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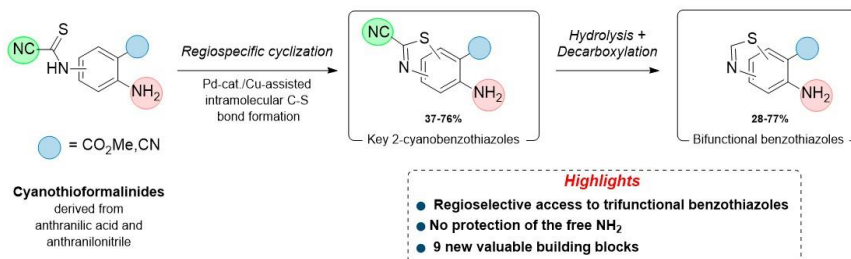
# Synthesis of trifunctional thiazole-fused anthranilonitrile and anthranilic acid derivatives.

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**Abstract** The synthesis of trifunctional isomeric benzothiazoles derived from nitroanthranilic acids and their corresponding anthranilonitrile analogues was studied. Compared to previous work, the reaction sequence afforded convenient access to hitherto undescribed 2-cyanobenzothiazoles. For further synthetic applications of these polyfunctional compounds, a hydrolysis-decarboxylation sequence was performed in acidic medium (HCl or HBr) and led to an enlarged array of relevant building blocks.

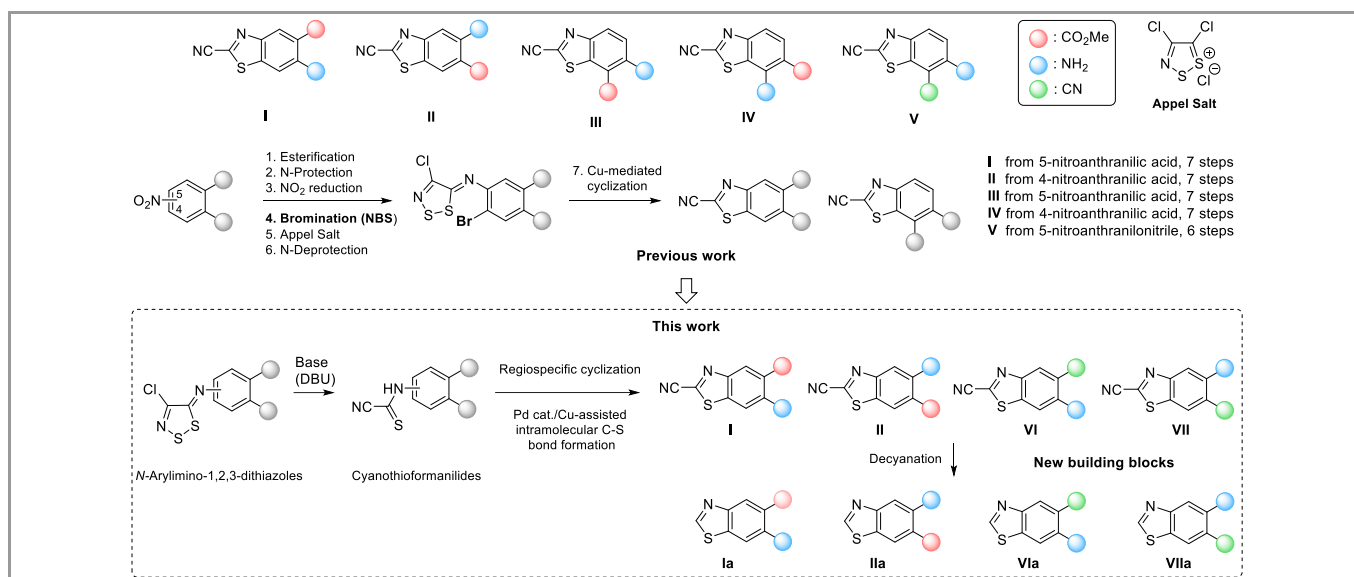
**Key words** *N*-arylcyanothioformamides, 4,5-dichloro-1,2,3-dithiazolium chloride, *N*-arylimino-1,2,3-dithiazoles, 2-cyanobenzothiazoles, anthranilic acid, anthranilonitrile, intramolecular C-S bond formation, decyanation.

The discovery of valuable new building blocks for the design of more complex heterocyclic systems is a major concern for medicinal chemistry in its search for novel therapeutic agents. Some years ago, we launched a research program on the synthesis and pharmacological evaluation of new *N*, *S*-containing heterocycles strongly inspired by natural marine or terrestrial benzothiazole derivatives,<sup>1</sup> which showed a real therapeutic potential.<sup>2</sup> This program led to the synthesis of an array of polyfunctionalized benzo[*d*]thiazoles **I-V** (Figure 1).<sup>3-5</sup> The last stage of the common strategy involved a regioselective copper(I)-mediated cyclization of *ortho*-brominated imino-1,2,3-dithiazoles resulting from the reaction of 4,5-dichloro-1,2,3-dithiazolium chloride (commonly called Appel salt)<sup>6</sup> with relevant methyl 4- or 5-aminoanthranilates, derived from 4- or 5-nitroanthranilic acids.<sup>7</sup> These compounds were synthesized following the specific multistep sequence: a) esterification of the starting acid, b) protection of the amine function, c) reduction of the nitro group and d) bromination with *N*-bromosuccinimide (NBS) to provide *o*-bromoanilines before condensation with Appel salt to give the corresponding *ortho*-brominated imino-

1,2,3-dithiazoles. The difficulties encountered in separating and purifying the *ortho*-brominated regioisomers were the main drawback for the synthesis of benzothiazoles **I-III**. Therefore, the next part of the synthetic route (Appel salt condensation and *N*-deprotection) had to be performed from mixtures of brominated reagents. Separation and purification of the transformed products were performed one or two steps later, prior to the copper (I)-mediated cyclization and generation of the targeted polyfunctional benzothiazoles.<sup>3-5</sup>

All these drawbacks have contributed to limiting the synthesis and the use of such molecular building blocks for the synthesis of more complex heterocyclic systems.

Recently, we described a Pd-catalyzed/Cu-assisted reaction to achieve the synthesis of 2-cyanobenzothiazoles via C-H functionalization/intramolecular C-S bond formation of *N*-arylcyanothioformamides derived from the corresponding *N*-arylimino-1,2,3-dithiazoles (see bottom part of Figure 1).<sup>8</sup> The cyclization was efficiently achieved in the presence of air and 2 equiv of an inorganic additive (KI). In these conditions, cyanothioformamides bearing halogen, alkyl or ether groups in position C3 and C4 regioselectively provided the corresponding 5,6-disubstituted 2-cyanobenzothiazoles. We therefore decided to apply these experimental conditions to the synthesis of polysubstituted benzothiazoles **I** and **II**, with the aim of suppressing the tricky bromination step and complicated purification of the resulting isomers. Seeking to open the chemical space, the synthesis of **VI** and **VII**, two novel regioisomers of benzothiazole **V**, was also envisioned (Figure 1). The removal of the carbonitrile function present at C2 of the thiazole moiety was also investigated, thus providing hitherto undescribed decyanated analogues (Figure 1).



**Figure 1** Synthesis of 2-cyanated benzothiazoles **I**, **II**, **III**, **IV** and **V** from brominated 5-*N*-arylimino-4-chloro-1,2,3-dithiazoles (previous work) and overview of the objectives of this work from *N*-arylcyanothioformamides

To achieve the envisioned synthesis of the target compounds it appeared necessary to first prepare the *N*-arylcyanothioformamides **3a-d** before achieving the fusion of the thiazole ring on the benzenic part (Figure 1).<sup>8</sup> Methyl 4- or 5-amino-2-[di(*tert*-butoxycarbonyl)amino] benzoates (**1a-d**) were reacted with Appel salt (1.1 equiv) in the presence of pyridine (2.0 equiv) in dichloromethane (0.3 M), at room temperature. After 1h of stirring, trifluoroacetic acid (15.0 equiv) was added and the resulting mixture was stirred again overnight at room temperature to yield the *N*-deprotected methyl-2-amino-5- or 4-[(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) amino]benzoates (**2a** and **2b**) in 95% and 87% yields, respectively. Treatment by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.0 equiv) at room temperature for 15 min afforded the corresponding cyanothioformanilides **3a** and **3b** in satisfactory yields (75% and 83% see Table 1). In a similar strategy, 2-amino-5- or 4-(cyanothioformamido)-benzonitrile **3c** and **3d** were synthesized in 57% and 21% yields, respectively. The reaction conditions (reagents, solvents and reaction time) and yields obtained are depicted in Table 1.

**Table 1** Synthetic route to *N*-arylcyanothioformamides (arylcarbamothioyl cyanides) **3a-d**: a) Appel salt (1.1 equiv), Pyr (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> [0.3 M], r.t., 1 h; b) TFA (15.0 equiv), rt, 16h or AcOH (0.3 M), reflux, 4 h; c) DBU (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> [0.2 M], r.t., 15 min.

Starting aniline <b>1<sup>a</sup></b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Yield in <b>2</b> (%) <sup>a</sup>	Yield in <b>3</b> (%) <sup>a,b</sup>
<b>a</b>	CO <sub>2</sub> Me	NBoc <sub>2</sub>	CO <sub>2</sub> Me	NH <sub>2</sub>	95	75
<b>b</b>	NBoc <sub>2</sub>	CO <sub>2</sub> Me	NH <sub>2</sub>	CO <sub>2</sub> Me	87	83
<b>c</b>	CN	NBoc <sub>2</sub>	CN	NH <sub>2</sub>	52	57
<b>d</b>	NBoc <sub>2</sub>	CN	NH <sub>2</sub>	CN	46	21

<sup>a</sup> Isolated yields. <sup>b</sup> tautomeric ratio major/minor 90:10 (estimated from <sup>1</sup>H NMR).

The reaction of DBU with imino-1,2,3-dithiazoles was previously described by Koutentis.<sup>9</sup> It suggests two nucleophilic attacks by the DBU amidine nitrogen on the same sulfur atom (initially the S2 of dithiazole ring). The third equivalent of DBU allows the removal of HCl that helps the conversion of the starting dithiazoles into disulfide intermediates before conversion into the expected cyanothioformamides. <sup>1</sup>H and <sup>13</sup>C NMR analysis of compounds **3a-d** indicate the presence of a tautomeric mixture, in which the thione form predominates (for more details see experimental section).<sup>10</sup>

In a first attempt, based on the experimental conditions previously described, **3a** was solubilized in a mixture of DMSO/DMF (1:1, v/v) (0.025M) and heated at 120 °C for 4 h in the presence of PdCl<sub>2</sub> (20 mol %), CuI (50 mol %) and an inorganic additive (KI, 2.0 equiv). After workup and purification on silica gel the desired methyl 6-amino-2-cyano-1,3-benzothiazole-5-carboxylate (**I**) was isolated in only 31% yield, together with a by-product identified as methyl 2-amino-5-isothiocyanatobenzoate (**4a**) (19%, entry 1, Table 2). This by-product was already described in chemical transformations of *N*-arylimino-1,2,3-dithiazoles or cyanothioformanilides.<sup>9,11</sup>

This disappointing result led us to optimize the reaction conditions and to test inorganic additives that previously allowed the synthesis of 2-cyanobenzothiazoles in yields close to those obtained with KI.<sup>8</sup> Table 2 reports our results with 2.0 equiv of KBr, LiI and LiBr as additives. The quantities of the other reactants and solvent proportions remained unchanged (see Table 2, entries 2, 3 and 4).

In the presence of KBr and LiI the yields in benzothiazole **I** were similar to those obtained with KI. Unfortunately, the unexpected isothiocyanate **4a** was also isolated in similar proportions (entries 2 and 3). Satisfyingly, when the reaction was carried out in the presence of LiBr, the benzothiazole **I** was obtained as the sole product in a fairly good yield of 55% (Table 2, entry 4).

**Table 2** Synthesis of benzothiazole **I** from **3a**: preliminary exploration of experimental conditions and effect of inorganic additives.

Entry	Additive	Yield in <b>I</b> (%) <sup>a</sup>	Yield in <b>4a</b> (%) <sup>a</sup>
1	KI	31	19
2	KBr	29	26
3	LiI	21	21
4	LiBr	55	0

<sup>a</sup> Isolated yields.

It should be noted that the cumulative yields of benzothiazole **I** and isothiocyanate **4a** were similar and in the range of 42-55% for each experiment, while conversion of the starting cyanothioformamide appeared to be complete (T.L.C. analysis). Despite our efforts, we were unable to improve this yield and it was considered as sufficiently acceptable to be extended to the preparation of the other isomer **II**. Each reaction was performed with two different additives (KI and LiBr) in equal proportions and the results obtained were compared. Products and yields are depicted in Table 3.

**Table 3** Synthesis of benzothiazole **II** from **3b**.

Entry	Additive	Yield in <b>II</b> (%) <sup>a</sup>	Yield in <b>IV</b> (%) <sup>a</sup>
1	KI	59	3
2	LiBr	76	0

<sup>a</sup> Isolated yields.

Here again, the addition of KI to the reaction mixture did not lead to an optimized synthesis of 2-cyanobenzothiazole derivative **II**. Thus, starting from methyl 2-amino-4-[(cyanothioformamido)benzoate] **3b**, product **II** was isolated in a good yield of 59%, but still accompanied by a by-product identified as its regioisomer **IV** (3% yield, entry 1). In these reactions, no traces of the corresponding isothiocyanate derivative **4b** were detected. Satisfyingly, replacing KI by LiBr led to the expected benzothiazole **II** in a good yield (76%, entry 2).

The benzonitrile derivatives **3c** and **3d** afforded similar results to those obtained for their methyl ester analogues. Thus, in the presence of KI, the cyclization process of cyanothioformanilide **3c** led to benzothiazole **VI** (13% yield), together with the corresponding isothiocyanate **4c** becoming the major product in 37% yield. In accordance with the preceding results, addition of LiBr to the starting mixture specifically provided the expected product **VI** in a yield of 38% (Table 4, entry 2).

**Table 4** Synthesis of benzothiazole **VI** from **3c**.

Entry	Additive	Yield in <b>VI</b> (%) <sup>a</sup>	Yield in <b>4c</b> (%) <sup>a</sup>
1	KI	13	37
2	LiBr	38	0

<sup>a</sup> Isolated yields.

Surprisingly, treatment of **3d** with the catalytic system (PdCl<sub>2</sub>/CuI) and LiBr (2.0 equiv) gave benzonitrile derivative **VII** regioselectively but in only 47% yield whilst addition of KI gave the expected product in a good yield of 61%. In the two cases no trace of any by-product was detected (Table 5).

**Table 5** Synthesis of benzothiazole **VII** from **3d**.

Entry	Additive	Yield in <b>VII</b> (%) <sup>a</sup>
1	KI	61
2	LiBr	47

<sup>a</sup> Isolated yields.

These results show that the main part of the reaction studied was favorably influenced by the addition of LiBr to the reaction mixture. Sometimes KI was the most effective additive, as in the transformation of **3d** to benzothiazole **VII**.

It may be noted that when the reaction was started from a trifluoroacetamide derivative of **3a** (NHCOCF<sub>3</sub>),<sup>3</sup> the corresponding benzothiazole was obtained in very low yields that did not exceed 12%, regardless of the additive (KI or LiBr) employed. The protection of N2 as a carbamate (NH-Boc)<sup>4</sup> allowed the synthesis of a 2-cyanobenzothiazole (NH-Boc in position 5) in a more interesting yield (close to 40-45%), but it appeared difficult to prevent hydrolysis of the carbamate group and the unexpected appearance of compound **I**. Moreover, whatever the additive (KI or LiBr), the cyclization process is more efficient when the free aromatic amine and the attracting group (CO<sub>2</sub>Me or CN) present on the reactant are in the *meta*- and the *para*-position of the cyanothioformamide group, respectively (e.g. **3b** and **3d**). According to the mechanism proposed in our previous study,<sup>8</sup> it can favour the formation of the Cu<sup>(I)</sup> thioamidate and the intermediate palladacycle before reductive elimination and generation of the 2-cyanobenzothiazole ring.

Pursuing our investigations and considering our recent work on metal-catalyzed C-H arylation at the C2 position of thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones,<sup>12</sup> we decided to treat all these polyfunctional 2-cyanobenzothiazoles with hydrobromic (HBr<sub>aq</sub> 48 %) or hydrochloric (HCl<sub>aq</sub> 37%) acid, in order to achieve hydrolysis of the CN function and decarboxylation of the resulting function that can lead to unprecedented decyanated analogues. All these experiments were carried out in a

microwave reactor and in a sealed tube, as usual thermal heating was not successful, even in sealed systems. It should be noted that the pressure due to the release of CO<sub>2</sub> in the reactor was measured in real time and never exceeded 10 bar.

In accordance with previous experiments,<sup>12</sup> compound **I** was heated in a sealed tube for 45 min in aqueous HBr at 100°C under microwave irradiation. The decyanated benzothiazole **Ia** was isolated in a low yield of 33%, when compared to the 90% previously reported for quinazolinone derivatives. Replacing HBr by HCl or extending the reaction time (75 min instead of 45 min) led to lower yields (23%). Satisfyingly, reducing the reaction time to 20 min and 10 min provided the expected product **Ia** in 57% and 77% yield, respectively (Table 6).

**Table 6** Study on the decyanation of **I** in the presence of HBr or HCl.<sup>a</sup>

Entry	HX <sup>a</sup>	time (min)	Yield in <b>Ia</b> (%) <sup>b</sup>
1	HBr	75	23
2	HBr	45	33
3	HBr	20	57
4	HBr	10	77
5	HCl	45	22

<sup>a</sup> HBr 48% in water; HCl 37% in water. <sup>b</sup> Isolated yields.

The same procedure (HBr<sub>aq</sub> 48 %, 100°C, 10 min) was applied to 2-cyanobenzothiazole **II**. Surprisingly, no trace of the decyanated product **Ila** was observed and the reactant could not be recovered. In this case, treatment with HCl was the sole method that allowed the synthesis of the expected benzothiazole in 28% yield, after heating at 100°C for 90 min. The yield did not exceed 10-12% when the heating time was reduced to 45 min or when the temperature was increased to 120°C. In all these experiments, the decyanated methyl 5-amino-1,3-benzothiazole-6-carboxylate **Ila** was accompanied by the 5-amino-6-(methoxycarbonyl)-1,3-benzothiazole-2-carboximidic acid **Iib** obtained in yields ranging from 11% to 18-20% after 90 min and 45 min of heating, respectively (the tautomeric amide form was not detected and <sup>1</sup>H-NMR analysis confirmed the presence of the carboximidic acid function, for details see SI section).

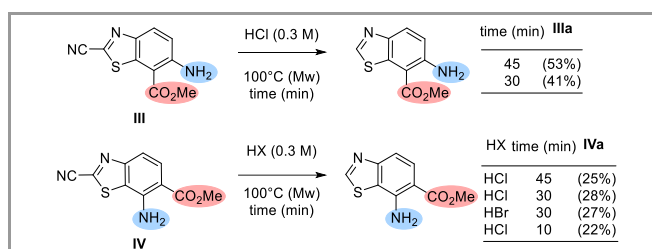
**Table 7** Study on the decyanation of **II** in the presence of HBr or HCl.<sup>a</sup>

HX (0.3 M)	time (min)	Yield in <b>Ila</b> (%) <sup>b</sup>	Yield in <b>Iib</b> (%) <sup>b</sup>
HBr	10	0	0
HCl	10	0	0
HCl	45	10	20
HCl	45 <sup>c</sup>	12	18
HCl	90	28	11

<sup>a</sup> HBr 48% in water; HCl 37% in water. <sup>b</sup> Isolated yields. <sup>c</sup> 120°C (Mw).

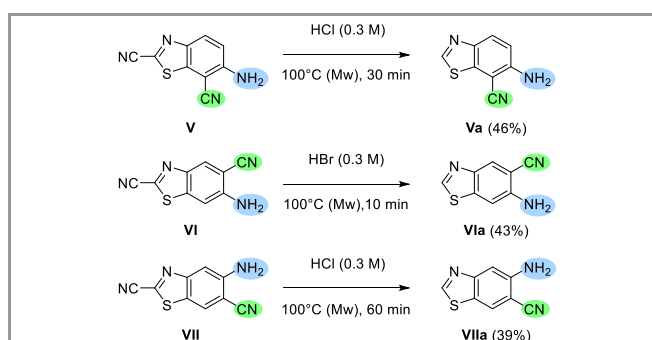
In this study, the decyanation of **III** and **IV** was also envisioned. These two regioisomers of compounds **I** and **II** were prepared as described in our previous investigations.<sup>5</sup> The route for benzothiazole **III** was the most studied. It contains a bromination step before Cu-mediated cyclization, allowing the expected product on a gram scale under good conditions. Benzothiazole **IV** cannot be obtained by the same routes as compounds **I**, **II** and **III**. In this case, fusion of the thiazole ring to the starting arene is accomplished by thermo-cyclization (115°C in pyridine, under microwave irradiation) of the intermediate imino-1,2,3-dithiazole precursor, leading to a separable mixture of **II** and **IV** (for experimental details see SI section).<sup>4</sup>

Removal of the cyano group on the thiazole ring was performed by heating 2-cyanobenzothiazoles **III** and **IV** in HCl (37% in water) for 45 min and yielded the corresponding carbonitrile-free analogues **IIIa** and **IVa** in yields of 53% and 28%, respectively. In the case of **IV**, reducing the heating time to 30 min and 10 min, or replacing HCl by HBr, did not increase the yields (Scheme 1).



**Scheme 1** Synthesis of **IIIa** and **IVa** from **III** and **IV** (Isolated yields).

The anthranilonitrile derivatives **V**, **VI** and **VII** were also submitted to the hydrolysis-decarboxylation sequence under the conditions described for their methyl ester analogues. As shown in Scheme 2, the decyanated amino-1,3-benzothiazole-7-, 5- or 6-carbonitriles **Va**, **Vla** and **VIIa** were isolated in 40% average yields (46%, 43% and 39%, respectively) (Scheme 2).



**Scheme 2** Synthesis of **Va**, **Vla** and **VIIa** from **V**, **VI** and **VII** (Optimized reaction times and isolated yields).

In summary, we have efficiently revised the synthesis of the trifunctional isomeric benzothiazoles **I** and **II** derived from anthranilic acids. Compared to previous studies,<sup>4,5</sup> the reaction sequence was reduced by one step and the overall yields improved. This new strategy also allowed the first synthesis of two additional 2-cyanobenzothiazoles **VI** and **VII**, regioisomers of **V**,<sup>1c</sup> itself derived from anthranilonitrile. These versatile compounds can be considered as 2-cyano-benzothiazoles which are very sensitive to nucleophilic attacks, becoming tools of

choice in the development of click chemistry methods under biocompatible conditions.<sup>13</sup> Moreover, these benzothiazoles are derivatives of anthranilic acid and anthranilonitrile, two major classes of molecular building blocks used for the preparation of molecules of interest in the pharmaceutical and cosmetic fields.<sup>14</sup> To study further synthetic applications of these polyfunctional benzothiazoles a hydrolysis-decarboxylation sequence in acidic medium (HCl or HBr) was applied to the studied compounds. This operation was found to be dependent on the starting isomer. The decyanated products were finally isolated with satisfactory yields. The reactivity and synthetic applications of these novel anthranilic acid and anthranilonitrile derivatives remain to be studied.

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Reagents were purchased from commercial suppliers and were used without further purification. Reactions were monitored by thin-layer chromatography with aluminium plates (0.25 mm) precoated with silica gel 60 F254 (Merck KGaA, Darmstadt, Germany). Visualization was performed with UV light at a wavelength of 254 nm. Purifications were conducted with a flash column chromatography system (PuriFlash, Interchim, Montluçon, France) using stepwise gradients of petroleum ether (also called light petroleum) (PE), and dichloromethane (DCM) as the eluent. Melting points were measured with an SMP3 Melting Point instrument (STUART, Bibby Scientific Ltd., Roissy, France) with a precision of 1.5 °C. IR spectra were recorded with a Spectrum 100 Series FTIR spectrometer (PerkinElmer, Villebon S/Yvette, France). Liquids and solids were investigated with a single-reflection attenuated total reflectance (ATR) accessory; the absorption bands are given in cm<sup>-1</sup>. NMR spectra (<sup>1</sup>H, <sup>13</sup>C) were acquired at 295 K using an AVANCE 300 MHz spectrometer (Bruker, Wissembourg, France) at 300 and 75.4 MHz using TMS as an internal standard. The coupling constant *J* is in Hz and chemical shifts are given in ppm. Mass (ESI, EI and field desorption (FD)) were recorded with an LCP 1er XR spectrometer (WATERS, Guyancourt, France). Mass spectrometry was performed by the Mass Spectrometry Laboratory of the University of Rouen. Normandie. Microwave-assisted reactions were carried out in sealed tubes with a Biotage Initiator microwave synthesis instrument, and temperatures were measured by IR-sensor (Biotage, Uppsala, Sweden). The time indicated in the various protocols is the time measured when the mixtures were at the programmed temperature. The pressure measured in the sealed tubes at the end of the reactions performed never exceeded 10 bar.

Anilines **1a-d** and 2-cyanobenzo[d]thiazoles **III**, **IV** and **V** were synthesized according to methods previously described.<sup>1c,4,5</sup> Detailed procedures of products **1a-d**, **4a**, **4c** and **IIb** and physicochemical characterization (<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra) of all compounds are available in the Supporting Information section. New compounds are described below.

#### Amino-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzene derivatives **2a - d**; general procedure

To a stirred solution of aniline **1** (1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.3M) were successively added Appel Salt (1.1 equiv) and pyridine (2.0 equiv). The reaction mixture was stirred at room temperature for 1h after which water was added. The resulting emulsion was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified on silica gel with petroleum ether (PE)/ CH<sub>2</sub>Cl<sub>2</sub> (100:0 to 0:100, v/v) as eluent.

#### Methyl-2-amino-5-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzoate (**2a**)

Brown solid; yield: 1.92 g (95%); m.p.: 100-101 °C.

IR (neat)  $\nu_{\max}$ : 3477, 3365, 1685, 1615, 1569, 1430, 1295, 1260, 1207, 1132, 855, 804, 768, 467 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.98 (d, *J* = 2.6 Hz, 1H), 7.37 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.95 (s, 2H), 3.89 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.1, 153.4, 149.5, 148.9, 138.2, 129.1, 122.7, 117.7, 110.4, 52.0.

HRMS (EI<sup>+</sup>) *m/z*, calcd for C<sub>10</sub>H<sub>9</sub>ClN<sub>3</sub>O<sub>2</sub>S [M]<sup>+</sup>: 301.9825, found: 301.9829.

#### Methyl-2-amino-4-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzoate (**2b**)<sup>4</sup>

Orange solid; yield: 1.76 g (87%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.95 (d, *J* = 8.5 Hz, 1H), 6.45 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 5.87 (s, 2H), 3.87 (s, 3H).

#### 2-Amino-5-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzonitrile (**2c**)

Yellow solid; yield: 1.16 g (52%). m.p.: 180-181 °C.

IR (neat)  $\nu_{\max}$ : 3471, 3370, 3225, 2988, 2207 (CN), 1619, 1603, 1572, 1492, 1420, 1266, 1243, 1149, 1120, 859, 596, 459 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.42 - 7.30 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.42 (s, 2H).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  155.2, 150.5, 147.4, 137.8, 128.3, 123.7, 117.5, 116.5, 93.2.

HRMS (EI<sup>+</sup>) *m/z*, calcd for C<sub>9</sub>H<sub>6</sub>ClN<sub>4</sub>S<sub>2</sub> [M]<sup>+</sup>: 268.9722, found: 268.9733.

#### 2-Amino-4-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzonitrile (**2d**)

Orange solid; yield: 1.13 g (46%). m.p.: 161-162 °C.

IR (neat)  $\nu_{\max}$ : 3463, 3366, 2210, 1637, 1580, 1441, 1186, 864, 528 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.51 - 7.45 (d, *J* = 8.3 Hz 1H), 6.53 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.48 (dd, *J* = 1.9, 0.5 Hz, 1H), 4.52 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  160.74, 156.68, 151.31, 147.74, 134.79, 117.49, 108.88, 105.28, 93.88.

HRMS (EI<sup>+</sup>) *m/z*, calcd for C<sub>9</sub>H<sub>4</sub>N<sub>4</sub>S<sub>2</sub><sup>35</sup>Cl [M]<sup>+</sup>: 266.9566, found: 266.9558.

#### Arylcyanothioformamide (arylcyanamidothioyl cyanides) derivatives **3a - d**; General Procedure

To a stirred solution of **2** (1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.2M) was added DBU (3.0 equiv). The reaction mixture was stirred under argon at room temperature for 15 min after which NaHSO<sub>4</sub> 1M was added. The resulting emulsion was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified on silica gel with PE/CH<sub>2</sub>Cl<sub>2</sub> (50:50 to 0:100, v/v) as eluent.

As described in previous studies,<sup>10</sup> <sup>1</sup>H and <sup>13</sup>C NMR analysis of cyanothioformanilides **3a-d** indicate the presence of a tautomeric mixture, in which the thione form predominates (average major/minor ratio estimated <sup>1</sup>H NMR, 90:10). The broad singlet at  $\delta$  13.3-13.5 ppm corresponds to the NH of the thioamide form and disappeared in the presence of D<sub>2</sub>O.

#### Methyl 2-amino-5-[(cyanocarbonothioyl)amino]benzoate (**3a**)

Red-brown solid; yield: 0.344 g (75%), m.p.: 187-188 °C.

IR (neat)  $\nu_{\max}$ : 3447, 3329, 3262, 3113, 3084, 2225 (CN), 1684, 1620, 1489, 1409, 1361, 1247, 1195, 1094, 821, 751, 599, 545 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.29 (s, 1H), 8.57 (d, *J* = 2.6 Hz, 1H, H6), 7.77 (dd, *J* = 9.1, 2.6 Hz, 2H, major and minor), 7.39 (dd, *J* = 8.9, 2.7 Hz, 1H, minor), 7.05 (s, 4H, major and minor), 6.84 (d, *J* = 9.1 Hz, 2H, major and minor), 3.80 (s, 6H, major and minor).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  167.1 (major), 163.7 (minor), 157.6 (major), 151.1 (minor), 150.6 (major), 129.7 (minor), 128.8 (major), 126.0 (major), 125.8 (minor), 125.7 (minor), 124.7 (major), 119.1 (minor), 117.3 (minor), 116.7 (major), 114.6 (minor), 114.0 (major), 108.1 (minor), 107.4 (major), 51.8 (major and minor).

HRMS (EI<sup>+</sup>) *m/z*, calcd for C<sub>10</sub>H<sub>10</sub>N<sub>3</sub>O<sub>2</sub>S [M]<sup>+</sup>: 236.0494, found: 236.0493.

#### Methyl 2-amino-4-[(cyanocarbonothioyl)amino]benzoate (**3b**)

Red-brown solid; yield: 0.448 g (83%), m.p.: 188-189 °C.

IR (neat)  $\nu_{\text{max}}$ : 3478, 3365, 3281, 3111, 2945, 2234 (CN), 1683, 1585, 1429, 1399, 1353, 1300, 1242, 1187, 1106, 774, 537  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.42 (s, 1H), 7.77 (d,  $J$  = 8.7 Hz, 2H, major and minor), 7.54 (d,  $J$  = 2.1 Hz, 1H, major), 6.93 (dd,  $J$  = 8.7, 2.1 Hz, 5H, major and minor), 6.82 (d,  $J$  = 2.2 Hz, 1H, minor), 6.62 (dd,  $J$  = 8.6, 2.2 Hz, 1H, minor), 3.79 (s, 3H, minor), 3.78 (s, 3H, major).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  167.1 (minor), 167.0 (major), 164.7 (minor), 161.8 (major), 151.9 (minor), 151.8 (major), 142.4 (minor), 142.2 (major), 132.4 (minor), 131.8 (major), 113.7 (major), 112.6 (minor), 109.3 (minor), 109.2 (minor), 109.1 (major), 108.8 (major), 108.1 (minor), 107.6 (major), 51.6 (minor), 51.5 (major).

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_{10}\text{H}_{10}\text{N}_3\text{O}_2\text{S}$  [M]<sup>+</sup>: 236.0494, found: 236.0493.

#### (4-Amino-3-cyanophenyl)carbamothioyl cyanide (3c)

Yellow solid; yield: 0.278 g (57%), m.p.: 172-173 °C.

IR (neat)  $\nu_{\text{max}}$ : 3453, 3362, 3254, 3070, 3014, 2225 (CN), 1631, 1503, 1411, 1349, 1233, 1099, 826, 491  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.35 (s, 1H), 8.17 (d,  $J$  = 2.5 Hz, 1H, major), 7.69 (dd,  $J$  = 9.1, 2.6 Hz, 1H, major), 7.60 (d,  $J$  = 2.6 Hz, 1H, minor), 7.40 (dd,  $J$  = 9.0, 2.6 Hz, 1H, minor), 6.84 (d,  $J$  = 9.1 Hz, 2H, major and minor), 6.55 (s, 2H, major), 6.50 (s, 2H, minor).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  164.4 (minor), 158.8 (major), 151.6 (minor), 151.0 (major), 130.1 (minor), 129.2 (major), 127.9 (minor), 126.6 (minor), 126.4 (major), 126.2 (minor), 117.3 (major), 117.1 (minor), 115.9 (minor), 115.5 (major), 113.9 (major), 112.7 (minor), 92.9 (minor), 92.1 (major).

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_9\text{H}_7\text{N}_4\text{S}$  [M]<sup>+</sup>: 203.0391, found: 203.0384.

#### (3-Amino-4-cyanophenyl)carbamothioyl cyanide (3d)

Yellow powder; yield: 0.136 g (21%), m.p.: 177-178 °C.

IR (neat)  $\nu_{\text{max}}$ : 3480, 3374, 3022, 2214, 1631, 1506, 1396, 1316, 1280, 845, 784  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.44 (s, 1H, major), 7.56 – 7.43 (m, 2H, major and minor), 7.01 (dd,  $J$  = 8.5, 2.0 Hz, 0.9H, major), 6.81 (d,  $J$  = 2.0 Hz, 0.1H, minor), 6.73 – 6.67 (dd,  $J$  = 8.5, 2.0 Hz, 0.1H, minor), 6.41 – 6.33 (s, 2H, major and minor).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  161.99 (major and minor), 152.42 (minor), 152.25 (major), 142.35 (major and minor), 134.22 (minor), 133.61 (major), 117.67 (major and minor), 113.73 (major and minor), 110.35 (minor), 110.17 (major), 108.16 (minor), 107.68 (major), 92.06 (major and minor).

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_9\text{H}_5\text{N}_4\text{S}$  [M]<sup>+</sup>: 201.0235, found: 201.0243.

#### 2-Cyanobenzo[d]thiazoles Derivatives I, II, V, VI and VII; general procedure

Cyanothioformamide **3** (1.0 equiv), CuI (50 mol %), LiBr or KI (2.0 equiv) and PdCl<sub>2</sub> (20 mol%) were dissolved in an anhydrous mixture of DMF/DMSO (1:1, v/v) (0.025 M). The resulting mixture was stirred at 120 °C for 4h after which it was diluted with AcOEt and washed with water (3 times) and brine (1 time), dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified on silica gel with PE/CH<sub>2</sub>Cl<sub>2</sub> (50:50 to 0:100, v/v) as eluent.

#### Methyl 6-amino-2-cyanobenzo[d]thiazole-5-carboxylate (I)<sup>4</sup>

White solid; yield: 0.056 g (55%).

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.72 (s, 1H), 7.07 (s, 1H), 6.12 (s, 2H), 3.96 (s, 3H).

#### Methyl 5-amino-2-cyanobenzo[d]thiazole-6-carboxylate (II)<sup>4</sup>

White solid; yield: 0.076 g (76%).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.73 (s, 1H), 7.49 (s, 1H), 6.81 (s, 2H), 3.87 (s, 3H).

#### Methyl 6-amino-2-cyanobenzo[d]thiazole-7-carboxylate (III)<sup>4</sup>

Pale brown solid; yield: 4.35 g (76%).

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.02 (d,  $J$  = 9.0 Hz, 1H), 6.93 (d,  $J$  = 9.0 Hz, 1H), 6.33 (s, 2H), 4.05 (s, 3H).

#### Methyl 7-amino-2-cyanobenzo[d]thiazole-6-carboxylate (IV)<sup>4</sup>

Orange solid; yield: 450 mg (28%).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.98 (d,  $J$  = 8.9 Hz, 1H), 7.58 (s, 2H), 7.39 (d,  $J$  = 8.9 Hz, 1H), 3.86 (s, 3H)

#### 6-Aminobenzo[d]thiazole-2,7-dicarbonitrile (V)<sup>1c</sup>

Pale brown solid; yield: 1.92 g (67%).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.11 (d,  $J$  = 9.3 Hz, 1H), 7.31 (s, 2H), 7.10 (d,  $J$  = 9.3 Hz, 1H).

#### 6-Aminobenzo[d]thiazole-2,5-dicarbonitrile (VI)

Brown powder; yield: 0.113 g (38%). m.p.: >350 °C.

IR (neat)  $\nu_{\text{max}}$ : 3426, 3343, 3231, 2222 (CN), 1653, 1600, 1529, 1472, 1260, 1304, 1260, 1130, 852, 895, 835, 852, 895, 835, 513, 416  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.47 (s, 1H), 7.45 (s, 1H), 6.71 (s, 2H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  150.4, 142.6, 142.4, 132.7, 130.0, 116.8, 113.5, 105.3, 97.5.

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_9\text{H}_5\text{N}_4\text{S}$  [M]<sup>+</sup>: 200.0157, found: 200.0162.

#### 5-Aminobenzo[d]thiazole-2,6-dicarbonitrile (VII)

Yellow solid; yield: 0.039 g (61%). m.p.: 243-244 °C.

IR (neat)  $\nu_{\text{max}}$ : 3449, 3358, 3243, 2216, 1633, 1448, 1331, 1133, 846, 519  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.49 (d,  $J$  = 1.6 Hz, 1H), 7.48 (d,  $J$  = 1.7 Hz, 1H), 6.33 (s, 2H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  155.81, 150.56, 141.49, 128.70, 122.30, 116.99, 113.20, 107.29, 98.41.

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_9\text{H}_3\text{N}_4\text{S}$  [M]<sup>+</sup>: 199.0078, found: 199.0085.

#### Benzo[d]thiazoles derivatives Ia – VIIa; general procedure

In a sealed vial, a solution of 2-cyanobenzo[d]thiazole **I-VII** (1.0 eq) in 48% HBr<sub>aq</sub> or 37% HCl<sub>aq</sub> (0.3M) was heated at 100 °C under microwave irradiation for a defined time. The resulting solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> and neutralized with an aqueous saturated solution of NaHCO<sub>3</sub>. The organic layer was washed with water, then dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. The crude product was purified on silica gel with CH<sub>2</sub>Cl<sub>2</sub>/AcOEt (100:0 to 50:50, v/v) as eluent.

#### Methyl 6-aminobenzo[d]thiazole-5-carboxylate (Ia)

Conditions: 48% HBr<sub>aq</sub> (0.3M), 10min

Beige product; yield: 0.067 g (77%); m.p.: 130-131 °C.

IR (neat)  $\nu_{\text{max}}$ : 3445, 3298, 2923, 690, 1613, 1433, 1294, 1225, 1167, 1079, 837, 785, 534  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.69 (s, 1H), 8.64 (s, 1H), 7.14 (s, 1H), 5.82 (s, 2H), 3.94 (d, 3H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  168.5, 150.7, 148.0, 145.4, 141.0, 126.5, 111.6, 106.9, 52.1.

HRMS (EI<sup>+</sup>)  $m/z$ , calcd for  $\text{C}_9\text{H}_9\text{N}_2\text{O}_2\text{S}$  [M]<sup>+</sup>: 209.0385, found: 209.0385.

#### Methyl 5-aminobenzo[d]thiazole-6-carboxylate (IIa)

Conditions: 37% HCl<sub>aq</sub> (0.3M), 90min

Beige product; yield: 0.038 g (28%). m.p.: 138-139 °C.

IR (neat)  $\nu_{\text{max}}$ : 3375, 3268, 3063, 2650, 1685, 1605, 1591, 1465, 1427, 1284, 1246, 1183, 1118, 855, 566  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.39 (s, 1H), 8.51 (s, 1H), 7.39 (s, 1H), 6.65 (s, 2H), 3.84 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  167.38, 161.07, 157.62, 149.76, 125.45, 120.25, 109.91, 107.92, 51.80.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>9</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>S [M]<sup>+</sup>: 209.0385, found: 209.0390.

#### Methyl 6-aminobenzo[d]thiazole-7-carboxylate (IIIa)

Conditions: 37% HCl<sub>aq</sub> (0.3M), 45min

Beige product; yield: 0.190 g (53%); m.p.: 112-113°C.

IR (neat)  $\nu_{\max}$  3495, 3373, 3042, 2962, 2120, 1682, 1600, 1554, 1454, 1420, 1269, 1117, 999, 846, 812 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  8.97 (s, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.11 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 3.92 (s, 3H).

<sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  166.74, 152.23, 151.08, 144.20, 135.47, 128.90, 117.43, 100.89, 51.83.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>9</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>S [M]<sup>+</sup>: 209.0385, found: 209.0388.

#### Methyl 7-aminobenzo[d]thiazole-6-carboxylate (IVa)

Conditions: 37% HCl<sub>aq</sub> (0.3M), 30min

Beige product; yield: 0.038 g (28%). m.p.: 166-167 °C.

IR (neat)  $\nu_{\max}$  3443, 3062, 1691, 1626, 1594, 1424, 1298, 1247, 855 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  9.45 (s, 1H), 7.89 (dd, *J* = 8.8 Hz, 1H), 7.34 – 7.24 (m, 3H), 3.84 (s, 3H).

<sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  168.04, 158.58, 157.10, 146.90, 128.79, 120.82, 110.43, 104.11, 51.71.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>9</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>S [M]<sup>+</sup>: 209.0385, found: 209.0378.

#### 6-Aminobenzo[d]thiazole-7-carbonitrile (Va)

Conditions: 37% HCl<sub>aq</sub> (0.3M), 30min

White powder; yield: 0.200 g (46%). m.p.: 215-216 °C.

IR (neat)  $\nu_{\max}$ : 3437, 3368, 3090, 2219, 1645, 1609, 1410, 875 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  9.07 (d, *J* = 1.5 Hz, 1H), 7.98 (dd, *J* = 9.1, 1.5 Hz, 1H), 6.95 (dd, *J* = 9.1, 1.5 Hz, 1H), 6.62 (s, 2H).

<sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  151.74, 150.63, 144.01, 137.71, 128.64, 116.83, 115.78, 83.72.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>8</sub>H<sub>6</sub>N<sub>3</sub>S [M]<sup>+</sup>: 176.0282, found: 176.0284.

#### 6-Aminobenzo[d]thiazole-5-carbonitrile (VIa)

Conditions: 48% HBr<sub>aq</sub> (0.3M), 10min

Beige powder; yield: 0.038 g (43%). m.p.: 235-236°C.

IR (neat)  $\nu_{\max}$ : 3446, 3363, 3086, 2217, 1640, 1611, 1482, 881, 841, 418 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  9.07 (s, 1H), 8.20 (s, 1H), 7.38 (s, 1H), 6.13 (s, 2H).

<sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  153.07, 148.53, 144.27, 141.13, 127.11, 117.68, 106.07, 94.95.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>8</sub>H<sub>6</sub>N<sub>3</sub>S [M]<sup>+</sup>: 176.0282, found: 176.0285.

#### 5-Aminobenzo[d]thiazole-6-carbonitrile (VIIa)

Conditions: 37% HCl<sub>aq</sub> (0.3M), 60min

Pale yellow powder; yield: 0.034 g (39%). m.p.: 216-217 °C.

IR (neat)  $\nu_{\max}$ : 3388, 3320, 3206, 2217, 1644, 1600, 1545, 1436, 1335, 1302, 855 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  9.43 (s, 1H), 8.32 (s, 1H), 7.40 (s, 1H), 6.04 (s, 2H).

<sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  161.19, 157.55, 149.81, 127.57, 121.15, 117.71, 107.14, 95.01.

HRMS (EI<sup>+</sup>) m/z, calcd for C<sub>8</sub>H<sub>6</sub>N<sub>3</sub>S [M]<sup>+</sup>: 176.0282, found: 176.0295.

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## Supporting Information

YES (this text will be updated with links prior to publication)

## Primary Data

NO.

## Conflict of Interest

The authors declare no conflict of interest.

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