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SYNTHESIS OF IN VIVO METABOLITES OF THE NEW ADENOSINE A_3 RECEPTOR PET-RADIOTRACER [^{18}F]FE@SUPPY

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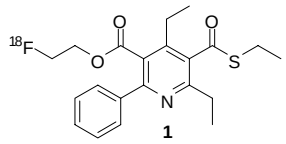
Abstract – The synthesis of three expected metabolites of the new adenosine A_3 receptor PET-radiotracer [^{18}F]FE@SUPPY is described. The target compounds – all pentasubstituted pyridines – were obtained via Hantzsch type synthesis of appropriate 1,4-dihydropyridines, followed by oxidation to the corresponding pyridines and subsequent modifications of the ester moieties.

INTRODUCTION

In contrast to adenosine receptor subtypes A_1 and A_{2A}, little is known about the distribution and absolute amounts of the A_3 subtype in humans. Fredholm *et al* found high expression of A_3 mRNA in rat testes, intermediate levels in human cerebellum and hippocampus, sheep lung and spleen and low levels in human liver, kidney, heart, intestine, testis and rest of the brain.[1] The reported data in the literature[1,2,3,4] so far are based on values of mRNA responsible for the expression rate of the A_3AR but do not represent the absolute receptor densities. For direct quantification of receptor densities autoradiography and positron emission tomography (PET) are available, but both methods require selective radiotracers.

In the last years a variety of compounds belonging to different chemical classes has been identified as selective A_3 adenosine antagonists such as adenines, xanthenes, triazoloquinazolines, flavonoids, thiazolopyridines, 6-phenyl-1,4-dihydropyridines, and 6-phenylpyridines.[5]

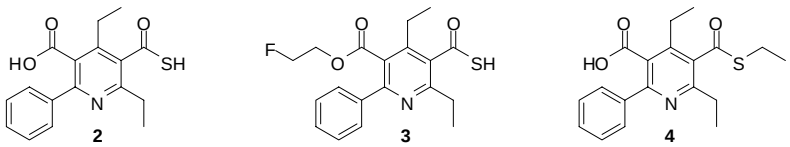
In our efforts to develop new PET-radiotracers, we focused our interest on [^{18}F]fluoride labeling of pentasubstituted pyridines, which exhibit high affinity and selectivity towards the A_3AR in a previous evaluation.[6] Most recently, we reported on 2-[^{18}F]fluoroethyl 4,6-diethyl-5-[(ethylsulfanyl)carbonyl]--2-phenylpyridine-3-carboxylate ([^{18}F]FE@SUPPY) (**1**) as the first A_3 adenosine receptor radiotracer, the establishment of its radiosynthesis, and a first biodistribution study in a rat model (Figure 1).[7]



1

Figure 1. [^{18}F]FE@SUPPY

In the course of our investigations it became obvious, that compounds (**2-4**) represent the expected *in vivo* phase I metabolites of parent compound (**1**) (Figure 2). Thus, synthetic pathways to these hitherto unknown target structures had to be developed. Whereas, **3** and **4** were needed as standards for potential radiometabolites, compound (**2**) additionally, serves as a versatile precursor for further syntheses of a variety of different pentasubstituted pyridines, for instance the alternative microwave enhanced synthesis of **3**. Detailed NMR spectroscopic studies with the target structures, including full and unambiguous assignments of all ^{1}H and ^{13}C-NMR resonances, was envisaged. Hence, aims of the present study were the preparation and structural analysis of compounds (**2-4**).

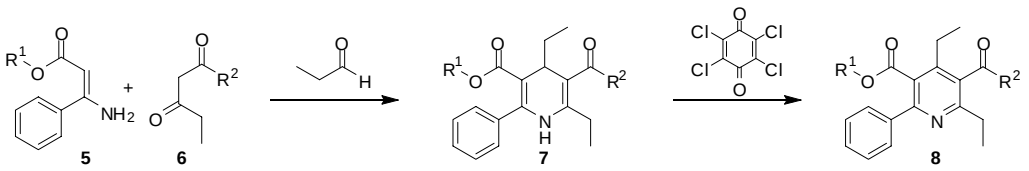


2 **3** **4**

Figure 2. Expected metabolites of FE@SUPPY

RESULTS AND DISCUSSION

In all synthetic pathways, the synthesis of the pyridine core was realized by reaction of a β-enaminoester, a β-ketoester, and an aldehyde in a straightforward Hantzsch reaction followed by oxidation of the thus resulting 1,4-dihydropyridines with tetrachloro-1,4-benzoquinone (Scheme 1, Table 1).

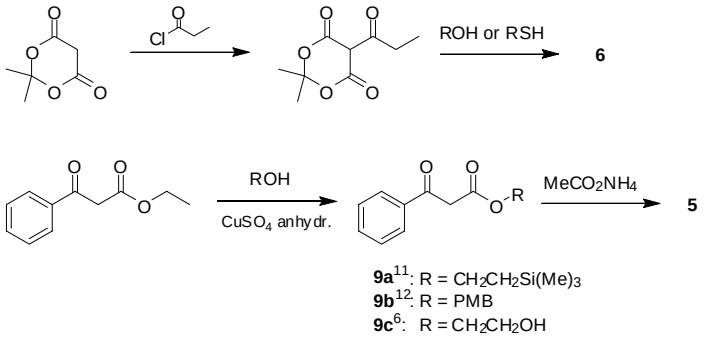


Scheme 1

	R^1	R^2		R^1	R^2
5a	$CH_2CH_2Si(Me)_3$	-	**7b**	PMB	OAllyl
5b	PMB	-	**7c**	CH_2CH_2OH	OPMB
5c[6]	CH_2CH_2OH	-	**7d**	PMB	SCH_2Me
6a	-	OPMB	**8a**	$CH_2CH_2Si(Me)_3$	OPMB
6b[8]	-	OAllyl	**8b**	PMB	OAllyl
6c[6]	-	SCH_2Me	**8c**	CH_2CH_2OH	OPMB
7a	$CH_2CH_2Si(Me)_3$	OPMB	**8d**	PMB	SCH_2Me

Table 1

β-Ketoesters (**6**) were prepared in a two-step route starting with the acylation of Meldrum's acid (Scheme 2), followed by a ring opening reaction with an appropriate alcohol and decarboxylation of the intermediately formed β-ketoacid.[9] In the synthesis of β-enaminoesters (**5**) the first reaction step consisted in the transesterification of the commercially available ethyl benzoylacetate into compound (**9**), which was realized according to Bandgar *et al* using $CuSO_4$ as catalyst.[10] The subsequent enamine formation was achieved by reaction of β-ketoesters (**9**) with ammonium acetate in a Dean-Stark trap in order to maximize yields (Scheme 2).



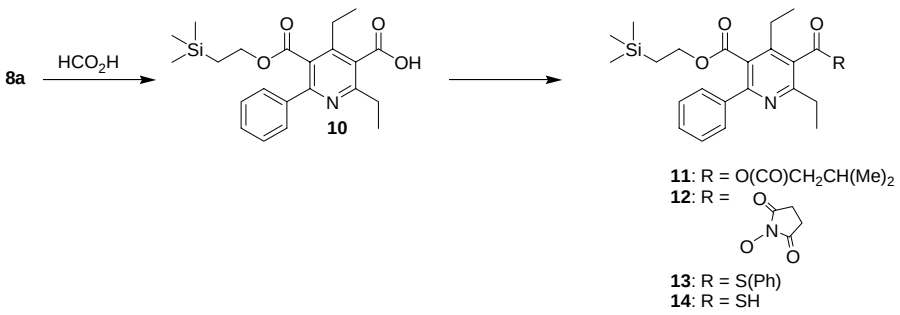
Scheme 2

The different ester groups in **8** had to be chosen carefully in order to permit selective cleavage after formation of the pyridine core, to obtain the crucial regioselective formation of the carbothioic acid group. Therefore, the fluorine-sensitive trimethylsilylethyl (TME) and the acid-sensitive *para*-methoxybenzyl esters (PMB) (**8a**) were selected at the first attempt to prepare title compound **2**.

The *para*-methoxybenzylester in compound (**8a**) was cleaved selectively with formic acid to afford

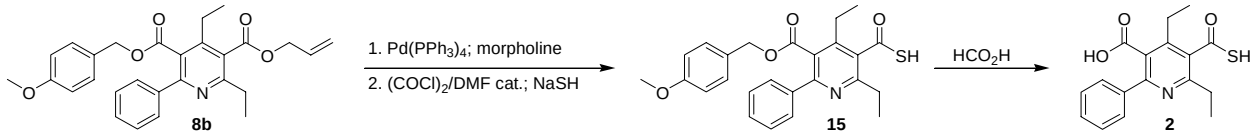
carboxylic acid (**10**). Established methods to convert **10** *via* **11**, **12**, or **13**, respectively, to thiocarboxylic acid (**14**) failed.[13,14,15]

The formation of the thiocarboxylic acid (**14**) was finally accomplished under mild conditions as described by Nomura *et al*[16] by direct sulfuration of the carboxylic acid (**10**) with P_4S_{10} catalyzed by Ph_3SbO (Scheme 3).



Scheme 3

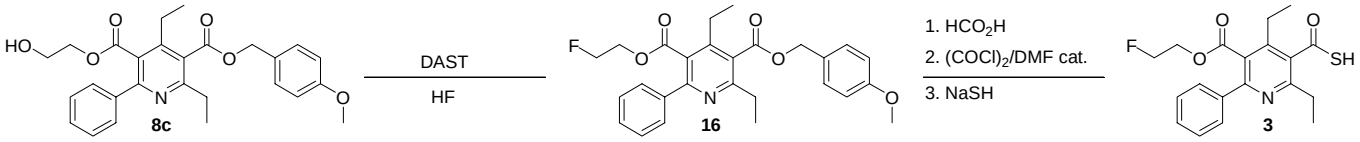
Since the subsequent attempt of the fluoride-induced cleavage of the trimethylsilylethyl ester (**14**) to **2** failed, **8b** was finally chosen as starting molecule for the synthesis of **2**. The allyl ester of **8b** was cleaved first with tetrakis(triphenylphosphine)palladium(0) exploiting the sensitivity of the allyl group towards transition metals. The resulting carboxylic acid could be easily converted to thiocarboxylic acid (**15**). Subsequently, the *para*-methoxybenzyl group was cleaved smoothly with formic acid at room temperature furnishing title compound (**2**) (Scheme 4).



Scheme 4

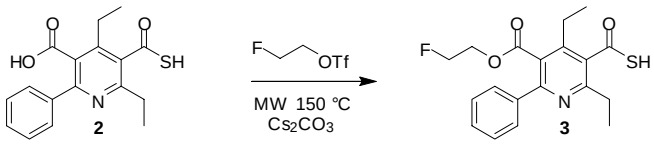
Title compound (**4**) could be made accessible by selective cleavage of the *para*-methoxybenzyl ester of **8d** again with formic acid.

Title compound (**3**) was synthesized starting from hydroxyethyl ester (**8c**), which was fluorinated with diethylaminosulfur trifluoride (DAST) to give fluoroethyl ester (**16**). The *para*-methoxybenzyl ester was treated with formic acid, thus furnishing the carboxylic acid, which was converted into carbothioic acid **3** (Scheme 5).



Scheme 5

The synthesis of derivative (**3**) was also achieved by treatment of carboxylic/carbothioic diacid (**2**) with 2-fluoroethyl trifluoromethanesulfonate under microwave-enhanced conditions. Due to the low dielectric loss (ε'') to dielectric constant (ε') ratio (tanδ = 0.062) of acetonitrile,[17] cesium ions (Cs_2CO_3) were added to improve the absorption and conversion of the microwave energy to heat by ionic conduction mechanism.[18,19] Under the investigated conditions the alkylation always occurred on the carboxylic acid and not on the thiocarboxy moiety, which can probably be explained by the stronger electronegativity of the oxygen atom and the higher acidity of the carboxylic acid. It should be emphasized that this approach appears to be well qualified also for radiochemical [^{18}F]fluoroethyl-labeling of compound **2** due to the short reaction time of only ten minutes (Scheme 6).



Scheme 6

NMR SPECTROSCOPIC INVESTIGATIONS

The NMR data of all compounds are given in the Experimental section. Complete assignment of signals of compound (**2**), (**3**), and (**4**) in ^{1}H and ^{13}C spectra was accomplished by combination of different NMR techniques. Figure 3 shows the ^3J (^{13}C, ^{1}H) - correlations used in the spectral assignment of **4**.

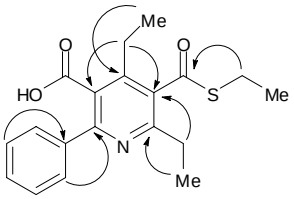


Figure 3

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS) and on a Finnigan MAT 900 S (ESI, 4 kV, 3 µA MeCN/MeOH, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR spectrum 1000 spectrometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX-200 spectrometer at 27 °C (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C), a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$), δ = 2.49 ppm (^{1}H in DMSO-d_6), δ = 77.0 ppm (^{13}C in $CDCl_3$), and δ = 39.5 ppm (^{13}C in DMSO-d_6). The starting materials were commercially available and/or prepared similar to literature procedures.

2-(Trimethylsilyl)ethyl 3-oxo-3-phenylpropanoate (**9a**)

Ethyl benzoylacetate (1.92 g, 10.00 mmol) and 2-(trimethylsilyl)ethanol (1.18 g, 10.00 mmol) were dissolved in 40 mL of toluene. After the addition of 100-200 mg of $CuSO_4$ the mixture was stirred for 72 h at 100 °C. A distillation condenser was used to remove emerging EtOH. After completion of the reaction the mixture was cooled, filtered and evaporated. The residue was chromatographed (silica gel, light petroleum ether/EtOAc 9/1) to afford **9a** as reddish liquid (2.10 g, 79 %). The spectroscopic data were in full accordance with the literature.[11]

2-(Trimethylsilyl)ethyl 3-amino-3-phenylprop-2-enoate (**5a**)

2-(Trimethylsilyl)ethyl 3-oxo-3-phenylpropanoate (**9a**) (4.01 g, 15.17 mmol) and ammonium acetate (3.51 g, 45.54 mmol) were mixed with toluene/AcOH (4/1) and refluxed for 6 h in a Dean-Stark apparatus, followed by removal of the solvent under reduced pressure and column chromatography (silica gel, light petroleum ether/EtOAc 9/1). The title compound (**5a**) was obtained as yellowish oil (3.11 g, 83 %). ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.52 (m, 2H), 7.40 (m, 3H), 4.95 (s, 1H), 4.22 (t, 2H, J = 8.32 Hz) 1.03 (t, 2H, J = 8.46 Hz), 0.06 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 170.5, 160.3, 137.7, 130.1, 128.8, 126.1, 84.8, 60.9, 17.5, -1.5. IR cm^{-1} (KBr): 3439, 3331, 3062, 2953, 2895, 1663, 1621, 1576, 1556, 1490, 1451, 1414, 1374, 1313, 1250, 1171, 1089, 1061. MS: m/z (%) 265 (M^+ + 2, 0.53), 263 (8), 221 (13), 220 (60), 145 (94), 104 (35), 91 (28), 73 (100); *Anal*. Calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04; N, 5.32. Found: C, 64.09; H, 7.93; N, 5.10.

4-Methoxybenzyl 3-oxopentanoate (6a)

To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (5.00 g, 34.72 mmol) and propionyl chloride (3.53 g, 38.15 mmol) in dry CH_2Cl_2 (70 mL), pyridine (5.49 g, 3.6 mL, 69.41 mmol) was added dropwise at 0 °C. After stirring for 1 h, the temperature was allowed to rise to rt and stirring was continued for 1 h. The reaction mixture was washed with 1N HCl (70 mL), water (40 mL) and then dried with Na_2SO_4. The solvent was evaporated and the crude product was used for the next step without further purification.

A solution of the crude product of the previous reaction and 4-methoxybenzyl alcohol (14.30 g, 103.50 mmol) was heated in toluene (100 mL) at 80 °C for 24 h. After removal of the solvent under reduced pressure, the remaining oil was subjected to column chromatography (silica gel, light petroleum ether/EtOAc 9/1) to afford 4.18 g (51 %) of **6a** as yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.29 (d, 2H, *J* = 6.68 Hz), 6.88 (d, 2H, *J* = 6.82 Hz), 5.09 (s, 2H), 3.78 (s, 3H) 3.45 (s, 2H), 2.51 (q, 2H, *J* = 7.34 Hz), 1.04 (t, 3H, *J* = 7.18 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 202.9, 167.0, 159.5, 130.0, 127.3, 113.7, 66.6, 55.0, 48.7, 36.0, 7.3. IR cm^{-1} (KBr): 2977, 2940, 2908, 2838, 1743, 1716, 1614, 1516, 1461, 1412, 1304, 1248, 1176, 1157, 1109, 1060, 1033, 965. MS: m/z (%) 236 (M^+, 11), 137 (76), 122 (9), 121 (100), 91 (10), 78 (12), 77 (15), 57 (12). *Anal*. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; Found: C, 65.95; H, 6.81.

4-Methoxybenzyl 3-amino-3-phenylprop-2-enoate (5b)

A mixture of 4-methoxybenzyl 3-oxo-3-phenylpropanoate (**9b**)[12] (5.80 g, 20.40 mmol) and ammonium acetate (7.86 g, 101.97 mmol) in toluene (100 mL) was refluxed overnight using a Dean-Stark trap. The solvent was removed *in vacuo* and the residue was submitted to column filtration (silica gel, light petroleum ether/EtOAc 8/2). The resulting crude product was used for the next step without further purification.

Allyl 3-oxopentanoate (4b)

To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (5.00 g, 34.69 mmol) and propionyl chloride (3.53 g, 38.15 mmol) in dry CH_2Cl_2 (70 mL), pyridine (5.49 g, 3.6 mL, 69.41 mmol) was added dropwise at 0 °C. After stirring for 1 h, the temperature was allowed to rise to rt and stirring was continued for 1 h. The reaction mixture was washed with 1N HCl (70 mL), water (40 mL) and was then dried with Na_2SO_4. The solvent was evaporated and the residue was used for the next step without further purification.

The crude product and allyl alcohol (6.01 g, 103.48 mmol) were dissolved in toluene (100 mL) and heated at 80 °C for 24 h. After removal of the solvent and excess allyl alcohol under reduced pressure, the remaining oil was subjected to column chromatography (silica gel, light petroleum ether/EtOAc 9/1) to afford 3.36 g (62 %) of **4b** as liquid. The spectroscopic data were in full accordance with the literature.[8]

3-(4-Methoxybenzyl) 5-[2-(trimethylsilyl)ethyl] 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**7a**)

A solution of 4-methoxybenzyl 3-oxopentanoate (**6a**) (1.35 g, 5.71 mmol), 2-(trimethylsilyl)ethyl 3-amino-3-phenylprop-2-enoate (**5a**) (1.51 g, 5.71 mmol) and propionaldehyde (0.32 g, 5.71 mmol) in 15 mL of absolute EtOH was stirred for 24 h in a sealed tube at 80 °C. After the solvent was removed under reduced pressure, the obtained crude product was chromatographed (silica gel, light petroleum ether/EtOAc 9/1) to afford 1.66 g (56 %) of **7a** as viscous liquid. For spectroscopic purposes 100 mg of this crude product were purified by preparative TLC (reversed phase C-18 silica gel MeCN/water 9/1). ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.35 (m, 7H), 6.89 (m, 2H), 5.85 (s, 1H), 5.13 (m, 2H) 4.06 (t, 1H, *J* = 5.42 Hz), 3.95 (m, 2H), 3.81 (s, 3H), 2.71 (m, 2H), 1.51 (m, 2H), 1.16 (t, 3H, *J* = 7.46 Hz), 0.87 (t, 3H, *J* = 7.32 Hz), 0.67 (m, 2H),- 0.05 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 167.4, 167.3, 159.2, 151.0, 146.6, 137.1, 129.6, 128.9, 128.2, 128.1, 113.7, 103.3, 101.2, 65.2, 61.7, 55.2, 34.3, 29.1, 25.9, 16.8, 13.0, 9.0, -1.6. IR cm^{-1} (KBr): 3312, 2956, 1682, 1614, 1515, 1485, 1249. MS: m/z (%) 522 (M^++ 1, 0.21), 521 (0.27), 493 (17), 492 (45), 464 (13), 392 (23), 122 (10), 121 (100), 77 (10), 73 (48). HRMS Calcd for $C_{28}H_{34}NO_5Si$ (M^+- C_2H_5): 492.2201. Found: 492.2180.

3-(4-Methoxybenzyl) 5-[2-(trimethylsilyl)ethyl] 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (8a)

Tetrachloro-1,4-benzoquinone (3.23 g, 13.14 mmol) and 3-(4-methoxybenzyl) 5-[2-(trimethylsilyl)ethyl] 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**7a**) (1.71 g, 3.28 mmol) in THF (50 mL) were refluxed overnight. Afterwards, the solvent was removed *in vacuo* and purified by column chromatography (silica gel, light petroleum ether/EtOAc 11/1). A sample was purified for spectroscopic purposes by reversed phase column chromatography (RP-18 silica gel, MeCN/water 8/2) giving 1.46 g (85 %) of **8a** as colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.56 (m, 2H), 7.40 (m, 5H), 6.91 (d, 2H, *J* = 8.58 Hz), 5.35 (s, 2H), 4.09 (m, 2H) 3.82 (s, 3H), 2.76 (q, 2H, *J* = 7.48 Hz), 2.62 (q, 2H, *J* = 7.44 Hz), 1.25 (t, 3H, *J* = 7.44 Hz), 1.14 (t, 3H, *J* = 7.58 Hz), 0.63 (m, 2H), -0.05 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.7, 168.4, 160.1, 159.9, 156.7, 148.4, 139.8, 130.8, 128.7, 128.4, 128.3, 127.3, 127.1, 126.7, 114.0, 67.4, 63.9, 55.3, 29.7, 24.6, 16.8, 15.2, 13.8, -1.7. IR cm^{-1} (KBr): 2954, 1724, 1612, 1562, 1515, 1463, 1251. MS: m/z (%) 520 (M^+ + 1, 1), 519 (3), 402 (2), 398 (2), 370 (3), 298 (2), 254 (3), 208 (3), 122 (10), 121 (100), 77 (5), 73 (28). *Anal*. Calcd for $C_{30}H_{37}NO_5Si$: C, 69.33; H, 7.18; N, 2.70. Found: C, 69.38; H, 6.95; N, 2.43. HRMS Calcd for $C_{30}H_{25}NO_5Si$: 519.2441. Found: 519.2437.

2,4-Diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carboxylic acid (**10**)

3-(4-Methoxybenzyl) 5-[2-(trimethylsilyl)ethyl] 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (**8a**) (1.20 g, 2.31 mmol) was stirred in formic acid (5.5 mL) for 5 h. Subsequently, formic acid was removed

under reduced pressure and the residue was purified by column chromatography (RP-18 silica gel, MeCN/water 9/1) furnishing 734 mg (80 %) of **10** as colorless crystals. Mp 169 – 171 °C. ^{1}H-NMR (200 MHz, DMSO): δ (ppm) 13.86 (s, 1H), 7.48 (m, 5H), 4.12 (t, 2H, *J* = 7.94 Hz), 2.73 (m, 4H), 1.20 (m, 6H), 0.67 (t, 2H, *J* = 8.20 Hz), -0.08 (s, 9H); ^{13}C-NMR (50 MHz, DMSO): δ (ppm) 169.3, 168.0, 158.6, 155.0, 146.7, 139.3, 128.9, 128.8, 128.3, 128.1, 126.3, 63.6, 28.9, 24.2, 16.3, 15.1, 13.4, -1.7. IR cm^{-1} (KBr): 3420, 2951, 2878, 2451, 1959, 1720, 1562, 1454. MS: m/z (%) 399 (M^+, 17), 371 (20), 356 (21), 342 (17), 326 (15), 298 (38), 282 (43), 73 (100). *Anal*. Calcd for $C_{22}H_{29}NO_4Si$: C, 66.13; H, 7.32; N, 3.51. Found: C, 65.99; H, 7.33; N, 3.41.

2-(Trimethylsilyl)ethyl 4,6-diethyl-5-({[(2-methylpropoxy)carbonyl]oxy}carbonyl)-2-phenylpyridine-3-carboxylate (11)

To a solution of 2,4-diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carboxylic acid (**10**) (0.74 g, 1.85 mmol) in THF (40 mL), triethylamine (TEA) (0.38 g, 3.76 mmol, 0.51 mL) and isobutyl carbonochloridate (0.25 g, 1.83 mmol, 0.24 mL) were added at -10 °C. The mixture was stirred for 2.5 h, filtrated and concentrated *in vacuo*. The residue was purified by column chromatography (RP-18 silica gel, MeCN/water 9/1) to furnish 900 mg (98 %) of **11** as colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.60 (m, 2H), 7.42 (m, 3H), 4.13 (m, 4H), 2.95 (q, 2H, *J* = 7.44 Hz) 2.80 (q, 2H, *J* = 7.44 Hz), 2.90 (m, 1H), 1.32 (m, 6H), 1.01 (d, 6H, *J* =6.70 Hz), 0.66 (m, 2H), -0.04 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.3, 163.2, 160.5, 157.7, 149.3, 148.6, 139.5, 129.0, 128.4, 128.3, 126.8, 124.8, 76.1, 64.2, 29.9, 27.6, 24.7, 18.7, 16.8, 15.4, 15.2, 13.7, -1.7. IR cm^{-1} (KBr): 2960, 2898, 2879, 1810, 1759, 1724, 1562, 1468, 1411, 1372, 1243, 1208, 1172, 1145, 1078, 1053, 1000, 940. MS: m/z (%) 501 (M^+ + 2, 0.43), 500 (2), 456 (6), 382 (57), 370 (18), 282 (33), 280 (25), 236 (25), 73 (100), 57 (58), 41 (28). *Anal*. Calcd for $C_{27}H_{37}NO_6Si$: C, 64.90; H, 7.46; N, 2.80. Found: C, 65.11; H, 7.40; N, 2.72.

2-(Trimethylsilyl)ethyl 5-{[(2,5-dioxopyrrolidin-1-yl)oxy]carbonyl}-4,6-diethyl-2-phenylpyridine--3-carboxylate (12)

2,4-Diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carboxylic acid (**10**) (2.28 g, 5.71 mmol) was dissolved in 110 mL of abs. THF. Afterwards, *N*-hydroxysuccinimide (0.79 g, 6.86 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride EDC (1.42 g, 7.41 mmol) were added to the solution and the resulting mixture was stirred at rt for 2 d. The solvent was removed by evaporation and the residue was dissolved in CH_2Cl_2 and washed with brine. The CH_2Cl_2 layer was separated, dried over anhydrous sodium sulfate, and evaporated to dryness. Recrystallization from petroleum ether/EtOAc afforded 2.69 g (95 %) of **12** as colorless crystals. Mp 139 – 140 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.62 (m, 2H), 7.42 (m, 3H), 4.13 (m, 2H), 3.07 (q, 2H, *J* = 7.44 Hz),

2.88 (m, 6H), 1.33 (m, 6H), 0.67 (m, 2H), -0.04 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.9, 168.2, 164.0, 161.6, 158.2, 150.5, 139.4, 129.0, 128.3, 126.7, 122.1, 64.2, 29.9, 25.7, 24.9, 16.8, 15.6, 14.1, -1.7. IR cm^{-1} (KBr): 3512, 3408, 2969, 2877, 2869, 1810, 1784, 1743, 1714, 1564, 1462, 1425, 1405, 1361, 1253. MS: m/z (%) 497 (M^+ + 1, 6), 496 (1), 383 (23), 382 (85), 355 (27), 354 (100), 282 (60), 264 (41), 236 (39), 73 (96). *Anal*. Calcd for $C_{26}H_{32}N_2O_6Si$: C, 62.88; H, 6.49; N, 5.64. Found: C, 62.61; H, 6.42; N, 5.50.

2-(Trimethylsilyl)ethyl 4,6-diethyl-2-phenyl-5-[(phenylsulfanyl)carbonyl]pyridine-3-carboxylate (**13**)

A solution of 2,4-diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carboxylic acid (**10**) (0.62 g, 1.55 mmol) in dry CH_2Cl_2 (7 mL) was treated with $SOCl_2$ (2.6 mL) and heated at reflux overnight under argon. After cooling to rt, the reaction mixture was concentrated under reduced pressure and the residue was dried under vacuum to remove traces of $SOCl_2$. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and added to a cooled (0 °C) solution of thiophenol (0.17 g, 1.55 mmol, 0.16 mL) and pyridine (0.12 g, 1.55 mmol, 0.13 mL) in CH_2Cl_2 (5 mL). After 5 min at 0 °C the reaction mixture was stirred at rt until completion (TLC). Then, it was washed with water and after separation of the layers, the aqueous phase was again extracted with CH_2Cl_2. The combined organic extracts were dried over sodium sulfate and after evaporation of the solvent to dryness, the residue was purified by column chromatography (RP-18 silica gel MeCN/water 9/1) to furnish 400 mg (52 %) of **13** as yellowish oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.53 (m, 10H), 4.14 (m, 2H), 3.01 (q, 2H, J = 7.56 Hz), 2.86 (q, 2H, J = 7.46 Hz), 1.35 (m, 6H), 0.67 (m, 2H), -0.02 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 193.6, 168.5, 159.2, 157.2, 148.0, 139.7, 134.3, 132.6, 129.9, 129.5, 128.8, 128.4, 128.3, 127.1, 126.7, 64.0, 29.3, 24.3, 16.8, 15.7, 14.0, -1.7. IR cm^{-1} (KBr): 3057, 2968, 2876, 1730, 1713, 1689, 1558, 1449, 1403, 1378, 1314, 1272, 1248, 1217, 1165, 1144, 1074, 1044. MS: m/z (%) 491 (M^+ + 1, 0.22), 449 (1), 448 (4), 383 (27), 382 (100), 354 (26), 282 (52), 264 (25), 236 (29), 109 (27), 73 (86). *Anal*. Calcd for $C_{28}H_{33}NO_3SSi$: C, 68.39; H, 6.67; N, 2.85. Found: C, 68.12; H, 6.87; N, 2.77.

2,4-Diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carbothioic *S*-acid (**14**)

To a suspension of P_4S_{10} (0.046 g, 0.13 mmol) and Ph_3SbO (0.028 g, 0.06 mmol) in 10 mL of benzene, was added 2,4-diethyl-6-phenyl-5-{[2-(trimethylsilyl)ethoxy]carbonyl}pyridine-3-carboxylic acid (**10**) (0.50 g, 1.25 mmol). The mixture was refluxed for 12 h and after cooling the solvent was removed under reduced pressure. The residue was applied onto a reversed phase silica gel column (RP-18 silica gel MeCN /water 9/1) for purification to obtain 327 mg (63 %) of **14** as pinkish oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.65 (m, 2H), 7.43 (m, 3H), 4.15 (m, 2H), 2.98 (m, 4H), 2.16 (s, 1H) 1.34 (m, 6H), 0.69 (m, 2H), -0.02 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 190.5, 169.3, 160.9, 159.0, 150.1, 140.5,

131.5, 130.0, 129.8, 129.5, 129.4, 128.0, 65.3, 30.4, 25.3, 17.9, 16.9, 15.2, -0.68. IR cm^{-1} (KBr): 3423, 2953, 2897, 1723, 1557, 1451, 1404, 1378, 1278, 1250, 1166, 1144, 1075. MS: m/z (%) 416 (M^+ + 1, 0.43), 415 (1), 414 (0.31), 413 (0.19), 385 (41), 383 (20), 382 (65), 354 (27), 296 (19), 282 (32), 236 (16), 73 (100). *Anal*. Calcd for $C_{22}H_{29}NO_3SSi$: C, 68.58; H, 7.03; N, 3.37. Found: C, 63.47; H, 6.79; N, 3.29.

3-Allyl 5-(4-methoxybenzyl) 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**7b**)

4-Methoxybenzyl 3-amino-3-phenylprop-2-enoate (**5b**) (2.57 g, 9.07 mmol), allyl 3-oxopentanoate (**6b**) (1.42 g, 9.07 mmol) and propionaldehyde (0.53 g, 9.07 mmol) were dissolved in 20 mL of absolute EtOH. The mixture was sealed in a Pyrex tube and stirred for 24 h at 80 °C. After cooling to rt, the solvent was evaporated and the oily residue was purified by column chromatography (silica gel, light petroleum ether/EtOAc 8/2) to give 3.61 g (86 %) of **7b** as greenish-yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.31 (m, 5H), 6.93 (d, 2H, *J* = 8.58 Hz), 6.76 (m, 2H, *J* = 8.58 Hz), 5.99 (m, 2H), 5.26 (m, 2H), 4.87 (d, 2H, *J* = 4.16 Hz), 4.65 (m, 2H), 4.10 (t, 2H, *J* = 4.44 Hz), 3.80 (s, 3H), 2.73 (m, 2H), 1.57 (m, 2H), 1.20 (t, 3H, *J* = 7.44 Hz), 0.94 (t, 3H, *J* = 7.38 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 167.6, 167.5, 159.5, 151.5, 147.4, 137.5, 133.3, 129.9, 129.5, 128.8, 128.7, 117.7, 113.9, 103.3, 101.7, 65.8, 64.8, 55.7, 34.9, 29.5, 26.3, 13.4, 9.6. IR cm^{-1} (KBr): 3418, 3323, 3055, 2963, 2934, 1684, 1615, 1516, 1464, 1442, 1266, 1248, 1207, 1110, 1086, 1066. MS: m/z (%) 460 (M^+ + 1, 1), 459 (2), 402 (2), 338 (1), 294 (7), 236 (1), 208 (2), 122 (19), 121 (100), 91 (3), 77 (4). *Anal*. Calcd for $C_{28}H_{31}NO_5 \cdot 0.2\ H_2O$: C, 72.30; H, 6.80; N, 3.01. Found: C, 72.41; H, 6.91; N, 2.91.

3-Allyl 5-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (**8b**)

A mixture of 3-allyl 5-(4-methoxybenzyl) 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**7b**) (3.61 g, 7.82 mmol) and tetrachloro-1,4-benzoquinone (2.13 g, 8.66 mmol) in THF (120 mL) was refluxed overnight. After the reaction mixture was allowed to cool, the solvent was removed *in vacuo* and purified by column chromatography (silica gel, light petroleum ether/EtOAc 9/1). A sample was subjected to reversed phase column chromatography (RP-18 silica gel MeCN/water 8/2) for spectroscopic purposes giving 1.70 g (47 %) of **8b** as an orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.60 (m, 2H), 7.38 (m, 3H), 6.94 (d, 2H, *J* = 8.70 Hz), 6.76 (d, 2H, *J* = 8.72 Hz), 6.04 (m, 2H) 5.41 (m, 2H), 5.00 (s, 2H), 4.86 (d, 2H, *J* = 6.06 Hz), 3.77 (s, 3H), 2.84 (q, 2H, *J* = 7.58 Hz), 2.67 (q, 2H, *J* = 7.58 Hz), 1.32 (t, 3H, *J* = 7.46 Hz), 1.19 (t, 3H, *J* = 7.46 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.3, 168.1, 160.2, 159.6, 156.7, 148.6, 139.7, 131.1, 130.3, 128.7, 128.3, 128.3, 127.2, 126.6, 126.2, 119.9, 113.7, 67.3, 66.3, 55.2, 29.7, 24.6, 15.2, 13.8. IR cm^{-1} (KBr): 2975, 2940, 2880, 2837, 1728, 1613, 1561, 1516, 1455, 1412, 1367, 1249, 1224, 1200, 1176, 1148, 1105, 1073, 1024, 973. MS: m/z (%) 462 (M^+ + 1, 0.10), 461 (0.12),

433 (22), 432 (74), 326 (14), 226 (15), 121 (100), 77 (14). *Anal*. Calcd for $C_{28}H_{29}NO_5 \cdot 0.4\ H_2O$: C, 72.05; H, 6.44; N, 3.00. Found: C, 72.06; H, 6.23; N, 2.94.

2,4-Diethyl-5-{[(4-methoxybenzyl)oxy]carbonyl}-6-phenylpyridine-3-carbothioic *S*-acid (18)

A solution of 3-allyl 5-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (**8b**) (0.93 g, 2.02 mmol) in 15 mL THF was stirred under an argon atmosphere at rt and tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.24 mmol, 10 mol %) and morpholine (2.11 g, 24.21 mmol, 2.12 mL) were added subsequently. After 30 min. the solvent was evaporated and the residue was dissolved in 2 N NaOH. The resulting solution was washed with CH_2Cl_2 and then, the aqueous phase was acidified with 6 N HCl and again extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The remaining residue was chromatographed (silica gel, light petroleum ether/EtOAc 8/2) giving 806 mg (95 %) of the carboxylic acid as yellowish crystals. Mp 137 – 139 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.53 (m, 2H), 7.32 (m, 3H), 6.87 (d, 2H, *J* = 8.60 Hz), 6.72 (d, 2H, *J* = 8.58 Hz), 4.93 (s, 2H), 3.74 (s, 3H), 2.75 (m, 4H), 1.17 (m, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 170.2, 168.8, 160.3, 159.8, 155.9, 147.9, 140.1, 131.4, 129.9, 129.8, 129.4, 129.0, 127.6, 126.9, 114.7, 68.0, 56.0, 29.9, 25.1, 16.1, 14.4. IR cm^{-1} (KBr): 3422, 2974, 2939, 2879, 1724, 1613, 1560, 1516, 1458, 1383, 1304, 1246, 1177, 1124, 1032. MS: m/z (%) 420 (M^+ + 1, 3), 419 (10), 278 (14), 277 (19), 144 (15), 122 (14), 121 (100), 100 (22), 86 (20), 77 (15), 57 (41). HRMS Calcd for $C_{25}H_{25}NO_5$: 419.1733. Found: 419.1727.

To 2,4-diethyl-5-{[(4-methoxybenzyl)oxy]carbonyl}-6-phenylpyridine-3-carboxylic acid (1.00 g, 2.38 mmol) from the previous reaction in benzene (10 mL) at -10 °C were added slowly oxalyl chloride (1 mL) and 1 drop of DMF. The solution was allowed to warm up to rt and stirring was continued for 2 h. Afterwards the solvent was removed under reduced pressure and the oily residue was coevaporated with toluene (three times). The acid chloride was used without further purification for the next reaction step.

NaSH hydrate (0.36 g, 6.45 mmol) was dissolved in absolute EtOH (10 mL) at -10 °C. Then, a solution of the crude acid chloride (**15**) in THF (4 mL) was added slowly. The reaction mixture was allowed to warm up to rt and stirring was continued for 1 h. The mixture was acidified with 6 N HCl, extracted with EtOAc, washed with brine twice and dried over Na_2SO_4. After evaporation of the solvent, the solid crude product was subjected to column chromatography (silica gel, light petroleum ether/EtOAc 8/2) to afford 480 mg (46 %) of **18** as brownish crystals. Mp 59 – 60 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.62 (m, 2H), 7.41 (m, 3H), 5.04 (s, 2H), 3.79 (s, 3H), 3.02 (q, 2H, *J* = 7.45 Hz), 2.88 (q, 2H, *J* = 7.3 Hz), 1.38 (t, 2H, *J* = 7.44 Hz), 1.23 (t, 2H, *J* = 7.45 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 189.3, 168.0, 160.0, 159.7, 158.0, 149.2, 139.3, 130.4, 129.1, 128.5, 128.4, 126.5, 113.8, 67.6, 55.2, 29.4, 24.3, 15.8, 14.2. IR cm^{-1} (KBr): 3403, 2973, 2936, 2877, 2836, 1725, 1613, 1556, 1515, 1462, 1403, 1376, 1303, 1246, 1165, 1142,

1074, 1034, 962. MS: m/z (%) 436 (M^+ + 1, 3), 435 (9), 432 (21), 402 (23), 311 (5), 121 (100), 76 (10). HRMS Calcd for $C_{25}H_{25}NO_4S$: 435.1504. Found: 435.1515.

4,6-Diethyl-2-phenyl-5-(sulfanylcarbonyl)pyridine-3-carboxylic acid (**2**)

2,4-Diethyl-5-{[(4-methoxybenzyl)oxy]carbonyl}-6-phenylpyridine-3-carbothioic *S*-acid (**15**) was stirred at rt in formic acid (5 mL) for 3 h. Subsequently, the formic acid was evaporated and the residue was dissolved in 2 N NaOH. The resulting solution was washed with CH_2Cl_2, acidified with 6 N HCl and again extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the crude product, which was purified by column chromatography (RP-18 silica gel MeCN/water 9/1) giving 200 mg (27 %) of **2** as colorless crystals. Mp 191 °C (decomp.). ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 13.84 (s, 1H, $CO_2\underline{H}$), 7.69 (m, 2H, Ph H-2/H-6), 7.49 (m, 3H, Ph H-3/H-4/H-5,), 2.92 (q, 2H, J = 7.50 Hz, C-6C$\underline{H}_2$), 2.82 (q, 2H, J = 7.50 Hz, C-4C$\underline{H}_2$) 1.30 (t, 3H, J = 7.50 Hz, C-6CH$_2\underline{Me}$), 1.21 (t, 3H, J = 7.50 Hz, C-4CH$_2\underline{Me}$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 189.8 (C=OSH), 168.9 ($\underline{C}O_2$), 158.3 (C-6), 156.2 (C-2), 147.4 (C-4), 138.8 (Ph C-1), 129.8 (C-5), 129.3 (Ph C-4), 128.3 (Ph C-2/C-3/C-5/C-6), 28.6 (C-6$\underline{C}H_2$), 23.9 (C-4$\underline{C}H_2$), 15.6 (C-4CH$_2\underline{Me}$), 13.7 (C-6CH$_2\underline{Me}$). IR cm^{-1} (KBr): 3414, 2977, 2939, 2878, 2580, 2498, 1958, 1910, 1720, 1551, 1448, 1250, 1172. MS: m/z (%) 317 (M^+ + 2, 1), 315 (9), 313 (100), 284 (11), 283 (16), 282 (97), 252 (14), 180 (10), 125 (27), 77 (35), 51 (14). *Anal*. Calcd for $C_{17}H_{17}NO_3S$•0.3 H_2O: C, 63.65; H, 5.53; N, 4.37. Found: C, 63.67; H, 5.44; N, 4.31.

2,4-Diethyl-5-[(2-fluoroethoxy)carbonyl]-6-phenylpyridine-3-carbothioic *S*-acid (**3**)

To a suspension of 4,6-diethyl-2-phenyl-5-(sulfanylcarbonyl)pyridine-3-carboxylic acid (**2**) (0.103 g, 0.33 mmol) and Cs_2CO_3 (0.215 g, 0.66 mmol) in MeCN (10-15 mL) was added 2-fluoroethyl trifluoromethanesulfonate (0.14 g, 0.72 mmol). The mixture was heated in a microwave oven to 150 °C (300 W) for 10 min. Afterwards, the reaction mixture was concentrated and the residue was purified by column chromatography (RP-18 silica gel, MeCN) to give 0.113 g (95 %) of **3** as colorless crystals. Mp 45 – 47 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (m, 2H, Ph H-2, H-6), 7.46 (m, 3H, Ph H-3, H-4, H-5), 4.39/4.29 (m, 2H, FC$\underline{H}_2$), 4.34/4.29 (m, 2H, CH_2O), 3.05 (q, 2H, J = 7.50 Hz, C-2C$\underline{H}_2$), 2.93 (q, 2H, J = 7.50 Hz, C-4C$\underline{H}_2$) 1.40 (t, 3H, J = 7.50 Hz, C-2CH$_2\underline{Me}$), 1.29 (t, 3H, J = 7.50 Hz, C-4CH$_2\underline{Me}$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 189.3 (C=OSH), 167.9 ($\underline{C}O_2$), 160.4 (C-2), 158.3 (C-6), 149.5 (C-4), 139.3 (Ph C-1), 130.6 (C-3), 129.3 (Ph C-4), 128.5 (Ph C-3, C-5), 128.3 (Ph C-2, C-6), 126.2 (C-5), 80.5 (d, F$\underline{C}H_2$, J = 172.0 Hz), 64.5 (d, $\underline{C}H_2O$, J = 20.2 Hz), 29.5 (C-2$\underline{C}H_2$), 24.4 (C-4$\underline{C}H_2$), 15.9 (C-4CH$_2\underline{Me}$), 14.3 (C-2CH$_2\underline{Me}$). IR cm^{-1} (KBr): 3439, 2975, 2938, 2877, 1731, 1556, 1495, 1448, 1403, 1377, 1278, 1250, 1166, 1144, 1077, 1060, 1033, 960. MS: m/z (%) 362 (M^+ + 1, 1), 361 (3), 359 (31), 329 (21), 328

(100), 312 (14), 254 (15), 236 (12), 77 (20), 47 (48). *Anal*. Calcd for $C_{19}H_{20}FNO_3S$•0.2 H_2O: C, 62.52; H, 5.63; N, 3.84. Found: C, 62.45; H, 5.44; N, 3.73.

4-Methoxybenzyl 4,6-diethyl-5-[(ethylsulfanyl)carbonyl]-2-phenyl-1,4-dihydropyridine-3-carboxylate (7d)

4-Methoxybenzyl 3-amino-3-phenylprop-2-enoate (**5b**) (12.00 g, 42.35 mmol), S-ethyl 3-oxopentanethioate (**6c**)[9] (6.79 g, 42.35 mmol), and propionaldehyde (2.46 g, 42.35 mmol) were dissolved in absolute EtOH and heated at 80 °C in a sealed tube for 24 h. After completion of the reaction, EtOH was removed *in vacuo* and the remaining oil was purified by column chromatography (silica gel, light petroleum ether/EtOAc 9/1) to furnish 12.60 g (64 %) of **7d** as greenish-yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.33 (m, 5H), 6.95 (d, 2H, *J* = 8.58 Hz), 6.76 (d, 2H, *J* = 8.70 Hz), 5.91 (s, 1H), 4.90 (m, 2H), 4.22 (t, 1H, *J* = 5.80 Hz), 3.80 (s, 3H), 2.93 (q, 2H, *J* = 7.34 Hz), 2.70 (m, 2H), 1.59 (m, 2H), 1.24 (m, 6H), 0.92 (t, 3H, *J* = 7.32 Hz; ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 190.8, 166.9, 159.0, 147.7, 146.6, 136.8, 129.4, 129.2, 128.4, 128.3, 113.5, 109.2, 102.9, 65.3, 55.2, 35.1, 29.4, 26.0, 23.0, 14.8, 12.8, 9.3. IR cm^{-1} (KBr): 3290, 2960, 2926, 2870, 1644, 1595, 1517, 1476, 1388, 1301, 1247, 1247, 1246, 1230, 1174, 1149, 1100, 1079, 1038, 973. MS: m/z (%) 466 (M^+ + 1, 0.11), 465 (0.19), 437 (19), 436 (65), 404 (6), 330 (11), 218 (4), 210 (16), 182 (11), 122 (9), 121 (100), 77 (15). HRMS Calcd for $C_{25}H_{26}NO_4S$: (M^+ - C_2H_5) 436.1582. Found: 436.1587.

4-Methoxybenzyl 4,6-diethyl-5-[(ethylsulfanyl)carbonyl]-2-phenylpyridine-3-carboxylate (8d)

A mixture of 4-methoxybenzyl 4,6-diethyl-5-[(ethylsulfanyl)carbonyl]-2-phenyl-1,4-dihydropyridine-3-carboxylate (**7d**) (12.60 g, 27.05 mmol) and tetrachloro-1,4-benzoquinone (7.32 g, 29.77 mmol) in THF (500 mL) was refluxed overnight. Subsequently, the solvent was evaporated and the oily residue was subjected to column chromatography (silica gel, light petroleum ether/EtOAc 8/2) to afford 8.50 g (68 %) of **8d** as colorless crystals. Mp 45 – 47 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.61 (m, 2H), 7.39 (m, 3H), 6.93 (d, 2H, *J* = 8.58 Hz), 6.76 (d, 2H, *J* = 8.58 Hz), 5.00 (s, 2H), 3.75 (s, 3H), 3.12 (q, 2H, *J* = 7.32 Hz), 2.88 (q, 2H, *J* = 7.56 Hz), 2.71 (q, 2H, *J* = 7.44 Hz), 1.29 (m, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 195.1, 168.2, 159.6, 159.2, 156.7, 147.9, 139.6, 133.0, 130.3, 128.7, 128.3, 126.5, 126.2, 113.7, 67.3, 55.1, 29.0, 24.4, 24.0, 15.6, 14.4, 13.9. IR cm^{-1} (KBr): 3428, 2973, 2935, 1725, 1663, 1613, 1560, 1517, 1463, 1411, 1372, 1278, 1245, 1170, 1150, 1076, 1076, 1034, 982. MS: m/z (%) 464 (M^+ + 1, 0.25), 463 (1), 403 (13), 402 (46), 236 (9), 122 (10), 121 (100), 91 (6), 78 (5), 77 (9). HRMS Calcd for $C_{27}H_{29}NO_4S$: 463.1817. Found: 463.1826.

4,6-Diethyl-5-[(ethylsulfanyl)carbonyl]-2-phenylpyridine-3-carboxylic acid (4)

4-Methoxybenzyl 4,6-diethyl-5-[(ethylsulfanyl)carbonyl]-2-phenylpyridine-3-carboxylate (**8d**) (2.70 g, 5.82 mmol) was dissolved in formic acid (25 mL) and stirred for 4 h at rt, followed by gentle removal of HCO_2H by Kugelrohr distillation at rt. The obtained solid was recrystallized from Et_2O to give 1.70 g (85 %) of **4** as colorless crystals. Mp 200 – 202 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 13.20 (br s, 1H, $CO_2\underline{H}$), 7.65 (m, 2H, Ph H-2/H-6), 7.45 (m, 3H, Ph H-3/H-4/H-5), 3.12 (q, 2H, J = 7.30 Hz, $SC\underline{H}_2$), 2.76 (q, 2H, J = 7.50 Hz, C-6$C\underline{H}_2$), 2.66 (q, 2H, J = 7.50 Hz, C-4$C\underline{H}_2$), 1.32 (t, 3H, J = 7.50 Hz, $SCH_2\underline{Me}$), 1.24 (t, 3H, J = 7.50 Hz, C-6$CH_2\underline{Me}$), 1.17 (t, 3H, J = 7.50 Hz, C-4$CH_2\underline{Me}$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ (ppm) 194.8 ($\underline{C}OS$, $^3J_{CO,SCH_2}$ = 4.90 Hz), 169.2 ($\underline{C}O_2$), 157.6 (C-6, $^2J_{C\text{-}6,CH_2}$ = 5.20 Hz, $^3J_{C\text{-}6,CH_3}$ = 5.20 Hz), 155.0 (C-2), 146.2 (C-4, $^2J_{C\text{-}4,CH_2}$ = 4.90 Hz, $^3J_{C\text{-}4,Me}$ = 4.90 Hz), 139.1 (Ph C-1), 132.6 (C-5), 132.6 (Ph C-4), 128.3 (Ph C-3/C-5), 128.2 (Ph C-2/Ph C-6), 127.9 (C-3), 28.2 (C-6$\underline{C}H_2$, $^1J_{CH_2}$ = 127.70 Hz, $^2J_{\underline{CH_2},Me}$ = 4.40 Hz), 24.2 ($S\underline{C}H_2$, $^1J_{CH_2}$ = 142.70 Hz, $^2J_{\underline{CH_2},Me}$ = 4.60 Hz), 23.6 (C-4$\underline{C}H_2$, $^1J_{CH_2}$ = 129.40 Hz, $^2J_{\underline{CH_2},Me}$ = 4.30 Hz), 15.5 (C-4$CH_2\underline{Me}$, $^1J_{Me}$ = 128.30 Hz, $^2J_{\underline{Me},CH_2}$ = 5.40 Hz), 14.4 ($SCH_2\underline{Me}$, $^1J_{Me}$ = 128.30 Hz, $^2J_{\underline{Me},CH_2}$ = 3.50 Hz), 13.7 (C-6$CH_2\underline{Me}$, $^1J_{Me}$ = 127.80 Hz, $^2J_{\underline{Me},CH_2}$ = 5.10 Hz). IR cm^{-1} (KBr): 3443, 2977, 2491, 1925, 1711, 1661, 1555, 1453, 1413, 1376, 1260, 1184, 1149, 1078. MS: m/z (%) 344 (M^+ + 1, 0.15), 343 (0.18), 327 (1), 326 (4), 283 (18), 282 (100), 236 (5), 180 (5), 126 (7), 91 (7), 77 (11). *Anal*. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.18; H, 6.21; N, 3.96.

5-(2-Hydroxyethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (7c)

2-Hydroxyethyl 3-amino-3-phenylprop-2-enoate (**5c**)[6] (2.65 g, 12.78 mmol), 4-methoxybenzyl-3-oxopentanoate (**6a**) (3.02 g, 12.78 mmol) and propionaldehyde (0.74 g, 12.78 mmol) were dissolved in abs. EtOH and heated in a sealed Pyrex tube at 80 °C for 24 h. After removal of the solvent, the crude product was subjected to column chromatography (silica gel, light petroleum ether/EtOAc 1/1) to yield 2.75 g (45 %) of **7c** as yellow-greenish oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.43 (m, 3H), 7.32 (m, 4H), 6.88 (d, J = 8.70 Hz, 2H), 5.93 (s, 1H), 5.12 (q, J = 12.12 Hz, 2H), 4.05 (t, J = 5.56 Hz, 1H), 3.90 (m, 2H), 3.80 (s, 3H), 3.34 (m, 2H), 2.71 (m, 2H), 1.51 (m, 3H), 1.16 (t, J = 7.44 Hz, 3H), 0.87 (t, J = 7.44 Hz, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 167.2, 167.2, 159.3, 150.7, 147.1, 137.7, 128.8, 102.6, 101.5, 65.6, 65.4, 61.0, 55.2, 34.4, 29.0, 25.8, 13.0, 9.1. IR cm^{-1} (KBr): 3301, 2962, 2925, 2874, 1720, 1686, 1612, 1560, 1515, 1461. MS: m/z (%) 464 (M^+ - 1, 1), 438 (1), 437 (3), 436 (10), 343 (2), 342 (5), 254 (4), 208 (4), 121 (100), 83 (17), 71 (24), 69 (24), 57 (42), 55 (28), 43 (35), 41 (19). HRMS Calcd for $C_{27}H_{31}NO_6Na$: (M^+ + Na) 488.2049. Found: 488.2033

5-(2-Hydroxyethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (8c)

A mixture of 5-(2-hydroxyethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**7c**) (2.50 g, 5.37 mmol) and tetrachloro-1,4-benzoquinone (1.32 g, 5.37 mmol) THF (100 mL) was refluxed for 24 h. Then, THF was evaporated and the residue was purified by column chromatography (silica gel, light petroleum ether/EtOAc 1/1) to give 1.70 g (73 %) of **8c** as colorless crystals. Mp 215 – 216 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.56 (m, 2H), 7.41 (m, 5H), 6.91 (d, *J* = 8.58 Hz, 2H), 5.35 (s, 2H), 4.08 (t, *J* = 4.42 Hz, 2H), 3.81 (s, 3H), 3.43 (t, *J* = 4.66 Hz, 2H), 2.77 (q, *J* = 7.58 Hz, 2H), 2.63 (q, *J* = 7.58 Hz, 2H), 1.19 (m, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.8, 168.1, 160.9, 160.4, 157.3, 149.4, 140.4, 131.3, 129.5, 129.0, 128.7, 128.0, 127.5, 126.5, 114.4, 67.9, 67.4, 60.7, 55.7, 30.1, 25.1, 15.7, 14.3. IR cm^{-1} (KBr): 3294, 3014, 2974, 2937, 2901, 2877, 2840, 1905, 1730, 1721, 1610, 1558, 1515, 1450. MS: m/z (%) 463 (M^+,3), 342 (6), 122 (9), 121 (100), 77 (8). HRMS Calcd for $C_{27}H_{29}NO_6$: 463.1995. Found: 463.2004.

5-(2-Fluoroethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (16)

5-(2-Hydroxyethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (**8c**) (1.60 g, 3.45 mmol) was dissolved in 90 mL of absolute CH_2Cl_2 under argon atmosphere and cooled to -78 °C. Subsequently, DAST (1.10 g, 0.9 ml, 6.83 mmol) was added dropwise. The resulting solution was stirred for 0.5 h at -78 °C, then warmed to rt and stirred until completion of the reaction, which was determined by TLC (silica gel, light petroleum ether/EtOAc 8/2). Afterwards, 1 mL of water was added at 0 °C and the reaction mixture was allowed to warm up to rt. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was achieved by column chromatography (silica gel, light petroleum ether/EtOAc 8/2) to give 0.76 g (47 %) of **19** as orange oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 7.58 (m, 2H), 7.41 (m, 5H), 6.92 (d, *J* = 8.58 Hz, 2H), 5.36 (s, 2H), 4.36 (m, 2H), 4.17 (s, 3H), 3.82 (s, 3H), 2.79 (q, *J* = 7.46 Hz, 2H), 2.63 (q, *J* = 7.58 Hz, 2H), 1.21 (m, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 168.1, 160.5, 160.0, 156.8, 148.8, 139.5, 130.8, 128.9, 128.3, 128.2, 127.4, 127.0, 125.9, 114.0, 80.5 (d, *J* = 170.52 Hz), 67.4, 64.0 (d, *J* = 20.36 Hz), 55.2, 29.6, 24.7, 15.1, 13.8. IR cm^{-1} (KBr): 2964, 2937, 2851, 2360, 2341, 1729, 1613, 1561, 1516, 1464, 1456. MS: m/z (%) 465 (M^+,5), 344 (12), 122 (10), 121 (100), 77 (6). HRMS Calcd for $C_{27}H_{28}NO_5F$: 465.1952. Found: 465.1946.

2,4-Diethyl-5-[(2-fluoroethoxy)carbonyl]-6-phenylpyridine-3-carbothioic acid (3)

5-(2-Fluoroethyl) 3-(4-methoxybenzyl) 2,4-diethyl-6-phenylpyridine-3,5-dicarboxylate (**16**) (0.60 g, 1.30 mmol) was dissolved in formic acid (15 mL) and the solution was stirred at rt until completion of the reaction (TLC silica gel light petroleum ether/EtOAc 2/8). The reaction solution was evaporated to

dryness using bulb-to-bulb distillation and purified through column chromatography (silica gel, light petroleum ether/EtOAc 2/8) to furnish 0.37 g (82 %) of the carboxylic acid as colorless crystals Mp 47 – 50 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) 9.87 (s, 1H), 7.55 (m, 2H), 7.40 (m, 3H), 4.34 (m, 2H), 4.15 (s, 2H), 2.88 (d, *J* = 6.94, 2H), 2.68 (d, *J* = 6.82, 2H), 1.23 (m, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) 172.2, 167.8, 159.4, 155.9, 140.0, 138.8, 129.1, 128.3, 126.7, 80.5 (d, *J* = 170.15 Hz), 64.1 (d, *J* = 20.36 Hz), 29.0, 24.9, 15.2, 14.1. IR cm^{-1} (KBr): 3441, 2978, 2941, 2879, 2506, 1956, 1732, 1559, 1448, 1382. MS: m/z (%) 345 (M^+, 75), 298 (100), 282 (36), 280 (28), 254 (65), 210 (19), 77 (20), 47 (24). HRMS Calcd for $C_{19}H_{20}NO_4F$: 345.1376. Found: 345.1372.

2,4-Diethyl-5-[(2-fluoroethoxy)carbonyl]-6-phenylpyridine-3-carboxylic acid (0.18 g, 0.52 mmol) from the previous reaction was dissolved in 15 mL of absolute benzene under argon atmosphere and cooled to -10 °C. Thereafter, oxalyl chloride (1.33 g, 0.9 ml, 10.48 mmol) and one drop of DMF were added. This solution was allowed to warm to rt and was stirred for further 2 h until the reaction was completed (TLC silica gel, light petroleum ether/EtOAc 2/8). The solvent was removed *in vacuo* and the oily residue repeatedly coevaporated with toluene. The crude product was used without further purification for the next reaction step.

To a solution of NaSH hydrate (0.08 g, 1.43 mmol) in absolute EtOH (10 mL) the crude product, obtained by the previous reaction, dissolved in THF (5 mL) was added dropwise. The resulting solution was stirred for 20 min. at -10 °C and further at rt until completion of the reaction (TLC, RP-18 silica gel, MeCN/water 9/1). Subsequently, the solution was acidified with 6N HCl and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to dryness. The solid residue was purified by reversed phase column chromatography (RP-18 silica gel, MeCN/water 9/1) to afford 0.15 g (83 %) of **3** as colorless crystals. Mp 45 – 47 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.64 (m, 2H, Ph H-2, H-6), 7.46 (m, 3H, Ph H-3, H-4, H-5), 4.39/4.29 (m, 2H, F$\underline{C}H_2$), 4.34/4.29 (m, 2H, CH_2O), 3.05 (q, 2H, *J* = 7.50 Hz, C-2$\underline{C}H_2$), 2.93 (q, 2H, *J* = 7.50 Hz, C-4$\underline{C}H_2$) 1.40 (t, 3H, *J* = 7.50 Hz, C-2$CH_2\underline{Me}$), 1.29 (t, 3H, *J* = 7.50 Hz, C-4CH_2Me); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 189.3 ($\underline{C}$OSH), 167.9 ($\underline{C}O_2$), 160.4 (C-2), 158.3 (C-6), 149.5 (C-4), 139.3 (Ph C-1), 130.6 (C-3), 129.3 (Ph C-4), 128.5 (Ph C-3, C-5), 128.3 (Ph C-2, C-6), 126.2 (C-5), 80.5 (d, F$\underline{C}H_2$, *J* = 172.0 Hz), 64.5 (d, $\underline{C}H_2O$ *J* = 20.2 Hz), 29.5 (C-2$\underline{C}H_2$), 24.4 (C-4$\underline{C}H_2$), 15.9 (C-4$CH_2\underline{Me}$), 14.3 (C-2$CH_2\underline{Me}$). IR cm^{-1} (KBr): 3439, 2975, 2938, 2877, 1731, 1556, 1495, 1448, 1403, 1377, 1278, 1250, 1166, 1144, 1077, 1060, 1033, 960. MS: m/z (%) 362 (M^+ + 1, 1), 361 (3), 359 (31), 329 (21), 328 (100), 312 (14), 254 (15), 236 (12), 77 (20), 47 (48). *Anal*. Calcd for $C_{19}H_{20}FNO_3S$•0.2 H_2O: C, 62.52; H, 5.63; N, 3.84. Found: C, 62.45; H, 5.44; N, 3.73.

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