Synthesis of new selenophene and thiazole analogues of the Tacrine series

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Dedicated to Professor Rainer Beckert on the occasion of his 60th birthday

Abstract

New 2-aminoselenophene-3-carbonitriles and 5-amino-1,3-thiazole-4-carbonitriles were made and reacted with cycloalkanones to give tetrahydroselenolo[2,3-*b*]quinolines, cycloalkene-fused selenolo[3,2-*e*]pyridines, [1,3]thiazolo[5,4-*b*]quinolines, thiazolo[4,5-*e*]pyridines and tetrahydro-[1,3]thiazolo[5,4-*b*]quinolines.

Keywords: 2-aminoselenophene-3-carbonitriles, 5-amino-1,3-thiazole-4-carbonitriles, Gewald reaction, fused pyridines, quinolines, thiazoles, selenophenes

Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of cognitive functions and has been associated with the impairment of the cholinergic system. Currently, therapeutic intervention still mainly involves the enhancement of the levels of the neurotransmitter acetylcholine (Ach) through the administration of acetylcholinesterase inhibitors. Tacrine (5-amino-1,2,3,4-tetrahydroacridine) **I** (commercial name Cognex[®]) belongs to this category of drugs and was authorized in 1993 for AD therapy. Our object was to look at structural modification of Tacrine which may have beneficial biological effects as enhanced acetylcholinesterase inhibition activity and/or diminished hepatotoxicity. We have described already the synthesis of tetrahydrothieno[3,2-*b*]quinolines **II**,¹ tetrahydrothieno[2,3-*b*]quinolines **III**,² tetrahydrothieno[3,4-*b*]quinolines **IV**,³ tetrahydroselenolo[3,2-*b*]quinolines **V**,⁴ and tetrahydrothiazolo[5,4-*b*]quinolines **VI**.⁵ (Fig. 1)

To extend our library of new analogues of Tacrine, we developed methods to prepare tetrahydroselenolo[2,3-*b*]quinolines and other cycloalkene-fused selenolo[3,2-*e*]pyridines **VII**, and tetrahydro[1,3]thiazolo[5,4-*b*]quinolines and other cycloalkene-fused [1,3]thiazolo[4,5-*e*]pyridine **VIII** (Fig. 1).

Figure 1

Results and discussion

Synthesis of 2-aminoselenophene-3-carbonitriles

The precursors of selenoloquinolines and cycloalkene-fused selenolo[3,2-*e*]pyridines **VII** are the substituted selenophenes **1**. They were obtained in one step in good yields using the method described by Gewald.⁶ (Scheme 1)

Scheme 1

Table 1. Yields obtained in the synthesis of 2-aminoselenophene-3-carbonitriles **1**

Entry	Substituent ^a	Yield
1a	R ¹ = R ² = -CH ₃	58%
1b	-R ¹ - R ² - = -(CH ₂) ₄ -	73%
1c	-R ¹ - R ² - = -(CH ₂) ₅ -	74%

^a We found it was not possible to obtain 2-aminoselenophene-3-carbonitriles with R = *p*-methoxyphenyl or R = *p*-chlorophenyl even in a two-step synthesis

Synthesis of 5-amino-1,3-thiazole-3-carbonitriles

The precursors of tetrahydro[1,3]thiazolo[5,4-*b*]quinolines and cycloalkene-fused [1,3]thiazolo[4,5-*e*]pyridines **VIII** are the substituted thiazoles **2**. They were obtained in one step (Scheme 2) in very good yields using methods described by Freeman and Kim⁷ or Hirota *et al.*⁸

Scheme 2

Table 2. Yields obtained in the synthesis of 5-amino-1,3-thiazole-4-carbonitriles **2**

Entry	Substituent	Yield
2a	R = -Ph	76%
2b	R = -C ₆ H ₄ OMe	83%
2c	R = -C ₆ H ₄ Cl	96%
2d	R = -CH ₂ Ph	68%

Synthesis of tetrahydroselenopheno[2,3-*b*]quinolines, cycloalkene-fused selenolo[3,2-*e*]pyridines, tetrahydro[1,3]thiazolo[5,4-*b*]quinolines and cycloalkene-fused [1,3]thiazolo[4,5-*e*]pyridines

To prepare these different compounds, we used Friedländer's reaction.⁹ 2-Aminoselenophene-3-carbonitriles (**1a-c**) and 5-amino-1,3-thiazole-4-carbonitriles (**2a-d**) were reacted with cycloalkanones in dichloroethane in the presence of aluminium chloride. After at least 6 hours of reflux the reaction had come to an end and the expected products (**3a-e**, Scheme 3, and **4a0-4d2**, Scheme 4) were obtained in good or moderate yields depending on the size of the ring of the cycloalkanone used.

Scheme 3

Table 3. Yields obtained for the synthesis of tetrahydroselenolo[2,3-*b*]quinolines and cycloalkene-fused selenolo[3,2-*e*]pyridines (**3a-e**)

Entry	Substituent	Yield
3a ($n = 1$)	$\text{R}^1 = \text{R}^2 = -\text{CH}_3$	73%
3b ($n = 0$)	$\text{R}^1 - \text{R}^2 = -(\text{CH}_2)_4-$	83%
3c ($n = 1$)	$\text{R}^1 - \text{R}^2 = -(\text{CH}_2)_4-$	88%
3d ($n = 2$)	$\text{R}^1 - \text{R}^2 = -(\text{CH}_2)_4-$	89%
3e ($n = 1$)	$\text{R}^1 - \text{R}^2 = -(\text{CH}_2)_5-$	86%

Scheme 4

Table 4. Yields obtained for the synthesis of tetrahydro[1,3]thiazolo[5,4-*b*]quinolines and cycloalkene-fused [1,3]thiazolo[4,5-*e*]pyridines (**4**)

Entry	Substituent	Yield
4a0 ($n=0$)		84%
4a1 ($n=1$)	$\text{R} = $	58%
4a2 ($n=2$)		84%
4b0 ($n=0$)		81%
4b1 ($n=1$)	$\text{R} = $	35%
4b2 ($n=2$)		87%

Table 4 (continued)

Entry	Substituent	Yield
4c0 (n=0)		85%
4c1 (n=1)	R =	33%
4c2 (n=2)		82%
4d0 (n=0)		87%
4d1 (n=1)	R =	31%
4d2 (n=2)		80%

Conclusions

Substituted 2-aminoselenophene-3-carbonitriles (**1a-c**) were obtained in good yields in one step by the Gewald reaction. The difference with the thiophene analogues prepared in ref. 2 is that only very few ketones gave the Gewald reaction with selenium. Substituted 5-amino-1,3-thiazole-4-carbonitriles (**2a-d**) were obtained in good yields in one step following refs 7 or 8. The substituted 2-aminoselenophene-3-carbonitriles gave substituted tetrahydroselenolo[2,3-*b*]quinolines and substituted cycloalkene-fused selenolo[3,2-*e*]pyridines (**3a-e**) and the substituted 5-amino-1,3-thiazole-3-carbonitriles gave substituted tetrahydro[1,3]thiazolo[5,4-*b*]quinolines and substituted cycloalkene-fused [1,3]thiazolo[4,5-*e*]pyridines (**4a0-d2**) by Friedländer's reaction in one step, the whole synthesis needing only two steps.

Experimental Section

General Procedures. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. IR spectra were recorded neat from 4400 to 600 cm⁻¹ on a Perkin Elmer FT-IR Baragon 1000PC equipped with a Graseby-Specac golden gate and treated with the Spectrum (Perkin-Elmer) software 5.3.1. ¹H and ¹³C NMR spectra were recorded on a Bruker AC 250 MHz spectrometer in CDCl₃ or DMSO-d₆. The coupling constants are in Hz. HMRS were collected on a Bruker MICROTOF-Q ESI/QqTOF spectrometer.

General procedure to obtain substituted 2-aminoselenophene-3-carbonitriles (1a-c) using Gewald's method⁶ (products listed in Table 1). The ketone (193 mmol), malonodinitrile (193 mmol), and powdered selenium 193 mg-atom) were dissolved / suspended in ethanol (100 ml).

Diethylamine or morpholine (100 mL) was added and the mixture was stirred and refluxed over *ca.* 18 h. After cooling to RT the mixture was filtered through Celite and poured into ice-water. The precipitation was collected by filtration, washed with cold water, dried and purified either by recrystallization from isopropanol or by silica gel column chromatography using dichloromethane as eluent. If there was no precipitation, the mixture was extracted with dichloromethane or diethyl ether. The organic layer was separated, dried on anhydrous sodium sulfate and filtered, and the solvent was evaporated to give the product which was then purified.

2-Amino-4,5-dimethylselenophene-3-carbonitrile (1a). Brownish solid, m.p. 143-145°C (isopropanol). IR: 3417 and 3323 (NH₂), 2193 (CN), 1717 (NH₂), 1341 (CH₃), 1317 (NH₂), cm⁻¹. ¹H NMR (CDCl₃): δ 2.0 (s, 3H, CH₃), 2.3 (s, 3H, CH₃), 5.3 (s, 2H, NH₂). ¹³C NMR (DMSO-*d*₆): δ 13.6, 14.1, 86.8, 117.6, 129.2, 158.5, 166.2.

2-Amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carbonitrile (1b). Red-brownish solid, m.p. 88-90°C. IR: 3420 and 3326 (NH₂), 2190 (CN), 1617 (NH₂), 1431 and 1379 (CH₂), 1325 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.75 (m, 4H, 2 × CH₂), 2.4 (t, 2H, CH₂), 2.5 (t, 2H, CH₂), 5.0 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.1, 23.8, 26.0, 26.5, 90.2, 116.4, 124.8, 133.0, 164.8.

2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]selenophene-3-carbonitrile (1c). Red-brownish solid, m.p. 94-96°C. IR: 3424 and 3329 (NH₂), 2191 (CN), 1615 (NH₂), 1439 and 1380 (CH₂), 1333 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.6 (m, 4H, 2 × CH₂), 1.8 (m, 2H, CH₂), 2.6 (m, 4H, 2 × CH₂), 4.9 (s, 2H, NH₂). ¹³C NMR (DMSO-*d*₆): δ 26.7, 27.7, 29.7, 30.6, 31.4, 88.0, 117.7, 123.9, 136.6, 166.0.

General procedure to obtain substituted 5-amino-1,3-thiazole-4-carbonitriles (2a-c) using the method of Freeman and Kim⁷ (products listed in Table 2). Aminomalononitrile tosylate (9.2 mmol) was dissolved in anhydrous 1-methyl-2-pyrrolidinone (30 mL). Aryl isothiocyanate (9.2 mmol) was added dropwise while stirring. The mixture was stirred for *ca.* 20 h at 22-24°C under stirring. It was then diluted with 1:1 ethyl acetate / diethyl ether (150 mL), transferred to a separatory funnel and washed with water (2 × 100 mL). The organic layer was separated, dried with anhydrous sodium sulfate and filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with EtOAc / dichloromethane (1:9 to 3:7) to afford the thiazoles.

5-Amino-2-(phenylamino)-1,3-thiazole-4-carbonitrile (2a). Red-brownish solid, m.p. 164-166°C (164-165⁷). IR: 3691 (NH), 3355 and 3289 (NH₂), 2198 (CN), 1597 (NH₂), 1575 (NH), 1345 (NH₂), 743 and 684 (monosubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 6.1 (s, 2H, NH₂), 6.8 (t, 1H, CH, *J* = 8.5 Hz), 7.1 (t, 2H, 2 × CH, *J* = 8.5 Hz), 7.4 (d, 2H, 2 × CH, *J* = 8.5 Hz), 9.3 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 95.6, 116.4, 116.6, 120.8, 128.9, 141.0, 147.8, 154.4.

5-Amino-2-[(4-methoxyphenyl)amino]-1,3-thiazole-4-carbonitrile (2b). Brownish solid, m.p. 200-202°C (199-200°C⁷). IR: 3414 (NH), 3324 and 3171 (NH₂), 2916 (CH₃), 1614 (NH₂), 1583

(NH), 1453 (CH₃), 1357 (NH₂), 753 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 3.7 (s, 3H, OCH₃), 6.7 (s, 2H, NH₂), 6.8 (d, 2H, 2 × CH, *J* = 8.5 Hz), 7.4 (d, 2H, 2 × CH, *J* = 8.5 Hz), 9.5 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 55.1, 95.6, 114.1, 115.7, 116.7, 118.0, 134.5, 148.7, 153.8.

5-Amino-2-[(4-chlorophenyl)amino]-1,3-thiazole-4-carbonitrile (2c). Brownish solid, m.p. 205-208°C (210-211°C⁷) IR: 3366 (NH), 3307 and 3178 (NH₂), 2199 (CN), 1600 (NH₂), 1573 (NH), 1320 (NH₂), 746 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 6.8 (s, 2H, NH₂), 7.4 (d, 2H, 2xCH, *J* = 7.8 Hz), 7.6 (d, 2H, 2xCH, *J* = 7.8 Hz), 9.9 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 95.6, 116.6, 117.8, 124.1, 128.7, 139.8, 147.4, 154.6.

Procedure to obtain substituted-5-amino-1,3-thiazole-4-carbonitrile (2d) using the method of Hirota *et al*⁸ *N,N*-Diisopropylethylamine (6.32 mmol) was added to a suspension of aminomalononitrile *p*-toluenesulfonate (7.9 mmol) in dry THF (20 mL), and the mixture was stirred under Ar at RT for 5 min. Benzyl thiocyanate (15.79 mmol) in dry THF was added and the mixture was stirred at *ca* 40°C for 72 hours. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and water (100mL). The organic layer was washed with brine (50 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel with EtOAc / dichloromethane (3:7).

5-Amino-2-(benzylamino)-1,3-thiazole-4-carbonitrile (2d). Red-brownish solid, m.p. 142-144°C. IR: 3406 (NH), 3185 and 3109 (NH₂), 2906 (CH₂), 2209 (CN), 1609 (NH₂), 1546 (NH), 1453 (CH₂), 1325 (NH₂), 756 and 689 (monosubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 4.3 (d, 2H, CH₂), 6.45 (s, 2H, NH₂), 7.3 (m, 5H, monosubstituted benzene), 7.55 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 46.7, 95.8, 116.9, 126.9, 127.42, 127.45, 139.1, 153.4, 153.6. HRMS (APCI) calcd for C₁₁H₁₁N₄S [M+H]⁺ 231.0699, found 231.0705.

General procedure to obtain substituted tetrahydroselenopheno[2,3-*b*]quinolines and cycloalkeno[*b*]selenopheno[3,2-*e*]pyridines (3a–3e, Table 3), substituted tetrahydro[1,3]-thiazolo[5,4-*b*]quinolines and substituted cycloalkeno[*b*]{1,3}thiazolo[4,5-*e*]pyridines (4a0 – 4d2, Table 4) by Friedländer reaction. Aluminum chloride (17 mmol for the selenophenes **1** and 34 mmol for the thiazoles **2**) was suspended in dry 1,2-dichloroethane (10 mL per mmol of aluminium chloride) at RT under Ar. The selenophene or thiazole (10 mmol) and ketone were added and the reaction mixture was heated under reflux for a minimum of 6 h. When the reaction was completed (monitoring by TLC), a mixture of THF / water (2:1) was added at RT and sodium hydroxide was added until the solution became alkaline. After stirring for at least 30 minutes, the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and solvent was evaporated to give the crude product which was purified by silica gel chromatography using dichloromethane (100%) for the selenopheno derivatives and EtOAc / dichloromethane (1:9 to 5:5) for the thiazolo derivatives.

2,3-Dimethyl-5,6,7,8-tetrahydroselenolo[2,3-*b*]quinolin-4-amine (3a). Brownish solid, m.p. 114-116°C. IR: 3357 and 3290 (NH₂), 2926 and 2855 (CH₃ and CH₂), 1617 (NH₂), 1267 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.8 (m, 4H, 2 × CH₂), 2.3 (m, 6H, 2 × CH₃), 2.5 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 4.7 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.6, 23.1, 26.8, 31.9, 42.0, 112.0, 121.4, 126.2, 132.3, 132.6, 148.3, 153.0, 160.2. HRMS (ESI) calcd for C₁₃H₁₇N₂Se [M+H]⁺ 281.0552, found 281.0548.

2,3,6,7,8,9-Hexahydro-1*H*-cyclopenta[*b*][1]benzoselenolo[3,2-*e*]pyridin-10-amine (3b). Beige solid, m.p. 198-200°C. IR: 3501 and 3295 (NH₂), 2932 and 2829 (CH₂), 1638 (NH₂), 1448 and 1398 (CH₂), 1275 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.8 (m, 4H, 2 × CH₂), 2.1 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 2.9 (m, 2H, CH₂), 3.0 (m, 4H, 2 × CH₂), 4.5 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.6, 22.8, 22.9, 27.0, 28.1, 28.4, 34.1, 117.1, 120.5, 128.7, 135.3, 146.2, 162.1, 163.8. HRMS (ESI) calcd for C₁₄H₁₇N₂Se [M+H]⁺ 293.0552, found 293.0558.

1,2,3,4,7,8,9,10-Octahydro[1]benzoselenolo[2,3-*b*]quinolin-11-amine (3c). Orange solid, m.p. 206-208°C. IR: 3470 and 3370 (NH₂), 2849 and 2923 (CH₂), 1612 (NH₂), 1430 (CH₂), 1273 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.8 (m, 6H, 3 × CH₂), 2.35 (m, 4H, 2 × CH₂), 2.8 (m, 4H, 2 × CH₂), 2.9 (m, 2H, CH₂), 4.5 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.7, 22.85, 22.89, 23.0, 28.1, 28.4, 32.9, 42.0, 111.8, 120.4, 128.6, 135.3, 147.8, 153.6, 161.8. HRMS (ESI) calcd for C₁₅H₁₉N₂Se [M+H]⁺ 307.0708, found 307.0732.

1,2,3,4,8,9,10,11-Octahydro-7*H*-cyclohepta[*b*][1]benzoselenolo[3,2-*e*]pyridin-12-amine (3d). Brownish solid, m.p. 222-224°C. IR: 3505 and 3295 (NH₂), 2908 and 2842 (CH₂), 1632 (NH₂), 1429 (CH₂), 1271 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.8 (m, 6H, 3 × CH₂), 2.1 (m, 4H, 2 × CH₂), 2.7 (m, 2H, CH₂), 3.05 (m, 2H, CH₂), 3.2 (m, 4H, 2 × CH₂), 4.9 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.8, 25.3, 26.5, 27.0, 28.2, 28.6, 30.3, 32.1, 38.5, 117.4, 121.4, 128.7, 136.4, 147.2, 159.8, 160.7. HRMS (ESI) calcd for C₁₆H₂₁N₂Se [M+H]⁺ 321.0865, found 321.0874.

1,2,3,4,8,9,10,11-Octahydro-7*H*-cyclohepta[4,5]selenolo[2,3-*b*]quinolin-12-amine (3e). Orange solid, m.p. 176-178°C. IR: 3501 and 3299 (NH₂), 2913 and 2846 (CH₂), 1632 (NH₂), 1428 (CH₂), 1278 (NH₂) cm⁻¹. ¹H NMR (CDCl₃): δ 1.6 (m, 6H, 3 × CH₂), 1.8 (m, 6H, 3 × CH₂), 2.4 (m, 4H, 2 × CH₂), 2.8 (m, 2H, CH₂), 4.6 (s, 2H, NH₂). ¹³C NMR (CDCl₃): δ 22.7, 23.1, 26.1, 27.0, 27.3, 30.6, 30.9, 32.7, 112.2, 122.1, 132.6, 133.6, 140.3, 147.7, 153.3, 161.2. HRMS (ESI) calcd for C₁₆H₂₁N₂Se [M+H]⁺ 321.0865, found 321.0866.

***N*²-Phenyl-6,7-dihydro-5*H*-cyclopenta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,8-diamine (4a0).** Orange solid, m.p. 248-250°C. IR: 3494 (NH), 3388 and 3241 (NH₂), 2954 (CH₂), 1597 (NH₂), 1589 (NH), 1443 (CH₂), 1342 (NH₂), 687 and 742 (monosubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.8 (m, 4H, 2 × CH₂), 3.3 (m, 2H, CH₂), 6.0 (s, 2H, NH₂), 7.0 (t, 1H, CH, *J* = 8.5 Hz), 7.3 (t, 2H, 2 × CH, *J* = 8.5 Hz), 7.8 (d, 2H, 2 × CH, *J* = 8.5 Hz), 10.2 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 22.2, 22.6, 23.2, 32.5, 112.0, 117.4, 121.4, 128.9, 130.3, 140.8, 142.9, 149.6, 151.4, 156.1. HRMS (ESI) calcd for C₁₅H₁₅N₄S [M+H]⁺ 283.1012, found 283.1005.

***N*²-Phenyl-5,6,7,8-tetrahydro[1,3]thiazolo[5,4-*b*]quinoline-2,9-diamine (4a1).** Beige solid, m.p. 200-202°C. IR: 3395 and 3214 (NH₂), 2359 (CH₂), 1588 (NH₂), 1537 (NH), 1445 (CH₂), 1312 (NH₂), 722 and 688 (monosubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.8 (m, 4H,

2 × CH₂), 2.4 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 5.8 (s, 2H, NH₂), 7.0 (t, 1H, CH, *J* = 8.5 Hz), 7.3 (t, 2H, 2 × CH, *J* = 8.5 Hz), 7.8 (d, 2H, 2 × CH, *J* = 8.5 Hz), 10.2 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 22.2, 22.6, 23.2, 32.5, 112.1, 117.4, 121.4, 128.9, 130.4, 140.7, 142.9, 149.6, 151.4, 156.2. HRMS (ESI) calcd for C₁₆H₁₇N₄S [M+H]⁺ 297.1168, found 297.1160.

***N*²-Phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,10-diamine**

(4a2). Beige solid, m.p. 212-214°C. IR: 3496 (NH), 3392 and 3257 (NH₂), 2909 (CH₂), 1587 (NH₂), 1529 (NH), 1444 (CH₂), 1310 (NH₂), 746 and 687 (monosubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.5 (m, 4H, 2 × CH₂), 1.7 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 2.7 (m, 2H, CH₂), 5.8 (s, 2H, NH₂), 6.8 (t, 1H, CH, *J* = 8.5 Hz), 7.2 (t, 2H, 2 × CH, *J* = 8.5 Hz), 7.7. (d, 2H, 2 × CH, *J* = 8.5 Hz), 10.1 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 20.6, 25.1, 26.5, 27.3, 31.8, 117.0, 117.3, 121.4, 128.8, 131.4, 140.8, 142.4, 148.4, 156.7, 158.5. HRMS (ESI) calcd for C₁₇H₁₉N₄S [M+H]⁺ 311.1325, found 311.1332.

***N*²-(4-Methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,8-diamine**

(4b0). Orange solid, m.p. 205-207°C. IR: 3448 (NH), 3377 and 3187 (NH₂), 2899 (CH₃ and CH₂), 1598 (NH₂), 1534 (NH), 1452 (CH₃), 1382 (NH₂), 751 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.0 (m, 2H, CH₂), 2.7 (m, 4H, 2 × CH₂), 3.7 (s, 3H, OCH₃), 5.9 (s, 2H, NH₂), 6.8 (d, 2H, 2 × CH, *J* = 8.2 Hz), 7.7. (d, 2H, 2 × CH, *J* = 8.2 Hz), 10.0 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 22.6, 27.2, 33.6, 45.1, 114.0, 116.3, 119.0, 130.6, 134.4, 141.3, 151.1, 154.0, 156.5, 158.6, 159.1. HRMS (ESI) calcd for C₁₆H₁₇ON₄S [M+H]⁺ 313.1118, found 313.1109.

***N*²-(4-Methoxyphenyl)-5,6,7,8-tetrahydro[1,3]thiazolo[5,4-*b*]quinoline-2,9-diamine**

(4b1). Beige solid, m.p. 195-197°C. IR: 3475 (NH), 3370 and 3186 (NH₂), 2920 (CH₃ and CH₂), 1594 (NH₂), 1535 (NH), 1462 (CH₃), 1311 (NH₂), 752 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.7 (m, 4H, 2 × CH₂), 2.5 (m, 2H, CH₂), 2.7 (m, 2H, CH₂), 3.7 (s, 3H, OCH₃), 5.7 (s, 2H, NH₂), 6.9 (d, 2H, 2 × CH, *J* = 8.2 Hz), 7.7 (d, 2H, 2 × CH, *J* = 8.2 Hz), 10.0 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 22.2, 22.6, 23.2, 32.5, 55.1, 112.1, 114.1, 119.1, 130.5, 134.3, 142.6, 149.5, 151.1, 154.1, 156.6. HRMS (ESI) calcd for C₁₇H₁₉ON₄S [M+H]⁺ 327.1279, found 327.1274.

***N*²-(4-Methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*][1,3]thiazolo[4,5-*e*]pyridine-**

2,10-diamine (4b2). Beige solid, m.p. 179-181°C. IR: 3481 (NH), 3372 and 3184 (NH₂), 2914 (CH₃ and CH₂), 1585 (NH₂), 1534 (NH), 1443 (CH₃), 1310 (NH₂), 723 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.5 (m, 4H, 2 × CH₂), 1.7 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 3.7 (s, 3H, OCH₃), 5.8 (s, 2H, NH₂), 6.9 (d, 2H, 2 × CH, *J* = 8.2 Hz), 7.8 (d, 2H, 2 × CH, *J* = 8.2 Hz), 10.1 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆): δ 20.7, 24.8, 26.5, 27.3, 31.9, 55.1, 114.0, 117.3, 118.7, 131.5, 134.2, 142.1, 148.2, 154.2, 157.2, 158.1. HRMS (ESI) calcd for C₁₈H₂₁N₄OS [M+H]⁺ 341.1431, found 341.1454.

***N*²-(4-Chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,8-diamine**

(4c0). Red-brownish solid, m.p. 294-296°C. IR: 3483 (NH), 3382 and 3296 (NH₂), 2892 (CH₂), 1594 (NH₂), 1538 (NH), 1487 (CH₂), 753 (disubstituted benzene) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.0 (m, 2H, CH₂), 2.7 (m, 4H, 2 × CH₂), 6.0 (s, 2H, NH₂), 7.3 (d, 2H, 2 × CH, *J* = 8.2 Hz), 7.9 (d,

2H, $2 \times \text{CH}$, $J = 8.2 \text{ Hz}$), 10.3 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 22.6, 27.3, 33.6, 116.5, 119.0, 124.6, 128.6, 130.3, 139.7, 141.7, 151.2, 155.7, 160.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{ClN}_4\text{S}$ $[\text{M}+\text{H}]^+$ 317.0628, found 317.0622.

***N*²-(4-Chlorophenyl)-5,6,7,8-tetrahydro[1,3]thiazolo[5,4-*b*]quinoline-2,9-diamine (4c1).**

Orange solid, m.p. 260-262°C. IR: 3486 (NH), 3385 and 3249 (NH₂), 2922 (CH₂), 1590 (NH₂), 1537 (NH), 1486 (CH₂), 1310 (NH₂), 722 (disubstituted benzene) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.6 (m, 4H, $2 \times \text{CH}_2$), 1.8 (m, 2H, CH₂), 2.5 (m, 2H, CH₂), 5.7 (s, 2H, NH₂), 7.1 (d, 2H, $2 \times \text{CH}$, $J = 8.2 \text{ Hz}$), 7.7. (d, 2H, $2 \times \text{CH}$, $J = 8.2 \text{ Hz}$), 10.2 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 20.7, 22.0, 23.2, 32.5, 112.1, 119.1, 124.7, 128.6, 130.1, 139.7, 143.1, 149.7, 151.6, 155.8. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{ClN}_4\text{S}$ $[\text{M}+\text{H}]^+$ 331.0772, found 331.0779.

***N*²-(4-Chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,10-diamine (4c2).** Red-brownish solid, m.p. 272-274°C. IR: 3483 (NH), 3368 and 3182 (NH₂), 2920 (CH₂), 1583 (NH₂), 1528 (NH), 1488 (CH₂), 1308 (NH₂), 735 (disubstituted benzene) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.5 (m, 4H, $2 \times \text{CH}_2$), 1.6 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 5.7 (s, 2H, NH₂), 7.1 (d, 2H, $2 \times \text{CH}$, $J = 8.2 \text{ Hz}$), 7.7 (d, 2H, $2 \times \text{CH}$, $J = 8.2 \text{ Hz}$), 10.2 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 20.7, 25.0, 26.6, 27.2, 31.8, 117.3, 119.0, 123.8, 124.7, 128.5, 139.4, 142.6, 145.4, 156.3, 158.7. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{ClN}_4\text{S}$ $[\text{M}+\text{H}]^+$ 345.0936, found 345.0935.

***N*²-Benzyl-6,7-dihydro-5H-cyclopenta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,8-diamine (4d0).**

Dark brownish solid, m.p. 143-145°C. IR: 3459 (NH), 3296 and 3163 (NH₂), 2952 (CH₂), 1562 (NH₂), 1531 (NH), 1348 (NH₂), 710 and 697 (monosubstituted benzene) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.8 (m, 2H, CH₂), 2.55 (m, 4H, $2 \times \text{CH}_2$), 4.4 (d, 2H, CH₂), 5.5 (s, 2H, NH₂), 7.15 (m, 5H, monosubstituted benzene), 8.0 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 22.7, 27.2, 33.5, 46.5, 116.3, 126.9, 127.6, 128.2, 130.8, 139.2, 140.6, 151.1, 158.5, 161.4. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_4\text{S}$ $[\text{M}+\text{H}]^+$ 297.1168, found 297.1178.

***N*²-Benzyl-5,6,7,8-tetrahydro[1,3]thiazolo[5,4-*b*]quinoline-2,9-diamine (4d1).**

Beige solid, m.p. 140-142°C. IR: 3401 (NH), 3339 and 3121 (NH₂), 2919 (CH₂), 1599 (NH₂), 1548 (NH), 1450 (CH₂), 1337 (NH₂), 737 and 694 (monosubstituted benzene) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.7 (m, 4H, $2 \times \text{CH}_2$), 2.5 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 4.6 (d, 2H, CH₂), 5.5 (s, 2H, NH₂), 7.3 (m, 5H, monosubstituted benzene), 8.2 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 22.2, 22.7, 23.1, 32.4, 46.5, 111.9, 126.9, 127.6, 128.3, 130.7, 139.2, 141.9, 149.7, 150.1, 161.4. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{N}_4\text{S}$ $[\text{M}+\text{H}]^+$ 311.1325, found 311.1331.

***N*²-Benzyl-6,7,8,9-tetrahydro-5H-cyclohepta[*b*][1,3]thiazolo[4,5-*e*]pyridine-2,10-diamine (4d2).**

Brownish solid, m.p. 198-200°C. IR: 3476 (NH), 3371 and 3164 (NH₂), 2925 (CH₂), 1613 (NH₂), 1451 (CH₂), 1345 (NH₂), 754 and 697 (monosubstituted benzene) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.5 (m, 4H, $2 \times \text{CH}_2$), 1.7 (m, 2H, CH₂), 2.6 (m, 2H, CH₂), 2.7 (m, 2H, CH₂), 4.5 (d, 2H, CH₂), 5.5. (s, 2H, NH₂), 7.3 (m, 5H, monosubstituted benzene), 8.2 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ 20.7, 25.1, 26.5, 27.3, 31.9, 46.5, 117.2, 126.9, 127.1, 128.2, 131.6, 139.2, 141.5, 148.2, 157.1, 161.9. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{N}_4\text{S}$ $[\text{M}+\text{H}]^+$ 325.1481, found 325.1490.

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