Experimental Section
EXPERIMENTAL SECTION.

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected.

Routine nuclear magnetic resonance spectra were recorded in DMSO-d₆ solution on a Varian Gemini 200 spectrometer operating at 200 MHz. Evaporation was performed in vacuo (rotary evaporator). Analytical TLC was carried out on Merck 0.2 mm precoated silica gel aluminum sheets (60 F-254). Combustion analyses on target compounds were performed by our Analytical laboratory in Pisa. All compounds showed ≥95% purity. All reagents used were obtained from commercial sources. All solvents were of an analytical grade.

**General procedure for the synthesis of 2-substituted-4-hydroxybenzothioamide 1-4, 4-aminobenzothioamide 5 and 2,5-substituted-4-metoxybenzothioamide 20-21.**

P₄S₁₀ (0,044 mol, 0,978 g) was added to a 10 ml of absolute ethanol, and this solution was allowed to stir for one hours. After one hours, 0.022 mol of appropriate benzonitrile was added and the reaction mixture was stirred at 70°C for 10 hours (TLC analysis: petroleum ether 60-80°C/ethyl acetate : 6/4). After cooling, the organic solvent was evaporated under reduced pressure, and the crude products were purified by flash chromatography (petroleum ether 60-80°C/ACOEt:6/4 as eluent) or by recrystallized from toluene.

**4-hydroxybenzothioamide 1.** Yield 68%; mp 200-202 °C (Toluene), lit.ref n.¹⁴: mp 206-207°C.

**2-fluoro-4-hydroxybenzothioamide 2.** Yield 58%; mp 275-277°C. ¹H NMR (200 MHz, DMSO-d₆, δ ppm): 6.51-6.66 (m, 2H, Ar-H); 7.66 (t, 1H, Ar-H, J = 8.8 Hz); 9.19 (bs exch., 1H, SH); 9.90 (bs exch.,1H, OH); 10.42 (bs exch.,1H, NH). Anal.Calcd. for C₇H₆FNOS: C, 49.11;H, 3.53; N, 8.18. Found: C, 49.25; H, 3.71; N, 8.29.

**2-chloro-4-hydroxybenzothioamide 3.** Yield 57 %; mp 138-140 °C. ¹H NMR (200 MHz, DMSO-d₆, δ ppm): 6.69-6.77 (m, 2H, Ar-H); 7.26 (d, 1H, Ar-H, J = 8.2 Hz); 9.43 (bs exch., 1H, SH); 9.99 (bs exch., 1H, OH); 10.13 (bs exch., 1H, NH). Anal. Calcd. for C₇H₆ClNOS: C, 44.80; H, 3.22; N, 7.46. Found: C, 44.96; H, 3.41; N, 7.69.
2-(trifluoromethyl)-4-hydroxybenzothioamide 4. Yield 57%; mp 167-169 °C. $^1$H NMR (200 MHz, DMSO-d$_6$, δ ppm): 6.99-7.03 (m, 2H, Ar-H); 7.24 (d, 1H, Ar-H, J = 7.8 Hz); 9.51 (bs exch., 1H, SH); 10.02 (bs exch., 1H, OH); 10.26 (bs exch., 1H, NH). Anal. Calcd. for C$_8$H$_6$F$_3$NOS: C, 43.44; H, 2.73; N, 6.33. Found: C, 43.66; H, 2.91; N, 6.59.

4-aminobenzothioamide 5. Yield 50%; mp 175-177 °C, lit ref n.$^{25}$: mp 188 °C.

2-nitro-4-methoxybenzothioamide 20. Yield 80%; mp 140-143°C.$^1$H NMR (200 MHz, DMSO-d$_6$, δ ppm): 3.86 (s, 3H,OCH$_3$); 7.23-7.29 (m,1H,Ar-H); 7.39-7.49 (m, 2H, Ar-H); 9.79 (bs exch., 1H, SH); 10.1 (bs exch., 1H, NH). Anal. Calcd. for C$_8$H$_8$N$_2$O$_3$S: C, 45.28; H, 3.80; N, 13.20; O, 22.62; S, 15.11. Found: C, 45.68; H, 3.40; N, 13.40; O, 22.42; S, 15.31.

2,5-dimethyl-4-methoxybenzothioamide 21. Yield 53%; mp 87-90°C. $^1$H NMR (200 MHz, DMSO-d$_6$, δ ppm): 2.07 (s, 3H, CH$_3$); 2.29 (s, 3H, CH$_3$); 3.76 (s, 3H, OCH$_3$); 6.72 (s, 1H, Ar-H); 7.04 (s, 1H, Ar-H); 9.23 (bs exch., 1H, SH); 9.81 (bs exch., 1H, NH). Anal. Calcd. for C$_{10}$H$_{13}$NOS: C,61.50; H,6.71; N,7.17; O,8.19; S,16.42. Found: C, 61.30; H, 6.91; N, 7.37; O, 8.39; S, 16.22.

**General procedure for the synthesis of 2,5-substituted-4-hydroxybenzothioamide 6-7**

To a stirred suspension of the appropriate 4-methoxybenzothioamide 20-21 (0.0010 mol) in 15 ml of dry Dichloromethane cooled at -10°C were added dropwise 1.26 ml of BBr$_3$. The mixture was left under stirring for 30 min. at -10°C, and subsequently at room temperature for 1h under nitrogen atmosphere (TLC analysis ACOEt/ petroleum ether 60-80°C =4/6). Finally, the solution was cooled again, and was added 10 ml of methanol to hydrolyze the excess of BBr$_3$. The solvent was evaporated at reduced pressure, and the solid precipitate was washed several times with methanol. The residues obtained were purified by flash chromatography (ACOEt/ petroleum ether 60-80°C =4/6 as eluent).

2,5-dimethyl-4-hydroxybenzothioamide 7. Yield 48%; mp 143-145°C.$^1$H NMR (200 MHz,DMSO-d$_6$, δ ppm): 2.04 (s, 3H, CH$_3$); 2.20 (s, 3H, CH$_3$); 6.52 (s, 1H, Ar-H); 6.99 (s, 1H, Ar-H); 9.13 (bs exch., 1H, SH); 9.42 (s exch., 1H, OH); 9.71 (bs exch., 1H, NH). Anal. Calcd.
for C₉H₁₁NOS: C, 59.64; H, 6.12; N, 7.73; O, 8.83; S, 17.69. Found: C, 59.79; H, 6.32; N, 7.83; O, 8.93; S, 17.79.

**General procedure for the synthesis of 2 or 3 or 4-Pyridinecarboxamide 22-24.**

A mixture of the appropriate carbonitrile (0.005 mol) and 3.0 g (0.015 mol) of potassium phosphate in 20 ml of H₂O/isopropyl alchol was heated at reflux for 2 h (TLC analysis: ethyl acetate/petroleum ether 60-80°C: 7/3). Then, the reaction mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate. The organic solvent was eliminated under vacuum and the products were isolated directly in a pure state.

**2-pyridinecarboxamide 22.** Yield 96 %; mp 105-107 °C, lit ref n.²⁶: mp 105-106 °C.

**3-pyridinecarboxamide 23.** Yield 90 %; mp123-125 °C, lit ref n.²⁷: mp 131-132 °C.

**4-pyridinecarboxamide 24.** Yield 88% ; mp 153-155 °C, lit ref n.²⁸: mp 154-155 °C

**General procedure for the synthesis of indole-2-carboxamide 25,**

**furan-2-carboxamide 26**

The appropriate carbossilic acid (0,003 mol) was solubilized in 10 ml of dry DMF in a nitrogen atmosphere; N,N’-carbonyldiimidazole (0.006 mol, 0.973 g) was added and the solution was stirred at room temperature for 2h. Then a solution of NH₄OH (0.003mol, 0.39 ml) in 5 ml of the same solvent was added dropwise. The compounds 25-26 formed almost quantitatively within 4-5h (TLC analysis). The solvent was evaporated at reduced pressure and the residue was triturated with saturated aqueous NaHCO₃ solution, washed with water and filtered, yielding compounds 25-26 in the desired purity of degree.

**Indole-2-carboxamide 25.** Yield 73%; mp 173-176°C. ¹H NMR (200 MHz, DMSO-d₆, δ ppm): 6.98-7.20 (m, 3H, Ar-H); 7.38-7.42 (m, 2H, Ar-H, NH); 7.57-7.61 (m, 1H, Ar-H); 7.96 (bs exch., 1H, OH); 11.54 (bs exch., 1H, NH) .Anal. Calcd. for C₉H₈N₂O: C, 67.49; H, 5.03; N,17.49; O, 9.99. Found: C, 67.29; H, 5.23; N, 17.29; O, 9.79.
**Furan-2-carboxamide 26.** Yield 55%; mp 139-141°C. \(^1\)H NMR (200 MHz, DMSO-\(d_6\), \(\delta\) ppm): 6.57-6.59 (m, 1H, Ar-H); 7.06-7.08 (m, 1H, Ar-H); 7.36 (bs exch., 1H, NH); 7.68-7.78 (m, 2H, Ar-H, OH). Anal. Calcd. for C\(_9\)H\(_8\)N\(_2\)O: C, 67.49; H, 5.03; N, 17.49; O, 9.99. Found: C, 67.29; H, 5.23; N, 17.69; O, 9.79.

**General procedure for the synthesis of:**

2 or 3 or 4-pyridinecarbothioamide 8-10, indole-2-carbothioamide 11, furan-2-carbothioamide 12, pyrazine-2-carbothioamide 13.

The appropriate carboxamide (0.001 mol) and Lawesson’s reagent (0.0012 mol, 0.490 g) were added to dry THF. The reaction mixture was stirred at room temperature for 1 h (TLC analysis: with appropriate eluent). The solvent was evaporated under reduced pressure and the residue was partitioned between aq. NaHCO\(_3\) and ethyl acetate. The organic solvent was separated and eliminated under vacuum. The crude products were further purified by flash chromatography (with appropriate eluent).

**2-pyridinecarbothioamide 8.** Yield 56%; mp 133-136 °C, lit ref n.\(^{29}\): mp 138-140 °C.

**3-pyridinecarbothioamide 9.** Yield 64%; mp 187-189 °C, lit ref n.\(^{30}\): mp 190-192 °C.

**4-pyridinecarbothioamide 10.** Yield 62%; mp 188-190 °C. (ACOEt as eluent). \(^1\)H NMR (200 MHz, DMSO-\(d_6\), \(\delta\) ppm): 7.72 (d, 2H, Ar-H, \(J = 4.6\) Hz); 8.66 (d, 1H, Ar-H, \(J = 4.6\) Hz); 9.81 (bs exch., 1H, SH); 10.24 (bs exch., 1H, NH). Anal. Calcd. for C\(_6\)H\(_7\)N\(_2\)S: C, 52.15; H, 4.38; N, 20.27. Found: C, 52.35; H, 4.61; N, 20.38.

**Indole-2-carbothioamide 11.** Yield 50%; mp 216-218 °C. (ACOEt/ petroleum ether 60-80°C =5/5 as eluent). \(^1\)H NMR (200 MHz, DMSO-\(d_6\), \(\delta\) ppm): 7.02 (t, 1H, Ar-H, \(J = 7.6\) Hz); 7.19 (t, 2H, Ar-H, \(J = 7.3\) Hz); 7.50-7.62 (m, 2H, Ar-H); 9.42 (bs exch., 1H, SH); 9.60 (bs exch., 1H, NH); 11.25 (bs exch., 1H, NH). Anal. Calcd. for C\(_9\)H\(_8\)N\(_2\)S: C, 61.34; H, 4.58; N, 15.90; S, 18.19. Found: C, 61.14; H, 4.88; N, 15.70; S, 18.39.

**Furan-2-carbothioamide 12.** Yield 51%; mp 128-130 °C. (ACOEt/ petroleum ether 60-80°C =6/4). \(^1\)H NMR (200 MHz, DMSO-\(d_6\), \(\delta\) ppm): 6.60-6.62 (m, 1H, Ar-H); 7.23-7.25 (m, 1H, Ar-H); 7.87 (s, 1H, Ar-H); 9.30 (bs exch., 1H, SH); 9.60 (bs exch., 1H, NH). Anal. Calcd. for C\(_9\)H\(_5\)NOS: C, 47.23; H, 3.96; N, 11.01; O, 12.58; S, 25.22. Found: C, 47.53; H, 3.76; N, 11.21; O, 12.78; S, 25.42.
**Pyrazine-2-carbothioamide 13.** Yield 52%; mp 198-200 °C. (ACOEt/ petroleum ether 60-80°C =5/5 as eluent). \(^1\)H NMR (200 MHz, DMSO-\(d_6\), \(\delta\) ppm): 8.66 (s, 1H, Ar-H); 8.84 (s,1H, Ar-H); 9.56 (s, 1H, Ar-H); 10.03 (bs exch., 1H, SH); 10.35 (bs exch., 1H, NH). Anal. Calcd. C\(_5\)H\(_5\)N\(_3\)S: C, 43.15; H, 3.62; N, 30.19; S, 23.04. Found: C, 43.35; H, 3.42; N, 30.39; S, 23.24.

**General procedure for the synthesis of N-benzyl-4-methoxybenzamide 29 and 4-methoxybenzamide 31**

A solution of appropriate amine (0.0013 mol) (benzylamina or NH\(_4\)OH), in 5 ml of dry toluene was added dropwise to a stirred suspension, cooled at 0°C, of the 4-methoxybenzoylchloride (0.0012 mol, 0.200 g) in 50 ml of the same solvent, followed by the addition of a solution of triethylamine (0.0014 mol, 0.19 ml). The reaction was left under stirring for 24h at room temperature (TLC analysis: with appropriate eluent), and then filtered. The collected precipitate were washed with a 5% NaHCO\(_3\) aqueous solution and collected to give compounds 29 and 31 in the desired purity of degree.

**N-benzyl-4-methoxybenzamide 29.** Yield 98%; mp 108-110°C. (ACOEt/ petroleum ether 60-80°C =7/3 as eluent). \(^1\)H NMR (200 MHz,DMSO-\(d_6\), \(\delta\) ppm):3.80 (s, 3H, OCH\(_3\)); 4.45 (d, 2H, CH\(_2\), \(J\) = 6 Hz); 6.99 (d, 2H,Ar-H, \(J\)=8.6 Hz); 7.22-7.32 (m, 5H, Ar-H); 7.87 (d, 2H, Ar-H, \(J\)= 8.4 Hz); 8.90 (bs exch., 1H, NH). Anal. Calcd. for C\(_{15}\)H\(_{15}\)NO\(_2\): C, 74.67; H, 6.27; N, 5.81; O, 13.26. Found: C, 74.47; H, 6.47; N, 5.61; O, 13.06.

**4-methoxybenzamide 31.** Yield 88%; mp 164-167°C.(ACOEt/ petroleum ether 60-80°C =5/5 as eluent). \(^1\)H NMR (200 MHz,DMSO-\(d_6\), \(\delta\) ppm): 3.79 (s, 3H, OCH\(_3\)); 6.96 (d, 2H, Ar-H, \(J\)=8.8 Hz); 7.18 (bs exch., 2H, NH\(_2\)); 7.84 (d, 2H, Ar-H, \(J\)= 8.8 Hz). Anal. Calcd. for C\(_8\)H\(_9\)NO\(_2\): C, 63.56; H, 6.00; N, 9.27; O, 21.17. Found: C,63.36; H, 6.20; N, 9.47; O, 21.37.
General procedure for the synthesis of:

N-benzylbenzothioamide 14, N-benzyl-4-methoxybenzothioamide 15,
Benzothioamide 32 and 4-methoxybenzothioamide 33.

The appropriate carboxamide (0.001 mol) and Lawesson’s reagent (0.0012 mol, 0.490 g) were added to dry THF. The reaction mixture was stirred at room temperature for 1 h (TLC analysis: with appropriate eluent). The solvent was evaporated under reduced pressure and the residue was partitioned between aq. NaHCO₃ and ethyl acetate. The organic solvent was separated and eliminated under vacuum. The crude products were further purified by flash chromatography (with appropriate eluent).

**N-benzylbenzothioamide 14.** Yield 89%; mp 72-74°C. (ACOEt as eluent). ¹H NMR (200 MHz,DMSO-d₆, δ ppm): 4.98 (s, 2H, CH₂); 7.26- 7.50 (m, 8H, Ar-H); 7.76- 7.80 (m, 2H, Ar-H); 10.78 (s exch., 1H, NH). Anal. Calcd. for C₁₄H₁₃NS: C, 73.97; H, 5.76; N, 6.16; S, 14.11. Found: C, 73.77; H, 5.96; N, 6.36; S, 14.31.

**N-benzyl-4-methoxybenzothioamide 15.** Yield 65%; mp 78-80°C.(ACOEt/ petroleum ether 60-80°C =5/5 as eluent). ¹H NMR (200 MHz,DMSO-d₆, δ ppm): 3.80 (s, 3H, OCH₃); 4.98 (d,2H,CH₂, J= 5.6 Hz); 6.97(d, 2H,Ar-H, J= 8.8 Hz); 7.24-7.35 (m, 5H, Ar-H); 7.85 (d, 2H, Ar-H, J=8.8 Hz); 10.58 (bs exch., 1H, NH). Anal. Calcd. for C₁₅H₁₅NOS: C, 70.91; H, 5.76; N, 6.16; S, 14.11. Found: C, 70.21; H, 5.67; N, 5.64; O, 6.44; S, 12.66.

**Benzothioamide 32.** Yield 58%; mp 96-98°C. (ACOEt/ petroleum ether 60-80°C =7/3 as eluent). ¹H NMR (200 MHz,DMSO-d₆, δ ppm): 7.36- 7.49 (m, 3H,Ar-H); 7.84- 7.88 (m, 2H, Ar-H);9.48 (bs exch., 1H, SH); 9.86 (bs exch., 1H, NH). Anal. Calcd. for: C₇H₇NS: C, 61.28; H, 5.14; N, 10.21; S, 23.17. Found: C, 61.48; H, 5.34; N, 10.01; S, 23.17.

**4-methoxybenzothioamide 33.** Yield 49%; mp 126-129 °C. (ACOEt/ petroleum ether 60-80°C =4/6 as eluent). ¹H NMR (200 MHz,DMSO-d₆, δ ppm): 3.80 (s, 3H, OCH₃); 6.95 (d, 2H, Ar-H; J= 8.8 Hz); 7.95 (d, 2H, Ar-H, J= 8.8 Hz); 9.34 (bs exch., 1H, SH); 9.67 (bs exch., 1H, NH). Anal. Calcd. for C₈H₉NOS: C, 57.46; H, 5.42; N, 8.38; O, 9.57; S, 19.17. Found: C, 57.26; H, 5.62; N, 8.18; O, 9.37; S, 19.37.
General procedure for the synthesis of Benzyl-benzothioimidate 17 and Benzyl-4-methoxybenzothioimidate 18

Benzyl Bromide (0.0010 mol, 0.12 ml) was added to a stirred solution of appropriate benzothioamide (0.0010 mol) in 10 ml of chloroform. The resulting mixture was refluxed for 12 h. (TLC analysis: ACOEt/ petroleum ether 60-80°C =5/5) After cooling to room temperature the reaction mixture was added with Et₂O (5 ml). The white precipitate was filtered and washed with Et₂O. The crude product was sufficiently pure to be used without further purification.

**Benzyl-benzothioimidate 17.** Yield 100%; mp 168-170°C. ¹H NMR (200 MHz, DMSO-d₆, δ ppm): 4.75 (s, 2H, CH₂); 7.39- 7.68 (m, 8H, Ar-H, NH); 7.70- 7.91 (m, 3H, Ar-H). Anal. Calcd. for C₁₄H₁₃NS: C, 73.97; H, 5.76; N, 6.16; S, 14.11. Found: C, 73.77; H, 5.96; N, 6.36; S, 14.31.

**Benzyl-4-methoxybenzothioimidate 18.** Yield 100%; mp 195-197°C. ¹H NMR (200 MHz, DMSO-d₆, δ ppm): 3.88 (s, 3H, OCH₃); 4.74 (s, 2H, CH₂); 7.18 (d, 2H, Ar-H, J= 8.8 Hz); 7.39-7.54 (m, 5H, Ar-H); 7.947 (d, 2H, Ar-H, J=8.8 Hz); 11.69 (bs exch., 1H, NH). Anal. Calcd. for C₁₅H₁₅NOS: C, 70.01; H, 5.87; N, 5.44; O, 6.22; S, 12.46. Found: C, 70.21; H, 5.67; N, 5.64; O, 6.44; S, 12.66.

**General procedure for the synthesis of N-benzyl-4-hydroxybenzothioamide 16 and Benzyl-4-hydroxybenzothioimidate 19**

To a stirred suspension of the appropriate 4-methoxybenzothioamide 15 and 18 (0.0010 mol) in 15 ml of dry Dichloromethane cooled at -10°C were added dropwise 1.26 ml of BBr₃. The mixture was left under stirring for 30 min. at -10°C, and subsequently at room temperature for 1h under nitrogen atmosphere (TLC analysis ACOEt/ petroleum ether 60-80°C =4/6). Finally, the solution was cooled again, and was added 10 ml of methanol to hydrolyze the excess of BBr₃. The solvent was evaporated at reduced pressure, and the solid precipitate was washed several times with methanol.
The residues obtained were purified by flash chromatography (ACOEt/ petroleum ether 60-80°C =4/6 as eluent).

**N-benzyl-4-hydroxybenzothioamide 16.** Yield 59%; mp 82-84 °C. $^1$H NMR (200 MHz,DMSO-d$_6$, $\delta$ ppm): 4.98 (d, 2H, CH$_2$, J = 6 Hz); 6.78 (d, 2H, Ar-H, J= 8.6 Hz); 7.25-7.36 (m, 5H, Ar-H); 7.77(d, 2H, Ar-H, J= 8.6 Hz); 10.053 (bs exch., 1H, OH); 10.48 (bs exch., 1H, NH). Anal. Calcd. for C$_{14}$H$_{13}$NOS: C, 69.11; H, 5.39; N, 5.76; O, 6.58; S, 13.18. Found: C, 69.31; H, 19; N, 5.56; O, 6.78; S, 13.38.

**Benzyl-4-hydroxybenzothioimidate 19.** Yield 50%, mp 133-136°C. $^1$H NMR (200 MHz,DMSO-d$_6$, $\delta$ ppm): 4.71 (s, 2H, CH$_2$); 6.97 (d, 2H, Ar-, J= 8.2 Hz); 7.38- 7.53 (m, 5H, Ar-H); 7.857 (d, 2H, Ar-H, J= 8.4 Hz); 11.09 (bs exch., 1H, NH); 11.52 (bs exch., 1H, OH). Anal. Calcd. for C$_{14}$H$_{13}$NOS: C, 69.11; H, 5.39; N, 5.76; O, 6.58; S, 13.18. Found: C, 69.31; H, 5.19; N, 5.76; O, 6.78; S, 13.38.