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Straightforward synthesis of PET tracer precursors used for the early diagnosis of Alzheimers disease through Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

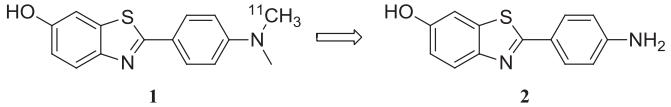
In positron emission tomography [^{11}C]PIB, Pittsburgh Compound-B, is currently the most widely used radiopharmaceutical for the early diagnosis of Alzheimer's disease. Synthetic routes for the preparation of the precursor of [^{11}C]PIB are reported in the literature. These strategies require multiple steps and the use of protecting groups. This paper describes a simple one-step synthesis of the precursor of [^{11}C]PIB through a Suzuki–Miyaura coupling reaction using thermal conditions or microwave activation. These methods were successfully applied to the synthesis of various 2-arylbenzothiazole and 2-pyridinylbenzothiazole compounds including [^{18}F] precursor derivatives of PIB containing a nitro function.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for 60%–70% of dementia cases. About 6% of the population aged 65 and older suffer from dementia, which represented 36 million people worldwide in 2010 with a total societal cost estimated to be US$ 604 billion. The number of AD patients is believed to double every 20 years to potentially reach 115 million in 2050.[1] AD has both human and economical impacts on our society and is expected to become one of the major health care problems for industrialized countries in the future.[2] As a matter of fact the research for a treatment and an early diagnosis of AD, with in vivo imaging of amyloid plaques as the most promising technique,[3] appears today as a priority.[4]

In the last 20 years, the research on AD focused on the development of different therapeutic approaches and diagnostic techniques to detect the pathology at an early stage.[5] However, to date the definitive diagnosis of AD can be performed *post-mortem* only.[6] An early diagnosis of AD would not only allow an intervention with future disease-modifying therapies right from the start of the disease, but also a relevant follow-up of drugs tested.[7] The 'amyloid hypothesis',[8] today well accepted by the scientific community, suggest that Aβ plaques appear in the brain 10–20 years before the clinical symptoms of AD. In vivo methods for amyloid imaging,[9] together with cerebrospinal fluid (CSF) biomarkers, as well as functional monitoring of the brain (glucose metabolism with [^{18}F]FDG or neurotransmitter activity),[10,11] are expected to have a high potential to specifically diagnose AD patients at a very early stage. During the last 10 years, various molecular imaging radiolabelled tracers have been reported for the early diagnosis of AD with single photon emission computed tomography (SPECT) and positron emission tomography (PET).[12–16]

Among them, the thioflavin-T derivative Pittsburgh Compound-B **1** ([^{11}C]PIB, Fig. 1), a carbon-11 radionuclide marker of Aβ plaques,[17,18] is currently the most widely used PET tracers in preclinical and clinical trials for the diagnosis of AD.[19–24]



1 **2**

Fig. 1. Chemicals structures of [^{11}C]PIB **1** used for the in vivo imaging of AD and the precursor **2** used for the radiosynthesis.

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[^{11}C]PIB showed high affinity for Aβ aggregates (two binding sites in AD human brain) and excellent pharmacokinetic profile.[25] Interestingly, around 20–30% of asymptomatic controls show a [^{11}C]PIB retention,[26–30] which suggests that this compound might be an efficient tracer for AD preclinical diagnosis since the major growth of amyloid burden seems to occur at this stage of the disease.[31,32] This radiopharmaceutical, which is today the gold-standard amyloid PET tracer,[33] is commonly used as a reference to compare the efficiency of new potent markers of Aβ aggregates.[34]

Important efforts have been made in the last 5 years to improve the synthesis of [^{11}C]PIB. The direct N-methylation of the 2-(4′-aminophenyl)-6-hydroxybenzothiazole **2** (Fig. 1) using [^{11}C] enriched isotope methylating agent, such as [^{11}C]-methyltriflate appeared to be the most straightforward method.[35,36] Today, this radiosynthesis can be performed routinely with an automate[37] using an HPLC loop to carry out the N-methylation.[38]

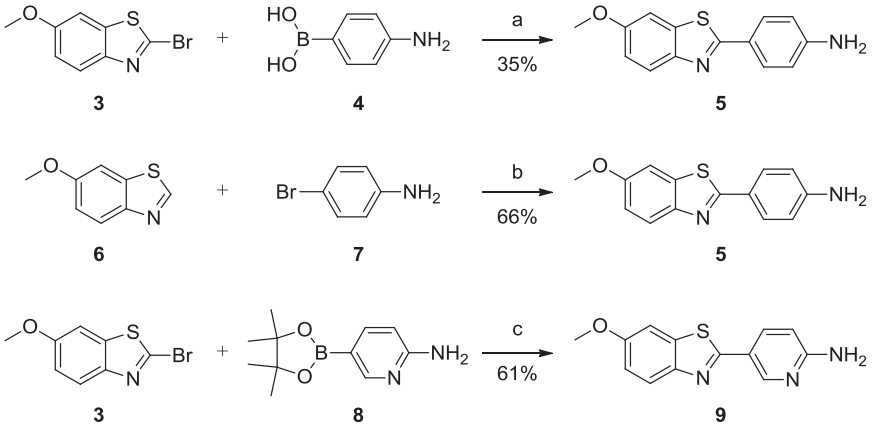
The commonly used method for the synthesis of the precursor **2** of [^{11}C]PIB requires the protection of the phenolic function or the use of a nitro group as precursor of the amine function. It involves a five-step synthesis with quite low overall yields ranging from 24 to 39% involving a Jacobson's oxidative cyclization of substituted thiobenzanilides.[17,39] Few improved syntheses of substituted 2-arylbenzothiazoles, which could be used as precursors for the radiosynthesis of [^{11}C]PIB are reported in the literature (Scheme 1). Kumar et al. described the synthesis of 2-(4-aminophenyl)-6-methoxybenzothiazole **5** in 35% yield via a Suzuki–Miyaura coupling reaction using $Pd_2(dba)_3$ in DME/water and aqueous K_2CO_3.[40] Another synthesis, reported by Tamagnan et al. affords the compound **5** through a Heck coupling reaction in 66% yield.[41] In the pyridinyl series, a Suzuki–Miyaura coupling reaction, reported by Svensson et al., leads to the 2-pyridinylbenzothiazole derivative **9** in 61% yield.[42] Other methods involving Suzuki–Miyaura,[43,44] Heck[45] or copper-catalyzed[46] conditions were reported for the synthesis of other 2-aryl-6-methoxybenzothiazole derivatives substituted with mono or dimethylamino functions on the aryl core, but these compounds cannot be used as precursor for the radiosynthesis of [^{11}C]PIB or derivatives because of the chemical functions present on these structures.

2. Results and discussion

Encouraged by the high interest in the [^{11}C]PIB for Alzheimer's disease diagnostic research and considering these previous studies, we decided to develop a direct synthesis of the precursor **2** of [^{11}C]PIB from two commercially available reagents, by a Suzuki–Miyaura coupling reaction. The one-step cross-coupling reported herein implies the use of the unprotected 2-bromo-6-hydroxybenzothiazole **10** and 4-aminophenylboronic acid pinacol ester **11**. Our first attempts with the catalyst $Pd_2(dba)_3$ led to the compound **2** in less than 15% yield, whereas the use of Pd(dppf)$Cl_2\cdot CH_2Cl_2$ led to a fast and total conversion of the starting material (controlled by HPLC) without affecting the hydroxyl and amino groups (Scheme 2).

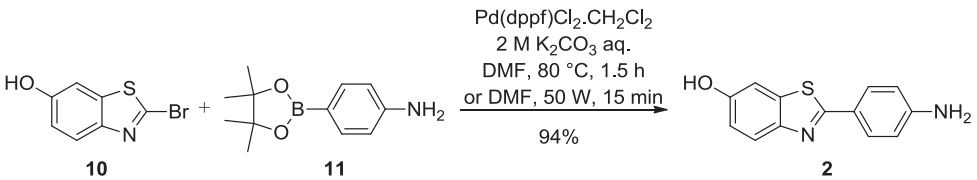
The 2-bromo-6-hydroxybenzothiazole **10** and the 4-aminophenylboronic acid pinacol ester **11** were stirred in a solution of DMF/2 M K_2CO_3. After degassing, the Pd(dppf)$Cl_2\cdot CH_2Cl_2$ was introduced and the reaction mixture was running for 1.5 h at 80 °C. After workup the desired compound **2** was isolated by precipitation in 94% yield. The compound **2** was isolated clean enough without additional purification as suggested HPLC and ^{1}H NMR analysis (Table 1).

These Suzuki–Miyaura conditions were successfully extended to the synthesis of several 2-arylbenzothiazole and 2-pyridinylbenzothiazole derivatives (Table 1). The hydroxyl and amino substituents were compatible with the used conditions. The synthesis of compounds containing nitro substituents (compounds **20**, **22**, **26** and **30**) was also very efficient using the conditions reported. This observation was particularly attractive because nitro function can be used to introduce fluorine-18, which suggests that the method developed could lead to efficient syntheses of various fluorine-18 tracers with chemical structure similar to PIB. The longer half-life of fluorine-18 (110 min) compared to carbon-11 (20 min) allows for a wider use in clinical settings. Fluorination



3 4 5 6 7 5 3 8 9

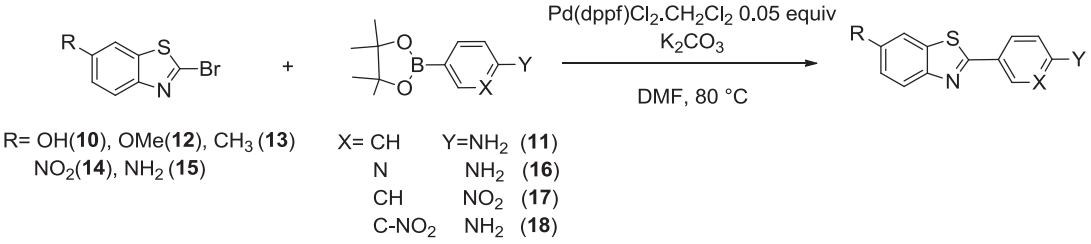
Scheme 1. a: $Pd_2(dba)_3\cdot CH_2Cl_2$, K_2CO_3, DME/water, 100 °C, 6 h. b: $Pd(OAc)_2$, P(*t*-Bu)$_3$, Cs_2CO_3, CuBr, DMF, 150 °C, 1 h. c: Pd(dppf)$Cl_2\cdot CH_2Cl_2$, K_2CO_3, DMF, 80 °C, 2 h.

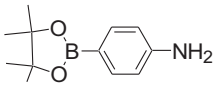
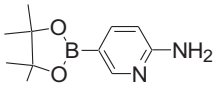
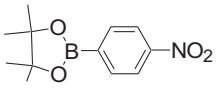
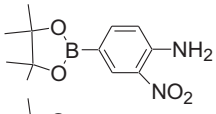
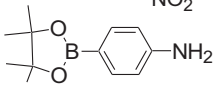
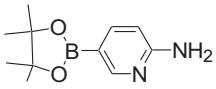
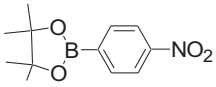
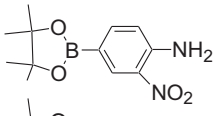
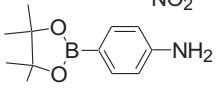
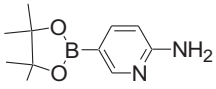
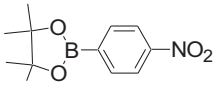
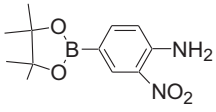
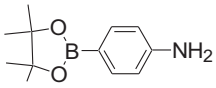
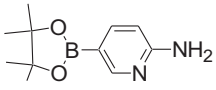


10 11 2

Scheme 2. Suzuki–Miyaura coupling reaction leading to the precursor **2** of the radiochemical tracer [^{11}C]PIB **1**.

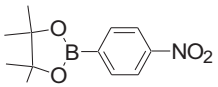
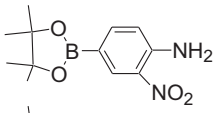
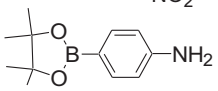
Table 1
Biaryl coupling of 2-bromobenzothiazoles (**10**, **12**–**15**) with various phenyl and pyridinylboronic acid pinacol esters



Entry	Aryl halide	Boronic acid pinacol ester	Time (h)	Product	Yield[a] (%)	HPLC purity (%)
1	**10** (OH)		1.5	**2**	94	92
2	**10**		1.5	**19**	95	99
3	**10**		1.5	**20**	70	99
4	**10**		1.5	**21**	98	99
5	**12** (OMe)		3	**5**	97	89
6	**12**		6	**9**	98	96
7	**12**		1.5	**22**	78	95
8	**12**		2	**23**	99	95
9	**13** (Me)		1.5	**24**	99	87
10	**13**		12	**25**	82	93
11	**13**		5	**26**	64	99
12	**13**		1	**27**	97	92
13	**14** (NO_2)		2	**28**	74	64
14	**14**		2	**29**	13[b]	62

(*continued on next page*)

Table 1 (*continued*)

Entry	Aryl halide	Boronic acid pinacol ester	Time (h)	Product	Yield[a] (%)	HPLC purity (%)
15	**14**		1	**30**	60[b]	99
16	**14**		1	**31**	78	87
17	**15** (NH_2)		4	**32**	70	95

[a] Yields refer to isolated products.
[b] Isolated yields after column chromatography.

by nucleophilic substitution of the nitro group was reported for the radiopharmaceuticals 2-(4-[^{18}F]fluorophenyl)-6-methoxybenzothiazole and 2-(4-[^{18}F]fluoro phenyl)-6-methylbenzothiazole, which showed high potential for PET amyloid imaging.[47] The precursors of these two radiopharmaceuticals were successfully synthesized here using the Suzuki–Miyaura approach proposed (compounds **22** and **26**).

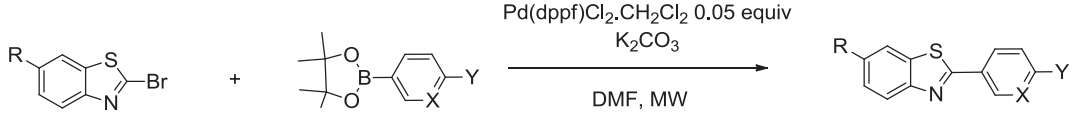
The Suzuki–Miyaura method described here offers a fast and easy access to key intermediates used in the synthesis of radiopharmaceuticals with chemical structures close to the PIB. Taking advantage of the presence of the amino or nitro substituent in the structure, some of them could directly be labelled.

Microwave-assisted heating under controlled conditions has gained importance in organic chemistry due to homogenous and short time heating and energy saving. Considering the results obtained under thermal conditions, the Suzuki cross-coupling reactions were undertaken under controlled microwave activation. Several examples of Suzuki–Miyaura reactions performed upon microwave activation for the synthesis of various heterocyclic scaffolds of pharmacological interest have been described in the literature.[48]

The microwave conditions for the synthesis of each series of arylbenzothiazoles were optimized. A preliminary study was developed using different conditions of temperature and activation power. The catalytic system (5 mol % of Pd(dppf)$Cl_2 \cdot CH_2Cl_2$) used for reactions under conventional heating was compatible with microwave conditions and rapid couplings were observed within 5 min at 60 °C and total conversion was obtained after 15 min.

The use of microwave activations resulted in a dramatic decrease of reaction times. When 2-bromo-6-hydroxybenzothiazole was used as reagent, this synthesis proved to be efficient with an irradiation of 10 W for 15 min at 60 °C. The best results were obtained for compounds **2** and **19** isolated in 93% and 92% yields, respectively, with an HPLC purity higher than 92%. Moreover microwave-assisted Suzuki–Miyaura reaction was found to be compatible with other series of 2-bromobenzothiazoles bearing methoxy and methyl groups. The reaction of aryl halide **12** and **13** with phenylboronic acid pinacol esters **11**, **16**–**18**, required an irradiation of 50 W for 15 min at 60 °C for total conversion. The best results were obtained for compounds **5** and **22** with 98% and 96% yields, respectively (Table 2).

Table 2
Biaryl coupling of 2-bromobenzothiazole (**10**, **12**, **13**) with various phenylboronic acid pinacol esters performed by microwave activation



R= OH (**10**), OMe(**12**), CH_3 (**13**)

X=	Y=	
CH	NH_2	(**11**)
N	NH_2	(**16**)
CH	NO_2	(**17**)
C-NO_2	NH_2	(**18**)

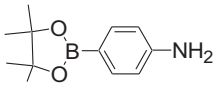
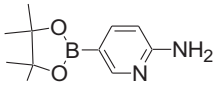
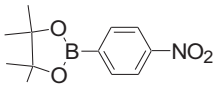
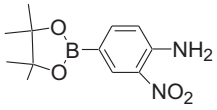
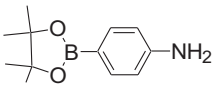
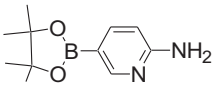
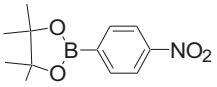
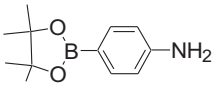
Entry	Aryl halide	Boronic acid pinacol ester	Conditions	Product	Yield[a] (%)	HPLC purity (%)
1	**10** (OH)		10 W, 60 °C, 15 min	**2**	93	94
2	**10**		10 W, 60 °C, 15 min	**19**	92	99
3	**10**		10 W, 60 °C, 15 min	**20**	87	96
4	**10**		10 W, 60 °C, 15 min	**21**	85	96

Table 2 (*continued*)

Entry	Aryl halide	Boronic acid pinacol ester	Conditions	Product	Yield[a] (%)	HPLC purity (%)
5	**12** (OMe)		50 W, 60 °C, 15 min	**5**	98	77
6	**12**		50 W, 150 °C, 15 min	**9**	68	88
7	**12**		50 W, 60 °C, 15 min	**22**	96	91
8	**13** (Me)		50 W, 80 °C, 15 min	**24**	84	81

[a] Yields refer to isolated products.

The high yields (68–98%) and short reaction times provided by the microwave-assisted Suzuki–Miyaura cross-coupling described here are decisive advantages. As expected, the unprotected phenol and amine functions are well tolerated by these coupling conditions, which makes this synthesis a very straightforward route to get the precursor of the [^{11}C]PIB and other derivatives. An extension of this method towards the synthesis of other functionalized arylbenzothiazoles is currently under study.

3. Conclusions

We have developed an efficient and rapid synthesis of the precursor of the widely used radionuclide [^{11}C]PIB, a PET tracer employed for the in vivo imaging of AD. This method was efficiently applied in the synthesis of various 2-arylbenzothiazole derivatives containing key functions for radiolabelling with carbon-11 (amino group) or fluorine-18 (nitro group). The Suzuki–Miyaura cross-coupling reaction can be performed from commercially available reactants to achieve the simple one-step synthesis of radiopharmaceutical precursors in high yields under conventional and microwave heating.

4. Experimental section

4.1. Chemicals

All reagents were obtained from commercial sources unless otherwise noted, and used as received. Heated experiments were conducted using thermostatically controlled oil baths and were performed under an atmosphere oxygen-free in oven-dried glassware. All reactions were monitored by analytical thin layer chromatography (TLC) or by Gas chromatography–Mass spectrometry (GC–MS). TLC was performed on aluminium sheets precoated silica gel plates ($60F_{254}$, Merck). TLC plates were visualized using irradiation with light at 254 nm, ninhydrin sprays or in an iodine chamber as appropriate. Frontal retention values R_f have been mentioned when necessary. Flash column chromatography was carried out when necessary using silica gel 60 (particle size 0.040–0.063 mm, Merck). The reactions using microwaves as the activating/heating source were accomplished using a microwave oven (CEM Discover 1™) under pressure and was monitored by ChemDriver.

4.2. Physical measurements

The structure of the products prepared by different methods was checked by comparison of their NMR, IR and MS data and by the TLC behaviour. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker BioSpin GmbH spectrometer 400 MHz, at room temperature. Chemical shifts are reported in δ units, parts per million (ppm). Coupling constants (J) are measured in hertz (Hz). Splitting patterns are designed as follows: s, singlet; d, doublet; dd, doublet of doublets, m, multiplet; br, broad. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. For the assignments of the NMR signals, we use the convention presented in Fig. 2. GC–MS analyses were performed with an Agilent 6890N instrument equipped with a 12 m×0.20 mm dimethyl polysiloxane capillary column and an Agilent 5973N MS detector-column temperature *gradient* 100–300 °C (method 100): 100 °C (1 min); 100 °C–220 °C (10 °C/min); 200 °C (2 min); *gradient* 160–280 °C (method 160): 160 °C (1 min); 160 °C–280 °C (10 °C/min); 280 °C (2 min); *gradient* 180–300 °C (method 180): 180 °C (1 min); 180 °C–300 °C (10 °C/min); 300 °C (2 min); *gradient* 220–325 °C (method 220): 220 °C (1 min); 220 °C–325 °C (10 °C/min); 325 °C (7.5 min), *gradient* 260–325 °C (method 260): 260 °C (1 min); 260 °C–325 °C (10 °C/min); 325 °C (7.5 min), low-resolution mass spectra (LRMS) resulting from ionization by electronic impact. Infrared spectra were recorded over the 400–4000 cm^{-1} range with an Agilent Technologies Cary 630 FTIR/ATR/ZnSe spectrometer. Low-resolution mass spectra (LRMS) were also performed from ionization by electrospray (ESI–LRMS) on a Waters Micromass ZQ2000 (mass) spectrometer. The mass analyses of compounds were made by direct introduction carried out by infusion over 2 min of the sample dissolved in methanol/HCO_2H 0.1% (1 mg/mL) within a flow rate of 30 μL/min. The abundance indicated for each mass number (m/z values) is given in percentage relative to the strongest peak of 100% abundance (base peak).

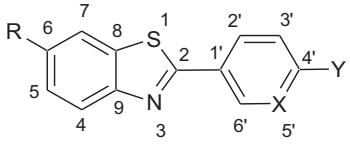


Fig. 2. Convention adopted to assign signals of ^{1}H and ^{13}C NMR spectra.

High-resolution mass spectra (HRMS) analyses were acquired on a Thermo Scientific LTQ Orbitrap mass spectrometer. The HPLC analyses were carried out on a normal phase column Kromasil (length: 250 mm, diameter: 4.6 mm, stationary phase: 5 μm) using a Water 2998 Photodiode Array Detector (260–370 nm) and an isocratic system of elution. The retention times t_R are expressed in minutes in the decimal system.

Chemical nomenclature of labelled compounds: [^{18}F]FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose; [^{11}C]PIB, Pittsburgh Compound-B or [*N*-[^{11}C]methyl]2-(4′-methylaminophenyl)-6-hydroxy benzothiazole; [^{125}I]IMPY, 6-[^{125}I]iodo-2-(4′-dimethylamino)phenylimidazo[1,2]pyridine.

4.3. General procedure for the preparation of benzothiazole derivatives by Suzuki–Miyaura coupling reaction

The corresponding 2-bromobenzothiazoles **10**, **12**–**15** (0.66 mmol, 1 equiv) and the corresponding phenylboronic acid pinacol ester (0.79 mmol, 1.2 equiv) were dissolved in anhydrous DMF in the presence of K_2CO_3 (6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (0.033 mmol, 0.05 equiv) was introduced and the mixture was stirred at 80 °C or under microwave irradiation (monitoring by TLC or by GC–MS). Later, the mixture was then filtered on Celite®, concentrated and dissolved in 4 mL of 1 N MeOH/HCl. Then 75 mL of Et_2O were introduced and a colour powder was isolated by filtration. The precipitate was poured into water and pH adjusted to 6. The expected compounds were isolated by filtration and purity was checked by HPLC.

*4.3.1. 2-(4′-Aminophenyl)-6-hydroxybenzothiazole (**2**).* 2-Bromo-6-hydroxybenzothiazole **10** was purchased from Bellenchem commercial source. 2-Bromo-6-hydroxybenzothiazole **10** (150.7 mg, 0.66 mmol) and 4-aminophenylboronic acid pinacol ester **11** (173.5 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1.5 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-aminophenyl)-6-hydroxybenzothiazole **2** was isolated by filtration as a grey amorphous powder. Yield 151 mg (94%). R_f=0.2, SiO_2 (cyclohexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.79 (s, 1H, OH), 7.73 (d, 1H, $J_{4\text{-}5}$=8.7 Hz, H_4), 7.70 (d, 2H, $J_{2'\text{-}3'\text{ or }6'\text{-}5'}$=8.2 Hz, $H_{2'}$ and $H_{6'}$), 7.36 (d, 1H, $J_{7\text{-}5}$=2.6 Hz, H_7), 6.95 (dd, 1H, $J_{5\text{-}7}$=2.4 Hz, $J_{5\text{-}4}$=8.7 Hz, H_5), 6.68 (d, 2H, $J_{3'\text{-}2'\text{ or }5'\text{-}6'}$=8.4 Hz, $H_{3'}$ and $H_{5'}$), 5.83 (s, 1H, NH_2), (similar to literature[49]); ^{13}C NMR (DMSO-d_6, 100 MHz): δ=164.6 (C_2), 154.9 (C_6), 151.5 ($C_{4'}$), 147.4 (C_9), 135.1 (C_8), 128.2 ($C_{2'}$ and $C_{6'}$), 122.3 (C_4), 120.6 ($C_{1'}$), 115.4 (C_5), 113.6 ($C_{3'}$ and $C_{5'}$), 106.7 (C_7). *m*/*z* (ESI$^+$): 243 (100%, $[M+H]^+$). HPLC purity: 92%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=12.3 min. GC/MS: method 180, t_R=9.01 min; *m*/*z*: 242 $[M]^+$(100), 226 $[M-NH_2]^+$ (0.1), IR (ATR): ν 3330 (νNH_2), 1601, 1570, 1483, 1454 (νC=C), 832 (δC–H). HRMS: calcd for $C_{13}H_{10}N_2OSH$ $[M+H]^+$ (243.05866); found (243.05864).

*4.3.2. 2-(6′-Aminopyridin-3-yl)-6-hydroxybenzothiazole (**19**).* 2-Bromo-6-hydroxybenzothiazole **10** (150.7 mg, 0.66 mmol) and 2-aminopyridine-5-boronic acid pinacol ester 97% **16** (179.7 mg, 0.79 mmol) were dissolved in 7 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1.5 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(6′-aminopyridin-3-yl)-6-hydroxybenzothiazole **19** was isolated by filtration as a green amorphous powder. Yield 152 mg (95%). R_f=0.1, SiO_2 (cyclohexane/EtOAc 1:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.84 (s, 1H, OH), 8.58 (s, 1H, $H_{6'}$), 7.97 (dd, 1H, $J_{4\text{-}5}$=8.8 Hz, $J_{4\text{-}7}$=2.4 Hz, H_4), 7.77 (d, 1H, J=8.8 Hz, $H_{2'}$), 7.41 (d, 1H, $J_{7\text{-}5}$=2.7 Hz, H_7), 7.05 (s_{broad}, 1H, NH_2); 7.00 (dd, 1H, $J_{5\text{-}7}$=2.5 Hz, $J_{5\text{-}4}$=8.5 Hz, H_5), 6.71 (d, 1H, $J_{3'\text{-}2'}$=8.9 Hz, $H_{3'}$), ^{13}C NMR (DMSO-d_6, 100 MHz): δ=161.1 (C_2), 159.5 (C_6), 155.4 ($C_{4'}$), 146.9 (C_9), 143.9 ($C_{6'}$), 136.7 ($C_{2'}$), 135.1 (C_8), 122.7 (C_4), 118.2 ($C_{1'}$), 115.8 (C_5), 109.6 ($C_{3'}$), 106.8 (C_7). HPLC purity: 99%, Krom Si 250, AcOEt 100%, 0.8 mL min^{-1}, λ=338 nm, t_R=11.4 min. GC/MS: method 180 (1 min); t_R=8.97 min *m*/*z*: 243 $[M]^+$(100), 242 $[M-H]^+$(100), 227 $[M-OH]^+$(5); IR (ATR): ν 3330 (νNH_2), 1630, 1561, 1451 (νC=C), 1250 (νC–N), 825 (δC–H). HRMS: calcd for $C_{12}H_9N_3OSH$ $[M+H]^+$ (244.05391); found (244.05396).

*4.3.3. 2-(4′-Nitrophenyl)-6-hydroxybenzothiazole (**20**).* 2-Bromo-6-hydroxybenzothiazole **10** (150.7 mg, 0.66 mmol) and 4-nitrophenylboronic acid pinacol ester **17** (196.8 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1.5 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-nitrophenyl)-6-hydroxybenzothiazole **20** was isolated by filtration as a yellow amorphous powder. Yield 126 mg (70%). R_f=0.5, SiO_2 (cyclohexane/EtOAc 1:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ=10.21 (s_{broad}, 1H, OH), 8.40 (d, 2H, $J_{3'\text{-}2'\text{ or }5'\text{-}6'}$=8.9 Hz, $H_{3'}$ and $H_{5'}$), 8.8 (d, 2H, $J_{2'\text{-}3'\text{ or }6'\text{-}5'}$=8.8 Hz, $H_{2'}$ and $H_{6'}$), 8.97 (d, 1H, $J_{4\text{-}5}$=8.8 Hz, H_4), 7.52 (d, 1H, $J_{7\text{-}5}$=2.4 Hz, H_7), 7.10 (dd, 1H, $J_{5\text{-}7}$=2.4 Hz, $J_{5\text{-}4}$=8.9 Hz, H_5), ^{13}C NMR (DMSO-d_6, 100 MHz): δ=160.8 (C_2), 156.5 (C_6), 148.2 ($C_{4'}$), 147.15 (C_9), 138.7 ($C_{1'}$), 136.8.1 (C_8), 128.6 ($C_{2'}$ and $C_{6'}$), 124.5.7 (C_4 and C_5), 106.8 (C_7). HPLC purity: 99%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=6.06 min. GC/MS: method 180; t_R=9.24 min *m*/*z*: 272 $[M]^+$(100), 242 $[M-NO]^+$(25), 226 $[M-NO_2]^+$(55). IR (ATR): ν 3431–3083 (νOH), 1657 (νC=C), 1513 ($\nu_{as}NO_2$), 1338 (ν_sNO_2), 849 (δCH). HRMS: calcd for $C_{13}H_8N_2O_3SH$ $[M+H]^+$ (273.03284); found (273.03278).

*4.3.4. 2-(4′-Amino-3-nitrophenyl)-6-hydroxybenzothiazole (**21**).* 2-Bromo-6-hydroxybenzothiazole **10** (150.7 mg, 0.66 mmol) and 4-amino-3-nitrophenylboronic acid pinacol ester **18** (208.6 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1.5 h (monitoring by TLC, cyclohexane/EtOAc 4:6). After workup 2-(4′-amino-3-nitrophenyl)-6-hydroxybenzothiazole **21** was isolated by filtration as a brown amorphous powder. Yield 185 mg (98%). R_f=0.4, SiO_2 (cyclohexane/EtOAc 4:6); ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.98 (s_{broad}, 1H, OH), 8.56 (d, 1H, $H_{6'}$, $J_{6'\text{-}2}$=2.4 Hz), 8.03 (dd, 1H, $J_{2'\text{-}3}$=9.04 Hz, $J_{2'\text{-}6'}$=2.3 Hz, $H_{2'}$), 7.97 (s_{broad}, 1H, NH_2); 7.83 (d, 1H, $J_{4\text{-}5}$=8.8 Hz, H_4), 7.44 (d, 1H, $J_{7\text{-}5}$=2.2 Hz, H_7), 7.21 (d, 1H, $J_{3'\text{-}2'}$=8.9 Hz, $H_{3'}$), 7.01 (dd, 1H, $J_{5\text{-}7}$=2.2 Hz, $J_{5\text{-}4}$=8.6 Hz, H_5), ^{13}C NMR (DMSO-d_6, 100 MHz): δ=161.9 (C_2), 155.5 (C_6), 147.4 (C_9), 146.9 ($C_{4'}$), 135.4 (C_8), 133.3 ($C_{2'}$), 129.9 ($C_{5'}$), 123.7 ($C_{6'}$), 122.9 (C_4), 120.6 ($C_{1'}$), 120.2 (C_3), 115.9 (C_5), 106.8 (C_7). HPLC purity: 99%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=10.65 min. GC/MS: method 220; t_R=8.00 min, *m*/*z*: 287 $[M]^+$(100), 257 $[M-NO]^+$(10), 241 $[M-NO_2]^+$(53). IR (ATR): ν 3464–3197 (νOH), 3344 (νNH_2), 1633, 1564 (νC=C), 1344 (ν_sNO_2), 819 (δ C–H). HRMS: calcd for $C_{13}H_9N_3O_3SNa$ $[M+Na]^+$ (310.02568); found (310.02580).

*4.3.5. 2-(4′-Aminophenyl)-6-methoxybenzothiazole (**5**).* 2-Bromo-6-methoxybenzothiazole **12** (167.8 mg, 0.66 mmol) previously synthesized from 2-amino-6-methoxybenzothiazole and 4-aminophenylboronic acid pinacol ester **11** (173.5 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 3 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-aminophenyl)-6-methoxybenzo-

thiazole **5** was isolated by filtration as a brown amorphous powder. Yield 164.3 mg (97%). R_f=0.4, SiO_2 (cyclohexane/EtOAc 1:1); Mp 97–99 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ=7.85 (d, 1H, $J_{4\text{-}5}$=8.9 Hz, H_4), 7.81 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.5 Hz, $H_{2'}$ and $H_{6'}$), 7.65 (d, 1H, $J_{7\text{-}5}$=2.5 Hz, H_7), 7.10 (dd, 1H, $J_{5\text{-}7}$=2.5 Hz, $J_{5\text{-}4}$=9.0 Hz, H_5), 6.84 (d, 2H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.7 Hz, $H_{3'}$ and $H_{5'}$), 3.84 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ=165.4 (C_2), 164.6 ($C_{4'}$), 149.4 (C_6), 148.1 (C_9), 135.2 (C_8), 128.3 ($C_{2'}$ and $C_{6'}$), 122.4 (C_4), 121.9 ($C_{1'}$), 115.2 (C_5), 115.0 ($C_{3'}$ and $_{5'}$), 104.9 (C_7), 55.7 (CH_3). HPLC purity: 89%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=9.57 min. GC/MS: method 160; t_R=10.80 min, m/z: 256 $[M]^+$(86), 241 $[M-CH_3]^+$(100), IR (ATR): ν 3427–3500 (νNH_2), 2835 (νOCH_3), 1603, 1463, 1433 (νC=C), 831 (δC–H). HRMS: calcd for $C_{14}H_{12}N_2OSH$ $[M+H]^+$ (257.07431); found (257.07462).

*4.3.6. 2-(6′-Aminopyridin-3-yl)-6-methoxybenzothiazole (**9**).* 2-Bromo-6-methoxybenzothiazole **12** (167.8 mg, 0.66 mmol) and 2-aminopyridine-5-boronic acid pinacol ester 97% **16** (179.7 mg, 0.79 mmol) were dissolved in 7 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 6 h (monitoring by GC–MS). After workup 2-(6′-aminopyridin-3-yl)-6-methoxybenzothiazole **9** was isolated by filtration as a brown amorphous powder. Yield 171.4 mg (98%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.63 (s, 1H, $H_{6'}$), 7.99 (d, 1H, $J_{2'\text{-}3'}$=8.7 Hz, $H_{2'}$), 7.99 (d, 1H, $J_{4\text{-}5}$=8.6 Hz, H_4), 7.67 (s, 1H, H_7), 7.10 (dd, 1H, $J_{5\text{-}7}$=2.3 Hz, $J_{5\text{-}4}$=8.7 Hz, H_5), 6.73 (s_{broad}, 1H, NH_2); 6.62 (d, 1H, $J_{3'\text{-}2'}$=8.6 Hz $H_{3'}$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=163.3 (C_2), 161.3 (C_6), 156.9 ($C_{4'}$), 147.9 (C_9), 147.3 ($C_{6'}$), 135.4 ($C_{2'}$), 134.9 (C_8), 122.4 (C_4), 117.8 ($C_{1'}$), 115.3 (C_5), 108.1 ($C_{3'}$), 104.9 (C_7), 55.7 (CH_3). HPLC purity: 96%, Krom Si 250, AcOEt 100%, 0.8 mL min^{-1}, λ=338 nm, t_R=10.8 min. GC/MS: method 160; t_R=10.65 min, m/z: 257 $[M]^+$(100), 242 $[M-CH_3]^+$(95). IR (ATR): ν 3428 (νNH_2), 2834 (νOCH_3), 1652, 1600, 1460, 1435 (νC=C), 813 (δC–H). HRMS: calcd for $C_{13}H_{11}N_3OSH$ $[M+H]^+$ (258.06956); found (258.06989).

*4.3.7. 2-(4′-Nitrophenyl)-6-methoxybenzothiazole (**22**).* 2-Bromo-6-methoxybenzothiazole **12** (106 mg, 0.43 mmol) and 4-nitrophenylboronic acid pinacol ester **17** (136 mg, 0.56 mmol) were dissolved in 4 mL of DMF in the presence of 1.3 mL of 2 M K_2CO_3 (2.6 mmol, 6.0 equiv). After 30 min under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 2 h (monitoring by GC–MS). After workup 2-(4′-nitrophenyl)-6-methoxybenzothiazole **22** was isolated by filtration as a yellow amorphous powder. Yield 96 mg (78%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.38 (d, 2H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.5 Hz, $H_{3'}$ and $H_{5'}$), 8.3 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.5 Hz, $H_{2'}$ and $H_{6'}$), 8.03 (d, 1H, $J_{4\text{-}5}$=8.9 Hz, H_4), 7.8 (d, 1H, $J_{7\text{-}5}$=2.6 Hz, H_7), 7.20 (dd, 1H, $J_{5\text{-}7}$=2.6 Hz, $J_{5\text{-}4}$=8.9 Hz, H_5), 3.88 ppm (s, 3H, CH_3) (similar to literature).[48] ^{13}C NMR (DMSO-d_6, 100 MHz): δ=162.1 (C_2), 158.2 (C_6), 148.3 ($C_{4'}$), 138.8 (C_9), 136.8 (C_8), 135.6 ($C_{2'}$), 127.8 (C_4), 126.2 ($C_{6'}$), 124.5 ($C_{1'}$), 124.1 ($C_{3'}$), 115.7 (C_5), 104.8 (C_7), 55.9 (CH_3). HPLC purity: 95%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=362 nm, t_R m/z (ESI$^+$): 287 (100%, $[M+H]^+$). GC/MS: method 100; t_R=16.83 min m/z: 286 $[M]^+$ (100), 271 $[M-CH_3]^+$ (25), 240 $[M-NO_2]^+$ (20). IR (ATR): ν 3081 (ν_C=$_C$), 2838 (νOCH_3), 1591, 1551 (νC=C), 1514 ($\nu_{as}NO_2$), 1313 (ν_sNO_2), 846 (δC–H). HRMS: calcd for $C_{14}H_{10}N_2O_3SH$ $[M+H]^+$ (287.04851); found (287.04849).

*4.3.8. 2-(4′-Amino-3-nitrophenyl)-6-methoxybenzothiazole (**23**).* 2-Bromo-6-methoxybenzothiazole **12** (106 mg, 0.43 mmol) and 4-amino-3-nitrophenylboronic acid pinacol ester **18** (208.6 mg, 0.79 mmol) were dissolved in 4.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 2 h (monitoring by GC–MS). After workup 2-(4′-amino-3-nitrophenyl)-6-methoxybenzothiazole **23** was isolated by filtration as a brown amorphous powder. Yield 211 mg (99%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.53 (s, 1H, $H_{6'}$), 7.99 (d, 1H, $J_{2'\text{-}3}$=8.4 Hz, $H_{2'}$), 7.86 (d, 1H, $J_{4\text{-}5}$=8.1 Hz, H_4), 7.64 (s, 1H, H_7), 7.19 (d, 1H, $J_{3'\text{-}2'}$=8.5 Hz, $H_{3'}$), 7.09 (d, 1H, $J_{5\text{-}4}$=8.3 Hz, H_5). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=163.1 (C_2), 157.2 (C_6), 147.7 (C_9), 147.5 ($C_{4'}$), 138.4 (C_8), 133.2 ($C_{2'}$), 129.8 ($C_{5'}$), 123.8 ($C_{6'}$), 122.8 (C_4), 120.3 ($C_{1'}$), 120.2 (C_3), 115.7 (C_5), 104.8 (C_7), 55.7 (CH_3). HPLC purity: 95%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=8.59 min. GC/MS: method 160; t_R=13.71 min, m/z: 301 $[M]^+$ (100), 286 $[M-CH_3]^+$ (43), 255 $[M-NO_2]^+$(20). IR (ATR): ν 3457 (νNH_2), 2834 (νOCH_3), 1628, 1561 (νC=C), 1512 ($\nu_{as}NO_2$), 1252 (ν_sNO_2), 818 (δC–H). HRMS: calcd for $C_{14}H_{11}N_3O_3SNa$ $[M+Na]^+$ (324.04133); found (324.04135).

*4.3.9. 2-(4′-Aminophenyl)-6-methylbenzothiazole (**24**).* 2-Bromo-6-methylbenzothiazole **13** previously synthesized from 2-amino-6-methylbenzothiazole (150.5 mg, 0.66 mmol) and 4-aminophenylboronic acid pinacol ester **11** (173.5 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1.5 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-aminophenyl)-6-methylbenzothiazole **24** was isolated by filtration as a yellow-brown amorphous powder. Yield 156.9 mg (99%). R_f=0.4, SiO_2 (cyclohexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=7.82 (d, 1H, H_7), 7.81 (d, 1H, $J_{4\text{-}5}$=8.6 Hz, H_4), 7.76 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.4 Hz, $H_{2'}$ and $H_{6'}$), 7.29 (dd, 1H, $J_{5\text{-}7}$=1.6 Hz, $J_{5\text{-}4}$=8.1 Hz, H_5), 6.70 (d, 2H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.4 Hz $H_{3'}$ and $H_{5'}$), 2.45 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=167 (C_2), 151.9 (C_9), 151.8 ($C_{4'}$), 133.9 (C_8), 133.8 (C_6), 128.5 ($C_{2'}$ and $C_{6'}$), 127.5 (C_5), 121.5 (C_7), 121.3 (C_4), 120.2 ($C_{1'}$), 113.6 ($C_{3'}$ and $C_{5'}$), 55.7 (CH_3). HPLC purity: 87%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=8.08 min. GC/MS: method 100; t_R=15.6 min, m/z: 240$[M]^+$ (100), 224 $[M-NH_2]^+$ (0.5). IR (ATR): ν 3464 (νNH_2), 1631, 1605, 1477, 1454 (νC=C), 813 (δC–H). HRMS: calcd for $C_{14}H_{12}N_2SH$ $[M+H]^+$ (241.07940); found (241.07942).

*4.3.10. 2-(6′-Aminopyridin-3-yl)-6-methylbenzothiazole (**25**).* 2-Bromo-6-methylbenzothiazole **13** (150.5 mg, 0.66 mmol) and 2-aminopyridine-5-boronic acid pinacol ester 97% **16** (179.7 mg, 0.79 mmol) were dissolved in 7 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2\cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 12 h (monitoring by GC–MS). After workup 2-(6′-aminopyridin-3-yl)-6-methylbenzothiazole **25** was isolated by filtration as a grey amorphous powder. Yield 130.8 mg (82%). R_f=0.3, SiO_2 (cyclohexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.63 (d, 1H, $J_{6'\text{-}2}$=2.5 Hz, $H_{6'}$), 8.02 (dd, 1H, $J_{2'\text{-}3'}$=8.6 Hz, $J_{2'\text{-}6'}$=2.5 Hz, $H_{2'}$), 7.85 (s, 1H, H_7), 7.84 (d, 1H, $J_{4\text{-}5}$=8.04 Hz, H_4), 7.32 (dd, 1H, $J_{5\text{-}7}$=1.5 Hz, $J_{5\text{-}4}$=8.9 Hz, H_5), 6.79 (s_{broad}, 1H, NH_2), 6.61 (d, 1H, $J_{3'\text{-}2'}$=8.6 Hz, $H_{3'}$), 2.47 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=167.4 ($C_{4'}$), 164.7 (C_2), 161.3 (C_9), 151.7 ($C_{6'}$), 135.6 ($C_{2'}$), 134.3 (C_8), 133.7 (C_6), 127.7 (C_5), 121.6 and 121.5 (C_4 and C_7), 117.6 ($C_{1'}$), 108.0 ($C_{3'}$), 20.9 (CH_3). HPLC purity: 93%, Krom Si 250, AcOEt 100%, 0.8 mL min^{-1}, λ=338 nm, t_R=10.02 min. GC/MS: method 100; t_R=15.45 min, m/z: 241 $[M]^+$ (100), 225 $[M-NH_2]^+$ (6). IR (ATR): ν 3385 (νNH_2), 1607, 1454 (νC=C), 1396 (νC–N), 808 (δC–H). HRMS: calcd for $C_{13}H_{11}N_3SH$ $[M+H]^+$ (242.07464); found (242.07465).

*4.3.11. 2-(4′-Nitrophenyl)-6-methylbenzothiazole (**26**).* 2-Bromo-6-methylbenzothiazole **13** (150.5 mg, 0.66 mmol) and 4-nitrophenylboronic acid pinacol ester **17** (196.8 mg, 0.79 mmol) were dissolved in 7 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)

$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 5 h (monitoring by GC–MS). After workup 2-(4′-nitrophenyl)-6-methylbenzothiazole **26** was isolated by filtration as a yellow amorphous powder. Yield 114.2 mg (64%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.42 (d, 2H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.8 Hz, $H_{3'}$ and $H_{5'}$), 8.38 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=9 Hz, $H_{2'}$ and $H_{6'}$), 8.06 (d, 1H, $J_{4\text{-}5}$=8.3 Hz, H_4), 8.05 (s, 1H, H_7), 7.46 (dd, 1H, $J_{5\text{-}7}$=1.8 Hz, $J_{5\text{-}4}$=8.2 Hz, H_5), 1.36 ppm (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=163.6 (C_2), 151.7 (C_9), 148.5 ($C_{4'}$), 138.4 ($C_{1'}$), 136.4 (C_8), 135.2 (C_6), 124.7 (C_5), 128.2 ($C_{2'}$ and $C_{6'}$), 124.6 ($C_{3'}$ and $C_{5'}$), 122.6 and 122.1 (C_4 and C_7), 24.6 (CH_3). HPLC purity: 99%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=345 nm, t_R=4.44 min. GC/MS: method 100, t_R=15.61 min, m/z: 270 $[M]^+$ (100), 224 $[M-NO_2]^+$ (45), 209 $[224-CH_3]^+$ (30), IR (ATR): ν 3079 (ν=C–H), 1515 ($\nu_{as}NO_2$), 1338 (ν_sNO_2), 849 (δC–H). HRMS: calcd for $C_{14}H_{10}N_2O_2SH$ $[M+H]^+$ (271.05357); found (271.05403).

*4.3.12. 2-(4′-Amino-3-nitrophenyl)-6-methylbenzothiazole (**27**).* 2-Bromo-6-methylbenzothiazole **13** (150.5 mg, 0.66 mmol) and 4-amino-3-nitrophenylboronic acid pinacol ester **18** (208.6 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1 h (monitoring by TLC, cyclohexane/EtOAc 5:5). After workup 2-(4′-amino-3-nitrophenyl)-6-methylbenzothiazole **27** was isolated by filtration as a brown amorphous powder. Yield 182.7 mg (97%). R_f=0.4, SiO_2 (cyclohexane/EtOAc 5:5). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=8.61 (d, 1H, $H_{6'}$, $J_{6'\text{-}2}$=2.2 Hz), 8.06 (dd, 1H, $J_{2'\text{-}3}$=8.9 Hz, $J_{2'\text{-}6'}$=2.3 Hz, $H_{2'}$), 7.97 (s_{broad}, 1H, NH_2); 7.90 (d, 1H, $J_{7\text{-}5}$=3.2 Hz, H_7), 7.83 (d, 1H, $J_{4\text{-}5}$=8.2 Hz, H_4), 7.35 (d, 1H, $J_{5\text{-}4}$=8.5 Hz, H_5), 7.20 (d, 1H, $J_{3'\text{-}2'}$=8.9 Hz, $H_{3'}$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=164.6 (C_2), 151.5 (C_9), 147.6 ($C_{4'}$), 134.8 (C_8), 134.0 ($C_{5'}$), 133.4 ($C_{2'}$), 129.9 (C_6), 128.0 (C_5), 124.13 ($C_{6'}$), 121.9 and 121.7 (C_7 and C_4), 120.2 ($C_{1'}$), 120.2 ($C_{3'}$), 21.1 (CH_3). HPLC purity: 92%, Krom Si 250, Heptane/AcOEt 30:70, 0.8 mL min^{-1}, λ=338 nm, t_R=5.58 min. GC/MS: method 180; t_R=10.36 min, m/z: 285 $[M]^+$ (100), 239 $[M-NO_2]^+$ (60). IR (ATR): ν 3447 (νNH_2), 1628, 1588 (νC=C), 1252 (ν_sNO_2), 764 (δ C–H). HRMS: calcd for $C_{14}H_{11}N_3O_2SNH$ $[M+H]^+$ (286.06447); found (286.06472).

*4.3.13. 2-(4′-Aminophenyl)-6-nitrobenzothiazole (**28**).* 2-Bromo-6-nitrobenzothiazole **14** previously synthesized from 2-amino-6-nitrobenzothiazole (170.9 mg, 0.66 mmol) and 4-aminophenylboronic acid pinacol ester **11** (173.5 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 2 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-aminophenyl)-6-nitrobenzothiazole **28** was isolated by filtration as a yellow amorphous powder. Yield 132.8 mg (74%). R_f=0.4, SiO_2 (cyclohexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.09 (s, 1H, H_7), 8.30 (d, 1H, $J_{5\text{-}4}$=9.1 Hz, H_5), 8.02 (d, 2H, $J_{4\text{-}5}$=9.1 Hz, H_4), 7.85 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.3 Hz, $H_{2'}$ and $H_{6'}$), 7.72 (d, 1H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.4 Hz, H_3), 6.22 (s, 1H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ=174.5 (C_2), 158.2 (C_9), 153.3 ($C_{4'}$), 143.3 (C_6), 134.3 (C_8), 129.6 ($C_{2'}$ and $C_{6'}$), 121.8 (C_4), 121.5 (C_5), 119.2 ($C_{1'}$), 118.8 (C_7), 113.6 ($C_{3'}$ and $C_{5'}$), HPLC purity: 64%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=345 nm, t_R=8.7 min. GC/MS: method, 180, t_R=10.14 min, m/z: 271 $[M]^+$ (100), 241 $[M-NO]^+$ (25), 225 $[M-NO_2]^+$(100). IR (ATR): ν3396 (νNH_2), 1636, 1570, 1502, 1436 (νC=C), 1328 (ν_sNO_2), 832 (δC–H). HRMS: calcd for $C_{13}H_9N_3O_2SH$ $[M+H]^+$ (272.04882); found (272.04899).

*4.3.14. 2-(6′-Aminopyridin-3-yl)-6-nitrobenzothiazole (**29**).* 2-Bromo-6-nitrobenzothiazole **14** (170.9 mg, 0.66 mmol) and 2-aminopyridine-5-boronic acid pinacol ester 97% **16** (179.7 mg, 0.79 mmol) were dissolved in 7 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 2 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(6′-aminopyridin-3-yl)-6-nitrobenzothiazole **29** was isolated by filtration as a beige solid. The crude was purified by flash chromatography on silica gel to afford the expected compound **29** as yellow oil. Yield 24 mg (13%). R_f=0.3, SiO_2 (cyclohexane/EtOAc 1:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.09 (s, 1H, H_7), 8.30 (d, 1H, $J_{5\text{-}4}$=9.1 Hz, H_5), 8.02 (d, 2H, $J_{4\text{-}5}$=9.1 Hz, H_4), 7.85 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.3 Hz, $H_{2'}$ and $H_{6'}$), 7.72 (d, 1H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.4 Hz, H_3), 6.22 (s, 1H, NH_2); HPLC purity: 62%, Krom Si 250, AcOEt 100%, 0.8 mL min^{-1}, λ=362 nm, t_R=8.11 min. IR (ATR): ν 3422 (νNH_2), 1656 (νC=C), 823 (δC–H). HRMS: calcd for $C_{12}H_9N_3OSH$ $[M+H]^+$ (272.03681); found (273.03685).

*4.3.15. 2-(4′-Nitrophenyl)-6-nitrobenzothiazole (**30**).* 2-Bromo-6-nitrobenzothiazole **14** (170.9 mg, 0.66 mmol) and 4-nitrophenylboronic acid pinacol ester **17** (196.8 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-nitrophenyl)-6-nitrobenzothiazole **30** was isolated by filtration as an amorphous solid. The crude was purified by flash chromatography on silica gel (cyclohexane/EtOAc 1:1) to afford the expected compound **30** as yellow amorphous powder. Yield 119 mg (60%). R_f=0.3, SiO_2 (cyclohexane/EtOAc 1:1); ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.35 (s, 1H, H_7), 8.47 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$), 8.43 (dd, 1H, $J_{5\text{-}4}$=9.0 Hz, $J_{5\text{-}7}$=2.3 Hz, H_5), 8.37 (d, 2H, $J_{4\text{-}5}$=8.9 Hz, H_4). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=166.6 (C_2), 160.5 (C_2), 145.7 (C_6), 148.3 ($C_{4'}$), 139.6 ($C_{1'}$), 136.8 (C_8), 133.3 ($C_{2'}$ and $C_{6'}$), 128.9 ($C_{3'}$ and $C_{5'}$), 128.3 (C_4), 126.6 (C_5), 124.0 (C_7). HPLC purity: 99%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=338 nm, t_R=4.62 min. GC/MS: method 180, t_R=9.95 min, m/z: 301 $[M]^+$ (100), 271 $[M-NO]^+$ (30), 255 $[M-NO_2]^+$ (10), 209$[M-2NO_2]^+$ (60). IR (ATR): ν 1602, 1514 (νC=C), 1514,($\nu_{as}NO_2$), 1330 (ν_sNO_2), 853 (δC–H).

*4.3.16. 2-(4′-Amino-3-nitrophenyl)-6-nitrobenzothiazole (**31**).* 2-Bromo-6-nitrobenzothiazole **14** (170.9 mg, 0.66 mmol) and 4-amino-3-nitrophenylboronic acid pinacol ester **18** (208.6 mg, 0.79 mmol) were dissolved in 3.3 mL of DMF in the presence of 2 mL of 2 M K_2CO_3 (4 mmol, 6.0 equiv). After 1 h under argon bubbling, Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (26.9 mg, 0.033 mmol) was introduced and the reaction was performed at 80 °C for 1 h (monitoring by TLC, cyclohexane/EtOAc 1:1). After workup 2-(4′-amino-3-nitrophenyl)-6-nitrobenzothiazole **31** was isolated by filtration as a yellow amorphous powder. Yield 163.4 mg (78%). R_f=0.3, SiO_2 (cyclohexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=9.10 (d, 1H, $J_{7\text{-}5}$=2.4 Hz, H_7), 8.63 (d, 1H, $J_{6'\text{-}2'}$=2.0 Hz, $H_{6'}$), 8.29 (dd, 1H, $J_{5\text{-}4}$=9 Hz, $J_{5\text{-}7}$=2.5 Hz, H_5), 8.10 (d, 1H, $J_{4\text{-}5}$=8.7 Hz), 8.04 (dd, 1H, $J_{2'\text{-}3'}$=8.9 Hz, $J_{2'\text{-}6'}$=2.9 Hz, $H_{2'}$ and $H_{6'}$), 7.18 (d, 1H, $J_{3'\text{-}2'}$=9 Hz, H_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=171.9 (C_2), 157.4 (C_9), 148.3 (C_6), 143.9 ($C_{4'}$), 134.6 (C_8), 133.6 ($C_{2'}$), 129.9 ($C_{5'}$), 125.3 ($C_{6'}$), 122.4 (C_4), 121.8 (C_5), 120.2 (C_7), 119.2 ($C_{1'}$), 119.17 ($C_{3'}$). HPLC purity: 87%, Krom Si 250, Heptane/AcOEt 50:50, 0.8 mL min^{-1}, λ=362 nm, t_R=9.38 min. GC/MS: method 260; t_R=5.33 min, m/z: 316 $[M]^+$ (100), 270 $[M-NO_2]^+$ (20), 224 $[M-2NO_2]^+$(50). IR (ATR): ν 3472 (νNH_2), 1638, 1502 (νC=C), 1335 (ν_sNO_2), HRMS: calcd for $C_{13}H_8N_4O_4SH$ $[M+H]^+$ (317.03390); found (317.03387).

*4.3.17. 2-(4′-Aminophenyl)-6-aminobenzothiazole (**32**).* 2-Bromo-6-aminobenzothiazole **15** (50 mg, 0.22 mmol) previously synthesized from 2-bromo-6-nitrobenzothiazole **14** and 4-aminophenylboronic acid pinacol ester 97% **11** (59.2 mg, 0.26 mmol) were dissolved in

1.5 mL of DMF in the presence of 0.7 mL of 2 M K_2CO_3 (1.32 mmol, 6.0 equiv). After 1 h under argon bubbling, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (9 mg, 0.011 mmol) was introduced and the reaction was performed at 80 °C for 4 h (monitoring by TLC, cyclohexane/EtOAc 4:6). After workup 2-(4′-aminophenyl)-6-aminobenzothiazole **32** was isolated by filtration as a brown amorphous powder. Yield 43.5 mg (70%). R_f=0.2, SiO_2 (cyclohexane/EtOAc 1:1). ^1H NMR (DMSO-d_6, 400 MHz) δ=7.66 (d, 2H, $J_{2'\text{-}3'}$ or $J_{6'\text{-}5'}$=8.4 Hz, $H_{2'}$ and $H_{6'}$), 7.59 (d, 1H, $J_{4\text{-}5}$=8.8 Hz, H_4), 7.08 (s, 1H, H_7), 6.76 (d, 1H, $J_{5\text{-}4}$=8.9 Hz, H_5), 6.67 (d, 2H, $J_{3'\text{-}2'}$ or $J_{5'\text{-}6'}$=8.5 Hz, $H_{3'}$ and $H_{5'}$), 5.64 (s, 1H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ=161.9 (C_2), 155.1 ($C_{4'}$), 146.4 ($C_{6'}$), 145.4 (C_9), 135.3 (C_8), 127.9 ($C_{2'}$ and $C_{6'}$), 122.1 (C_4), 120.9 ($C_{1'}$), 114.5 (C_5), 113.6 ($C_{3'}$ and $C_{5'}$) 104.1 (C_7). HPLC purity: 95%, Krom Si 250, AcOEt 100%, 0.8 mL min^{-1}, λ=345 nm, t_R=7.37 min. GC/MS: method 180, t_R=9.42 min, m/z: 241 $[M]^+$ (100), IR (ATR): ν 3455 (νNH_2), 1604, 1462 (νC=C), 1288 (νC–N), 820 (δC-H). HRMS: calcd for $C_{13}H_{11}N_3SH$ $[M+H]^+$ (242.07464); found (242.07464).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.085. These data include MOL files and InChiKeys of the most important compounds described in this article.

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