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A tandem aza-Friedel–Crafts reaction/Hantzsch cyclization: a simple procedure to access polysubstituted 2-amino-1,3-thiazoles

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ABSTRACT

A tandem aza-Friedel–Crafts reaction/Hantzsch cyclization is described to access various polysubstituted 2-amino-1,3-thiazoles from electron-rich (hetero)-aromatic rings, aldehydes, thiourea and α-chloroketones.

1. Introduction

The 2-amino-1,3-thiazoles are biologically important compounds with a broad range of activity like antiviral,[1] antifungal,[2] antiprion,[3] anti-inflammatory[4] and antibacterial activities.[5] Some 2-amino-1,3-thiazole derivatives have been reported as ligands of thrombopoietin,[6] neuropeptide Y5[7] and adenosine receptors[8] and as inhibitors of several physiological important enzymes like cyclin-dependant kinase,[9] tyrosine kinases (in the antitumoral agent dasatinib),[10] poly (ADP-Ribose) polymerase,[11] urokinase[12] etc. 2-amino-1,3-thiazole is also considered as a heterocyclic bioisostere of the phenol moiety in the widely used anti-parkinsonian agent pramipexol[13] and in morphinan derivatives.[14] Due to their broad utility in the pharmaceutical industry, the development of methods that give quick access to diverse 2-amino-1,3-thiazole libraries would provide additional lead molecules for drug discovery.

The Hantzsch reaction of α-halocarbonyl compounds with thioureas is the most commonly used method for the synthesis of 2-amino-1,3-thiazoles. However preparation of diverse monosubstituted thiourea libraries is time consuming and is often limited by the low solubility of compounds making them difficult to purify. In this report, we considered adapting aza-Friedel–Crafts reaction (AFCR) to access diverse methylene thiourea precursors, that could react to lead to substituted 2-amino-1,3-thiazoles in a one-pot process without any hazardous purification of the intermediates. In AFCR, three different molecules including a nitrogen source (amine, amide, urea), an aldehyde and an electron-rich aromatic ring (naphtol,[15] indole,[16] pyrrole[17] and furan,[18] etc…) are put together to yield one final product and water as the only byproduct. It is catalyzed by many Brønsted as well as Lewis acids.[15–18] More recently, it has been demonstrated that vitamin B1, also known as Thiamine hydrochloride, could catalyze the reaction.[19] To the best of our knowledge, although AFCRs are well described on amines, amides or urea only one example of AFCR with thiourea[15i] has been reported so far. In this case, solid silica sulfuric acid was used as catalyst to condense in a solvent-free procedure thiourea, liquid aldehydes, and β-naphthol. However, the reported condition is hardly compatible with our second objective, i.e., telescoping two reactions (AFCR and Hantzsch to heterocyclization) in a one-pot procedure.

This study is devoted to a tandem AFCR/Hantzsch reaction in a one-pot procedure to quickly access polysubstituted 2-amino-1,3-thiazoles (Scheme 1). In a first step, an electron-rich aromatic ring (ArH **1**) reacted with an aldehyde **2** and the thiourea **3** to afford a substituted methylene thiourea **4**. In a second step, the thiourea intermediate reacted in a one-pot procedure with an α-chloroketone **5** to lead to 2-amino-1,3-thiazole **6**. Three electron-rich aromatic rings, i.e., imidazo[1,2-*a*]pyridine (IP), β-naphthol and indole were considered as privileged structure because of their association with a variety of biological activities.[20] We were mainly interested by the IP derivatives since some 4-(2-methylimidazo[1,2-*a*]pyridin-3-yl) aminothiazoles have recently been reported as highly potent inhibitors of Hedgehog pathway-dependent cell proliferation.[20h,i]

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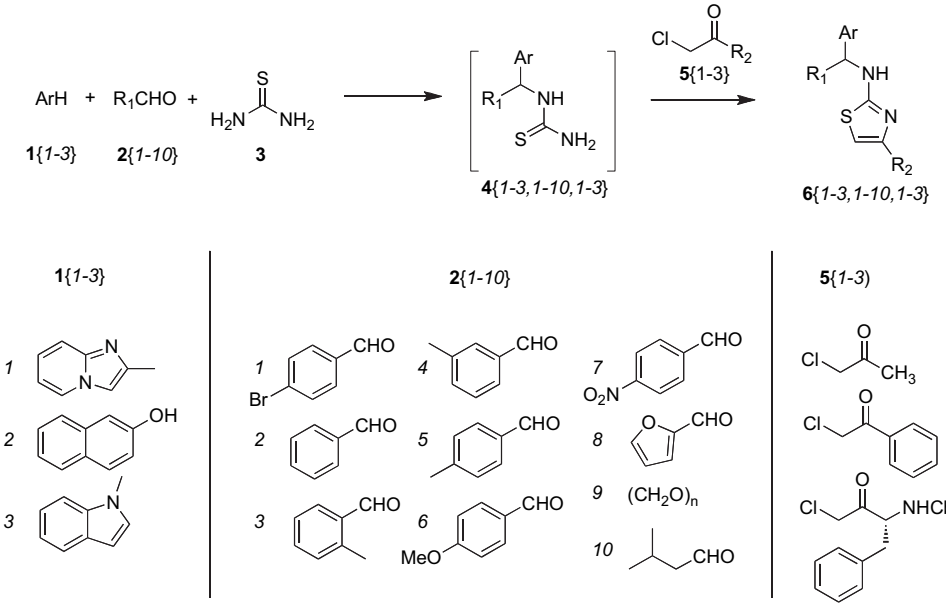
However, while IP is considered as an electron-rich aromatic ring,[21] no example of AFCR has been reported so far. Therefore, the first part of this paper is dedicated to the study of the aza-Friedel–Crafts reaction on the IP heterocycle to access imidazo[1,2-*a*]pyridin-3-yl methylene thioureas. The second part deals on the synthesis of polysubstituted 2-amino-1,3-thiazoles through a tandem AFCR/Hantzsch reaction without purification of the thiourea intermediates.

addition of 0.1 equiv $TiCl_4$ inhibited the reaction. We assumed that it results from a complexation of the titanium salts with the imidazo[1,2-*a*]pyridin-3-yl methylene thiourea.

Therefore we turned out our attention on the use of Thiamine, HCl as a promising alternative to $TiCl_4$ for a tandem AFCR/Hantzsch cyclization. We first controlled that Thiamine, HCl did not inhibit the Hantzsch reaction of thiourea **4**{1,1} and chloroacetone (data



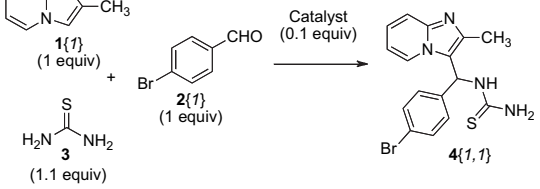
Scheme 1. Strategy for the synthesis of polysubstituted 2-amino-1,3-thiazoles. Chemset numbering of compounds **4**{*x*,*y*} and **6**{*x*,*y*,*z*} is standardized as follows: **4**{building block **1**, building block **2**} and **6**{building block **1**, building block **2**, building block **5**}.

2. Results and discussion

In order to access imidazo[1,2-*a*]pyridin-3-yl methylene thioureas by aza-Friedel–Crafts reaction, we initiated our study by subjecting 2-methylimidazo[1,2-*a*]pyridine **1**{1}, *p*-bromo-benzaldehyde **2**{1} and thiourea to various reaction conditions (Table 1). Several catalysts including Brønsted acids (Table 1, entries 2 and 4) and Lewis acids (Table 1, entries 5–12) were screened at 10 mol %. While all tested catalysts provided the desired thiourea **4**{1}, the best results were obtained using $TiCl_4$ (Table 1, entries 10–12). It appeared that the reaction was highly dependent on temperature limiting solvents to those having a boiling point higher than 100 °C, i.e., *n*-butanol or 1,4-dioxane (Table 1, entries 10–12). Since the reaction was not performed in anhydrous conditions, $TiCl_4$ could generate hydrochloride acid. However, when using 0.4 equiv HCl as catalyst the yield of the AFCR was decreased to 24% (data not shown) compared to 82% yield obtained with 0.1 equiv $TiCl_4$. This result suggested a catalytic effect of the titanium species.

We explored the scope of the AFCR on a set of various aromatic and aliphatic aldehydes, i.e., benzaldehyde **2**{2}, *o*-, *m*-, *p*-tolualdehyde **2**{3–5}, *p*-anisaldehyde **2**{6}, 4-nitrobenzaldehyde **2**{7} and isovaleraldehyde **2**{10} with $TiCl_4$ as catalyst. 1,4-Dioxane was preferred to *n*-butanol since in this solvent several compounds spontaneously precipitated at room temperature. Purities were higher than 85% determined by analytical HPLC for all thiourea derivatives. A fraction of each compound was purified by reverse phase preparative HPLC for characterization (Table 2). Encouraged by the results obtained from AFCRs, we turned our attention to the Hantzsch heterocyclization. The cyclization of thiourea **4**{1,1} and chloroacetone occurred at temperature higher than 70 °C in protic solvents, i.e., ethanol or *n*-butanol. We were surprised that the

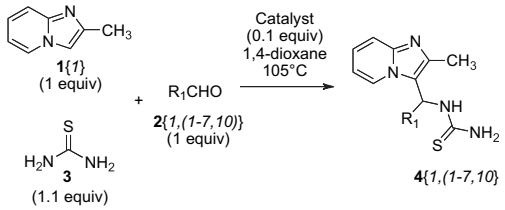
Table 1
aza-Friedel–Crafts reaction on imidazo[1,2-*a*]pyridine **1**{1} using various reaction conditions



Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield[a] (%)
1	None	AcOH	80	24	0[b]
2	None	AcOH	117	24	22[b]
3	None	*n*-BuOH	117	24	22[b]
4	*p*-TSA	*n*-BuOH	117	24	43[b]
5	$BiCl_3$	*n*-BuOH	117	3	52[b]
6	$FeCl_3$	*n*-BuOH	117	3	53[b]
7	$Yb(OTf)_3$	*n*-BuOH	117	3	31[b]
8	$InCl_3$	*n*-BuOH	117	3	39[b]
9	$SnCl_2$	*n*-BuOH	117	3	35[b]
10	$TiCl_4$	EtOH	80	3	0[b]
11	$TiCl_4$	*n*-BuOH	117	3	80[b]
12	$TiCl_4$	1,4-Dioxane	105	3	82[b]
13	Thiamine, HCl	EtOH	80	24	0[b]
14	Thiamine, HCl	DMF	120	3	30[b]
15	Thiamine, HCl	*n*-BuOH	117	3	36[b]
16	Thiamine, HCl	*n*-BuOH	117	3	89[c]
17	Thiamine, HCl	1,4-Dioxane	105	3	80[c]

[a] Experimental conditions: see Experimental section 4.2.
[b] Volume of solvent 2 mL; concentration of **1**{1}: 0.2 M.
[c] Volume of solvent 0.5 mL; concentration of **1**{1}: 0.8 M.

Table 2
aza-Friedel–Crafts reaction of aryl and alkyl aldehydes, thiourea and imidazo[1,2-*a*]pyridine **1**{1}



Entry	Compound	R_1	Catalyst	Isolated yield (%)
1	**4**{1,1}	4-BrC_6H_4	$TiCl_4$	71
			Thiamine, HCl	64
2	**4**{1,2}	C_6H_5	$TiCl_4$	79
			Thiamine, HCl	60
3	**4**{1,3}	2-MeC_6H_4	$TiCl_4$	73
			Thiamine, HCl	55
4	**4**{1,4}	3-MeC_6H_4	$TiCl_4$	84
			Thiamine, HCl	35
5	**4**{1,5}	4-MeC_6H_4	$TiCl_4$	72
			Thiamine, HCl	81
6	**4**{1,6}	4-MeOC_6H_4	$TiCl_4$	63
			Thiamine, HCl	34
7	**4**{1,7}	4-$NO_2C_6H_4$	$TiCl_4$	52
			Thiamine, HCl	NR[a]
8	**4**{1,10}	$(CH_3)_2CHCH_2$	$TiCl_4$	15
			Thiamine, HCl	NR[a]

[a] NR: no reaction.

not shown) then we focused on its catalytic activity for the AFCRs. Solvent, temperature and concentration effects were investigated. Like with $TiCl_4$, reaction was highly dependent on temperature conditions (Table 1, entries 13–17). Reaction concentration showed to be another crucial parameter: crude yields increased when changing concentration of 2-methylimidazo[1,2-*a*]pyridine from 0.2 M to 0.8 M (Table 1, entries 15–16). Best results were obtained at 0.8 M 2-methylimidazo[1,2-*a*]pyridine in refluxing 1,4-dioxane or n-butanol with 10 mol % Thiamine, HCl. Although yields of AFCRs were often lower than with $TiCl_4$ (Table 2), Thiamine, HCl was chosen as catalyst for the tandem AFCR/Hantzsch procedure. 2-Methylimidazo[1,2-*a*]pyridine **1**{1}, aldehydes and thiourea were stirred in refluxing 1,4-dioxane with 10 mol % of Thiamine, HCl. After 3 h stirring, the mixture was cooled down to 80 °C, then a solution of α-chloroketone in ethanol was added. Addition of ethanol as cosolvent was required for conversion of the methylene thioureas **4**{1,1–5}. Cyclizations were completed after 3.5 h leading to 2-amino-1,3-thiazole derivatives with 37%–50% yields after purification (Fig. 1, **6**{1,1–5,1-2}).

The procedure was tested on two more electron-rich aromatic rings, i.e., β-naphtol **1**{2} and *N*-methylindole **1**{3}. A variety of starting materials including 10 aldehydes **2**{1–10} and three α-chloroketones **5**{1–3} were used. With β-naphthol **1**{2}, the AFCRs occurred smoothly at 78 °C using Thiamine, HCl or $TiCl_4$. Optimization of the experimental conditions of the all process indicated that ethanol was the best solvent whatever the catalyst used (data not shown). After cooling the reaction mixture to 40 °C, the Hantzsch cyclization was performed by simply adding the α-chloroketone. With Thiamine, HCl, three different amino-1,3-thiazole derivatives (Fig. 1, **6**{2,1,1}, **6**{2,2,1}, **6**{2,8,1}) were obtained in low to moderate yields (31%–53%). This resulted from a long AFCR time (almost one day) leading to some degradation and making compounds hard to purify (Fig. 1, **6**{2,6,1}, **6**{2,7,1}). By using 10 mol % of $TiCl_4$ instead of Thiamine, HCl, the AFCR time was overall divided by 5 limiting byproduct formation. The optimized procedure tolerated the use of aromatic aldehydes, as well as paraformaldehyde (Fig. 1, **6**{2,9,1}) and aliphatic aldehydes (Fig. 1, **6**{2,10,1}). Such a result was unexpected since only few examples of AFCRs with aliphatic aldehydes have been reported so far. The presence of a *p*-electron donating group on benzaldehyde led to a decrease in yield (Fig. 1, **6**{2,5,1}, **6**{2,6,1}),

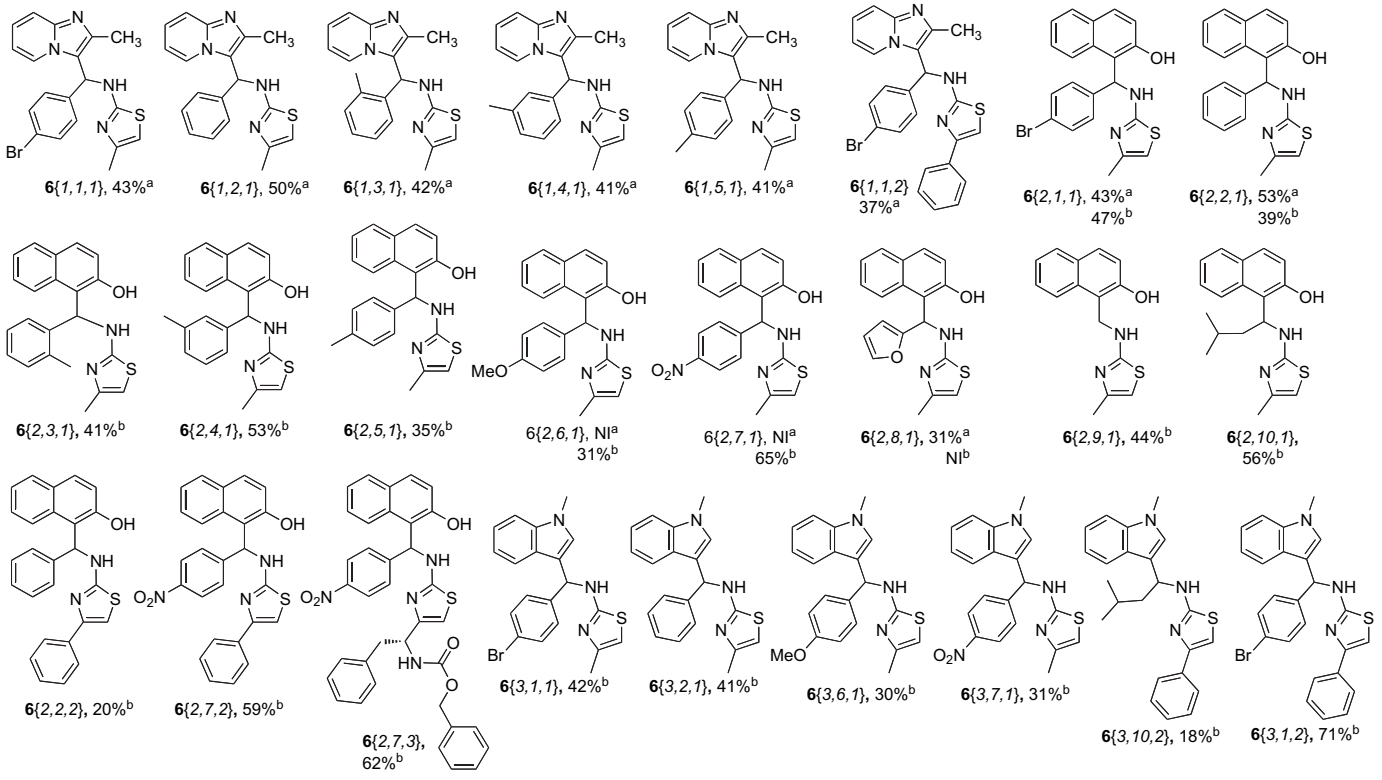


Fig. 1. Library of polysubstituted 2-Amino-1,3-thiazoles (Isolated yield of analytically pure compounds. [a]Method A: Thiamine, HCl (0.1 equiv) was used as catalyst. [b]Method B: $TiCl_4$ (0.1 equiv) was used as catalyst. NI: not isolated).

while a *p*-electron withdrawing group increased the yield (Fig. 1, **6**{2,1,1}, **6**{2,7,1}). The Hantzsch cyclization proceeded with diverse α-chloroketones like chloroacetone, chloroacetophenone and functionalized reagents (Fig. 1, **6**{2,2,2}, **6**{2,7,2}, **6**{2,7,3}). Finally, the overall process was also tested on *N*-methylindole (Fig. 1, **6**{3,*x*,*y*}). This electron-rich aromatic ring appeared much more reactive than β-naphthol and IP. Best results were obtained when performing the AFCR in THF at 0 °C using $TiCl_4$ as catalyst. However, the formation of the well-known 3,3′-(arylmethylene)bis(1-methyl-1*H*-indole) byproduct[22] is observed in the range of 10–20% yield. The Hantzsch cyclization was done at 70 °C with ethanol as cosolvent, leading to 2-amino-1,3-thiazole derivatives with 18%–71% yields after purification.

3. Conclusion

We developed a new tandem procedure consisting on an aza-Friedel–Crafts reaction and a Hantzsch cyclization to access polysubstituted 2-amino-1,3-thiazoles from simple precursors. An electron-rich aromatic ring, i.e., IP, β-naphthol or indole reacted with an aldehyde and the thiourea to afford a substituted methylene thiourea intermediate that reacted in a one-pot procedure with an α-chloroketone to lead to the desired product. To the best of our knowledge, this is the first time that IP was submitted to AFCRs. While IP is considered as an aza-indole analogue, it presented some significant differences in reactivity compared to indole. The key of the procedure was the choice of the appropriate catalyst for the AFCR, i.e., Thiamine, HCl for IP and $TiCl_4$ for β-naphthol or indole. The reaction, which was simple and allowed the introduction of at least three diversity points, has been exemplified on 25 compounds. A following study will be devoted to the development of an asymmetric version of this process.

4. Experimental section

4.1. General information

Commercially available reagents and solvents were used without further purification. Reactions were monitored by HPLC using an analytical Chromolith Speed Rod RP-C18 185 Pm column (50×4.6 mm, 5 μm) using a flow rate of 3.0 mL/min, and gradients of 100/0 to 0/100 eluants A/B over 5 min, in which eluants A=H_2O/0.1% TFA and BCH_3CN/0.1% TFA. Detection was at 214 nm using a Photodiode Array detector. Retention times are reported as follows: t_R (min). ^1H and ^{13}C NMR spectra were recorded at room temperature in deuterated solvents. Chemical shifts (δ) are given in parts per million relative to TMS or relative to the solvent [^1H: δ ($CDCl_3$)=7.24 ppm; ^{13}C: δ ($CDCl_3$)=77.2 ppm]. The following abbreviations are used to designate the signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Analytical thin-layer chromatography (TLC) was performed using aluminium-backed silica gel plates coated with a 0.2 mm thickness of silica gel or with aluminium oxide 60 F_{254}, neutral. LC–MS spectra (ESI) were recorded on an HPLC using an analytical Chromolith Speed Rod RP-C18 185 Pm column (50×4.6 mm, 5 μm); solvent A, water/HCOOH 1‰; solvent B, CH_3CN/HCOOH 1‰; gradient, 0% solvent B to 100% solvent B in solvent A in 3 min; flow rate, 3.0 mL min^{-1}. Melting points (mp) are uncorrected and were recorded on a capillary melting point apparatus.

4.2. Condition screening of the aza-Friedel–Crafts reaction on imidazo[1,2-*a*]pyridine 1a (Table 1)

To a solution of 2-methylimidazo[1,2-*a*]pyridine **1**{*1*} (50 mg; 0.38 mmol) were added thiourea (32 mg; 1.1 equiv), *p*-bromobenzaldehyde (70 mg; 1.0 equiv) and the catalyst (0.1 equiv). The reaction mixture was stirred for 3–24 h under reflux. Crude yield was determined by HPLC analysis using 4-hydroxymethylbenzoate as internal standard: 15 μL sample was dissolved in 4 mL methanol containing 4-hydroxymethylbenzoate (0.1 mg/mL) as internal standard. Crude yield was determined by quantitative HPLC titration at 254 nm relatively to the standard.

4.3. Synthesis of methylene thiourea derivatives 4{1,*x*}

To a solution of 2-methylimidazo[1,2-*a*]pyridine **1**{1} (100 mg; 0.76 mmol) in 1,4-dioxane (1 mL) was added thiourea (64 mg; 1.1 equiv), aldehyde (1.0 equiv) and the catalyst $TiCl_4$ or Thiamine, HCl (0.1 equiv). The reaction mixture was stirred for 3 h at 105 °C then cooled down to room temperature. After addition of 10 mL water, pH was adjusted to 10 by addition of 28% aqueous ammonia. The precipitate was collected by filtration, dried and washed by ~2 mL of diethylether (purities >85% by HPLC).

For full characterization, a fraction of each compound was dissolved in DMSO/TFA (5% v/v) and purified by semi-preparative reverse phase chromatography (RP-C18 Delta-Pak 15 μm, 100 Å, 25×100 mm; solvent A, water/TFA 1‰; solvent B, acetonitrile/TFA 1‰; gradient, 5% solvent B to 15% in 5 min then 15%–40% solvent B in solvent A in 30 min; flow rate, 20 mL min^{-1}).

*4.3.1. N-[(4-Bromophenyl)(2-methylimidazo[1,2-a]pyridin-3-yl) methyl]thio urea **4**{1,1}.* White solid. Using $TiCl_4$ as catalyst: isolated yield: 71%. Using Thiamine, HCl as catalyst: isolated yield: 64%. ^1H NMR (DMSO, 300 MHz): δ ppm 2.17 (3H, s); 7.31 (1H, d, *J*=8 Hz); 7.32 (2H, d, *J*=8.5 Hz); 7.51 (1H, td, *J*=6.5, 1.5 Hz); 7.64 (2H, d, *J*=8.5 Hz); 7.90–8.00 (2H, m); 8.61 (1H, d, *J*=6.5 Hz); 9.10 (1H, d, *J*=8 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 10.6; 51.0; 112.3; 116.8; 118.8; 121.3; 121.5; 126.5; 129.0 (2C); 131.8 (2C); 132.3; 132.4; 136.6; 138.6; 183.1. HPLC, t_R=1.27 min. HPLC, t_R=1.18 min. LC–MS (ESI^+): *m*/*z* 375.0, 377.0 $[M+H]^+$. HRMS calcd for $C_{16}H_{16}N_4BrS$ 375.0279, found 375.0273. FT-IR: ν_{max} (cm^{-1}) 3301; 3055; 1673; 1529; 1449; 1397; 1357; 1199; 1176; 1128; 1024; 1006; 823; 799; 158; 719. Mp: 194.8 °C.

*4.3.2. N-[(2-Methylimidazo [1,2-a]pyridin-3-yl)(phenyl)methyl]thiourea **4**{1,2}.* White solid. Using $TiCl_4$ as catalyst: isolated yield: 79%. Using Thiamine, HCl as catalyst: isolated yield: 60%. ^1H NMR (DMSO, 300 MHz): δ ppm 2.19 (3H,s); 7.27 (1H, d, *J*=6 Hz); 7.28–7.50 (7H, m); 7.86–7.97 (2H, m); 8.60 (1H, d, *J*=5 Hz); 8.95 (1H, d, *J*=6 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 10.7; 51.6; 112.5; 114.9; 116.5; 121.8; 126.3; 126.8 (2C); 128.2; 128.9 (2C); 131.8; 137.0; 138.8; 183.0. HPLC, t_R=1.05 min. LC–MS (ESI^+): *m*/*z* 297.2 $[M+H]^+$. HRMS calcd for $C_{16}H_{17}N_4S$ 297.1174, found 297.1172. FT-IR: ν_{max} (cm^{-1}) 3290; 1672; 1623; 1568; 1529; 1418; 1193; 1130; 836; 799; 760; 748; 721. Mp: 175.3 °C.

*4.3.3. N-[(2-Methylimidazo [1,2-a]pyridin-3-yl)(2-methylphenyl)methyl] thiourea **4**{1,3}.* White solid. Using $TiCl_4$ as catalyst: isolated yield: 73%. Using Thiamine, HCl as catalyst: isolated yield: 55%. ^1H NMR (DMSO/TFA, 300 MHz): δ ppm 2.10 (3H, s); 2.28 (3H, s); 7.13–7.33 (5H, m); 7.55 (1H, td, *J*=6.5, 1.5 Hz); 7.96 (2H, m); 8.58 (1H, d, *J*=6.5 Hz); 8.87 (1H, d, *J*=7.0 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 13.0; 18.9; 50.9; 113.7; 115.9; 118.9; 124.9; 126.2; 126.6 (2C); 128.3; 131.2; 136.4; 137.4; 139.5; 142.6; 183.0. HPLC, t_R=0.84 min. LC–MS (ESI^+): *m*/*z* 311.2 $[M+H]^+$. HRMS calcd for $C_{17}H_{19}N_4S$ 311.1330, found 311.1335. FT-IR: ν_{max} (cm^{-1}) 3284; 3170; 1667; 1620; 1585; 1417; 1188; 1134; 836; 801; 751; 720. Mp: 208.6 °C.

*4.3.4. N-[(2-Methylimidazo [1,2-a]pyridin-3-yl)(3-methylphenyl) methyl] thiourea **4**{1,4}.* White solid. Using $TiCl_4$ as catalyst: isolated yield: 84%. Using Thiamine, HCl as catalyst: isolated yield: 35%. ^1H NMR (DMSO, 300 MHz): δ ppm 2.21 (3H, s); 2.31 (3H, s); 7.12–7.34

(6H, m); 7.47 (1H, td, *J*=6.5, 1 Hz); 7.89–7.97 (2H, m); 8.59 (1H, d, *J*=5 Hz); 8.95 (1H, d, *J*=6 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 11.1; 21.5; 52.0; 112.8; 116.9; 124.2; 126.7; 127.7; 129.2 (2C); 132.3; 132.9; 137.4; 138.7; 139.1; 183.5. HPLC, t_R=1.02 min. LC–MS (ESI$^+$): *m*/*z* 311.2 [M+H]$^+$. HRMS calcd for $C_{17}H_{19}N_4S$ 311.1330, found 311.1323. FT-IR: ν_{max} (cm^{-1}) 3282; 3178; 1672; 1621; 1575; 1416; 1199; 1134; 836; 801; 751; 720. Mp: 162.9 °C.

4.3.5. N-[(2-Methylimidazo [1,2-a]pyridin-3-yl)(4-methylphenyl) methyl] thiourea ***4****{1,5}*. White solid. Using $TiCl_4$ as catalyst: isolated yield: 72%. Using Thiamine, HCl as catalyst: isolated yield: 81%. ^{1}H NMR (DMSO, 300 MHz): δ ppm 2.07 (3H, s); 2.29 (3H, s); 6.85 (1H, t, *J*=6.5 Hz); 7.07 (2H, d, *J*=8.0 Hz); 7.19 (3H, m); 7.48 (2H, d, *J*=6.5 Hz); 8.05 (1H, d, *J*=6.05 Hz); 8.59 (1H, d, *J*=7 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 14.6; 21.0; 52.2; 112.3; 116.7; 120.0; 124.2; 124.6; 126.8; 129.7; 136.5; 137.0; 141.3; 143.8; 183.2. HPLC, t_R=1.10 min. LC–MS (ESI$^+$): *m*/*z* 311.2 [M+H]$^+$. HRMS calcd for $C_{17}H_{19}N_4S$ 311.1330, found 311.1324. FT-IR: ν_{max} (cm^{-1}) 3280; 3180; 1672; 1618; 1575; 1200; 1134; 840; 811; 753. Mp: 190.1 °C.

4.3.6. N-[(4-Methoxyphenyl)(2-methylimidazo [1,2-a]pyridin-3-yl) methyl]thiourea ***4****{1,6}*. White solid. Using $TiCl_4$ as catalyst: isolated yield: 63%. Using Thiamine, HCl as catalyst: isolated yield: 34%. ^{1}H NMR (DMSO, 300 MHz): δ ppm 2.23 (3H, s); 3.76 (3H, s); 6.97 (2H, d, *J*=9.0 Hz); 7.14 (1H, d, *J*=5.5 Hz); 7.26 (2H, d, *J*=9.0 Hz); 7.47 (1H, td, *J*=6.5, 1.5 Hz); 7.88–7.94 (2H, m); 8.58 (1H, d, *J*=5.5 Hz); 8.85 (1H, d, *J*=5.5 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 10.7; 51.2; 55.2; 112.4; 114.1 (2C); 114.15; 114.5; 116.5; 121.9; 126.3; 128.2 (2C); 131.8; 138.6; 159.11; 183.1. HPLC, t_R=1.15 min. LC–MS (ESI$^+$): *m*/*z* 327.1 [M+H]$^+$. HRMS calcd for $C_{17}H_{19}N_4OS$ 327.1280, found 327.1280. FT-IR: ν_{max} (cm^{-1}) 3358; 3296; 3183; 1671; 1622; 1566; 1513; 1434; 1256; 1205; 1177; 1131; 1034; 834; 798; 748; 722. Mp: 157.9 °C.

4.3.7. N-[(4-Nitrophenyl)(2-methylimidazo[1,2-a]pyridin-3-yl) methyl]thiourea ***4****{1,7}*. White solid. Using $TiCl_4$ as catalyst: isolated yield: 52%. ^{1}H NMR (DMSO, 300 MHz): δ ppm 1.95 (3H, s); 6.89 (1H, td, *J*=6.0, 1.0 Hz); 7.23 (1H, td, *J*=7.0, 1.0 Hz); 7.35 (1H, d, *J*=8.0 Hz); 7.45–7.52 (3H, m); 8.09 (1H, dd, *J*=6.0, 1.0 Hz); 8.21 (2H, d, *J*=9.0 Hz); 8.74 (1H, d, *J*=8.0 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 14.1; 51.7; 112.2; 116.1; 118.6; 123.8 (2C); 124.3; 124.7; 127.8 (2C); 140.7; 143.3; 146.8; 147.1; 183.2. HPLC, t_R=1.08 min. LC–MS (ESI$^+$): *m*/*z* 342.2 [M+H]$^+$. HRMS calcd for $C_{16}H_{16}N_5O_2S$ 342.1025, found 342.1024. Mp: 174.4 °C.

4.3.8. N-[3-Methyl-1-(2-methylimidazo[1,2-a] pyridin-3-yl)butyl] thiourea ***4****{1,10}*. White solid. Using $TiCl_4$ as catalyst: isolated yield: 15%. ^{1}H NMR (DMSO, 300 MHz): δ ppm 0.94 (6H, d, *J*=6.5 Hz); 1.62–1.71 (2H, m); 1.99–2.05 (1H, m); 2.57 (3H, s); 5.74 (1H, br); 7.36 (2H, br); 7.51 (1H, td, *J*=6.5, 1 Hz); 7.87 (1H, m); 8.0 (1H, d, *J*=5 Hz); 8.95 (1H, d, *J*=6 Hz). ^{13}C NMR (DMSO, 75 MHz): δ ppm 10.5; 21.7; 22.5; 24.5; 40.4; 47.0; 112.1; 116.6; 123.3; 126.5; 130.5; 131.8; 138.1; 183.1. HPLC, t_R=0.94 min. LC–MS (ESI$^+$): *m*/*z* 277.2 [M+H]$^+$. HRMS calcd for $C_{14}H_{21}N_4S$ 277.1487, found 277.1484. FT-IR: ν_{max} (cm^{-1}) 3188; 29,955; 1605 (br); 1501; 1397; 1354; 1051; 734. Mp: 201.9 (dec).

4.4. Synthesis of 2-amino-1,3-thiazoles 6{1,*x*,*y*}

To a solution of 2-methylimidazo[1,2-*a*]pyridine **1**{1} (100 mg; 0.76 mmol) in 1,4-dioxane (1 mL) were added thiourea (64 mg; 1.1 equiv), aldehyde (1.0 equiv) and Thiamine, HCl (26 mg; 0.1 equiv). The reaction mixture was stirred for 3 h at 105 °C then cooled down to 80 °C. A solution of α-chloromethylketone (0.91 mmol, 1.2 equiv) in 2 mL ethanol was added. The mixture was stirred at 80 °C for 3–3.5 h (monitoring by HPLC). Addition of 10 mL *n*-hexane and evaporation of the solvent under reduce pressure (13 Mbar, 40 °C) allowed complete removal of 1,4-dioxane. The residue was dissolved in DCM and purified by chromatography on neutral aluminium oxide gel (30 g aluminium oxide; eluant: DCM).

4.4.1. N-[(4-Bromophenyl)(2-methylimidazo[1,2-a]pyridin-3-yl) methyl]-4-methyl-1,3-thiazol-2-amine ***6****{1,1,1}*. White solid. recovering mass: 136 mg; yield 43%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.09 (3H, s); 2.67 (3H, s); 6.06 (1H, b); 6.21 (1H, s); 7.14–7.19 (3H, m); 7.55 (2H, d, *J*=8 Hz); 7.67–7.73 (1H, ddd, *J*=9, 7, 1 Hz); 8.13 (1H, dd, *J*=9, 1 Hz); 8.18 (1H, dd, *J*=7, 1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 10.9; 14.2; 54.6; 101.0; 114.2; 117.1; 117.3; 124.3; 126.6 (2C); 128.0; 131.5; 132.6 (2C); 133.3; 140.0; 141.0; 170.0. HPLC, t_R=1.13 min. LC–MS (ESI$^+$): *m*/*z* 413.1, 415.1 [M+H]$^+$. HRMS calcd for $C_{19}H_{18}N_4BrS$ 413.0436, found 413.0432. FT-IR: ν_{max} (cm^{-1}) 3175; 2920; 1636; 1516; 1487; 1439; 1393; 1355; 1301; 1209; 1131; 1072; 1010; 827; 736. Mp: 175 °C.

4.4.2. N-[(2-Methylimidazo[1,2-a]pyridin-3-yl)(phenyl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{1,2,1}*. White solid. m: 127 mg; yield 50%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.09 (3H, d, *J*=1.0 Hz); 2.25 (3H, s); 5.98 (1H, q, *J*=1.0 Hz); 6.16 (1H, s); 6.58 (1H, td, *J*=7.0, 1.5 Hz); 7.06 (1H, ddd, *J*=9.0, 7.0, 1.5 Hz); 7.24–7.31 (5H, m); 7.46 (1H, dt, *J*=9.0, 1.5 Hz); 7.88 (1H, td, *J*=7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.2; 17.2; 54.8; 102.2; 112.1; 117.0 (2C); 117.4; 124.0; 124.3; 126.7 (2C); 128.2; 129.1 (2C); 136.8; 137.7; 148.8. HPLC, t_R=1.02 min. LC–MS (ESI$^+$): *m*/*z* 335.3 [M+H]$^+$. HRMS calcd for $C_{19}H_{19}N_4S$ 335.1330, found 335.1331. FT-IR: ν_{max} (cm^{-1}) 3168; 2963; 2923; 1634; 1556; 1527; 1496; 1441; 1393; 1299; 1275; 1213; 1132; 836; 754; 743; 718; 682. Mp: 166 °C (dec).

4.4.3. N-[(2-Methylimidazo[1,2-a]pyridin-3-yl)(2-methylphenyl) methyl]-4-methyl-1,3-thiazol-2-amine ***6****{1,3,1}*. White solid. m: 111 mg; yield 42%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 1.98 (3H, s); 2.09 (3H, d, *J*=1.0 Hz); 2.19 (3H, s); 6.01 (1H, q, *J*=1.0 Hz); 6.14 (1H, s); 6.69 (1H, td, *J*=7.0, 1.5 Hz); 7.11–7.25 (4H, m); 7.34 (1H, d, *J*=7.5 Hz); 7.50 (1H, dt, *J*=9.0, 1.5 Hz); 7.95 (1H, dt, *J*=7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.3; 17.4; 19.1; 53.2; 102.0; 112.5; 116.6; 117.1; 123.9; 124.5; 126.5; 126.6; 128.6; 131.4; 135.8; 136.8; 142.7; 144.9; 149.3; 167.7. HPLC, t_R=0.99 min. LC–MS (ESI +): 349.1 [M+H]$^+$, 235.2. HRMS calcd for $C_{20}H_{21}N_4S$ 349.1487, found 349.1491. FT-IR: ν_{max} (cm^{-1}) 3163; 2920; 1630; 1559; 1521; 1500; 1395; 1377; 1345; 1299; 1274; 1217; 1140; 837; 734. Mp: 201 °C (dec).

4.4.4. N-[(2-Methylimidazo[1,2-a]pyridin-3-yl)(3-methylphenyl) methyl]-4-methyl-1,3-thiazol-2-amine ***6****{1,4,1}*. White solid. m: 109 mg; yield 41%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.13 (3H, d, *J*=1.0 Hz); 2.27 (3H, s); 2.41 (3H, s); 6.02 (1H, q, *J*=1.0 Hz); 6.14 (1H, s); 6.63 (1H, td, *J*=7.0, 1.0 Hz); 7.05–7.14 (4H, m); 7.20 (1H, d, *J*=8.0 Hz); 7.52 (1H, dt, *J*=9.0, 1.0 Hz); 7.94 (1H, dt, *J*=7.0, 1.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.2; 17.1; 21.5; 54.8; 102.2; 112.1; 116.9; 117.3; 123.6; 124.1; 124.3; 127.4; 129.0; 129.1; 137.5; 139.0; 142.8; 144.9; 148.7; 167.8. HPLC, t_R=1.03 min. HRMS calcd for $C_{20}H_{21}N_4S$ 349.1487, found 349.1493. FT-IR: ν_{max} (cm^{-1}) 3171; 2921; 1634; 1607; 1560; 1524; 1502; 1449; 1356; 1295; 1275; 1218; 1141; 1130; 785; 748; 734. Mp: 140–146 °C.

4.4.5. N-[(2-Methylimidazo[1,2-a]pyridin-3-yl)(4-methylphenyl) methyl]-4-methyl-1,3-thiazol-2-amine ***6****{1,5,1}*. White solid. m: 108 mg; yield 41%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.16 (3H, d, *J*=1.0 Hz); 2.32 (3H, s); 2.34 (3H, s); 6.03 (1H, q, *J*=1.0 Hz); 6.14 (1H, s); 6.64 (1H, tt, *J*=7.0, 1.5 Hz); 7.10–7.20 (6H, m); 7.52 (1H, d, *J*=9.0 Hz); 7.93 (1H, dt, *J*=7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 14.09; 17.1; 21.1; 54.6; 102.2; 112.1; 116.8; 117.4; 124.1; 124.4; 126.6 (2C); 129.8 (2C); 134.5; 138.1; 142.5; 144.7; 148.6; 167.8.

HPLC, t_R=1.03 min. LC–MS (ESI^+): 349.1 $[M+H]^+$, 235.3. HRMS calcd for $C_{20}H_{21}N_4S$ 349.1487, found 349.1496. FT-IR: ν_{max} (cm^{-1}) 3170; 2923; 1630; 1610; 1560; 1527; 1500; 1449; 1300; 1275; 1215; 1139. Mp: 135 °C (dec).

4.4.6. N-[(4-Bromophenyl)(2-methylimidazo[1,2-a]pyridin-3-yl) methyl]-4-phenyl-1,3-thiazol-2-amine ***6****{1,1,2}*. White solid. m: 133 mg; yield 37%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.69 (3H, s); 6.18 (1H, s); 6.69 (s, 1H); 7.13–7.21 (4H, m); 7.45–7.49 (2H, m); 7.57 (2H, d, *J*=8.0 Hz); 7.68–7.71 (3H, m); 8.13 (1H, d, *J*=8 Hz); 8.25 (1H, d, *J*=8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 11.1; 54.5; 100.4; 114.1; 117.8; 117.9; 124.3; 126.3(2C); 126.6; 128.1(2C); 129.6; 130.3(2C); 132.1; 132.4; 133.3(2C); 135.8; 140.8; 145.2; 170.0. HPLC, t_R=1.61 min. LC–MS (ESI^+): *m/z* 475.2, 477.2 $[M+H]^+$. HRMS calcd for $C_{24}H_{20}N_4BrS$ 475.0592, found 475.0596. FT-IR: ν_{max} (cm^{-1}) 1661; 1528; 1489; 1435; 1188; 1130; 1075; 1010; 829; 797; 747; 719. Mp: 80 °C.

4.5. Synthesis of 2-amino-1,3-thiazoles 6{2,*x*,*y*}

To a suspension of β-naphtol (1.39 mmol, 200 mg, 1.0 equiv) in ethanol (2 mL) were added thiourea (3.05 mmol, 233 mg, 2.2 equiv), aldehyde (1.39 mmol, 1.0 equiv) and $TiCl_4$ (0.139 mmol, 15.3 μL, 0.1 equiv). The heterogeneous mixture was stirred at 78 °C for 3 h. The reaction mixture was then cooled down to 40 °C and α-chloromethylketone (3.19 mmol, 2.3 equiv) was added and the reaction was stirred until the complete conversion of the previous intermediate (monitoring by HPLC). After evaporation of the solvent under reduce pressure (13 Mbar, 40 °C), the residue was dissolved in 50 mL DCM/Methanol (9/1 v/v) and extracted with saturated sodium hydrogenocarbonate solution (3×50 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent is evaporated in vacuo. The resulting crude mixture was purified by chromatography on silica gel (DCM, 100%, then DCM/ethyl acetate, 95/5 v/v, DCM/methanol, 98/2 v/v and DCM/methanol, 95/5 v/v).

4.5.1. N-[(4-Bromophenyl)(2-hydroxynaphth-1-yl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,1,1}*. White solid. Mp: 94.2 °C. Using Thiamine, HCl as catalyst: m: 253 mg; yield 43%. Using $TiCl_4$ as catalyst: m: 276 mg; yield 47%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.21 (3H, s); 5.91 (1H, s); 6.25 (1H, s); 7.10 (1H, d, *J*=8.7 Hz); 7.13–7.21 (4H, m); 7.32 (1H, t, *J*=7.4 Hz); 7.48 (1H, t, *J*=7.8 Hz); 7.71 (1H, d, *J*=9.2 Hz); 7.79 (1H, d, *J*=8.3 Hz); 7.86 (1H, d, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 13.8; 58.9; 99.5; 114.3; 119.0; 121.0; 121.9; 123.2; 127.5; 128.3 (2C); 128.7; 129.3; 131.0; 131.7 (2C); 132.4; 137.1; 138.4; 153.4; 169.7. LC–MS (ESI^+): *m/z* 425.04 $[M+H]^+$. HRMS calcd for $C_{21}H_{18}N_2OSBr$ 425.0317, found 425.0323. FT-IR: ν_{max} (cm^{-1}) 3115; 1663; 1597; 1438; 1185; 1132; 1010; 816; 720. Mp: 94.2 °C.

4.5.2. N-[(2-Hydroxynaphth-1-yl)(phenyl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,2,1}*. White solid. Using Thiamine, HCl as catalyst: m: 255 mg; yield 53%. Using $TiCl_4$ as catalyst: m: 187 mg; yield 39%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.21 (3H, d, *J*=1.0 Hz); 6.01 (1H, q, *J*=1.0 Hz); 6.63 (1H, s); 7.18–7.36 (6H, m); 7.68–7.77 (3H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.1; 57.5; 101.5; 122.9; 123.0; 126.6; 126.7; 127.3; 127.6; 128.7; 129.2; 129.4; 129.5; 129.6; 130.2; 141.0; 147.5; 154.7; 171.3. LC–MS (ESI^+): *m/z* 347.18 $[M+H]^+$. HRMS calcd for $C_{21}H_{19}N_2OS$ 347.1218; found 347.1225. FT-IR: ν_{max} (cm^{-1}) 3560; 2916; 2537; 1732; 1625; 1538; 1514; 1436; 1331; 1264; 1135; 1064; 1029; 978; 811; 740; 695. Mp: 115.7 °C.

4.5.3. N-[(2-Hydroxynaphth-1-yl)(2-methylphenyl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,3,1}*. White solid. m: 205 mg; yield 41%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.04 (3H, s); 2.17 (3H, s); 6.10 (1H, s); 6.84 (1H, s); 7.07–7.12 (3H, m) 7.16–7.40 (4H, m); 7.72 (1H, d, *J*=8.9 Hz); 7.76 (1H, d, *J*=7.8 Hz); 7.98 (1H, d, *J*=8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.4; 19.2; 53.5; 100.3; 117.4; 118.9; 121.9; 123.5; 125.3; 125.8; 126.6; 127.4; 128.3; 128.4; 129.2; 130.4; 132.7; 136.2 (2C); 139.9; 147.5; 167.8. LC–MS (ESI^+): *m/z* 361.2 $[M+H]^+$. HRMS calcd for $C_{22}H_{21}N_2OS$ 361.1375; found 361.1371. FT-IR: ν_{max} (cm^{-1}) 3346; 2954; 2581; 1735; 1540; 1435; 1331; 1270; 1136; 979; 812; 728; 700. Mp: 174.3 °C.

4.5.4. N-[(2-Hydroxynaphth-1-yl)(3-methylphenyl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,4,1}*. White solid. m: 265 mg; yield 53%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.21 (3H, s); 2.21 (3H, s); 6.00 (1H, d, *J*=1.2 Hz); 6.53 (1H, s); 6.99 (1H, d, *J*=6.4 Hz); 7.07–7.12 (2H, m); 7.20 (1H, s); 7.26–7.31 (2H, m); 7.38 (1H, t, *J*=7.5 Hz); 7.69 (1H, d, *J*=8.9 Hz); 7.76 (1H, d, *J*=8.1 Hz); 7.81 (1H, d, *J*=8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.1; 21.7; 58.0; 101.2; 118.6; 118.9; 122.7; 122.9; 123.8; 126.8; 127.3; 128.2; 128.6; 129.1; 129.3; 130.1; 132.7; 138.3; 140.9; 147.5; 154.6; 170.9. LC–MS (ESI^+): *m/z* 361.2 $[M+H]^+$. HRMS calcd for $C_{22}H_{21}N_2OS$ 361.1363; found 361.1375. FT-IR: ν_{max} (cm^{-1}) 3333; 2915; 2554; 1548; 1516; 1437; 1333; 1268; 1134; 1071; 983; 819; 808; 746; 695. Mp: 151.4 °C.

4.5.5. N-[(2-Hydroxynaphth-1-yl)(4-methylphenyl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,5,1}*. White solid. m: 175 mg; yield 35%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.22 (3H, s); 2.26 (3H, s); 6.00 (1H, s); 6.50 (1H, s,); 7.02 (2H, d, *J*=8.0 Hz); 7.26 (2H, d, *J*=8.0 Hz); 7.28–7.31 (2H, m); 7.40 (1H, t, *J*=7.5 Hz); 7.69 (1H, d, *J*=8.9 Hz); 7.76 (1H, d, *J*=8.0 Hz); 7.85 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.2; 21.2; 58.0; 101.0; 118.5; 119.7; 122.5; 122.9; 126.6 (2C); 126.9; 129.1; 129.2; 129.4 (2C); 130.0; 132.7; 136.9; 138.0; 147.5; 154.4; 171.1. LC–MS (ESI^+): *m/z* 361.2 $[M+H]^+$. HRMS calcd for $C_{22}H_{21}N_2OS$ 361.1369; found 361.1375. FT-IR: ν_{max} (cm^{-1}) 3338; 2917; 2540; 1625; 1531; 1511; 1436; 1375; 1328; 1270; 1254; 1135; 1063; 978; 810; 742; 695. Mp: 139.1 °C.

4.5.6. N-[(4-Methoxyphenyl)(2-hydroxynaphth-1-yl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,6,1}*. White solid. Using Thiamine, HCl as catalyst: not isolated. Using $TiCl_4$ as catalyst: m: 162 mg; yield 31%. m: 276 mg; yield 47%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.22 (3H, s); 3.71 (3H, s); 6.00 (1H, s); 6.45 (1H, s); 6.75 (2H, d, *J*=9.0 Hz); 7.26–7.32 (4H, m); 7.42 (1H, t, *J*=8.0 Hz); 7.69 (1H, d, *J*=9.0 Hz); 7.76 (1H, d, *J*=8.0 Hz); 7.90 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.2; 55.4; 58.0; 100.9; 114.0; 118.5; 119.6; 122.4; 122.9; 126.9; 128.0; 129.1; 130.0; 131.9; 132.7; 133.1; 147.4; 154.3; 158.9; 171.2. LC–MS (ESI^+): *m/z* 377.18 $[M+H]^+$. HRMS calcd for $C_{22}H_{21}N_2O_2S$ 377.1328; found 377.1324. FT-IR: ν_{max} (cm^{-1}) 3357; 2916; 2537; 1609; 1508; 1437; 1246; 1175; 1030; 811. Mp: 98.1 °C.

4.5.7. N-[(4-Nitrophenyl)(2-hydroxynaphth-1-yl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,7,1}*. White solid. Using Thiamine, HCl as catalyst: not isolated. Using $TiCl_4$ as catalyst: m: 353 mg; yield 65%. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.26 (3H, s); 6.00 (1H, s); 6.33 (1H, s); 7.11 (1H, d, *J*=8.9 Hz); 7.37 (1H, t); 7.46 (2H, d, *J*=8.9 Hz); 7.54 (1H, t, *J*=7.4 Hz); 7.73 (3H, d, *J*=8.9 Hz); 7.82 (1H, d, *J*=8.1 Hz); 7.91 (1H, d, *J*=8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 13.6; 58.4; 99.3; 114.0; 118.4; 120.2; 123.1; 123.2; 126.9; 127.6; 128.4; 129.2; 131.0; 131.9; 138.6; 145.1; 146.7; 153.0; 169.6. LC–MS (ESI^+): *m/z* 392.15 $[M+H]^+$. HRMS calcd for $C_{21}H_{18}N_3O_3S$ 392.1067; found 392.1069. FT-IR: ν_{max} (cm^{-1}) 2989; 1667; 1592; 1438; 1344; 1188; 1134; 828. Mp: 123.6 °C.

4.5.8. N-[(2-Hydroxynaphth-1-yl)(furanl-2-yl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,8,1}*. White solid. Using Thiamine, HCl as catalyst: m: 145 mg; yield 31%. Using $TiCl_4$ as catalyst: not isolated. ^1H NMR ($CDCl_3$, 300 MHz): δ ppm 2.08 (3H, d, *J*=0.7 Hz); 6.16 (1H, d, *J*=1.0 Hz); 6.21 (1H, d, *J*=3.3 Hz); 6.37 (1H, dd, *J*=3.3 Hz); 6.94 (1H, d, *J*=5.3 Hz); 7.20 (1H, d, *J*=9.0 Hz); 7.26 (1H, t, *J*=7.1 Hz); 7.37 (1H, t, *J*=8.1 Hz); 7.48 (1H, s); 7.76 (1H, d, *J*=9.0 Hz); 7.79 (1H, d, *J*=8.1 Hz);

8.04 (1H, d, J=8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.2; 49.3; 100.9; 106.3; 110.4; 116.7; 118.6; 122.4; 123.5; 126.1; 128.4; 128.6; 129.6; 132.3; 141.8; 147.1; 153.4; 154.7; 167.7. LC–MS (ESI$^+$): m/z 337.16 $[M+H]^+$. HRMS calcd for $C_{19}H_{17}N_2O_2S$ 337.1011; found 337.1001. FT-IR: ν_{max} (cm^{-1}) 3335; 2914; 2581; 1627; 1539; 1516; 1437; 1265; 1138; 1010; 812; 738; 707. Mp: 122.8 °C.

4.5.9. N-[(2-Hydroxynaphth-1-yl)methyl]-4-methyl-1,3-thiazol-2-amine ***6****{2,9,1}*. White solid. m: 165 mg; yield 44%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.27 (3H, s); 4.90 (2H, s); 5.94 (1H, s); 7.24 (1H, t, J=4.4 Hz); 7.32 (1H, t, J=6.8 Hz); 7.48 (1H, t, J=6.8 Hz); 7.71–7.82 (3H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 16.9; 40.4; 101.4; 117.1; 121.6 (2C), 123.1; 126.9; 127.9; 129.1; 130.3; 133.5; 146.9; 154.7; 169.4. LC–MS (ESI$^+$): m/z 271.2$[M+H]^+$. HRMS calcd for $C_{15}H_{15}N_2OS$ 271.0897; found 271.0905. FT-IR: ν_{max} (cm^{-1}) 3354; 2918; 2556; 1622; 1597; 1531; 1462; 1346; 1304; 1223; 1134; 1071; 1023; 841; 814; 737. Mp: 128.2 °C.

4.5.10. N-[3-Methyl-1-(2-hydroxynapht-1-yl)butyl]thiourea ***6****{2,10,1}* . White solid. m: 253 mg; yield 56%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 0.97 (3H, d, J=6.5 Hz); 1.06 (3H, d, J=6.5 Hz); 1.66 (1H, m); 1.81 (1H, m); 2.22 (3H, s); 2.26 (1H, m); 5.17 (1H, dd, J=4.9 Hz); 5.98 (1H, s); 7.29 (1H, t, J=7.5 Hz); 7.35 (1H, d, J=8.7 Hz); 7.51 (1H, t, J=7.5 Hz); 7.64 (1H, d, J=8.9 Hz); 7.75 (1H, d, J=8.1 Hz); 8.01 (1H, d, J=8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 17.1; 22.5; 23.7; 25.4; 43.9; 55.5; 100.2; 118.8; 119.5; 121.4; 122.7; 126.9; 128.5; 129.0; 129.2; 132.6; 147.35; 154.2; 172.5. LC–MS (ESI$^+$): m/z 327.3 $[M+H]^+$. HRMS calcd for $C_{19}H_{23}N_2OS$ 327.1533; found 327.1531. FT-IR: ν_{max} (cm^{-1}) 3336; 2955; 2867; 2540; 1740; 1628; 1542; 1436; 1330; 1258; 1062; 978; 809; 743; 697. Mp: 140.6 °C.

4.5.11. N-[(2-Hydroxynaphth-1-yl)(phenyl)methyl] -4-phenyl-1,3-thiazol-2-amine ***6****{2,2,2}*. White solid. m: 113 mg; yield 20% ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 6.62 (1H, s); 6.62 (1H, s); 7.01 (1H, d, J=8.9 Hz); 7.22–7.38 (8H, m); 7.40–7.50 (2H, m); 7.54 (1H, d, J=9.0 Hz); 7.60 (2H, dd, J=7.0 Hz); 7.73 (1H, d, J=7.9 Hz); 7.95 (1H, d, J=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 58.4; 101.4; 118.5; 119.7; 122.3; 123.0; 126.4; 126.8; 127.0; 127.5; 128.2; 128.7; 128.8; 129.1; 129.1; 130.1; 132.5; 134.1; 140.9; 150.7; 154.0; 171.5. LC–MS (ESI$^+$): m/z 409.20 $[M+H]^+$. HRMS calcd for $C_{26}H_{21}N_2OS$ 409.1375; found 409.1368. FT-IR: ν_{max} (cm^{-1}) 3331; 3060; 1544; 1516; 1436; 1267; 1252; 1049; 1026; 950; 906; 807; 738; 707; 696. Mp: 125.4 °C.

4.5.12. N-[(4-Nitrophenyl)(2-hydroxynaphth-1-yl)methyl]-4-phenyl-1,3-thiazol-2-amine ***6****{2,7,2}*. White solid. m: 371 mg; yield 59%. ^{1}H NMR (DMSO-d_6; 300 MHz): δ ppm 5.78 (1H, br); 7.10–8.61 (17H, m). ^{13}C NMR (DMSO-d_6; 75 MHz): δ ppm 53.3; 102.2; 118.4; 122.6; 123.3 (2C); 123.4; 124.1; 125.6 (2C); 127.2; 127.3 (2C); 128.1; 128.4 (2C); 128.5; 128.6; 128.7; 129.9; 134.7; 145.9; 149.4; 151.3; 153.2; 167.7. LC–MS (ESI$^+$): m/z 454.10 $[M+H]^+$. HRMS calcd for $C_{26}H_{20}N_3O_3S$ 454.1225; found 454.1221. FT-IR: ν_{max} (cm^{-1}) 3298; 3106; 3062; 2527; 1625; 1598; 1510; 1318; 1246; 1165; 1050; 825; 810; 721; 685. Mp: 199.7 °C.

4.5.13. Compound ***6****{2,7,3}*. Mixture of diastereoisomers. m: 543 mg; yield 62%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 2.89 (2H, m); 4.73–5.02 (4H, m); 5.87 (1H, d, J=11 Hz); 6.78–7.95 (21H, m). LC–MS (ESI$^+$): m/z 631.2 $[M+H]^+$. HRMS calcd for $C_{36}H_{31}N_4O_5S$ 631.2015; found 631.2010. FT-IR: ν_{max} (cm^{-1}) 3322; 3029; 1694; 1627; 1599; 151; 14,154; 1438; 1343; 1229; 1110; 1079; 1028; 852; 817; 739; 696.

4.6. Synthesis of 2-amino-1,3-thiazoles 6{3,*x*,*y*}

To a solution of *N*-methylindole (0.76 mmol, 100 mg, 96 μL) in THF (1 mL) at 0 °C were added thiourea (0.76 mmol, 58 mg, 1.0 equiv), aldehyde (0.76 mmol, 1.0 equiv) and finally $TiCl_4$ (0.08 mmol, 9 μL, 0.1 equiv). The heterogeneous mixture was stirred at 0 °C for 3 h. After return to room temperature, a solution of α-chloromethylketone (0.91 mmol, 1.2 equiv) in 1 mL ethanol was added. The reaction was stirred at 70 °C until the complete conversion of the previous intermediate (monitoring by HPLC). After evaporation of the solvent under reduced pressure (13 Mbar, 40 °C), the residue was dissolved in DCM (20 mL) and washed with a solution of $KHSO_4$ 1 M in water (2×20 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated. The resulting crude mixture was purified by chromatography on neutral aluminium oxide gel (30 g aluminium oxide; eluant: DCM and then DCM/EtOH 99/1 v/v).

4.6.1. 4-Methyl-N-[(4-bromophenyl)(1-methyl-1H-indol-3-yl) methyl]-1,3-thiazol-2-amine ***6****{3,1,1}*. Red solid. m: 131 mg; yield 42%; Mp: 199.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.14 (s, 3H); 3.70 (s, 3H); 4.75 (br s, 1H); 5.61 (s, 1H;); 6.58 (s, 1H); 7.00 (ddd, 1H, J=8.0, 6.9, 1.2 Hz); 7.15 (d, 2H, J=8.4 Hz); 7.22 (m, 3H); 7.27 (dd, 1H, J=8.0, 1.2 Hz); 7.40 (d, 2H, J=8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.2; 32.9; 40.2; 109.5; 117.3; 119.3; 119.8; 120.6; 122.1; 124.9; 126.9; 128.1; 130.1(2C); 131.7 (2C); 137.6; 142.8; 143.1; 165.3. HPLC: rt=1.79 min. LC–MS (ESI$^+$): m/z 412.1 $[M+H]^+$, 414.1 $[M+H+2]^+$. HRMS calcd for $C_{20}H_{19}BrN_3S^+$: 412.0483, found 412.091. FT-IR: ν_{max} (cm^{-1}) 3435; 3254; 3056; 2920; 1614; 1523; 1485; 1329; 1261; 1106; 1070; 1010; 799; 760. Mp: 199.3 °C.

4.6.2. 4-Methyl-N-[(1-methyl-1H-indol-3-yl)(phenyl)methyl]-1,3-thiazol-2-amine ***6****{3,2,1}*. Orange solid. m: 104 mg; yield 41%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.15 (s, 3H); 3.69 (s, 3H); 4.72 (br s, 1H); 5.66 (s, 1H); 6.59 (s, 1H); 6.99 (dd, 1H, J=7.9, 7.0 Hz); 7.16–7.30 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.2; 32.8; 40.8; 109.4; 117.9; 119.1; 119.9; 121.9; 125.7; 126.7; 127.2; 128.1; 128.3 (2C); 128.6 (2C); 137.5; 142.8; 143.7; 165.2. HPLC: rt=1.61 min. LC–MS (ESI$^+$): m/z 334.2 $[M+H]^+$. HRMS calcd for $C_{20}H_{20}N_3S^+$ 334.1378, found 334.1372. FT-IR: ν_{max} (cm^{-1}) 3425; 3269; 3057; 2919; 1624; 1523; 1327; 1229; 1113; 910; 790; 760. Mp: 184.8 °C (dec).

4.6.3. 4-Methyl-N-[(1-methyl-1H-indol-3-yl)(4-methoxyphenyl) methyl]-1,3-thiazol-2-amine ***6****{3,6,1}*. Red solid. m: 83 mg; yield 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.15 (s, 3H); 3.69 (s, 3H); 3.77 (s, 3H); 4.78 (br s, 1H); 5.61 (s, 1H); 6.59 (s, 1H); 6.82 (d, 1H, J=8.7 Hz); 6.99 (t, 1H, J=7.8 Hz); 7.22 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.2; 32.8; 40.0; 55.4; 109.3; 113.9 (2C); 118.2; 119.1; 120.0; 121.9; 126.1; 127.1; 128.1; 129.3 (2C); 136.0; 137.6; 142.5; 158.4; 165.2. HPLC: t_R=1.78 min. LC–MS (ESI$^+$): m/z 364.1 $[M+H]^+$. HRMS calcd for $C_{21}H_{22}N_3OS^+$ 364.1484, found 364.1494. FT-IR: ν_{max} (cm^{-1}) 3425; 2930; 1608; 1507; 1463; 1327; 1243; 1175; 1108; 1029; 907; 803; 760. Mp: 68.2 °C.

4.6.4. 4-Methyl-N-[(1-methyl-1H-indol-3-yl)(4-nitrophenyl) methyl]-1,3-thiazol-2-amine ***6****{3,7,1}*. Yellow solid. m: 89 mg; yield 31%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.17 (s, 3H); 3.74 (s, 3H); 4.86 (br s, 1H); 5.78 (s, 1H); 6.62 (s, 1H); 7.03 (dd, 1H, J=8.0, 7.0 Hz); 7.22 (m, 3H); 7.46 (d, 2H, J=8.7 Hz); 8.16 (d, 2H, J=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 15.2; 33.0; 40.7; 109.7 (2C); 116.4; 119.6 (2C); 122.4; 126.6; 123.9; 126.7; 127.1; 128.1; 129.2 (2C); 137.6; 143.6; 151.2; 165.6. HPLC: rt=1.67 min. LC–MS (ESI$^+$): m/z 379.2 $[M+H]^+$. HRMS calcd for $C_{20}H_{19}N_4O_2S^{++}$ 379.1229, found 379.1221. FT-IR: ν_{max} (cm^{-1}) 3432; 3259; 3072; 2925; 1618; 1593; 1511; 1342; 1262; 1108; 1013; 858; 823; 798; 750. Mp: 198.2 °C (dec).

4.6.5. N-[3-Methyl-1-(1-methyl-1H-indol-3-yl)butyl]-4-phenyl-1,3-thiazol-2-amine ***6****{3,10,2}*. Yellow solid. m: 52 mg; yield 18%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.63 (d, 3H, J=6.4 Hz); 0.72 (d, 3H, J=6.4 Hz); 1.50 (m, 2H); 1.64 (m, 1H); 3.59 (s, 3H); 4.45 (t, 1H,

J=7.3 Hz); 6.91 (s, 1H); 6.99 (t, 1H, *J*=6.8 Hz); 7.19 (m, 6H); 7.33 (m, 2H); 9.39 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 22.1; 22.8; 25.8; 32.4; 32.8; 47.2; 109.6; 116.7; 118.8; 119.2; 121.9; 125.3; 126.4; 126.7; 128.6 (2C); 128.9 (2C); 129.0; 129.2; 139.9; 137.2; 168.6. HPLC: rt=1.68 min. LC–MS (ESI^+): *m/z* 376.2 $[M+H]^+$. HRMS calcd for $C_{23}H_{26}N_3S^+$ 376.1847, found 376.1849. FT-IR: ν_{max} (cm^{-1}) 2954; 1601; 1466; 1367; 1330; 1085; 907; 771; 750. Mp: 154.0 °C.

4.6.6. 4-Phenyl-N-[(4-bromophenyl)(1-methyl-1H-indol-3-yl) methyl]-1,3-thiazol-2-amine ***6****{3,1,2}*. White solid. m: 255 mg; yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 3.71 (s, 3H); 5.16 (br s, 1H); 5.80 (s, 1H); 6.71 (s, 1H); 6.97 (t, 1H, *J*=7.3 Hz); 7.08 (d, 1H, *J*=7.8 Hz); 7.17 (d, 2H, *J*=8.4 Hz,); 7.20 (dd, 1H, *J*=7.8, 7.3 Hz); 7.30(m, 4H); 7.40 (d, 2H, *J*=8.4 Hz); 7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 32.9; 40.9; 109.4; 117.8; 119.3; 119.9; 120.7; 122.1; 126.8; 126.8; 127.8; 128.3; 128.5 (2C); 128.6 (2C); 130.1 (2C); 131.7 (2C); 135.1; 137.6; 143.2; 146.4; 165.9. HPLC: rt=1.98 min. LC–MS (ESI^+): *m/z* 474.0 $[M+H]^+$, 476.0 $[M+H+2]^+$. HRMS calcd for $C_{25}H_{21}BrN_3S^+$ 474.0640, found 474.0631. FT-IR: ν_{max} (cm^{-1}) 3420; 3115; 2926; 1613; 1525; 1484; 1329; 1068; 1009; 854; 818; 801; 770; 750; 701. Mp: 211.2 °C (dec).

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Supplementary data

Analytical data including NMR data and spectra for all reported thioureas **4** and polysubstituted 2-amino-1,3-thiazoles **6**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.090.

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