Synthesis of Selenophene Analogues of the Tacrine Series: Comparison of Classical Route and Microwave Irradiation

David Thomae,[a] Gilbert Kirsch,*[a] Pierre Seck[b]

[a] Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, FR CNRS 2843, 1 Boulevard Arago, 57070 Metz, France
Fax +33(3)87315801; E-mail: kirsch@univ-metz.fr

[b] Laboratoire de Chimie, Faculté des Sciences, de la Technologie et de la Communication, Université du Luxembourg, 162a Avenue de la Faïencerie, 1511 Luxembourg, Grand-Duché de Luxembourg

Received 28 January 2008

In memory of Ariane Beutler

Abstract: New 3-amino-2-selenophenecarbonitriles condensed with cyclanones to afford, in one step, analogues of Tacrine. A comparison between classical heating and microwave irradiation for the Friedländer condensation is presented.

Key words: Alzheimer disease, Tacrine analogues, Friedländer reaction, 3-amino-2-cyanoselenophenes, sodium selenide, microwave irradiation

Alzheimer's disease is a form of dementia of older people and will be a major problem in the coming decade.[1] One possible treatment is to inhibit acetylcholinesterase, which plays a role in the formation of the β-amyloïd plaque. The first acetylcholinesterase inhibitor used was Tacrine (**I**) sold under the name COGNEX® (Figure 1). However, this drug has side effects.[2] Our aim was to look at the effects of structural modifications of Tacrine on its biological activity. Recently, we described the synthesis of thiophene analogues of Tacrine,[3] based on the thieno[3,2*b*]quinoline moiety **II** (Figure 1). To extend our library of new analogues of Tacrine, we have developed a method with which to prepare the selenophenes analogues **3**, **4** and **5** (Figure 1).

The precursors of **3**, **4** and **5** were the substituted selenophenes **2a–f** (Scheme 2) and the first step of the synthesis was thus to prepare these new 3-amino-2-selenophenecarbonitriles. In the literature, access to 5-substituted 3-aminoselenophenes is described starting from ketene dithioacetals,[4] 2-cyano-3-phenyl-3-chloroacrylonitrile[5] or 3-aryl-3-chloroacrylonitrile[6] and these strategies have been used for the synthesis of 3-amino-2-nitroselenophenes **III** (Scheme 1). To obtain **2a–f**, we applied the same strategy. Thus, β-chloroacrylonitriles **1a–f** were obtained in three steps by a method previously established by different groups and also used in our laboratory.[3,6,7] Freshly prepared sodium selenide, prepared by a known method,[4a,6] was reacted with β-chloroacrylonitriles **1a–f** in *N*,*N*-dimethylformamide (DMF) at 60 °C, to form the intermediate selenolate. After two hours, chloroacetonitrile was added dropwise at 60 °C and stirring was continued for two more hours. Cyclization was performed by addition of a solution of sodium ethanolate. Pouring the reaction mixture in to water gave the compounds **2a–f** as solids in good yields (Table 1).

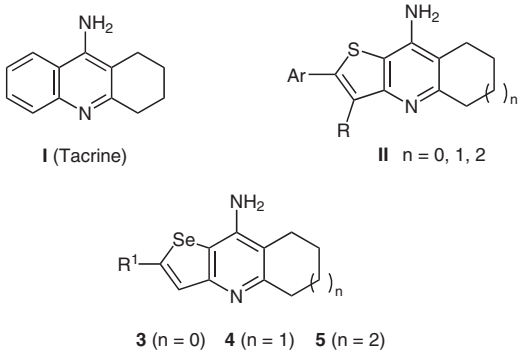
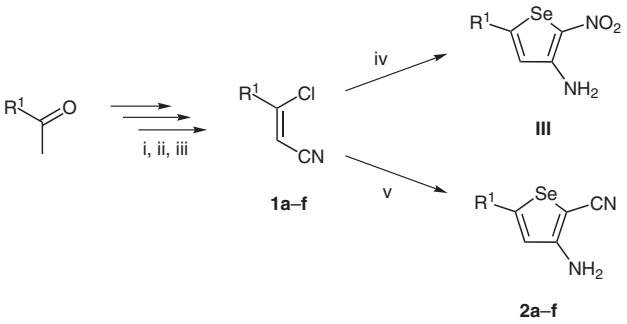


Figure 1 Strucure of Tacrine, thiophene analogues and new selenophene analogues



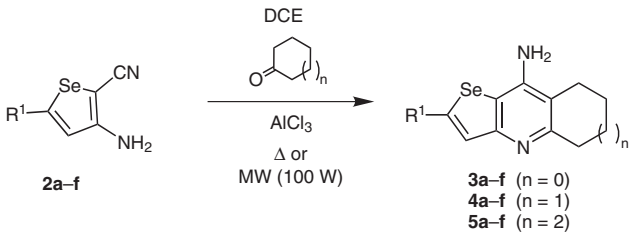
Scheme 1 *Reagents and conditions*: i) $POCl_3$, DMF, 60 °C, 5 h; ii) hydroxylamine chloride, EtOH, reflux; iii) Ac_2O; iv) Na_2Se, DMF, $BrCH_2NO_2$, NaOH; v) Na_2Se, DMF, $ClCH_2CN$, NaOEt.

Table 1 Formation of the Selenophenes **2a–f**

Entry	**1**	R^1	Yield of **2** (%)[a]
1	**1a**	Ph	64
2	**1b**	4-MeC_6H_4	76
3	**1c**	4-$MeOC_6H_4$	80
4	**1d**	4-ClC_6H_4	77
5	**1e**	*t*-Bu	68
6	**1f**	4-$O_2NC_6H_4$	77

[a] Crude product, analytically pure and used without purification.

SYNTHESIS 2008, No. 10, pp 1600–1606
Advanced online publication: 27.03.2008
DOI: 10.1055/s-2008-1067001; Art ID: Z03108SS

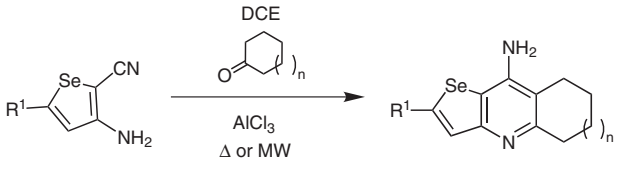


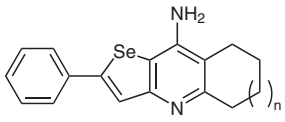
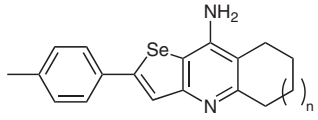
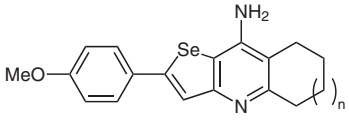
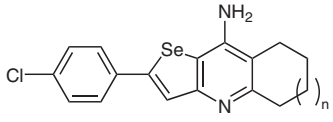
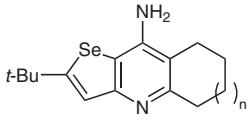
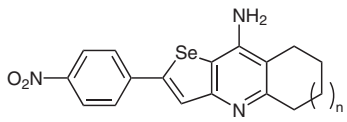
Scheme 2 The Friedländer condensation

The second step of our synthesis was to prepare the selenophene analogues of Tacrine **3a–f**, **4a–f** and **5a–f** (Scheme 2). As for thieno[3,2*b*]quinolines,[3] the Friedländer reaction was used. Substituted 3-amino-2-selenophenecarbonitriles reacted with cyclanones in the presence of aluminium chloride. The first attempt at cyclization was realized with **2d** under the conditions previously described in the litterature.[2,8] To aluminium chloride suspended in anhydrous dichloroethane under an argon atmosphere, **2d** and cyclopentanone were added. The solution was heated for 12 hours at reflux to give **3d** in 75% yield. In order to improve the reaction, the order of addition of the reagents was reversed. Thus, when **2** was dissolved in dichloroethane and the cyclanone was then added followed by aluminium chloride, the reaction was complete in 1–2 hours, instead of 12 hours, and compounds **3–5** were obtained in good yields (Table 2).

Since the pioneering work of Gedye in 1986,[9] the use of microwave irradiation in organic reactions has become very important.[10] Our laboratory has ongoing research in the microwave field, focussing on improving heterocyclic synthesis.[11] Moreover, some research on the microwave-assisted synthesis of quinolines have already been published.[12] After some attempts, we optimised the experi-

Table 2 Yields of the Friedländer Reaction

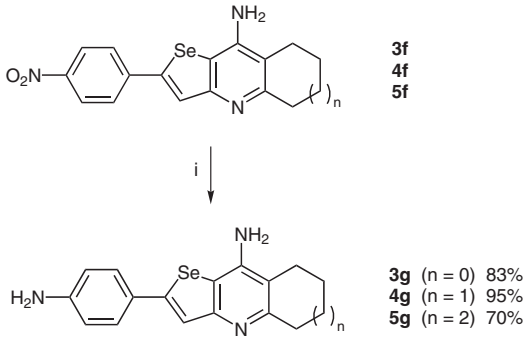


Tacrine analogue	Compound	Classical heating Method A		Microwave irradiation (100 W) Method B	
		Time (min)	Yield (%)	Time (min)	Yield (%)
	n = 0, **3a**	120	65	2 × 8	70
	n = 1, **4a**	120	85	2 × 8	95
	n = 2, **5a**	120	78	2 × 8	97
	n = 0, **3b**	60	83	1 × 8	93
	n = 1, **4b**	60	80	1 × 8	89
	n = 2, **5b**	60	76	1 × 8	91
	n = 0, **3c**	120	85	2 × 8	75
	n = 1, **4c**	60	73	2 × 8	84
	n = 2, **5c**	60	75	2 × 8	82
	n = 0, **3d**	120	84	1 × 10	94
	n = 1, **4d**	120	94	1 × 10	79
	n = 2, **5d**	120	90	1 × 10	88
	n = 0, **3e**	120	92	1 × 8	93
	n = 1, **4e**	120	95	1 × 8 + 3	94
	n = 2, **5e**	120	91	1 × 8	91
	n = 0, **3f**	120	85	2 × 8[a]	86
	n = 1, **4f**	120	95	2 × 8[a]	95
	n = 2, **5f**	120	85	2 × 8[a]	88

[a] Reaction performed in THF with $AlCl_3$ (6 equiv).

mental conditions through which to prepare **3**, **4** and **5** under microwave irradiation. Thus, **2a–f** were reacted with cyclanones in dichloroethane in the presence of aluminium chloride in the same proportions used for refluxing. The solution was heated between 8 and 16 minutes at constant power (100W). **3f**, **4f** and **5f** were not soluble enough in dichloroethane and the Friedländer reaction did not go to completion. In this case, when the solvent was changed to THF, however, **2f** rapidly gave the expected compounds **3f**, **4f** and **5f** in high yields (Table 2). Microwave irradiation helped to reduce the time of reaction and, in most cases, the yields were better than those obtained following the classical route (Table 2).

Nitro derivatives **3f**, **4f** and **5f** were transformed into the previously unknown amino compounds **3g**, **4g** and **5g**, respectively, in good yields, using hydrazine hydrate and palladium on activated carbon (Scheme 3).[13]



Scheme 3 *Reagents and conditions:* i) $N_2H_4 \cdot H_2O$, Pd/C (5%), EtOH, reflux.

In conclusion, substituted 3-amino-2-cyanoselenophenecarbonitriles **2a–f** were synthesized in four steps with good yields. Experimental conditions for the Friedländer reaction under microwave irradiation have been developed, which allow very rapid access to the target molecules **3–5** in high yields. The expected compounds were obtained faster and with better yields than those obtained through classical heating. Biological tests using Ellman's test on acetylcholinesterase inhibition procedure[14] are underway.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. IR spectra were performed using a Perkin–Elmer Spectrum BxFT-IR spectrophotometer or were recorded neat from 4400 to 600 cm^{-1} on an Perkin–Elmer FT-IR Baragon 1000PC equipped with a Graseby–Specac golden gate and treated with the Spectrum (Perkin–Elmer) software version 5.3.1. ^1H and ^{13}C NMR spectra were recorded on a 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, 6890N 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. Elemental analyses were determined with a LECO CHNS 932 elemental analyzer. A CEM Discover oven was used for reactions requiring microwave irradiation.

Preparation of Sodium Selenide

Selenium (0.04 mol) was added to a solution of NaOH (0.224 mol) and sodium formaldehyde sulfoxylate (0.096 mol) in H_2O (40 mL). After stirring for 1 h at 50 °C, the white precipitate was filtered under an argon atmosphere and rapidly used for the next step.

Synthesis of Substituted 3-Aminoselenophenecarbonitrile (2a–f); General Procedure

Na_2Se (0.04 mol) was suspended in DMF (40 mL) and the corresponding β-chloroacrylonitrile **1a–f** (0.04 mol) dissolved in DMF (15 mL) was added. The mixture was heated at 60 °C for 2 h then choroacetonitrile (0.04 mol) was added dropwise. After addition, the mixture was stirred for 2 h at 60 °C then a solution of EtONa (0.04 mol) in absolute EtOH (25 mL) was added and stirring was continued for 1 h at the same temperature. The mixture was poured onto H_2O (300 mL) under vigorous stirring and the precipitate was filtered, washed with H_2O (2 × 50 mL), dried at r.t. until constant weight and recrystallized (EtOH).

3-Amino-5-phenyl-2-selenophenecarbonitrile (2a)

Yield: 64%; brown solid; mp 110–112 °C (dec).

IR (neat): 3429 (s), 3332 (s), 3229 (s), 2959 (s), 2197 (s), 1563 (s) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 6.58 (s, 2 H, NH_2), 7.20 (s, 1 H, CH), 7.41 (m, 3 H, CH), 7.42 (m, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 72.32, 117.15, 119.31, 125.78, 129.30, 129.41, 134.00, 153.11, 159.48.

GC-MS (EI, 70 eV): *m*/*z* = 248 [M^+], 168, 77.

Anal. Calcd for $C_{11}H_8N_2Se$: C, 56.46; H, 3.26; N, 11.33. Found: C, 56.66; H, 3.23; N, 10.30.

3-Amino-5-(4-methylphenyl)-2-selenophenecarbonitrile (2b)

Yield: 76%; brown solid; mp 190–192 °C.

IR (KBr): 3428 (s), 3345 (s), 3242 (s), 2178 (s), 1566 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.30 (s, 3 H, CH_3), 6.54 (s, 2 H, NH_2), 7.15 (s, 1 H, CH), 7.22 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.42 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 20.77, 71.67, 117.26, 118.64, 125.68, 129.71, 131.31, 138.34, 153.26, 159.53.

GC-MS (EI, 70 eV): *m*/*z* = 262 [M^+], 182, 115.

Anal. Calcd for $C_{12}H_{10}N_2Se$: C, 55.18; H, 3.86; N, 10.73. Found: C, 55.05; H, 4.01; N, 10.78.

3-Amino-5-(4-methoxyphenyl)-2-selenophenecarbonitrile (2c)

Yield: 80%; brown solid; mp 220–222 °C.

IR (KBr): 3458 (s), 3339 (s), 3234 (s), 2182 (s), 1565 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.77 (s, 3 H, CH_3), 6.52 (s, 2 H, NH_2), 6.96 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.11 (s, 1 H, CH), 7.46 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 55.33, 113.47, 114.59, 117.20, 117.94, 126.54, 126.54, 126.97, 157.21, 159.67, 160.20.

GC-MS (EI, 70 eV): *m*/*z* = 278 [M^+], 263, 198.

Anal. Calcd for $C_{12}H_{10}N_2OSe$: C, 52.00; H, 3.64; N, 10.11. Found: C, 52.16; H, 3.78; N, 10.99.

3-Amino-5-(4-chlorophenyl)-2-selenophenecarbonitrile (2d)

Yield: 77%; green solid; mp 204–206 °C.

IR (KBr): 3429 (s), 3333 (s), 3229 (s), 2198 (s), 1566 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 6.62 (s, 2 H, NH_2), 7.25 (s, 1 H, CH), 7.46 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.55 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 72.72, 117.07, 120.00, 127.70, 128.73, 132.90, 133.87, 151.39, 159.49.

GC-MS (EI, 70 eV): *m*/*z* = 282 [M$^+$], 202.

Anal. Calcd for $C_{11}H_7ClN_2Se$: C, 46.92; H, 2.51; N, 9.95. Found: C, 46.81; H, 2.24; N, 9.88.

3-Amino-5-*tert*-butyl-2-selenophenecarbonitrile (2e)
Yield: 68%; brown solid; mp 122–124 °C.

IR (KBr): 3414 (s), 3334 (s), 3227 (s), 2959 (s), 2185 (s), 1570 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.32 (s, 9 H, 3 × CH_3), 4.44 (s, 2 H, NH_2), 6.59 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 32.32, 36.94, 79.61, 116.85, 117.68, 156.60, 172.16.

GC-MS (EI, 70 eV): *m*/*z* = 228 [M$^+$], 213, 147, 132.

Anal. Calcd for $C_9H_{12}N_2Se$: C, 47.58; H, 5.32; N, 12.33. Found: C, 47.84; H, 5.44; N, 12.28.

3-Amino-5-(4-nitrophenyl)-2-selenophenecarbonitrile (2f)
Yield: 77%; orange solid; mp 198–200 °C.

IR (KBr): 3431(s), 3312 (s), 1557 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.66 (s, 2 H, NH_2), 7.41 (s, 1 H, CH), 7.80 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 8.23 (d, *J* = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 75.06, 116.74, 122.03, 124.48, 126.62, 140.01, 147.28, 149.92, 159.38.

GC-MS (EI, 70 eV): *m*/*z* = 293 [M$^+$], 263, 247, 220, 140.

Anal. Calcd for $C_{11}H_7N_3O_2Se$: C, 45.22; H, 2.42; N, 14.38. Found: C, 45.84; H, 2.45; N, 14.27.

Friedländer Reaction (Method A: Refluxing); General Procedure
Cyclanone (1.1 mmol) was added to a solution of selenophene **1** (1 mmol) in CH_2Cl_2 (25 mL). After stirring 5 min at r.t., aluminium chloride (1.7 mmol) was added and the mixture was heated at reflux for 1–2 h. When the reaction was complete (TLC), aq NaOH (10%, 25 mL) was added. After stirring for 30 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous $NaSO_4$, filtered and the solvent was evaporated. The resultant solid was purified by column chromatography (EtOAc, 100%) or heated in MeCN (2 mL) and filtered while hot.

Friedländer Reaction (Method B: Microwave Irradiation); General Procedure
In a 100 mL round-bottom flask equipped with a condenser, cyclanone (2.2 mmol) was added to a solution of selenophene **2** (2 mmol) in CH_2Cl_2 (34 mL) (or THF when **2f** was used). Aluminium chloride (3.4 mmol or 12 mmol for **2f**) was added and the mixture was heated at reflux for 8–16 min under microwave irradiation (constant power of 100 W). When the reaction was complete (TLC), aq NaOH (10%, 34 mL) was added and stirring was continued for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried over anhydrous $NaSO_4$, filtered and the solvent was evaporated. The resultant solid was purified by column chromatography (EtOAc, 100%) or heated in MeCN (2 mL) and filtered while hot.

8-Amino-2-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno[2,3-*e*]pyridine (3a)
Yield: 65% (Method A), 70% (Method B); brown solid; mp 234–236 °C.

IR (neat): 2949 (m), 1638 (s), 1563 (s), 1540 (s), 753 (s), 680 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.10 (m, 2 H, CH_2), 2.75 (m, 2 H, CH_2), 2.78 (m, 2 H, CH_2), 6.23 (s, 2 H, NH_2), 7.38 (m, 3 H, 3 × CH), 7.52 (m, 2 H, 2 × CH), 7.52 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 24.65, 27.45, 33.70, 114.54, 117.54, 124.33, 125.91, 127.83, 129.14, 135.50, 146.64, 146.95, 158.78, 163.76.

GC-MS (EI, 70 eV): *m*/*z* = 314 [M$^+$], 233.

Anal. Calcd for $C_{16}H_{14}N_2Se$: C, 61.35; H, 4.50; N, 8.94. Found: C, 61.43; H, 4.49; N, 8.89.

9-Amino-2-phenyl-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4a)
Yield: 85% (Method A), 95% (Method B); brown solid; mp 228–230 °C.

IR (neat): 2926 (m), 164 (s), 1559 (s), 1529 (s), 753 (s), 684 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.80 (m, 4 H, 2 × CH_2), 2.49 (m, 2 H, CH_2), 2.75 (m, 2 H, CH_2), 6.09 (s, 2 H, NH_2), 7.39 (m, 3 H, 3 × CH), 7.68 (m, 2 H, 2 × CH), 7.80 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.38, 22.59, 23.32, 32.52, 110.03, 116.82, 124.30, 125.97, 128.54, 129.14, 135.46, 146.83, 148.70, 154.53, 156.89.

GC-MS (EI, 70 eV): *m*/*z* = 328 [M$^+$], 312, 300.

Anal. Calcd for $C_{17}H_{16}N_2Se$: C, 62.39; H, 4.93; N, 8.56. Found: C, 62.34; H, 4.74; N, 8.65.

10-Amino-2-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5a)
Yield: 78% (Method A), 97% (Method B); brown solid; mp 216–218 °C.

IR (neat): 2918 (m), 1631 (s), 1558 (s), 1528 (s), 753 (s), 687 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.56 (m, 4 H, 2 × CH_2), 1.80 (m, 2 H, CH_2), 2.73 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 6.20 (s, 2 H, NH_2), 7.42 (m, 3 H, 3 × CH), 7.68 (m, 2 H, 2 × CH), 7.82 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 23.63, 24.99, 26.45, 27.29, 31.74, 115.31, 118.87, 124.61, 125.94, 128.47, 129.15, 135.52, 146.79, 147.70, 156.37, 161.72.

GC-MS (EI, 70 eV): *m*/*z* = 342 [M$^+$], 327, 313, 288, 77.

Anal. Calcd for $C_{18}H_{18}N_2Se$: C, 63.34; H, 5.32; N, 8.21. Found: C, 63.57; H, 5.13; N, 8.14.

8-Amino-2-(4-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno[2,3-*e*]pyridine (3b)
Yield: 83% (Method A), 93% (Method B); light-brown solid; mp 264–266 °C.

IR (neat): 2949 (m), 1645 (s), 1561 (s), 1538 (s), 800 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.14 (m, 2 H, CH_2), 2.17 (s, 3 H, CH_3), 2.77 (m, 2 H, CH_2), 3.00 (m, 2 H, CH_2), 4.05 (s, 2 H, NH_2), 7.18 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.46 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.57 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 20.76, 22.44, 27.47, 33.81, 114.40, 117.18, 123.89, 125.81, 129.69, 132.84, 138.04, 146.56, 146.76, 159.26, 163.95.

GC-MS (EI, 70 eV): *m*/*z* = 328 [M$^+$], 247, 163, 115, 91.

Anal. Calcd for $C_{17}H_{16}N_2Se$: C, 62.39; H, 4.93; N, 8.56. Found: C, 62.66; H, 5.14; N, 8.29.

9-Amino-2-(4-methylphenyl)-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4b)
Yield: 80% (Method A), 89% (Method B); colorless solid; mp 254–256 °C.

IR (neat): 2929 (m), 1646 (s), 1559 (s), 153 (s), 807 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.79 (m, 4 H, 2 × CH_2), 2.34 (s, 3 H, CH_3), 2.50 (m, 2 H, CH_2), 2.75 (m, 2 H, CH_2), 6.02 (s, 2 H, NH_2), 7.26 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.58 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.76 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 20.75, 22.43, 22.66, 23.34, 32.67, 109.92, 116.48, 123.82, 125.85, 130.67, 132.80, 138.10, 146.73, 148.50, 154.63, 157.29.

GC-MS (EI, 70 eV): *m*/*z* = 342 [M^+], 326, 314, 163, 115, 91.

Anal. Calcd for $C_{18}H_{18}N_2Se$: C, 63.34; H, 5.32; N, 8.21. Found: C, 63.38; H, 5.33; N, 8.35.

10-Amino-2-(4-methylphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5b)
Yield: 76% (Method A), 91% (Method B); light-brown solid; mp 276–278 °C.

IR (neat): 2917 (m), 1648 (s), 1559 (s), 1534 (s), 809 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.55 (m, 4 H, 2 × CH_2), 1.58 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.72 (m, 2 H, CH_2), 2.89 (m, 2 H, CH_2), 5.99 (s, 2 H, NH_2), 7.25 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.56 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.75 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 20.74, 25.00, 26.47, 27.32, 31.75, 32.07, 115.20, 118.55, 124.01, 125.68, 129.66, 132.83, 138.04, 146.79, 147.58, 156.60, 161.75.

GC-MS (EI, 70 eV): *m*/*z* = 356 [M^+], 341, 327, 163, 115, 91.

Anal. Calcd for $C_{19}H_{20}N_2Se$: C, 64.22; H, 5.67; N, 7.88. Found: C, 64.08; H, 5.57; N, 7.98.

8-Amino-2-(4-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno [2,3-*e*]pyridine (3c)
Yield: 83% (Method A), 75% (Method B); light-brown solid; mp 236–238 °C.

IR (neat): 2944 (m), 1647 (m), 1562 (s), 1540 (s), 810 (s) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.22 (m, 2 H, CH_2), 2.82 (m, 2 H, CH_2), 3.05 (m, 2 H, CH_2), 3.87 (s, 3 H, CH_3), 4.18 (s, 2 H, NH_2), 6.96 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.64 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.96, 27.27, 34.38, 55.41, 114.36, 115.65, 123.36, 127.86, 128.63, 129.59, 145.00, 147.76, 159.85, 160.04, 165.15.

GC-MS (EI, 70 eV): *m*/*z* = 344 [M^+], 329, 300, 219, 207.

Anal. Calcd for $C_{17}H_{16}N_2OSe$: C, 59.48; H, 4.70; N, 8.16. Found: C, 59.61; H, 4.52; N, 8.13.

9-Amino-2-(4-methoxyphenyl)-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4c)
Yield: 73% (Method A), 84% (Method B); colorless solid; mp 246–248 °C.

IR (neat): 2933 (m), 1646 (m), 1532 (s), 1499 (s), 822 (s) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.79 (m, 2 H, CH_2), 1.81 (m, 2 H, CH_2), 2.47 (m, 2 H, CH_2), 2.86 (m, 2 H, CH_2), 3.73 (s, 3 H, CH_3), 4.13 (s, 2 H, NH_2), 6.83 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.49 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.66 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.71, 22.92, 23.38, 33.04, 55.40, 110.96, 114.35, 123.23, 127.77, 128.55, 129.59, 147.28, 147.91, 155.79, 157.80, 160.07.

GC-MS (EI, 70 eV): *m*/*z* = 358 [M^+], 343, 330, 315, 219, 207.

Anal. Calcd for $C_{18}H_{18}N_2OSe$: C, 60.51; H, 5.08; N, 7.84. Found: C, 60.78; H, 5.26; N, 7.94.

10-Amino-2-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5c)
Yield: 75% (Method A), 82% (Method B); colorless solid; mp 240–242 °C.

IR (neat): 2918 (m), 1650 (m), 1533 (s), 1498 (s), 825 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.54 (m, 2 H, CH_2), 1.56 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 2.72 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 5.97 (s, 2 H, NH_2), 7.00 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.60 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.67 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 26.04, 26.64, 27.29, 32.22, 39.05, 55.41, 116.50, 119.92, 123.51, 127.51, 127.76, 128.59, 146.16, 148.08, 157.06, 160.05, 162.65.

GC-MS (EI, 70 eV): *m*/*z* = 372 [M^+], 357, 343, 328, 315, 300, 219, 207.

Anal. Calcd for $C_{19}H_{20}N_2OSe$: C, 61.45; H, 5.43; N, 7.54. Found: C, 61.25; H, 5.53; N, 7.72.

8-Amino-2-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno[2,3-*e*]pyridine (3d)
Yield: 84% (Method A), 94% (Method B); brown solid; mp 270–272 °C.

IR (neat): 2952 (m), 1642 (s), 1539 (s), 1562 (s), 814 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.04 (m, 2 H, CH_2), 2.75 (m 2 H, CH_2), 2.83 (m, 2 H, CH_2), 6.22 (s, 2 H, NH_2), 7.57 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.62 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.71 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.41, 27.47, 33.76, 114.67, 117.80, 125.28, 127.56, 129.08, 132.88, 134.46, 144.87, 146.83, 158.93, 164.10.

GC-MS (EI, 70 eV): *m*/*z* = 348 [M^+], 331, 311, 267.

Anal. Calcd for $C_{16}H_{13}ClN_2Se$: C, 55.27; H, 3.77; N, 8.06. Found: C, 55.54; H, 3.83; N, 8.09.

9-Amino-2-(4-chlorophenyl)-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4d)
Yield: 94% (Method A), 79% (Method B); brown solid; mp 258–260 °C.

IR (neat): 2932 (m), 1628 (m), 1557 (s), 1528 (s), 814 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.77 (m, 4 H, 2 × CH_2), 2.48 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 6.08 (s, 2 H, NH_2), 7.50 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.67 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.84 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.37, 22.59, 23.35, 32.60, 110.16, 117.05, 125.22, 127.61, 129.09, 132.94, 134.43, 145.07, 148.63, 154.76, 156.95.

GC-MS (EI, 70 eV): *m*/*z* = 362 [M^+], 346, 334, 281.

Anal. Calcd for $C_{17}H_{15}ClN_2Se$: C, 56.45; H, 4.18; N, 7.74. Found: C, 56.61; H, 4.16; N, 7.49.

10-Amino-2-(4-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5d)
Yield: 90% (Method A), 88% (Method B); brown solid; mp 274–276 °C.

IR (neat): 2917 (m), 1648 (m), 1559 (s), 1531 (s), 820 (s) cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.57 (m, 4 H, 2 × CH_2), 1.79 (m, 2 H, CH_2), 2.38 (m, 2 H, CH_2), 2.89 (m, 2 H, CH_2), 6.06 (s, 2 H,

NH_2), 7.55 (d, J = 7.5 Hz, 2 H, 2 × CH), 7.63 (d, J = 7.5 Hz, 2 H, 2 × CH), 7.85 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 23.63, 25.00, 26.45, 27.28, 30.36, 115.46, 119.15, 125.47, 127.59, 129.09, 132.89, 134.48, 145.06, 147.66, 156.36, 161.95.

GC-MS (EI, 70 eV): m/z = 376 [M$^+$], 361, 347, 207.

Anal. Calcd for $C_{18}H_{17}ClN_2Se$: C, 57.54; H, 4.56; N, 7.46. Found: C, 57.65; H, 4.50; N, 9.43.

8-Amino-2-*tert*-butyl-3-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]seleno[2,3-*e*]pyridine (3e)
Yield: 92% (Method A), 93% (Method B); beige solid; mp 212–214 °C.

IR (neat): 2951 (s), 1646 (s), 1563 (s), 1537 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.35 (s, 9 H, 3 × CH_3), 2.01 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 2.79 (m, 2 H, CH_2), 5.97 (s, 1 H, NH_2), 7.14 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.44, 27.36, 32.13, 32.78, 36.09, 113.58, 116.31, 122.68, 146.70, 158.59, 162.53, 163.25.

GC-MS (EI, 70 eV): m/z = 294 [M$^+$], 279, 263, 251, 237, 199.

Anal. Calcd for $C_{14}H_{18}N_2Se$: C, 57.34; H, 6.19; N, 9.55. Found: C, 57.30; H, 6.11; N, 9.37.

9-Amino-2-*tert*-butyl-3-methyl-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4e)
Yield: 95% (Method A), 94% (Method B); beige solid; mp 198–200 °C.

IR (neat): 2928 (s), 1641 (s), 1562 (s), 1527 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.35 (s, 9 H, 3 × CH_3), 1.74 (m, 4 H, 2 × CH_2), 2.48 (m, 2 H, CH_2), 2.70 (m, 2 H, CH_2), 5.84 (s, 1 H, NH_2), 7.11 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 22.49, 22.71, 23.22, 32.10, 32.61, 36.08, 109.17, 115.74, 122.57, 148.48, 153.93, 156.60, 162.80.

GC-MS (EI, 70 eV): m/z = 308 [M$^+$], 293, 277, 265, 213.

Anal. Calcd for $C_{15}H_{20}N_2Se$: C, 58.63; H, 6.56; N, 9.12. Found: C, 58.52; H, 6.40; N, 9.06.

10-Amino-2-*tert*-butyl-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5e)
Yield: 91% (Method A), 91% (Method B); beige solid; mp 192–194 °C.

IR (neat): 2916 (s), 1680 (s), 1562 (s), 1528 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.35 (s, 9 H, 3 × CH_3), 1.52 (m, 4 H, 2 × CH_2), 1.74 (m, 2 H, CH_2), 2.68 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 5.85 (s, 1 H, NH_2), 7.12 (s, 1 H, CH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 24.95, 26.51, 27.40, 31.76, 32.13, 36.07, 38.35, 114.49, 117.72, 122.81, 147.53, 155.87, 161.11, 162.82.

GC-MS (EI, 70 eV): m/z = 322 [M$^+$], 307, 293, 277, 263, 227.

Anal. Calcd for $C_{17}H_{22}N_2Se$: C, 59.81; H, 6.90; N, 8.72. Found: C, 70.22; H, 6.04; N, 8.87.

8-Amino-2-(4-nitrophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno[2,3-*e*]pyridine (3f)
Yield: 85% (Method A), 86% (Method B); brown solid; mp 286–288 °C (MeCN).

IR (neat): 2922 (m), 1590 (s), 1562 (s), 1511 (s), 1337 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.08 (m, 2 H, CH_2), 2.75 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 6.35 (s, 2 H, NH_2), 7.95 (d, J = 7.5 Hz, 2 H, 2 × CH), 8.11 (s, 1 H, CH), 8.26 (d, J = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.38, 27.50, 33.71, 115.20, 119.24, 124.39, 126.81, 127.90, 141.82, 143.59, 146.67, 146.98, 158.43, 164.43.

GC-MS (EI, 70 eV): m/z = 248, 168.

Anal. Calcd for $C_{15}H_{13}N_3O_2Se$: C, 53.64; H, 3.66; N, 11.73. Found: C, 53.46; H, 3.85; N, 11.42.

9-Amino-2-(4-nitrophenyl)-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4f)
Yield: 95% (Method A), 95% (Method B); brown solid; mp 276–278 °C (MeCN).

IR (neat): 2932 (m), 1592 (s), 1561 (s), 1511 (s), 1338 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.78 (m, 4 H, 2 × CH_2), 2.48 (m, 2 H, CH_2), 2.76 (m, 2 H, CH_2), 6.17 (s, 2 H, NH_2), 7.96 (d, J = 7.5 Hz, 2 H, 2 × CH), 8.10 (s, 1 H, CH), 8.26 (d, J = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.32, 22.56, 23.19, 32.68, 110.64, 118.39, 124.39, 126.86, 128.11, 141.85, 143.61, 146.70, 148.66, 155.30, 156.73.

Anal. Calcd for $C_{17}H_{15}N_3O_2Se$: C, 54.85; H, 4.06; N, 11.29. Found: C, 55.12; H, 4.30; N, 11.23.

10-Amino-2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5f)
Yield: 85% (Method A), 88% (Method B); brown solid; mp 272–274 °C (MeCN).

IR (neat): 2918 (m), 1591 (s), 1560 (s), 1514 (s), 1338 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.57 (m, 4 H, 2 × CH_2), 1.78 (m, 2 H, CH_2), 2.76 (m, 2 H, CH_2), 2.82 (m, 2 H, CH_2), 6.17 (s, 2 H, NH_2), 7.95 (d, J = 7.5 Hz, 2 H, 2 × CH), 8.10 (s, 1 H, CH), 8.26 (d, J = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 25.03, 26.42, 27.22, 29.82, 31.69, 115.94, 120.54, 124.41, 126.83, 128.25, 141.87, 143.67, 146.58, 147.74, 156.07, 162.38.

GC-MS (EI, 70 eV): m/z = 357, 342, 328.

Anal. Calcd for $C_{18}H_{17}N_3O_2Se$: C, 55.96; H, 4.44; N, 10.88. Found: C, 55.84; H, 4.59; N, 10.98.

Reduction of the Nitro Group; General Procedure
In a three-necked round-bottom flask equipped with a magnetic stirrer, condenser and stoppers, Pd/C (5%, 60 mg) was added to a solution of **2f**, **3f** or **4f** (0.5 mmol) in absolute EtOH (10 mL). Hydrazine hydrate (98%, 1.35 mmol) was added dropwise at r.t. and the mixture was stirred for 30 min. The mixture was then heated at reflux for 4 h, and every hour, additional hydrazine hydrate (1.35 mmol) was added. When the reaction was complete, EtOH was evaporated under vacuum and H_2O (30 mL) was added. The precipitate was filtered, washed with H_2O (2 × 10 mL), dried at r.t. until constant weight and recrystallized (EtOH).

8-Amino-2-(4-aminophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]selenopheno[2,3-*e*]pyridine (3g)
Yield: 83%; orange solid; mp 210–212 °C.

IR (neat): 3338 (m), 3209 (m), 2949 (m), 1604 (s), 1562 (s), 1502 (s), 821 (s) cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.03 (m, 2 H, CH_2), 2.73 (m, 2 H, CH_2), 2.81 (m, 2 H, CH_2), 5.47 (s, 2 H, NH_2), 6.08 (s, 2 H, NH_2), 6.58 (d, J = 7.5 Hz, 2 H, 2 × CH), 7.33 (d, J = 7.5 Hz, 2 H, 2 × CH), 7.48 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.41, 27.42, 33.64, 113.86, 113.92, 115.73, 119.96, 122.91, 126.98, 146.85, 148.50, 149.57, 159.22, 163.04.

GC-MS (EI, 70 eV): *m*/*z* = 329 [M^+], 313, 207.

Anal. Calcd for $C_{16}H_{15}N_3Se$: C, 58.54; H, 4.61; N, 12.80. Found: C, 58.61; H, 4.68; N, 12.79.

9-Amino-2-(4-nitrophenyl)-5,6,7,8-tetrahydroselenopheno[3,2-*b*]quinoline (4g)
Yield: 95%; orange solid; mp 208–210 °C.

IR (neat): 3338 (m), 3208 (m), 2924 (m), 2856 (m), 1603 (s), 1531(s), 1500 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.76 (m, 4 H, 2 × CH_2), 2.48 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 5.48 (s, 2 H, NH_2), 5.96 (s, 2 H, NH_2), 6.58 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.33 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.45 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.41, 22.60, 23.23, 32.35, 109.42, 113.85, 115.14, 119.83, 122.86, 127.04, 148.56, 148.65, 149.62, 153.83, 157.32.

Anal. Calcd for $C_{17}H_{17}N_3Se$: C, 59.65; H, 5.01; N, 12.28. Found: C, 59.74; H, 5.32; N, 12.39.

10-Amino-2-(4-nitrophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]selenopheno[2,3-*e*]pyridine (5g)
Yield: 70%; orange solid; mp 212–214 °C.

IR (neat): 3341 (m), 3193 (m), 2916 (m), 2847 (m), 1601 (s), 1529 (s), 1500 (s), 816 (s) cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 (m, 4 H, 2 × CH_2), 1.78 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 2.86 (m, 2 H, CH_2), 5.47 (s, 2 H, NH_2), 5.91 (s, 2 H, NH_2), 6.58 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.33 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.45 (s, 1 H, CH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 18.51, 24.95, 26.41, 27.29, 31.74, 113.75, 114.72, 117.12, 119.92, 123.66, 126.97, 147.77, 149.60, 150.42, 154.84, 160.86.

GC-MS (EI, 70 eV): *m*/*z* = 220.

Anal. Calcd for $C_{18}H_{19}N_3Se$: C, 60.67; H, 5.37; N, 11.79. Found: C, 60.62; H, 5.27; N, 1.84.

Acknowledgment

We thank to the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche for a PhD grant to D.T. We thank also the Université du Luxembourg for financial support to P.S. We are grateful to Ms. Veronique Poddig for recording NMR spectra and Dr Serge Schneider and Dr Marc Schuman from the Laboratoire de Toxicologie at the Laboratoire National de Santé (Luxembourg) for recording the IR and MS spectra.

References

(1) Francotte, P.; Grandorge, E.; Boverie, S.; De Tullio, P.; Pirotte, B. *Curr. Med. Chem.* **2004**, *11*, 1757.
(2) Augry, F.; Darch, A.; De Routou, J.; Guelfi, M. C.; Forette, F. *J. Pharm. Clin.* **1997**, *16*, 183.
(3) Thomae, D.; Kirsch, G.; Seck, P. *Synthesis* **2007**, 1027.
(4) (a) Sommen, G.; Comel, A.; Kirsch, G. *Synlett* **2003**, 855. (b) Sommen, G.; Comel, A.; Kirsch, G. *Synthesis* **2004**, 451.
(5) Gewald, K.; Hain, U. *Monatsh. Chem.* **1992**, *123*, 455.
(6) Thomae, D.; Rodriguez Dominguez, J. C.; Kirsch, G.; Seck, P. *Tetrahedron* **2008**, *64*, 3232.
(7) (a) Thomae, D.; Kirsch, G.; Seck, P. *Synthesis* **2007**, 2153. (b) Migianu, E.; Kirsch, G. *Synthesis* **2002**, 1096. (c) Ren, W.-Y.; Rao, K.; Kein, R. *J. Heterocycl. Chem.* **1986**, *23*, 1757. (d) Vega, S.; Gil, M. S. *J. Heterocycl. Chem.* **1991**, *28*, 1757. (e) Hartmann, H.; Liebscher, J. *Synthesis* **1984**, 275. (f) Hartmann, H.; Liebscher, J. *Synthesis* **1984**, 276. (g) Liebscher, J.; Neumann, B.; Hartmann, H. *J. Prakt. Chem.* **1983**, *325*, 915. (h) Hartmann, H.; Liebscher, J. *Synthesis* **1979**, 241.
(8) (a) Marco-Contelles, J.; Leon, R.; De los Rios, C.; Garcia, A. G.; Lopez, M. G.; Villarroya, M. *Bioorg. Med. Chem.* **2006**, *14*, 8176. (b) Marco-Contelles, J.; Leon, R.; De los Rios, C.; Garcia, A. G.; Lopez, M. G.; Villarroya, M. *Eur. J. Med. Chem.* **2006**, *41*, 1464. (c) Leon, R.; Marco-Contelles, J.; Garcia, A. G.; Villarroya, M. *Bioorg. Med. Chem.* **2005**, *13*, 1167. (d) Marco, J. L.; De Los Rios, C.; Garcia, A.; Villarroya, M.; Carreiras, C.; Martins, C.; Eleutério, A.; Morreale, A.; Orozco, M.; Luque, F. J. *Bioorg. Med. Chem.* **2004**, *12*, 2199. (e) De Los Rios, C.; Marco, J. L.; Carreiras, M. D. C.; Chinchon, P. M.; Garcia, A.; Villarroya, M. *Bioorg. Med. Chem.* **2002**, *10*, 2077. (f) Marco, J. L.; De Los Rios, C.; Carreiras, C.; Baños, J. E.; Badia, A.; Vivas, N. M. *Bioorg. Med. Chem.* **2001**, *9*, 727. (g) Grau, A. M.; Marco, J. L. *Bioorg. Med. Chem.* **1997**, *24*, 3165.
(9) Gedye, R. N.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.
(10) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
(11) (a) Hesse, S.; Perspicaco, E.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5261. (b) Begouin, A.; Hesse, S.; Kirsch, G. *ARKIVOC* **2008**, *(vii)*, 84.
(12) (a) Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. *Tetrahedron Lett.* **2003**, *44*, 255. (b) Muscia, G. C.; Bollini, M.; Carnevale, J. P.; Bruno, A. M.; Asis, S. E. *Tetrahedron Lett.* **2006**, *44*, 8811. (c) Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. *Org. Biomol. Chem.* **2006**, *4*, 104. (d) Frideling, A.; Faure, R.; Galy, J. P.; Kenz, A.; Alkorta, I.; Elguero, J. *Eur. J. Med. Chem.* **2004**, *39*, 37.
(13) (a) Yun, Y. K.; Porco, J. A. Jr.; Labadie, J. *Synlett* **2002**, 742. (b) Borza, I.; Bozo, E.; Barta-Szalaï, G.; Kiss, C.; Tarkani, G.; Demeter, A.; Gati, T.; Hada, V.; Kolok, S.; Gere, A.; Fodor, L.; Nagy, J.; Gagoczy, K.; Magdo, I.; Bela, A.; Fetter, J.; Bertha, F.; Kerserü, G. M.; Horvath, C.; Farkas, S.; Greiner, I.; Domany, G. *J. Med. Chem.* **2007**, *50*, 901.
(14) Ellman, G. L.; Courtney, K. D.; Andres, V.; Feather-Stone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88.