared from imidoyl chloride **1b** (17.00 g, 74 mmol), NaSCN (6.00 g, 74 mmol) in acetonitrile (100 mL), and *p*-anisidine (9.11 g, 74 mmol) in acetonitrile (40 mL)

following the typical procedure given for **2a**; yield 96% (26.62 g). Colorless crystals, mp 126-127 °C (from EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, CH_3), 3.82 (s, CH_3), 6.74 (d, J_{HH} 7.6 Hz, 2Har.), 6.93 (d, J_{HH} 8.8 Hz, 2Har.), 7.00 (t, J_{HH} 7.4 Hz, 1Har.), 7.11 (d, J_{HH} 7.6 Hz, 2Har.), 7.15-7.18 (m, 4Har.), 7.59 (d, J_{HH} 8.8 Hz, 2Har.), 8.11 (s, NH), 13.88 (s, NH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.1, 55.1, 113.6, 122.1, 123.6, 125.4, 127.7, 128.5, 128.7, 129.2, 131.0, 140.8, 146.0, 155.5, 157.4, 178.6, 186.2. Calcd for $C_{22}H_{21}N_3OS$ (375.49): C 70.37, H 5.64, N 11.19, S 8.54. Found: C 70.64, H 5.83, N 11.09, S 8.53.

***N*^{1}-(Benzylcarbamothioyl)-*N*^{2}-phenylbenzimidamide (2c).** This compound was prepared from imidoyl chloride **1a** (11.65 g, 54 mmol), NaSCN (4.38 g, 54 mmol), and benzylamine (5.90 mL, 54 mmol) following the typical procedure given for **2a**; yield 90% (16.75 g). Colorless crystals, mp 148-149 °C (from EtOH) (lit. 159 °C[12]). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.99 (d, J_{HH} 5.5 Hz, CH_2), 6.63 (d, J_{HH} 8.0 Hz, 2Har.), 6.95 (t, J_{HH} 8.0 Hz, 1Har.), 7.11 (t, J_{HH} 7.5 Hz, 2Har.), 7.24 (d, J_{HH} 7.5 Hz, 2Har), 7.29-7.31 (m, 3Har.), 7.35-7.38 (m, 3Har.), 7.43 (d, J_{HH} 7.5 Hz, 2Har.), 8.09 (s, NH), 12.41 (s, NH).

2,3-Diphenyl-5-(phenylamino)-1,2,4-thiadiazolium bromide (3a) (typical procedure). To a stirred at room temperature suspension of **2a** (22.21 g, 67 mmol) in $CHCl_3$ (70 mL), pyridine (5.42 mL, 67 mmol) was added in one portion. Then a solution of bromine (3.43 mL, 67 mmol) in $CHCl_3$ (30 mL) was added dropwise for 1 h. The resulting mixture was stirred for 2 h and the precipitate was filtered off and washed with EtOH to obtain the product (22.29 g, 81%). The filtrate was concentrated in vacuum and the residue was washed with EtOH to afford an additional amount of the product (2.70 g, 10%). Colorless crystals, mp 217-218 °C (lit. 207-208 °C[13], 230-232 °C[14]). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.29 (t, J_{HH} 7.5 Hz, 1Har.), 7.44 (t, J_{HH} 7.5 Hz, 2Har.), 7.50-7.58 (m, 8Har.), 7.64 (d, J_{HH} 8.0 Hz, 2Har.), 7.81 (d, J_{HH} 7.5 Hz, 2Har.), 12.90 (s, NH).

5-((4-Methoxyphenyl)amino)-2-phenyl-3-(*p*-tolyl)-1,2,4-thiadiazolium bromide (3b). This compound was prepared by bromination of **2b** (30.04 g, 80 mmol) in a solution of $CHCl_3$ (80 mL) according to the typical procedure given for **3a**; total yield 91% (33.00 g). Slightly yellow crystals, mp 222-223 °C (from MeCN). ^{1}H NMR (500 MHz, DMSO-d_6,): δ 2.31 (s, CH_3), 3.79 (s, CH_3), 7.08 (d, J_{HH} 9.0 Hz, 2Har.), 7.24 (d, J_{HH} 8.0 Hz, 2Har.), 7.44 (d, J_{HH} 8.0 Hz, 2Har.), 7.56-7.64 (m, 5Har.), 7.72 (d, J_{HH} 8.5 Hz, 2Har.), 12.18 (s, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.1, 55.4, 114.7, 121.6, 123.6, 127.6, 129.3, 130.3, 130.4, 130.9, 134.3, 143.4, 157.1, 165.3, 171.5, 186.4. Calcd for $C_{22}H_{20}BrN_3OS\cdot$(454.38): Br 17.59, N 9.25, S 7.06. Found: Br 17.90, N 9.14, S 7.27.

5-(Benzylamino)-2,3-diphenyl-1,2,4-thiadiazolium bromide (3c). This compound was prepared by bromination of **2c** (15.25 g, 44 mmol) according to the typical procedure given for **3a**; yield 90% (16.78 g). Colorless crystals, mp 206-207 °C dec (from EtOH) (lit. 239 °C[12], 226-227 °C[15]). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.97 (d, J_{HH} 5.0 Hz, CH_2), 7.34 (t, J_{HH} 7.0 Hz, 1Har.), 7.40-7.43 (m, 4Har.), 7.47 (d, J_{HH} 7.0 Hz, 2Har.), 7.52-7.55 (m, 6Har.), 7.60 (d, J_{HH} 6.5 Hz, 2Har.), 10.38 (s, NH).

***N*-(2,3-Diphenyl-1,2,4-thiadiazol-5(2*H*)-ylidene)aniline (4a).** To a suspension of salt **3a** (23.51 g, 57 mmol) in EtOH (120 mL), triethylamine (10.07 mL, 72 mmol) was added dropwise for 0.5 h at room temperature. The mixture was stirred for 6 h and filtered to separate the product which was washed with EtOH; yield 89% (16.72 g). Yellow crystals, mp 125-126 °C (lit. 142-143 °C[1]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05-7.10 (m, 5Har.), 7.23-7.39 (m, 8Har.), 7.55 (d, J_{HH} 8.0 Hz, 2Har.).

4-Methoxy-*N*-(2-phenyl-3-(*p*-tolyl)-1,2,4-thiadiazol-5(2*H*)-ylidene)aniline (4b). This base was obtained from salt **3b** (27.95 g, 62 mmol) following the procedure given for **4a**; yield 94% (21.67 g). Yellow crystals, mp 126-127 °C. ^{1}H (500 MHz, $CDCl_3$): δ 2.33 (s, CH_3), 3.79 (s, CH_3), 6.90 (d, J_{HH} 9.0 Hz, 2Har.), 7.04-7.14 (m, 6Har.), 7.28-7.31 (m, 3Har.), 7.48 (d, J_{HH} 8.0 Hz, 2Har.). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.1, 55.1, 114.5, 121.2, 125.0, 126.6, 128.1, 128.6, 129.3, 129.8, 138.7, 141.6, 145.0, 156.1, 166.0. Calcd for $C_{22}H_{19}N_3OS$ (373.47): C 70.75, H 5.13, N 11.25, S 8.59. Found: C 70.67, H 5.37, N 11.46, S 8.49.

***N*^{1}-(4-Amino-5-cyano-3-phenylthiazol-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (5a).** A stirred mixture of **4a** (9.88 g, 30 mmol), malononitrile (1.98 g, 30 mmol), and dioxane (15 mL) was heated under reflux for 4 h, cooled, and filtered to separate the product, which was washed with dioxane and dried at 100 °C; yield 88% (10.39 g). Slightly yellow crystals, mp 208-209 °C dec. IR (CH_2Cl_2, ν_{max}, cm^{-1}): 2190 (CN), 2700-3500 (CH, NH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.61 (s, NH_2), 6.81 (d, J_{HH} 7.5 Hz, 2Har.), 7.03 (t, J_{HH} 6.5 Hz, 1Har.), 7.12 (t, J_{HH} 7.5 Hz, 2Har.), 7.19-7.29 (m, 5Har.), 7.46 (d, J_{HH} 7.5 Hz, 2Har.), 7.56-7.65 (m, 3Har.). ^{13}C NMR (126 MHz, $CDCl_3$): δ 62.3, 115.2, 121.3, 122.6, 127.3, 128.1, 128.6, 128.9, 129.3, 129.88, 129.93, 134.09, 134.13, 144.3, 146.9, 149.2, 157.2, 159.9. Calcd for $C_{23}H_{17}N_5S$ (395.48): C 69.85, H 4.33, N 17.71, S 8.11. Found: C 69.89, H 4.44, N 17.72, S 8.37.

***N*^{1}-(4-Amino-5-cyano-3-(4-methoxyphenyl)thiazol-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (5b).** This compound was prepared from **4b** (11.20 g, 30 mmol) and malononitrile (1.98 g, 30 mmol) following the procedure given for **5a**; yield 86% (11.40 g). Yellow crystals, mp 205-206 °C dec (from MeCN). IR (CH_2Cl_2, ν_{max}, cm^{-1}): 2190 (CN), 2700-3500 (CH, NH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 (s, CH_3), 3.90 (s, CH_3), 4.61 (s, NH_2), 6.81 (d, J_{HH} 7.0 Hz, 2Har.), 6.93 (d, J_{HH} 7.5 Hz, 2Har.), 7.02 (t, J_{HH} 7.5 Hz, 1Har.), 7.09 (d, J_{HH} 8.0 Hz, 2Har.), 7.19-7.27 (m, 4Har.), 7.35 (d, J_{HH} 8.0 Hz, 2Har.). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.7, 55.3, 57.4, 114.9, 116.0, 121.4, 122.4, 127.2, 128.2, 128.8, 128.9, 129.9, 132.1, 138.8, 147.6, 151.6, 157.9, 159.8, 160.0. Calcd for $C_{25}H_{21}N_5OS$ (439.53): C 68.32, H 4.82, N 15.93, S 7.30. Found: C 68.68, H 4.82, N 15.88, S 7.13.

***N*^{1}-(4-Amino-3-benzyl-5-cyanothiazol-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (5c).** To a stirred mixture of salt **3c** (6.36 g, 15 mmol) and malononitrile (0.99 g, 15 mmol) in CH_2Cl_2 (20 mL), a solution of triethylamine (2.10 mL, 15 mmol) in CH_2Cl_2 (10 mL) was added dropwise for 0.5 h at room temperature. The reaction mixture was stirred for 15 h then the precipitate was filtered off and washed with water to afford the product (4.68 g, 76%). Yellow crystals, mp 210-211 °C dec (from MeCN). IR (CH_2Cl_2, ν_{max}, cm^{-1}): 2190 (CN), 2800-3400 (CH, NH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.52 (s, NH_2), 5.55 (s, CH_2), 6.83 (d, J_{HH} 6.5 Hz, 2Har.), 7.03 (t,

J_{HH} 6.5 Hz, 1Har.), 7.23-7.29 (m, 5Har.), 7.35-7.47 (m, 7Har.). ^{13}C NMR (126 MHz, $CDCl_3$): δ 47.9, 64.5, 114.8, 121.6, 122.7, 126.5, 127.4, 128.3, 128.5, 129.0, 129.2, 134.0, 134.7, 144.3, 146.9, 150.0, 157.9, 159.7. Calcd for $C_{24}H_{19}N_5S$ (409.51): C 70.39, H 4.68, N 17.10, S 7.83. Found: C 70.54, H 4.76, N 17.02, S 7.55.

***N*-(5-Cyano-3-phenyl-2-((phenyl(phenylimino)methyl)imino)-2,3-dihydrothiazol-4-yl)acetamide (6a).** A solution of **5a** (1.98 g, 5 mmol) and acetic anhydride (0.94 mL, 10 mmol) in pyridine (6 mL) was heated under reflux for 5 h. The reaction mixture was poured on ice and a precipitated solid was separated and washed with MeCN to give the pure product (1.62 g, 74%). Yellow powder, mp 248-249 °C dec (from MeCN). IR (KBr, ν_{max}, cm^{-1}): 1700 (CO), 2235 (CN), 3290 (NH). ^{1}H NMR (500 MHz DMSO-d_6,): δ 1.83 (s, CH_3), 6.74 (d, J_{HH} 7.0 Hz, 2Har.), 7.01 (t, J_{HH} 7.0 Hz, 1Har.), 7.19-7.25 (m, 7Har.), 7.44 (d, J_{HH} 8.0 Hz, 2Har.), 7.52-7.56 (m, 3Har.), 10.35 (s, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 22.2, 86.8, 112.8, 121.6, 123.1, 127.9, 128.2, 128.9, 129.2, 129.4, 129.5, 134.4, 135.2, 141.9, 146.6, 158.0, 159.2, 169.1, 186.1. Calcd for $C_{25}H_{19}N_5OS$ (437.52): C 68.63, H 4.38, N 16.01, S 7.33. Found: C 68.62, H 4.49, N 15.84, S 7.30.

***N*^{1}-(5-Methyl-7-oxo-3-phenyl-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (7a).** (a) A stirred mixture of **5a** (1.08 g, 2.7 mmol) and acetic anhydride (5 mL) was heated under reflux for 4 h, then cooled and filtered to separate the product which was washed with EtOH; yield 33% (0.40 g). (b) Through a boiling stirred suspension of **6a** (1.09 g, 2.5 mmol) in 1,2-dichloroethane (8 mL), gaseous HCl was bubbled during 5 h. After cooling, the precipitate was filtered off, dried, and added to a solution of triethylamine (0.70 mL, 5.0 mmol) in ethanol (10 mL). This mixture was stirred, heated under reflux for 2 h, then cooled and filtered to separate the product; yield 70%, (0.76 g). Yellow crystals, mp 317-318 °C dec (from DMF). IR (KBr, ν_{max}, cm^{-1}): 1670 (CO), 2400-3200 (CH, NH). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C): δ 2.28 (s, CH_3), 6.80 (d, J_{HH} 7.8 Hz, 2Har.), 6.99 (t, J_{HH} 7.5 Hz, 1Har.), 7.21-7.58 (m, 12Har.), 12.38 (s, NH). Calcd for $C_{25}H_{19}N_5OS$ (437.52): C 68.63, H 4.38, N 16.01, S 7.33. Found: C 68.81, H 4.41, N 16.19, S 7.54.

***N*^{1}-(5-(4-Nitrophenyl)-7-oxo-3-phenyl-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (7b).** A stirred mixture of **5a** (2.37 g, 6 mmol), *p*-nitrobenzoyl chloride (2.23 g, 12 mmol), and pyridine (7 mL) was heated under reflux for 2 h, then cooled and diluted with EtOH (15 mL). The precipitated product was filtered off and dried at 100 °C; yield 56% (1.82 g). Yellow powder, mp 305-306 °C dec (from DMF). IR (KBr, ν_{max}, cm^{-1}): 1660 (CO), 2800-3150 (CH, NH). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C): δ 6.84 (d, J_{HH} 7.8 Hz, 2Har.), 7.02 (t, J_{HH} 7.4 Hz, 1Har.), 7.24-7.69 (m, 12Har.), 8.20-8.30 (m, 4Har.), 12.83 (br. s, NH). Calcd for $C_{30}H_{20}N_6O_3S$ (544.58): C 66.16, H 3.70, N 15.43, S 5.89. Found: C 66.33, H 3.70, N 15.11, S 5.99.

***N*^{1}-(3-(4-Methoxyphenyl)-7-oxo-5-phenyl-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (7c).** This compound was synthesized from **5b** (1.10 g, 2.5 mmol) and benzoyl chloride (0.58 mL, 5.0 mmol) following the procedure given for **7b**; yield 51% (0.70 g). Slightly yellow powder, mp 314-315 °C dec. IR (KBr, ν_{max}, cm^{-1}): 1680

(CO), 2800-3250 (CH, NH). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C): δ 2.27 (s, CH_3), 3.88 (s, CH_3), 6.83 (d, J_{HH} 7.2 Hz, 2Har.), 6.98-7.55 (m, 14Har.), 7.98 (d, J_{HH} 7.5 Hz, 2Har.), 12.56 (br. s, NH). Calcd for $C_{32}H_{25}N_5O_2S$ (543.64): C 70.70, H 4.64, N 12.88. Found: C 71.06, H 4.93, N 12.67.

2-Imino-5-methyl-3-phenyl-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8a). To a suspension of **7a** (0.35 g, 0.8 mmol) in ethanol (8 mL), concd hydrochloric acid (0.8 mL) was added. A resulting solution was heated under reflux for 1 h, then cooled, added by 2 M Na_2CO_3 (5 mL), and filtered to separate a solid, which was recrystallized from DMF to give the pure product (0.04 g, 19%). Colorless powder, mp 264-266 ºC dec (lit. 245 ºC[6]). IR (KBr, ν_{max}, cm^{-1}): 1680 (CO), 2500-3140 (CH, NH), 3300 (NH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (s, CH_3), 7.36-7.51 (m, 5Har.), 8.85 (s, NH), 12.60 (s, NH).

2-Imino-3-(4-methoxyphenyl)-5-phenyl-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8c). To a suspension of **7c** (0.71 g, 1.3 mmol) in acetic acid (6 mL), concd hydrochloric acid (1 mL) was added. A resulting solution was heated under reflux for 8 h, evaporated in vacuum and the residue was treated with ethanol to give a solid, which was separated. To a suspension of this solid in acetonitrile (5 mL), triethylamine (0.36 mL) was added, the mixture was stirred for 24 h then the precipitate was filtered off and washed with water to give the pure product (0.05 g, 11%). Colorless powder, mp 277-279 ºC dec. IR (KBr, ν_{max}, cm^{-1}): 1650 (CO), 3210-3320 (NH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, CH_3), 7.06 (d, J_{HH} 8.0 Hz, 2Har.), 7.36 (d, J_{HH} 8.0 Hz, 2Har.), 7.45 (t, J_{HH} 6.3 Hz, 2Har.), 7.52 (t, J_{HH} 7.0 Hz, 1Har.), 7.89 (d, J_{HH} 7.5 Hz, 2Har.). Calcd for $C_{18}H_{14}N_4O_2S$ (350.39): C 61.70, H 4.03, N 15.99. Found: C 61.55, H 4.00, N 15.85.

***N*^{1}-(5-Cyano-4-(((dimethylamino)methylene)amino)-3-(4-methoxyphenyl)thiazol-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (9b)**. A mixture of **5b** (3.30 g, 7.5 mmol) and DMF dimethyl acetal (1.10 mL, 8.3 mmol) in dioxane (20 mL) was heated under reflux for 3 h. The resulting solution was diluted with water (5 mL) and kept at room temperature to precipitate the product, which was separated and dried at 100 °C; yield 76% (2.55 g). Slightly yellow crystals, mp 222-223 °C. IR (CH_2Cl_2, ν_{max}, cm^{-1}): 2180 (CN). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, CH_3), 2.74 (s, CH_3), 3.06 (s, CH_3), 3.79 (s, CH_3), 6.70 (d, J_{HH} 7.5 Hz, 2Har.), 6.95-7.08 (m, 7Har.), 7.20 (t, J_{HH} 7.5 Hz, 2Har.), 7.33 (d, J_{HH} 9.0 Hz, 2Har.), 8.17 (s, CH=N). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.7, 34.0, 40.0, 55.1, 67.9, 113.6, 116.5, 121.4, 122.5, 128.2, 128.8, 128.9, 129.2, 129.6, 132.1, 138.9, 147.4, 156.3, 156.5, 158.1, 158.8, 159.6. Calcd for $C_{28}H_{26}N_6OS$ (494.61): C 67.99, H 5.30, N 16.99, S 6.48. Found: C 68.19, H 5.19, N 17.33, S 6.61.

***N*^{1}-(3-Benzyl-5-cyano-4-((dimethylamino)methylene)amino)thiazol-2(*3H*)-ylidene)-*N*^{2}-phenylbenzimidamide (9c).** This compound was prepared from **5c** (2.91 g, 7.1 mmol) and DMF dimethyl acetal (1.13 mL, 8.5 mmol) according to the procedure given for **9b**; yield 75% (2.48 g). Yellow crystals, mp 159-160 °C (from MeCN). IR (CH_2Cl_2, ν_{max}, cm^{-1}): 2170 (CN). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.05 (s, CH_3), 3.15 (s, CH_3), 5.38 (s, CH_2), 6.69 (d, J_{HH} 7.0 Hz, 2Har.), 6.96 (t, J_{HH} 7.0 Hz, 1Har.), 7.17-7.40 (m, 12Har.), 8.34 (s, CH=N). ^{13}C NMR

(126 MHz, DMSO-d_6): δ 34.4, 40.3, 47.8, 67.4, 116.5, 121.5, 122.6, 127.4, 127.8, 127.9, 128.3, 128.8, 129.1, 129.2, 135.0, 136.7, 147.4, 155.5, 156.9, 158.0, 158.5. Calcd for $C_{27}H_{24}N_6S$ (464.58): C 69.80, H 5.21, N 18.09, S 6.90. Found: C 69.69, H 5.24, N 18.14, S 6.80.

***N*^{1}-(7-Chloro-3-(4-methoxyphenyl)thiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (10b).** Through a boiling stirred solution of **9b** (1.50 g, 3.03 mmol) in benzene (50 mL), gaseous hydrogen chloride was bubbled during 2 h. After cooling of the resulting mixture, the precipitate was filtered off and washed with water; yield 96 % (1.41 g). Slightly yellow crystals, mp 218-219 ºC dec (from MeCN). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25, 2.39 (s, 8:1, CH_3), 3.89 (s, CH_3), 6.86-7.80 (m, 13Har.), 8.44, 8.63 (s, 1:5, CH-5). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.3, 56.0, 114.8, 118.6, 121.6, 123.8, 128.5, 129.0, 129.7, 130.0, 131.9, 140.3, 147.6, 152.0, 156.2, 158.2, 158.4, 158.7, 159.3, 160.0. Calcd for $C_{26}H_{20}ClN_5OS$ (485.99): C 64.26, H 4.15, Cl 7.30, N 14.41, S 6.60. Found: C 63.92, H 4.37, Cl 7.21, N 14.15, S 6.53.

***N*^{1}-(3-Benzyl-7-chlorothiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (10c).** This compound was prepared from **9c** (1.22 g, 2.63 mmol) according to the procedure given for **10b**; yield 97% (1.16 g). Yellow crystals, mp 205-206 °C (from MeCN). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (s, CH_2), 6.88 (d, J_{HH} 7.5 Hz, 2Har.), 7.09 (t, J_{HH} 7.0 Hz, 1Har.), 7.29-7.37 (m, 8Har.), 7.52 (d, J_{HH} 7.5 Hz, 2Har.), 7.61 (d, J_{HH} 6.5 Hz, 2Har.), 8.79 (s, CH-5). ^{13}C NMR (126 MHz, $CDCl_3$): δ 47.7, 118.8, 121.3, 123.0, 127.6, 127.8, 128.2, 128.6, 128.7, 129.4, 134.4, 135.3, 146.9, 152.4, 155.0, 156.6, 157.8, 157.9. MALDI–TOF MS, *m/z*: calcd for $[C_{25}H_{18}ClN_5S]^+$ 455.097, found 455.10. Calcd for $C_{25}H_{18}ClN_5S$ (455.96): C 65.85, H 3.98, Cl 7.78, S 7.03. Found: C 65.79, H 4.03, Cl 7.88, S 7.16.

***N*^{1}-(3-(4-Methoxyphenyl)-7-(morpholin-4-yl)thiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (11a).** To a solution of **10b** (0.17 g, 0.35 mmol) in THF (5 mL), morpholine (0.06 mL, 0.70 mmol) was added. The mixture was left to stand for 4 d at room temperature then filtered. The filtrate was concentrated in vacuum and the residue was treated with ethanol (5 mL) to crystallize the product; yield 92% (0.17 g). Yellow crystals, mp 230-231 ºC (from MeCN). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C): δ 2.28 (s, CH_3), 3.70-3.79 (m, 4CH_2), 3.86 (s, CH_3), 6.83 (d, J_{HH} 7.5 Hz, 2Har.), 6.97–7.10 (m, 5Har.), 7.23-7.35 (m, 6Har.), 8.24 (s, CH-5). Calcd for $C_{30}H_{28}N_6O_2S$ (536.65): C 67.14, H 5.26, N 15.66, S 5.98. Found: C 67.17, H 5.46, N 15.45, S 6.02.

***N*^{1}-(3-(4-Methoxyphenyl)-7-(phenylsulfanyl)thiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-4-methyl-*N*^{2}-phenylbenzimidamide (11b).** A mixture of **10b** (0.52 g, 1.07 mmol), thiophenol (0.12 mL, 1.2 mmol), and triethylamine (0.42 mL, 3.0 mmol) in acetonitrile (10 mL) was heated under reflux for 2 h. The resulting solution was left to stand at room temperature to precipitate the product, which was separated and washed with water; yield 77% (0.46 g). Yellow crystals, mp 188-189 °C (from MeCN). ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C): δ 2.27 (s, CH_3), 3.86 (s, CH_3), 6.76 (br. s, 2Har.), 7.03-7.11 (m, 6Har.), 7.27-7.42 (m, 8Har.), 7.64 (br. s, 2Har.), 8.54 (s, CH-5). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.3, 55.9, 114.7, 116.0, 121.7, 123.4, 126.8, 128.6, 129.0, 129.4, 129.7, 130.06, 130.14, 130.8, 132.2, 136.2, 140.0, 147.8, 155.5, 156.4, 158.2,

159.6, 159.8, 161.3. Calcd for $C_{32}H_{25}N_5OS_2$ (559.70): C 68.67, H 4.50, N 12.51, S 11.46. Found: C 69.04, H 4.64, N 12.29, S 11.57.

***N*^{1}-(3-Benzyl-7-methoxythiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)-*N*^{2}-phenylbenzimidamide (11c).** To a suspension of **10c** (0.43 g, 0.94 mmol) in THF (8 mL), 2.3 M MeONa/MeOH (0.82 mL) was added. The mixture was stirred for 6 d at room temperature then the precipitate was filtered off and washed with water to give the product (0.21 g, 49%). The filtrate was concentrated in vacuum and the residue was washed with water to obtain an additional amount of the product (0.16 g, 37%). Slightly yellow crystals, mp 202-203 °C (from AcOEt). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.09 (s, CH_3), 5.64 (s, CH_2), 6.78 (br. s, 2Har.), 7.02 (t, J_{HH} 9.2 Hz, 1Har.), 7.25-7.43 (m, 12Har.), 8.72 (s, CH-5). MALDI-TOF MS, *m/z*: calcd for $[C_{26}H_{21}N_5OS]^+$ 451.147, found 451.14. Calcd for $C_{26}H_{21}N_5OS$ (451.54): C 69.16, H 4.69, N 15.51, S 7.10. Found: C 69.56, H 4.63, N 15.49, S 7.06.

Supplementary Material

^{1}H NMR spectra of compounds **7a-c, 10b, 11a-c** at 20 (25), 50, 70, and 90 ºC.

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