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Synthesis of substituted [1,3]thiazolo[4,5-*b*]pyridines and [1,3]thiazolo-[4,5-*d*][1,2,3]triazines

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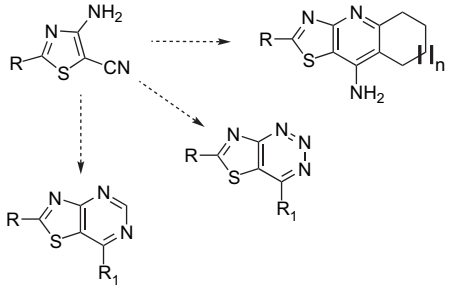
ABSTRACT

In this work, we described an easy preparation of substituted 4-amino-5-cyano-1,3-thiazoles. These compounds have been used as starting materials to obtain two classes of compounds. New substituted [1,3]thiazolo[4,5-*e*]pyridines were synthesized in one step via Friedländer reaction. Diazotation of 4-amino-5-cyano-1,3-thiazoles afforded 4-chloro[1,3]thiazolo[4,5-*d*][1,2,3]triazines in one step. The later was substituted by a secondary amine to obtain substituted 4-amino[1,3]thiazolo[4,5-*d*][1,2,3]triazines.

1. Introduction

Since a few years, we are interested in the many possibilities that heterocyclic analogs of anthranilonitriles or anthraniloesters allow. Especially, *ortho*-amino-cyano-thiophenes were used to synthesize analogues of Tacrine,[1,2] thienopyridinones,[3] and thienopyrimidinones.[4] Several analogues of Tacrine synthesized in the thiophene series are currently under biological investigation. As the 1,3-thiazole ring is also present in many pharmacological active substances,[5] we decided to extend our library of Tacrine analogues to the thiazole series. Those new analogues could be obtained starting from 4-amino-1,3-thiazole-5-carbonitrile. This interesting starting material would also allow access to thiazolocondensed heterocyclic systems like thiazolopyrimidines or thiazolotriazines (Scheme 1).



Scheme 1. Targeted compounds starting from amino-cyano-thiazole.

2. Results and discussion

The first step of our strategy was the formation of 4-amino-1,3-thiazole-5-carbonitriles **2**. Their preparation is well described in the literature[6] and usually, compound **2a** is obtained from cyanodithiocarbamic acid methyl ester potassium salt and chloroacetonitrile.[6a,c] Here, we proposed an alternative route via dimethyl cyanodithioimidocarbonate **1** (Scheme 2). As reported in the literature,[7] **1** was obtained easily and in good yield from cyanamide (Scheme 2). We applied the same methodology, we used few years ago to synthesize amino-cyano-thiophenes from ketene *S*,*S*-dimethylthioacetals:[8] compound **1** was reacted with sodium sulfide, an activated halide and potassium carbonate. Compound **2a** was obtained in good yield with this one-pot three-step sequential procedure (Scheme 2).

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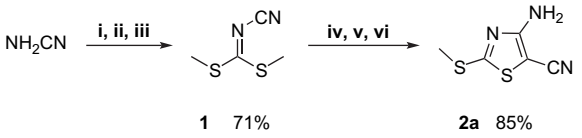
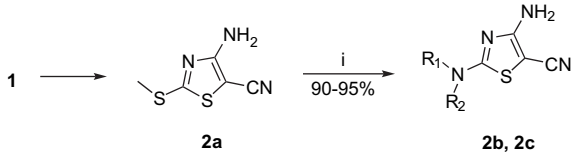


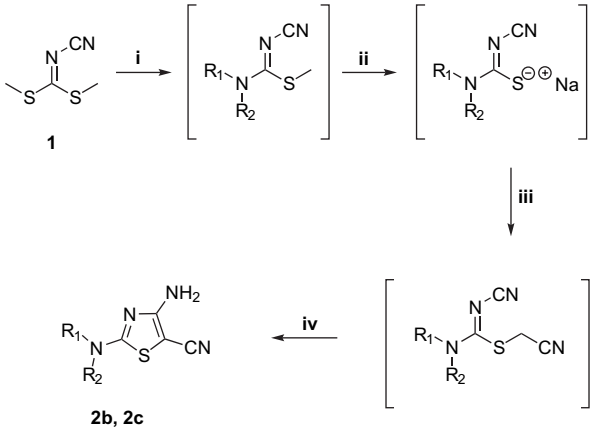
Scheme 2. Reagents and conditions: (i) KOH; (ii) CS_2; (iii) MeI; (iv) $Na_2S{\cdot}9H_2O$, DMF; (v) $ClCH_2CN$; (vi) K_2CO_3.

Taking advantage of the good leaving group property of the methylsulfanyl group in compound **2a** and as described before on similar compounds,[6k,l,9] S_NAr reaction with secondary amines were realized. Compound **2a** was dissolved in 10 equiv of amine and refluxed overnight to yield **2b** and **2c** in high yields (method A, Scheme 3).



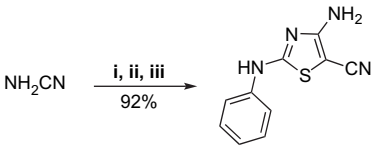
Scheme 3. Method A: synthesis of **3** (R_1–R_2=4-morpholinyl) and **4** (R_1–R_2=1-pyrrolidinyl) starting from **2**. Reagents: (i) excess of amine, reflux.

Ried et al. described the synthesis of 4-amino-2-morpholin-4-yl-thiazole-5-carboxylic acid methyl ester from methyl *N*-cyano-4-morpholinecarbimidothioate and methylthioglycolate.[10] We have presumed that compounds **2b** and **2c** could be synthesized directly from **1** via a one-pot four-step sequential procedure (method B, Scheme 4). Compound **1** was dissolved in DMF, then morpholine or pyrrolidine was added and heated at 70 °C during 1 h. After this time, sodium sulfide was introduced to form the thiolate that reacted with chloroacetonitrile and finally, potassium carbonate was added to complete the cyclization (Scheme 4). Compounds **2**(**b** and **c**) were obtained in good yields. In the literature, there is only one example of solid phase synthesis to access 2,4,5-trisubstituted thiazoles in a one-pot four-step reaction.[11] In terms of overall yields, methods A and B were equivalent but method B was shorter.



Scheme 4. Method B: synthesis of **3** (R_1–R_2=4-morpholinyl) and **4** (R_1–R_2=1-pyrrolidinyl) starting from **1**. Reagents: (i) morpholine or pyrrolidine, DMF; (ii) $Na_2S{\cdot}9H_2O$; (iii) $ClCH_2CN$; (iv) K_2CO_3.

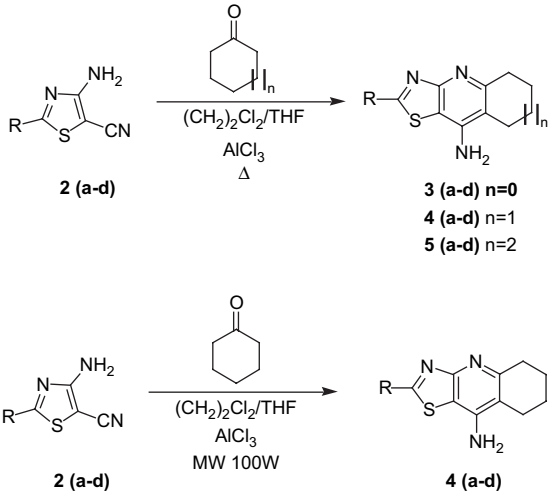
Thiazole **2d** was synthesized by a method described by Gewald.[6d] Cyanamide, potassium carbonate, phenyl isothiocyanate, and chloroacetonitrile afforded in one step and in high yield thiazole **2d** (Scheme 5).



Scheme 5. i) DMF, K_2CO_3; (ii) phenyl isothiocyanate; (iii) $ClCH_2CN$.

In the literature, 1,3-thiazolopyridines are obtained by cyclization of the suitable thioacetamidopyridine.[12] The second step of our strategy was to use thiazoles **2**(**a**–**d**) as starting material to access new classes of compounds like thiazole analogues of Tacrine and [1,3]thiazolo[4,5-*d*][1,2,3]triazines.

Friedländer reaction on thiazoles **2** has allowed formation of new Tacrine's analogues. As we have shown recently in the selenophene series,[13] Friedländer reaction can be performed under classical heating or under microwave irradiation. We decided to study those two methods on thiazoles **2**. Using classical heating, thiazoles **2a** and **2d** were dissolved in dichloroethane, and cyclanones and aluminum chloride were added. For thiazoles **2b** and **2c**, we have chosen THF because **2**(**b** and **c**) were not enough soluble in dichloroethane. In both cases, the reaction mixture was refluxed for 4 h and compounds **3**–**5**(**a**–**d**) were obtained in high yields (Scheme 6 and Table 1). Under microwave irradiation, we choose a mixture of solvent to be able to finish the reaction in about 30 min (THF for solubility and DCE for the higher boiling point). With microwave irradiation, the time of reaction was reduced from 4 h to about 30 min and compounds **4**(**a**–**d**) were obtained in high yields too (Scheme 6 and Table 2).



Scheme 6. Friedländer reaction: R=MeS–, 4-morpholinyl, 1-pyrrolidinyl, PhNH–.

As explained before, amino-cyano-thiazoles could also be used to synthesize thiazolocondensed systems. For example, thiazolopyrimidines have shown interesting biological activity such as antagonist of CXCR2 receptor.[14] This bicyclic core has been built starting either from substituted pyrimidines[15] or from 4-amino-5-cyanothiazole.[16] On another hand, in several publications, aza analogues of condensed pyrimidines were synthesized for studying the modulation of biological activities: pyrazolo[3,4-*d*]-1,2,3-triazin-4-one nucleosides[17] or pyrrolo[2,3-*d*]-1,2,3-triazine[18] were explored for their antiviral/antitumor activity.

So we planned to synthesize new thiazolotriazines. Few years ago, pyridothienotriazines were described as anti-histaminic[19] and antifungal[20] compounds; in these publications, the 4-chlorotriazine ring was prepared in one-pot starting from 3-amino-2-

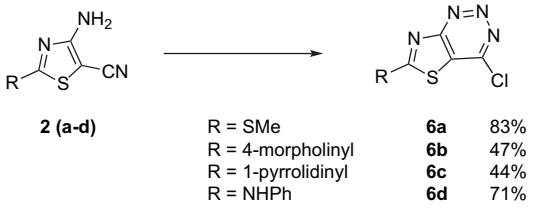
Table 1
Friedländer reaction under classical heating

Thiazole	Ketone (*n*)	Solvent	Substituted [1,3]thiazolo [4,5-*b*]pyridine	Yield (%)
2a, R=MeS–	0	$(CH_2)_2Cl_2$	**3a**	96
	1		**4a**	77
	2		**5a**	87
2b, R=4-morpholinyl	0	THF	**3b**	98
	1		**4b**	98
	2		**5b**	92
2c, R=1-pyrrolidinyl	0	THF	**3c**	98
	1		**4c**	95
	2		**5c**	97
2d, R=Ph–NH–	0	$(CH_2)_2Cl_2$	**3d**	85
	1		**4d**	80
	2		**5d**	97

Table 2
Friedländer reaction under microwave irradiation

Thiazole	Solvent	Substituted [1,3]thiazolo [4,5-*b*]pyridine	Time (min)	Yield (%)
2a, R=MeS–	$(CH_2)_2Cl_2$	**4a**	3×8	93
2b, R=4-morpholinyl	$(CH_2)_2Cl_2$/THF (4:1)	**4b**	2×16	93
2c, R=1-pyrrolidinyl	$(CH_2)_2Cl_2$/THF (4:1)	**4c**	2×16	80
2d, R=Ph–NH–	$(CH_2)_2Cl_2$/THF (3:1)	**4d**	1×16	79

cyanothiophenes. To the best of our knowledge, chlorothiazolotriazines are not described in the literature. 2-Substituted 4-amino-5-cyanothiazoles **2**(**a**–**d**) were converted into chlorothiazolotriazines **6**(**a**–**d**) in moderate to good yields via a one-pot process of diazotation and dediazo-chlorination (Scheme 7).[21]



Scheme 7. $NaNO_2$, HCl 37%, 0–5 °C.

We next wanted to study the reactivity of the chlorine atom in compounds **6**(**a**–**d**). When compound **6a** was subjected to the action of pyrrolidine, both the methylsulfanyl group and the chlorine atom were displaced (Scheme 8). The chlorine atom was also substituted by a secondary amine in compounds **6b**–**d** (Scheme 8).

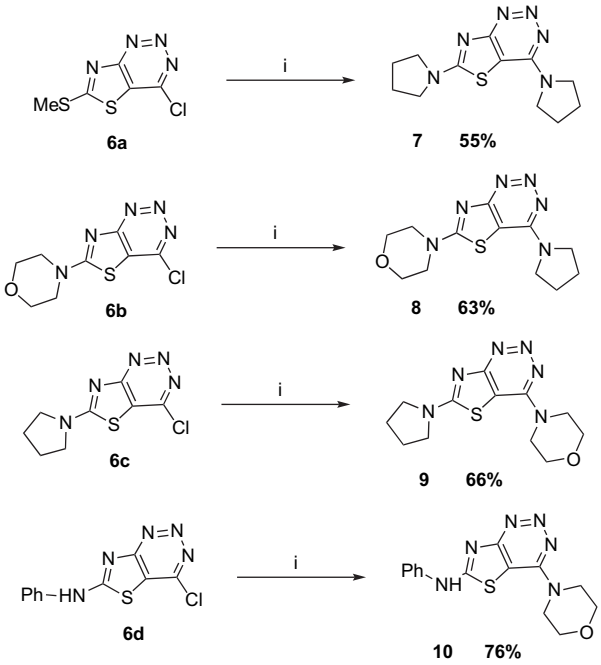
3. Conclusion

We have developed a one-pot four-steps sequential synthesis of trisubstituted [1,3]thiazoles. Those 4-amino[1,3]thiazole-5-carbonitriles have allowed access to several thiazolocondensed systems. We have prepared 12 new analogues of Tacrine in thiazole series and 8 new thiazolotriazines in good yields.

4. Experimental section

4.1. General

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. IR spectra were performed on a Perkin–Elmer FTIR Baragon 1000PC equipped with a Graseby-Specac golden gate and treated with the Spectrum (Perkin–Elmer) software version



Scheme 8. (i) RR′NH 10 mL, reflux.

5.3.1. ^1H and ^{13}C NMR spectra (δ in parts per million) were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6. MS spectra were recorded on an Agilent Technologies GC–MS instrument equipped with a 7683 injector, 6890 N gas chromatograph and a 5973 mass selective detector. The mass spectrometer was operated in EI mode at 70 eV and MS spectra were recorded from m/z 50 to 650. A CEM Discover oven was used for Friedländer's reaction under microwave irradiation.

4.2. Synthesis of dimethyl cyanodithioimidocarbonate (1)

Cyanamide (0.02 mol, 50% aqueous solution) was dissolved in 80 mL of water. Potassium hydroxide (0.04 mol) was added and the solution was stirred for 45 min at room temperature. Carbon disulfide was added. The reaction was heated at 40 °C. When all carbon disulfide was dissolved (2 h are required), methyl iodide (0.04 mol) was added and the reaction was stirred at room temperature overnight. The precipitate was filtered and the solid was washed with water, dried at room temperature until constant weight, and purified by recrystallization in EtOH.

Yield: 71%. Colorless solid; mp: 58 °C; mp_{lit}: 57 °C.[8] IR: 2176 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.70 (s, 6H, 2×CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.82, 112.25, 193.77. GC–MS (EI, 70 eV): m/z (%): 143 (23), 99 (100), 74 (23).

4.3. Synthesis of 4-amino-2-(methylsulfanyl)-1,3-thiazole-5-carbonitrile (2a)

$Na_2S·9H_2O$ (0.04 mol) was suspended in DMF (53 mL), dimethyl cyanodithioimidocarbonate **1** (0.04 mol) was dissolved in 13 mL of DMF and added. The mixture is heated at 70 °C for 2 h. Chloroacetonitrile (0.08 mol) is slowly dropped at 70 °C. The reaction was stirred for 2 h and potassium carbonate was added (0.04 mol). The reaction was stirred at 70 °C for 1 h more. The mixture was poured onto water (400 mL) under good stirring. The precipitated was filtered, washed with water, dried at room temperature until constant weight, and purified by recrystallization in EtOH.

Yield: 85%. Colorless solid; mp: 205 °C; mp_{lit}: 204–206 °C.[2] IR: 3308 (s), 3171 (s), 2192 (s), 1641 (s), 1534 (s) cm^{-1}. ^1H NMR

(250 MHz, DMSO-d_6): δ 2.62 (s, 3H, CH_3), 7.22 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.52, 67.16, 114.43, 165.52, 172.25. GC–MS (EI, 70 eV): m/z (%): 171 (100), 156 (30), 138 (48).

4.4. Synthesis of 2-substituted 4-amino-1,3-thiazole-5-carbonitrile 2(b and c)

4.4.1. Method A

4-Amino-2-(methylsulfanyl)-1,3-thiazole-5-carbonitrile **2a** (2.92 mmol) and corresponding amine (10 mL) were refluxed for 6 h. The mixture was poured onto water (80 mL) under stirring. The precipitated was filtered, washed with water, and dried at room temperature overnight.

4.4.2. Method B

Dimethyl cyanodithioimidocarbonate **1** (0.04 mol) was dissolved in DMF (53 mL). Amine (0.04 mol) was added and the mixture was heated at 70 °C for 1 h. Then, $Na_2S\cdot 9H_2O$ (0.04 mol) was added and heated for 2 h at 70 °C. Chloroacetonitrile (0.12 mol) was added dropwise at 50 °C. The mixture was heated at 50 °C for 2 h and the potassium carbonate was added (0.04 mol). The reaction was stirred at 50 °C for 1 h more. The mixture was poured onto water (400 mL) with good stirring. The precipitated was filtered, washed with water, dried at room temperature until constant weight, and purified by recrystallization in EtOH.

4.4.3. 4-Amino-2-(4-morpholinyl)-1,3-thiazole-5-carbonitrile (*2b*)

Yield: 90% (method A), 78% (method B). Colorless solid; mp: 236 °C. IR: 3320 (s), 3205 (s), 1641 (s), 1563 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.39 (t, J=5.0 Hz, 4H, 2×CH_2), 3.65 (t, J=5.0 Hz, 4H, 2×CH_2), 6.81 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 47.36, 56.92, 65.15, 116.49, 165.06, 170.01.

4.4.4. 4-Amino-2-(1-pyrrolidinyl)-1,3-thiazole-5-carbonitrile (*2c*)

Yield: 99% (method A), 67% (method B). Colorless solid; mp: 299 °C; mp_{lit}: 303–305 °C.[2] IR: 3323 (s), 3168 (s), 2170 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.94 (t, J=7.5 Hz, 4H, 2×CH_2), 3.33 (t, J=5.0 Hz, 4H, 2×CH_2), 6.75 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 25.03, 49.10, 56.18, 116.90, 165.47, 166.18. GC–MS (EI, 70 eV): m/z (%): 194 (100), 166 (43), 139 (16), 97 (17), 70 (18), 55 (24).

4.5. Synthesis of 4-amino-2-anilino-1,3-thiazole-5-carbonitrile (2d)

Cyanamide 99% (0.01 mol) was dissolved in 53 mL of dry DMF. Potassium carbonate (0.01 mol) was added and the reaction was stirred for 2 h at room temperature. Phenyl isothiocyanate was added dropwise and the reaction was heated at 60 °C for 1 h. Chloroacetonitrile (0.01 mol) is slowly dropped and the temperature increased to 75 °C. The mixture was stirred for 1 h more at this temperature. After completion, the mixture was poured onto water (60 mL) with good stirring. The precipitated was filtered, washed with water, dried at room temperature until constant weight, and purified by recrystallization in EtOH.

Yield: 92% (method B). Yellow solid; mp: 212 °C. IR: 2171 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.92 (s, 2H, NH_2), 7.03 (t, J=7.5 Hz, 1H, CH), 7.32 (t, J=7.5 Hz, 2H, 2×CH), 7.57 (d, J=7.5 Hz, 2H, 2×CH), 10.63 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 56.68, 116.28, 118.24, 124.36, 129.46, 139.70, 164.46, 164.52. GC–MS (EI, 70 eV): m/z (%): 216 (100), 119 (31), 77 (19).

4.6. General procedure for Friedländer's reaction

4.6.1. Classical conditions (method C)

Cyclanone (2.8 mmol) was added to a solution of 2-substituted-1,3-thiazole-5-carbonitrile **2–4** (2 mmol) in a mixture of dichloroethane/THF. After stirring 5 min at room temperature, aluminum chloride (4 mmol) was added and the mixture was heated at reflux for 2 h. The mixture was cooled at room temperature and 4 mmol of aluminum chloride was added, the mixture was heated at reflux 2 h more. The solvent was removed under reduced pressure. An aqueous solution of sodium hydroxide (50 mL, 10%) was added. After stirring for 30 min, the precipitate was filtered, washed twice with 25 mL of water and washed twice with 10 mL of ether, and dried at room temperature until constant weight, purified in 5 mL of acetonitrile, and filtered while hot.

4.6.2. Microwave irradiation (method D)

In a round bottom flask of 100 mL equipped with a condenser, cyclohexanone (1.4 mmol) was added to a solution of 2-substituted-1,3-thiazole-5-carbonitrile **2–4** (1 mmol) in 25–40 mL of a mixture of dichloroethane/THF. Aluminum chloride (4 mmol otherwise specified) was added and the mixture was heated at reflux during 16 and 32 min (Table 2) under microwave irradiation (at a constant power of 100–150 W). The solvent was removed under reduce pressure. An aqueous solution of sodium hydroxide (30 mL, 10%) was added. After stirring for 30 min, the precipitate was filtered, washed twice with 12 mL of water and washed twice with 5 mL of ether, and dried at room temperature until constant weight, purified in 2 mL of acetonitrile, and filtered while hot.

4.6.3. 8-Amino-2-(methylsulfanyl)-6,7-dihydro-5H-cyclopenta[b][1,3]thiazolo[4,5-b]pyridine (*3a*)

Yield: 96% (method C: 60 mL of $(CH_2)_2Cl_2$). Colorless solid; mp: 266 °C (dec). IR: 3320 (s), 3205 (s), 1641 (s), 1563 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.03 (q, J=7.5 Hz, 2H, CH_2), 2.72 (t, J=7.5 Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), 2.82 (t, J=7.5 Hz, 2H, CH_2), 6.34 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.31, 22.33, 27.26, 33.98, 109.65, 114.42, 144.87, 163.75, 164.72, 167.66. GC–MS (EI, 70 eV): m/z (%): 237 (100), 204 (19), 191 (28).

4.6.4. 9-Amino-2-(methylsulfanyl)-5,6,7,8-tetrahydro[1,3]thiazolo[4,5-b]quinoline (*4a*)

Yield: 77% (method C: 60 mL of $(CH_2)_2Cl_2$). Yield: 93% (method D: 25 mL of $(CH_2)_2Cl_2$, 6 mmol $AlCl_3$, 150 W, 3×8 min). Colorless solid; mp: 215 °C. IR: 3318 (s), 32 (s), 1643 (s), 1571 (s), 1541 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.76 (m, 4H, 2×CH_2), 2.45 (m, 2H, CH_2), 2.73 (m, 5H, CH_2+CH_3), 6.22 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.27, 22.26, 22.52, 23.14, 32.72, 109.06, 110.06, 146.87, 154.57, 162.50, 168.10. GC–MS (EI, 70 eV): m/z (%): 251 (100).

4.6.5. 10-Amino-2-(methylsulfanyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b][1,3]thiazolo[4,5-b]pyridine (*5a*)

Yield: 87% (method C: 60 mL of $(CH_2)_2Cl_2$). Colorless solid; mp: 234 °C. IR: 3323 (s), 3202 (s), 1645, 1564 (s), 1543 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.52 (m, 4H, 2×CH_2), 1.76 (m, 2H, CH_2), 2.72 (m, 5H, CH_2+CH_3), 2.88 (m, 2H, CH_2), 6.22 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.35, 24.71, 26.30, 27.16, 31.68, 31.80, 110.76, 115.37, 146.03, 161.79, 161.89, 167.78. GC–MS (EI, 70 eV): m/z (%): 265 (100), 250 (19), 236 (28).

4.6.6. 8-Amino-2-(4-morpholinyl)-6,7-dihydro-5H-cyclopenta[b][1,3]thiazolo[4,5-b]pyridine (*3b*)

Yield: 98% (method C: 50 mL of THF). Colorless solid; mp 311 °C. IR: 1628 (s), 1569 (s), 1534 (s) cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.03 (q, J=7.5 Hz, 2H, CH_2), 2.68 (t, J=7.5 Hz, 2H, CH_2), 2.74 (t, J=7.5 Hz, 2H, CH_2), 3.47 (t, J=5.0 Hz, 4H, 2×CH_2), 3.72 (t, J=5.0 Hz, 4H, 2×CH_2), 6.01 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.22, 27.28, 33.94, 47.55, 65.41, 104.13, 112.98, 144.68, 162.06, 164.13, 168.28. GC–MS (EI, 70 eV): m/z (%): 276 (100), 219 (100), 190 (15).

*4.6.7. 9-Amino-2-(4-morpholinyl)-5,6,7,8-tetrahydro[1,3]-thiazolo[4,5-b]quinoline (**4b**)*

Yield: 98% (method C: 50 mL of THF). Yield: 93% (method D: 20 mL of $(CH_2)_2Cl_2$+5 mL of THF, 4 mmol $AlCl_3$, 100 W, 2×16 min). Colorless solid; mp: 318 °C. IR: 3302 (s), 3209 (s), 1629 (s), 1567 (s), 1532 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.72 (m, 4H, 2×CH_2), 2.41 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 3.48 (t, J=5.0 Hz, 4H, 2×CH_2), 3.72 (t, J=5.0 Hz, 4H, 2×CH_2), 5.87 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.45, 22.68, 23.01, 32.61, 47.60, 65.42, 104.05, 108.76, 146.45, 153.14, 162.03, 168.30. GC–MS (EI, 70 eV): m/z (%): 290 (100), 233 (88), 204 (17).

*4.6.8. 10-Amino-2-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b][1,3]thiazolo[4,5-b]pyridine (**5b**)*

Yield: 92% (method C: 50 mL of THF). Colorless solid; mp: 314 °C. IR: 1633 (s), 1565 (s), 1526 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.51 (m, 4H, 2×CH_2), 1.75 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 3.47 (t, J=5.0 Hz, 4H, 2×CH_2), 3.72 (t, J=5.0 Hz, 4H, 2×CH_2), 5.87 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.69, 26.38, 27.37, 31.81, 40.48, 47.70, 65.40, 105.53, 114.03, 145.70, 160.47, 161.32, 168.32. GC–MS (EI, 70 eV): m/z (%): 304 (100), 247 (63).

*4.6.9. 8-Amino-2-(1-pyrrolidinyl)-6,7-dihydro-5H-cyclopenta[b][1,3]thiazolo[4,5-b]pyridine (**3c**)*

Yield: 98% (method C: 50 mL of THF). Colorless solid; mp: 369 °C. IR: 1632 (s), 1573 (s), 1535 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.99 (m, 6H, 3×CH_2), 2.67 (t, J=7.5 Hz, 2H, CH_2), 2.72 (t, J=7.5 Hz, 2H, CH_2), 3.43 (m, 4H, 2×CH_2), 5.91 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.24, 24.79, 27.25, 33.96, 67.22, 104.10, 112.35, 144.54, 161.71, 164.13, 164.92. GC–MS (EI, 70 eV): m/z (%): 260 (100), 232 (42), 205 (74), 55 (19).

*4.6.10. 9-Amino-2-(1-pyrrolidinyl)-5,6,7,8-tetrahydro[1,3]-thiazolo[4,5-b]quinoline (**4c**)*

Yield: 95% (method C: 50 mL of THF). Yield: 80% (method D: 20 mL of $(CH_2)_2Cl_2$+5 mL of THF, 4 mmol $AlCl_3$, 100 W, 2×16 min). Colorless solid; mp: 346 °C. IR: 1629 (s), 1576 (s), 1522 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.73 (m, 4H, 2×CH_2), 1.98 (m, 4H, 2×CH_2), 2.40 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 3.43 (m, 4H, 2×CH_2), 5.77 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.51, 22.73, 22.95, 25.06, 32.62, 48.79, 104.07, 108.16, 146.27, 152.76, 162.06, 164.14. GC–MS (EI, 70 eV): m/z (%): 274 (100), 246 (45), 219 (49), 70 (12).

*4.6.11. 10-Amino-2-(1-pyrrolidinyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b][1,3]thiazolo[4,5-b]pyridine (**5c**)*

Yield: 97% (method C: 50 mL of THF). Colorless solid; mp: 336 °C. IR: 1630 (s), 1571 (s), 1524 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.50 (m, 4H, 2×CH_2), 1.75 (m, 2H, CH_2), 1.99 (m, 4H, 2×CH_2), 2.63 (m, 2H, CH_2), 2.78 (m, 2H, CH_2), 3.41 (t, J=5.0 Hz, 4H, 2×CH_2), 5.77 (s, 2H, NH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.69, 25.07, 26.40, 27.44, 31.87, 40.48, 48.82, 105.47, 113.42, 145.57, 160.10, 162.06, 164.18. GC–MS (EI, 70 eV): m/z (%): 288 (100), 273 (16), 260 (44), 233 (25).

*4.6.12. 8-Amino-2-anilino-6,7-dihydro-5H-cyclopenta[b][1,3]thiazolo[4,5-b]pyridine (**3d**)*

Yield: 85% (method C: 50 mL of $(CH_2)_2Cl_2$+10 mL of THF). Orange solid. Colorless solid; mp: 274 °C. IR: 1623 (s), 1564 (s), 1526 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.01 (q, J=7.5 Hz, 2H, CH_2), 2.70 (t, J=7.5 Hz, 2H, CH_2), 2.77 (t, J=7.5 Hz, 2H, CH_2), 6.01 (s, 2H, NH_2), 6.97 (m, 1H, CH), 7.31 (m, 2×CH), 7.73 (m, 2H, 2×CH), 10.50 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.26, 27.32, 33.89, 103.82, 113.48, 117.88, 121.67, 128.80, 141.21, 144.60, 161.90, 164.11.

*4.6.13. 9-Amino-2-anilino-5,6,7,8-tetrahydro[1,3]-thiazolo[4,5-b]quinoline (**4d**)*

Yield: 80% (method C: 50 mL of $(CH_2)_2Cl_2$+10 mL of THF). Yield: 79% (method D: 30 mL of $(CH_2)_2Cl_2$+10 mL of THF, 2 mmol $AlCl_3$, 100 W, 16 min). Orange solid; mp: 280 °C. IR: 1617 (s), 1563 (s), 1519 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.75 (m, 4H, 2×CH_2), 2.43 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 5.99 (s, 2H, NH_2), 7.00 (m, 1H, CH), 7.33 (m, 2H, 2×CH), 7.76 (m, 2×CH), 10.48 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 22.45, 22.69, 23.07, 32.56, 103.76, 109.44, 117.77, 121.83, 128.80, 140.73, 146.48, 153.05, 16.73, 161.87.

*4.6.14. 10-Amino-2-anilino-6,7,8,9-tetrahydro-5H-cyclohepta[b][1,3]thiazolo[4,5-b]pyridine (**5d**)*

Yield: 97%. Colorless solid; mp: 275 °C. IR: 1634 (s), 1564 (s), 1542 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.50 (m, 4H, 2×CH_2), 1.77 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 5.92 (s, 2H, NH_2), 6.99 (m, 1H, CH), 7.33 (m, 1H, 2×CH), 7.75 (m, 2H, 2×CH), 10.42 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.75, 26.39, 27.34, 31.84, 40.48, 105.23, 114.73, 117.71, 121.81, 128.82, 140.71, 145.73, 160.38, 161.17, 161.67.

4.7. Synthesis of chlorothiazolotriazines 6(a–d): general procedure

A solution of sodium nitrite (11.4 mmol) in water (7 mL) was added over 15 min to a suspension of the foregoing 2-substituted 4-amino-1,3-thiazole-5-carbonitrile (8.1 mmol) at 0–5 °C in concentrated hydrochloric acid (16 mL). The resulting mixture was stirred at 0 °C for a further 40 min and then allowed to stand at room temperature overnight. The reaction mixture was quenched in water (100 mL). The precipitate was washed twice with 15 mL of water, and dried under room temperature, purified in 2 mL of acetonitrile, and filtered while hot.

*4.7.1. 4-Chloro-6-(methylsulfanyl)[1,3]thiazolo[4,5-d]-[1,2,3]triazine (**6a**)*

Yield: 83%. Orange solid; mp: 190 °C. IR: 1516 (s), 1460 (s), 1359 (br) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.49 (s, 3H, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 16.65, 129.18, 150.73, 165.18, 183.03. GC–MS (EI, 70 eV): m/z (%): 190 (97), 175 (23), 157 (100).

*4.7.2. 4-Chloro-6-(4-morpholinyl)[1,3]thiazolo[4,5-d]-[1,2,3]triazine (**6b**)*

Yield: 47%. Beige solid; mp: 243 °C. IR: 1592 (s), 1530 (s), 1417 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.47 (m, 4H, 2×CH_2), 3.76 (m, 4H, 2×CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 65.25, 105.89, 124.53, 148.41, 166.07, 171.87. GC–MS (EI, 70 eV): m/z (%): 229 (100), 171 (83), 144 (36).

*4.7.3. 4-Chloro-6-(1-pyrrolidinyl)[1,3]thiazolo[4,5-d]-[1,2,3]triazine (**6c**)*

Yield: 44%. Orange solid; mp: 219 °C. IR: 1560 (s), 1526 (s), 1412 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 2.52 (m, 4H, 2×CH_2), 3.56 (m, 2H, CH_2), 3.80 (m, 2H, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 25.12, 50.83, 124.64, 148.15, 166.07, 167.80. GC–MS (EI, 70 eV): m/z (%): 213 (97), 185 (100), 158 (60).

*4.7.4. 4-Chloro-N-phenyl[1,3]thiazolo[4,5-d][1,2,3]-triazin-6-amine (**6d**)*

Yield: 71%. Orange solid; mp: 208 °C. IR: 1602 (s), 1567 (s), 1500 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 7.22 (m, 1H, CH), 7.47 (m, 2H, 2×CH), 7.78 (m, 2H, 2×CH), 12.03 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 118.70, 119.68, 124.97, 129.38, 138.39, 140.37, 148.85, 166.19. GC–MS (EI, 70 eV): m/z (%): 235 (100), 200 (52).

4.8. Synthesis of aminothiazolotriazine derivatives

The chlorothiazolotriazines **6**(**a**–**d**) (1 mmol) and corresponding amine (10 mL) were refluxed for 6 h. The mixture was cooled at room temperature and poured onto water (80 mL) under stirring. When a precipitated was formed, it was filtered, washed twice with 15 mL of water and twice with 8 mL of diethyl ether, and dried at room temperature overnight. When a precipitated wasn't formed, the aqueous layer was extracted trice with 25 mL of CH_2Cl_2. The organic layers were washed twice with 30 mL of HCl 2 N and once with 80 mL of water, dried over $MgSO_4$ and concentrated under reduce pressure. The products were purified in 2 mL of acetonitrile and filtered while hot to give products **7**–**10**.

*4.8.1. 4,6-Di(1-pyrrolidinyl)[1,3]thiazolo[4,5-d][1,2,3]triazine (**7**)*

Yield: 55%. Pale yellow solid; mp: 178 °C. IR: 1556 (s), 1457 (s), 1422 (s), 1325 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.97–2.03 (m, 8H, 4×CH_2), 3.32 (m, 4H, 2×CH_2), 3.71 (m, 4H, 2×CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.68, 25.08, 46.91, 49.74, 102.98, 150.90, 164.05, 167.51.

*4.8.2. 6-(4-Morpholinyl)-4-(1-pyrrolidinyl)[1,3]thiazolo-[4,5-d][1,2,3]triazine (**8**)*

Yield: 63%. Pale orange solid; mp: 178 °C (dec). IR: 1536 (s), 1413 (br), 1329 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.86 (m, 2H, CH_2), 1.97 (m, 2H, CH_2), 3.42 (m, 2H, CH_2), 3.51 (m, 2H, CH_2), 3.66 (m, 4H, 2×CH_2), 3.72 (m, 4H, 2×CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.96, 47.37, 48.58, 65.28, 117.77, 161.26, 168.83, 171.76. GC–MS (EI, 70 eV): *m*/*z* (%): 264 (100).

*4.8.3. 4-(4-Morpholinyl)-6-(1-pyrrolidinyl)[1,3]thiazolo-[4,5-d][1,2,3]triazine (**9**)*

Yield: 66%. Pale orange solid; mp: 203 °C. IR: 1543 (br), 1489 (s), 1421 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 1.95–2.03 (m, 4H, 2×CH_2), 3.32 (m, 8H, 4×CH_2), 3.75 (m, 4H, 2×CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 25.06, 45.30, 49.74, 65.73, 112.61, 147.37, 166.80, 167.32. GC–MS (EI, 70 eV): *m*/*z* (%): 213 (98), 185 (100), 158 (58).

*4.8.4. 4-(4-Morpholinyl)-N-phenyl[1,3]thiazolo[4,5-d]-[1,2,3]triazin-6-amine (**10**)*

Yield: 76%. Pale brown solid; mp: 297 °C. IR: 1535 (s), 1417 (s) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 3.47 (m, 4H, 2×CH_2), 3.70–3.79 (m, 4H, 2×CH_2), 7.15 (m, 1H, C*H*), 7.43 (m, 2H, 2×C*H*), 7.74 (m, 2H, 2×C*H*). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 45.35, 65.72, 103.43, 119.19, 123.97, 129.28, 139.21, 153.16, 165.14, 166.60.

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