

# Agonists for the Adenosine A<sub>1</sub> Receptor with tunable residence time. A case for non-ribose 4-amino-6-aryl-5-cyano-2-thiopyrimidines

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## Supplementary Information

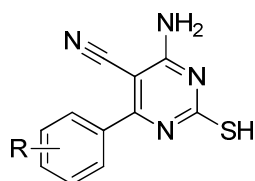
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### Chemistry

All reagents used were obtained from commercial sources and all solvents are of analytical grade. Ethyl acetate (EtOAc) was redistilled before use. Demineralised water is simply referred to as H<sub>2</sub>O. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature on a Bruker AC 400 (<sup>1</sup>H NMR, 400MHz; <sup>13</sup>C NMR, 100MHz) spectrometer unless specified otherwise. Chemical shifts are reported in δ (ppm) and the following abbreviations are used: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quadruplet; m, multiplet, br s, broad singlet. Coupling-constants are reported in Hz and are designated as *J*. High resolution mass spectrometry was performed by Leiden Institute of Chemistry and recorded by direct injection (2 μL of a 2 μM solution in water/MeCN; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275°C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and calibrated for dioctylphthalate (m/z = 391.28428). Analytical purity of the final compounds was determined by high pressure liquid chromatography (HPLC) with a Phenomenex Gemini 3u C18 110A column (50 x 4.6 mm, 3 μm), measuring UV absorbance at 254 nm. Sample preparation and HPLC method is - unless stated otherwise - as follows: 0.3-0.8 mg of compound was dissolved in 1 mL of a 1:1:1 mixture of CH<sub>3</sub>CN/H<sub>2</sub>O/tBuOH and eluted from the column within 15 minutes, with a three component system of H<sub>2</sub>O/CH<sub>3</sub>CN/1% TFA in H<sub>2</sub>O, decreasing polarity of the solvent mixture in time from 80/10/10 to 0/90/10. LCMS analysis was performed on a Finnigan Surveyor HPLC system with a Gemini C18 50 x 4.60 mm column (detection at 200-600 nm), coupled to a Finnigan LCQ Advantage Max mass spectrometer with ESI. The applied buffers were H<sub>2</sub>O, CH<sub>3</sub>CN and 1.0% aq. TFA. All compounds show

a single peak with at the designated retention time and are at least 95% pure. Thin-layer chromatography (TLC) was routinely consulted to monitor the progress of reactions, using aluminium coated Merck silica gel F<sup>254</sup> plates. Purification by column chromatography was achieved by use of Grace Davison DAVISIL silica column material (LC60A 30-200 micron). Solutions were concentrated using a Heidolph laborota W8 2000 efficient rotary evaporation apparatus and by a high vacuum on a Binder APT line Vacuum Drying Oven. The procedure for a series of similar compounds is given as a general procedure for all within that series, annotated by the numbers of the compounds. Procedures are not optimized.



**General procedures for the synthesis of 4-Amino-6-benzo[substituted]-5-yl-2-mercapto-pyrimidine-5-carbonitrile 14–23.** A mixture of aldehyde (50 mmol, 1 equiv.), malononitrile (50 mmol, 1 equiv.) and thiourea (50 mmol, 1 equiv.) in EtOH (25 mL) containing potassium carbonate (50 mmol, 1 equiv.) was heated at reflux for 5 h. The reaction was monitored by TLC, eluent: ethylacetate : petroleum ether (1 : 2). At the end of the reaction the precipitate was collected and washed with EtOH. The crude salt was stirred in warm water and filtered. The filtrate, after cooling, was acidified with acetic acid until pH = 1. The deposited precipitate was collected, washed with water and dried under high vacuum.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-mercaptopyrimidine-5-carbonitrile 14.** Reagent: piperonal 3. Yield: 42%. <sup>1</sup>H NMR (DMSO) δ 7.26 (s, 1H), 7.24 (s, 1H), 6.14 (s, 2H) ppm.

**4-Amino-6-benzo-5-yl-2-mercapto-pyrimidine-5-carbonitrile 15.** Reagent: benzaldehyde 4. Yield: 13%. <sup>1</sup>H NMR (DMSO) δ 7.96 (br s, 2H), 7.68 (s, 2H), 7.59 (s, 1H), 7.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ: 181.9, 161.8, 159.6, 131.5, 131.3, 128.8, 128.4, 115.6, 79.8 ppm.

**4-amino-2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile 16.** Reagent: 4-methoxybenzaldehyde 5. Yield: 13%. <sup>1</sup>NMR (DMSO) δ 7.87 (br s, 2H), 7.68 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 3.84 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO) δ: 182.2, 161.9, 161.3, 159.9, 130.7, 123.5, 116.1, 113.8, 78.9, 55.5 ppm.

**4-Amino-6-(4-hydroxyphenyl)-2-mercaptopyrimidine-5-carbonitrile 17.** Reagent: 4-hydroxybenzaldehyde 6. Yield: 25%. <sup>1</sup>NMR (DMSO) δ 12.83 (s, 1H), 10.33 (s, 1H), 8.39 (s, 1H), 7.78 (s, 1h), 7.55 (d, J = 6.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H) ppm.

**4-Amino-6-(4-(2-hydroxyethoxy)phenyl)-2-mercaptopyrimidine-5-carbonitrile 18.** Reagent: 4-(2-hydroxyethoxy)benzaldehyde 7. Yield: 13%. <sup>1</sup>NMR (DMSO) δ 12.91 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 4.96 (t, J = 5.6 Hz, 1H), 4.08 (t, J = 4.8 Hz, 2H), 3.74 (q, J = 4.8, 2H) ppm.

***N*-(4-(6-Amino-5-cyano-2-mercaptopyrimidin-4-yl)phenyl)acetamide 19.** Reagent: 4-(*N*-acetyl)benzaldehyde **8**. Yield: 7%. <sup>1</sup>NMR (DMSO) δ 12.99 (s, 1H), 10.30 (s, 1H), 8.37 (s, 1H), 7.92 (s, 1h), 7.72 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 2.10 (s, 3H) ppm.

**4-Amino-6-(4-ethoxyphenyl)-2-mercaptopyrimidine-5-carbonitrile 20.** Reagent: 4-ethoxybenzaldehyde **9**. Yield: 28%. <sup>1</sup>NMR (DMSO) δ 12.93 (s, 1H), 7.95 (br s, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.12 (d, *J* = 6.8 Hz, 2H), 1.35 (s, 3H) ppm.

**4-Amino-2-mercapto-6-(4-(trifluoromethoxy)phenyl)pyrimidine-5-carbonitrile 21.** Reagent: 4-hydroxybenzaldehyde **10**. Yield: 4%. <sup>1</sup>NMR (DMSO) δ 12.96 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H) ppm.

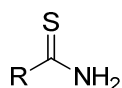
**4-Amino-6-(4-(dimethylamino)phenyl)-2-mercaptopyrimidine-5-carbonitrile 22.**

Reagent: 4-dimethylaminobenzaldehyde **11**. Filtration at pH = 7. Yield: 1%. <sup>1</sup>NMR (DMSO) δ 12.69 (s, 1H), 8.35 (s, 1H), 7.71 (s, 1h), 7.56 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.03 (s, 7H) ppm.

**4-Amino-2-mercapto-6-(*p*-tolyl)pyrimidine-5-carbonitrile 23.**

Reagent: *p*-tolylaldehyde **12**. Yield: 14%. <sup>1</sup>NMR (DMSO) δ 13.01 (s, 1H), 8.00 (br s, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H) ppm.

**4-Fluorobenzamide 58.** 4-Fluorobenzoyl chloride (31.6 mmol) was dissolved in dry EtOAc (50 mL) and added dropwise to an ice-cold solution of NH<sub>4</sub>OH (50 mL of 33% solution in H<sub>2</sub>O) in EtOAc (250 mL) over 30 min. After addition the mixture was stirred on ice for 30 min. The layers were separated, the organic layer was washed two times with H<sub>2</sub>O, two times with brine, dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. Yield: 81%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85–7.82 (m, 2H), 7.15–7.11 (m, 2H), 6.00–5.90 (m, 2H) ppm.



**General procedures for the synthesis of substituted thioamides 75-89.** An appropriate nitrile (1 equiv, 30 mmol) was dissolved in pyridine (20 mL) then triethylamine (1.1 equiv, 33 mmol) and ammonium sulfide 20% wt solution in water (1.1 equiv, 33 mmol) were added into the mixture. The reaction mixture was stirred at 50 °C for 3-6 h and monitored by TLC, eluent: DCM. After cooling to rt, the mixture was diluted with cold water (50 mL). In case of precipitation the precipitated solid was filtered off and washed with cold water (procedure a). If there was no precipitation the product was extracted with ethyl acetate (3 x 50mL). The organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuum to give the thioamide (procedure b).

**4-Chloro-benzothioamide 75.** Reagent: 4-chlorobenzonitrile **59**. Procedure b. Yield: 96%. Spectral data was identical to the commercially available material.

**Thiobenzamide 76.** Reagent: benzonitrile **60**. Procedure b. Yield: 100%. <sup>1</sup>H NMR (MeOD) δ 7.90–7.88 (m, 2H), 7.50–7.46 (m, 1H), 7.46–7.36 (m, 2H) ppm.

**4-Fluorobenzothioamide 77.** Reagent: 4-fluorobenzonitrile **61**. Procedure a. Yield: 82%.  $^1\text{H}$  NMR (MeOD)  $\delta$  8.00 (dd,  $J = 9.2, 5.6$  Hz, 2H), 7.16 (t,  $J = 10.0$  Hz, 2H) ppm.

**3-Chlorobenzothioamide 78.** Reagent: 3-chlorobenzonitrile **62**. Procedure a. Yield: 73%.  $^1\text{H}$  NMR (MeOD)  $\delta$  7.92 (t,  $J = 1.2$  Hz, 1H), 7.81 (ddt,  $J = 8.0, 2.4, 1.2$  Hz, 1H), 7.52 (ddt,  $J = 8.0, 2.4, 1.2$  Hz, 1H), 7.41 (t,  $J = 8.0$  Hz, 2H) ppm.

**3-Fluorobenzothioamide 79.** Reagent: 3-fluorobenzonitrile **63**. Procedure b. Yield: 82%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (tt,  $J = 8.0, 1.6$  Hz, 1H), 7.62–7.60 (m, 1H), 7.39–7.33 (m, 1H), 7.31–7.27 (m, 1H) ppm.

**2-Chlorobenzothioamide 80.** Reagent: 2-chlorobenzonitrile **64**. Procedure b. Yield: 83%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71–7.66 (m, 1H), 7.40–7.26 (m, 3H) ppm.

**2-Fluorobenzothioamide 81.** Reagent: 2-fluorobenzonitrile **65**. Procedure b. Yield: 73%.  $^1\text{H}$  NMR (MeOD)  $\delta$  8.52–8.51 (m, 1H), 7.46–7.40 (m, 1H), 7.21–7.1 (m, 2H) ppm.

**4-Methylbenzothioamide 82.** Reagent: *p*-tolunitrile **66**. Procedure a. Yield: 79%.  $^1\text{H}$  NMR (MeOD)  $\delta$  7.82 (d,  $J = 7.6$  Hz, 2H), 7.20 (d,  $J = 7.6$  Hz, 2H), 2.35 (s, 3H) ppm.

**4-Methoxybenzothioamide 83.** Reagent: 4-methoxy-benzonitrile **67**. Procedure b. Yield: 79.6%.  $^1\text{H}$  NMR (MeOD)  $\delta$  7.95 (d,  $J = 8.8$  Hz, 2H), 6.91 (d,  $J = 8.8$  Hz, 2H), 3.82 (s, 3H) ppm.

**3,4-Dichlorobenzothioamide 84.** Reagent: 3,4-dichloro-benzonitrile **68**. Procedure a. Yield: 83%.  $^1\text{H}$  NMR (MeOD)  $\delta$  8.05 (s, 1H), 7.79 (d,  $J = 8.4$  Hz, 1H), 7.53 (d,  $J = 8.4$  Hz, 1H) ppm.

**4-Bromobenzothioamide 85.** Reagent: 4-bromobenzonitrile **69**. Yield: 100%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.4$  Hz, 2H), 7.54 (d,  $J = 8.4$  Hz, 2H) ppm.

**4-Iodobenzothioamide 86.** Reagent: 4-iodobenzonitrile **70**. Yield 71%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.92 (s, 1H), 9.55 (s, 1H), 7.80 (d,  $J = 8.0$  Hz, 2H), 7.65 (d,  $J = 8.0$  Hz, 2H) ppm.

**Benzo[*d*][1,3]dioxole-5-carbothioamide 87.** Reagent: piperonylonitrile **71**. Procedure a. Yield: 84%.  $^1\text{H}$  NMR (MeOD)  $\delta$  7.49 (br s, 2H), 6.82 (br s, 1H), 6.02 (s, 2H) ppm.

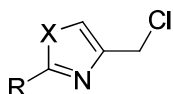
**Cyclohexanecarbothioamide 88.** Reagent: cyclohexanecarbonitrile **72**. Procedure a. Yield: 57%.  $^1\text{H}$  NMR (MeOD)  $\delta$  2.60 (t,  $J = 7.6$  Hz, 1H), 1.81 (s, 2H), 1.78 (s, 2H), 1.68 (d,  $J = 12.8$  Hz, 1H), 1.62–1.54 (m, 2H), 1.38–1.22 (m, 3H) ppm.

**4-(Trifluoromethyl)benzothioamide 89.** Reagent: 4-trifluoromethylbenzonitrile **73**. Procedure b. Yield: 100%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.96 (d,  $J = 8.0$  Hz, 2H), 7.68 (d,  $J = 8.0$  Hz, 2H) ppm.

**4-Nitrobenzothioamide 90.** A solution of  $\text{P}_4\text{S}_{10}$  (100 mmol) in EtOH (50 mL) was stirred for 1 h. 4-Nitrobenzonitrile **74** (50 mmol) was added and the resulting solution was heated to reflux for 6.5 h. The solvent was evaporated in vacuo and water (75 mL) was added. The mixture was extracted with EtOAc (3 x 75 mL), the organic layers gathered and washed with brine (75 mL), dried over  $\text{MgSO}_4$ ,

filtered, and the volatiles were removed in vacuo, affording **91** in 19% yield.  $^1\text{H NMR}$  ( $\text{CDCl}_3 + \text{MeOD}$ )  $\delta$  8.30 (d,  $J = 8.8$  Hz, 2H), 8.05 (d,  $J = 8.8$  Hz, 2H) ppm.

**Morpholine-4-carbothioamide 92.** Thiocarbonyldiimidazole (3.96 g, 20 mmol, 1 equiv.) was dissolved in THF and morpholine (1.74 mL, 20 mmol, 1equiv.) was added. After 1 hour the mixture was heated to 55°C, and after 3 hours 50 mL of THF was evaporated in vacuo (yielding intermediate (a)). Ammonia (40 mL of 2M solution in EtOH, 80 mmol, 4 eq.) was added to the mixture and after overnight stirring, the mixture was heated at 55 °C for 1 hour. After cooling to rt, the precipitate was filtered off. The filtrate was concentrated in vacuo and recrystallized from THF, yielding the product as an off-white powder (1.904 g, 13 mmol). Yield: 65%.  $^1\text{H NMR}$  (400 MHz, MeOD)  $\delta$  3.81 (s, 4H), 3.69–3.67 (m, 4H) ppm.



**General procedure for the synthesis of 4-chloromethyl-oxazole and 4-chloromethyl-thiazole derivatives 93–111.** A mixture of (thio)amide (1 equiv, 15 mmol) and 1,3-dichloroacetone (0.99 equiv, 14.9 mmol) in toluene (15 mL) was refluxed for 2-18 h. After completion of the reaction, monitored by TLC (petroleum ether : ethyl acetate), toluene was evaporated under reduced pressure and water was added. The mixture was extracted three times with ethyl acetate (50 mL). The organic layer was washed (brine) and dried ( $\text{MgSO}_4$ ). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using ethyl acetate/petroleum ether (1:99) as an eluent to give **93–111**.

**4-Chloromethyl-2-(4-chloro-phenyl)-thiazole 93.** Reagent: **75**. Yield: 72%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.89 (d,  $J = 8.8$  Hz, 2H), 7.42 (d,  $J = 8.8$  Hz, 2H), 7.32 (s, 1H), 4.74 (s, 2H) ppm.

**4-Chloromethyl-2-phenylthiazole 94.** Reagent: **76**. Yield 79%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.92–7.90 (m, 2H), 7.41–7.38 (m, 3H), 7.24 (s, 1H), 4.71 (s, 2H) ppm.

**4-Chloromethyl-2-(4-fluoro-phenyl)-thiazole 95.** Reagent: **77**. Yield 57%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.94 (dd,  $J = 8.0, 1.6$  Hz, 2H), 7.28 (s, 1H), 7.14 (t,  $J = 8.4$  Hz, 2H), 4.73 (s, 2H) ppm.

**4-Chloromethyl-2-(3-chloro-phenyl)-thiazole 96.** Reagent: **78**. Yield 50%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.97 (t,  $J = 1.6$  Hz, 1H), 7.82 (dt,  $J = 8.0, 1.6$  Hz, 1H), 7.42–7.37 (m, 2H), 7.34 (s, 1H), 4.75 (s, 2H) ppm.

**4-Chloromethyl-2-(3-fluoro-phenyl)-thiazole 97.** Reagent: **79**. Yield 73%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.67–7.66 (m, 2H), 7.43–7.37 (m, 1H), 7.33 (s, 1H), 7.15–7.10 (m, 1H), 4.74 (s, 2H) ppm.

**4-Chloromethyl-2-(2-chloro-phenyl)-thiazole 98.** Reagent: **80**. Yield 70%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.24–8.22 (m, 1H), 7.54–7.46 (m, 2H), 7.39–7.35 (m, 2H), 4.78 (s, 2H) ppm.

**4-Chloromethyl-2-(2-fluoro-phenyl)-thiazole 99.** Reagent: **81**. Yield 56%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.31–8.27 (m, 1H), 7.43–7.39 (m, 2H), 7.28–7.17 (m, 2H), 4.78 (s, 2H) ppm.

**4-Chloromethyl-2-(4-methyl-phenyl)-thiazole 100.** Reagent: **82**. Yield: 95%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J = 8.0$  Hz, 2H), 7.23 (s, 1H), 7.21 (s, 2H), 4.72 (s, 2H), 2.37 (s, 3H) ppm.

**Chloromethyl-2-(4-methoxy-phenyl)-thiazole 101.** Reagent: **83**. Yield: 72%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.83 (d,  $J = 8.8$  Hz, 2H), 7.16 (s, 1H), 6.88 (d,  $J = 8.8$  Hz, 2H), 4.68 (s, 2H), 3.76 (s, 3H) ppm.

**Chloromethyl-2-(3,4-dichloro-phenyl)-thiazole 102.** Reagent: **84**. Yield: 83%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.07 (d,  $J = 1.6$  Hz, 1H), 7.77 (dd,  $J = 8.4, 1.6$  Hz, 1H), 7.52 (d,  $J = 8.4$  Hz, 1H), 7.35 (s, 1H), 4.73 (s, 2H) ppm.

**Chloromethyl-2-(4-bromo-phenyl)-thiazole 103.** Reagent: **85**. Yield 87%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.80 (d,  $J = 6.8$  Hz, 2H), 7.56 (d,  $J = 6.8$  Hz, 2H), 7.31 (s, 1H), 4.73 (s, 2H) ppm.

**Chloromethyl-2-(4-iodo-phenyl)-thiazole 104.** Reagent: **86**. Yield 65%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J = 8.4$  Hz, 2H), 7.67 (d,  $J = 8.4$  Hz, 2H), 7.32 (s, 1H), 4.74 (s, 2H) ppm.

**Chloromethyl-2-(3,4-dioxo-phenyl)-thiazole 105.** Reagent: **87**. Yield: 69%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.43–7.41 (m, 2H), 7.20 (s, 1H), 6.84 (d,  $J = 8.4$  Hz, 1H), 6.00 (s, 2H), 4.70 (s, 2H) ppm.

**Chloromethyl-2-(4-chloro-phenyl)-oxazole 106.** Reagent: 4-chloro-benzamide **56**. After the addition of water, the precipitate was filtered and recrystallised from MeOH, giving the pure product. Yield: 84%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J = 8.4$  Hz, 2H), 7.71 (s, 1H), 7.44 (d,  $J = 8.8$  Hz, 2H), 4.57 (s, 2H) ppm.

**Chloromethyl-2-(4-fluoro-phenyl)-oxazole 107.** Reagent: 4-fluoro-benzamide **58**. After the addition of water, the precipitate was filtered, giving the pure product. Yield: 16%.  $^1\text{H NMR}$  (MeOD)  $\delta$  8.07–8.03 (m, 2H), 7.99 (s, 1H), 7.25 (t,  $J = 8.8$  Hz, 2H), 4.62 (s, 2H) ppm.

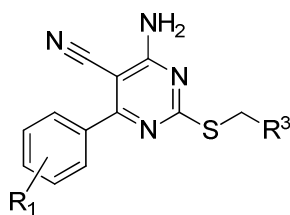
**Chloromethyl-2-(3-fluoro-phenyl)-oxazole 108.** Reagent: 3-fluoro-benzamide **57**. Yield: 63%.  $^1\text{H NMR}$  (MeOD)  $\delta$  8.02 (s, 1H), 7.84–7.82 (m, 1H), 7.74–7.70 (m, 1H), 7.55–7.50 (m, 1H), 7.28–7.23 (m, 1H), 4.63 (s, 2H) ppm.

**Chloromethyl-2-cyclohexyl-thiazole 109.** Reagent: **88**. Yield: 44%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.15 (d,  $J = 3.6$  Hz, 1H), 4.66 (d,  $J = 3.6$  Hz, 2H), 2.99 (br s, 1H), 2.12 (br s, 2H), 1.83 (br s, 2H), 1.72 (br s, 1H), 1.49 (br s, 2H), 1.41–1.39 (m, 2H), 1.28–1.27 (m, 1H) ppm.

**4-Chloromethyl-2-(4-trifluoromethylphenyl)-thiazole 110.** Reagent: **89**. Yield: 97%.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.07 (d,  $J = 8.0$  Hz, 2H), 7.70 (d,  $J = 8.4$  Hz, 2H), 7.39 (s, 1H), 4.76 (s, 2H) ppm.

**4-Chloromethyl-2-(4-nitrophenyl)-thiazole 111.** Reagent: **90**. Column eluent: ethyl acetate : petroleum ether (40:60), Yield: 20%,  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.43 (s, 1H) 8.39 (d,  $J = 9.2$  Hz, 2H), 8.23 (d,  $J = 8.8$  Hz, 2H), 4.79 (s, 2H) ppm.

**4-(4-(Chloromethyl)thiazol-2-yl)morpholine 112.** Morpholine-4-carbothioamide **92** (1.90 g, 13 mmol, 1 equiv.) and dichloroacetone (1.74 g, 13 mmol, 1 equiv.) were dissolved in EtOH (18 mL) and heated to reflux (90°C). After 1.5 hr. the mixture was cooled to rt, and the white precipitate in the pink mixture was filtered off. The filtrate was concentrated in vacuo, and the product was recrystallized from EtOH, yielding the product as an off-white powder (1.25 g, 5.7 mmol, 44%).  $^1\text{H NMR}$  (MeOD)  $\delta$  7.16 (s, 1H), 4.67 (s, 2H), 3.89–3.87 (m, 4H), 3.71–3.69 (m, 4H) ppm.



**General procedure for the synthesis of 5-substituted thiopyrimidines 24–54.** A mixture of thiopyrimidine **14–23** (1 equiv, 0.5 mmol), Na<sub>2</sub>CO<sub>3</sub> (1 equiv, 0.5 mmol) and the appropriate alkylating agent (1 equiv, 0.5 mmol) in DMF (2 mL) was stirred at 50 °C for 3–4 h. After completion of the reaction, monitored with TLC (DCM:MeOH 9:1), water (10 ml) was added. The precipitate was filtered off and washed with EtOAc. It was then collected, dissolved in DMF (1 mL) and EtOAc (1 mL). Water was added, causing precipitation. After filtration the pure final compound was obtained as a solid.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-(2-hydroxyethoxy)phenyl)pyrimidine-5-carbonitrile 24.** Reagent: **18, 93**. Yield: 8%. <sup>1</sup>H NMR (DMSO) δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.75 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.93 (t, *J* = 5.2 Hz, 1H), 4.55 (s, 2H), 4.08 (t, *J* = 9.6 Hz, 2H), 3.75 (q, *J* = 5.2 Hz, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 174.3, 172.3, 166.5, 163.5, 153.4, 145.6, 134.8, 131.7, 130.4, 129.3, 127.8, 118.0, 114.4, 106.5, 92.5, 91.3, 69.8, 59.4, 30.2 ppm. HPLC: 10.92 min.

**N-(4-(6-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-5-cyanopyrimidin-4-yl)phenyl)acetamide 25.** Reagent: **19, 93**. Yield: 7%. <sup>1</sup>H NMR (DMSO) δ 10.25 (s, 1H), 8.18 (br s, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.74 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 2.09 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.8, 169.3, 167.0, 166.0, 164.0, 153.8, 142.5, 135.2, 132.2, 130.5, 129.9, 129.8, 128.2, 118.8, 118.5, 117.0, 80.2, 30.6, 24.6 ppm. HPLC: 10.92 min.

**4-Amino-2-((2-(4-chlorophenyl)thiazol-4-yl)methylthio)-6-phenylpyrimidine-5-carbonitrile 26.** Reagents: **15, 93**. Yield: 43%. <sup>1</sup>H NMR (DMSO) δ 8.21 (br s, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 6.0 Hz, 2H), 7.74 (s, 1H), 7.56 (s, 2H), 7.54 (s, 3H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.5, 167.4, 165.5, 163.3, 153.3, 135.9, 134.8, 131.7, 131.1, 129.3, 128.5 (2 peaks), 127.7, 118.0, 116.2, 82.6, 30.2 ppm. HPLC: 12.49 min.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile 27.** Reagents: **16, 93**. Yield: 13%. <sup>1</sup>H NMR (DMSO) δ 8.50–7.50 (br s, 2H), 7.91 (br s, 2H), 7.72 (s, 1H), 7.55 (s, 2H), 7.07 (s, 2H), 4.53 (s, 2H), 3.82 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.5, 165.5, 163.6, 161.7, 153.4, 134.8, 131.7, 130.4, 129.3, 128.0, 127.7, 117.9, 116.6, 113.9, 55.4, 30.2 ppm. HPLC: 12.59 min.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-hydroxyphenyl)pyrimidine-5-carbonitrile 28.** Reagent: **17, 93**. Yield: 13.3%. <sup>1</sup>H NMR (DMSO) δ 10.20 (br s, 1H), 8.00–7.40 (m, 7H), 6.89 (s, 2H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 170.9, 166.6, 163.6, 134.8, 130.5, 129.5, 129.3, 128.0, 127.8, 126.4, 118.0, 116.8, 115.2, 107.9, 107.3, 80.0, 30.2 ppm. HPLC: 11.12 min.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-ethoxyphenyl)pyrimidine-5-carbonitrile 29.** Reagent: **20, 93**. Yield: 7%. <sup>1</sup>H NMR (DMSO) δ 8.15 (br s, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 6.9 Hz, 2H), 7.73 (s, 1H), 7.56 (d, *J* = 6.6 Hz, 2H), 7.04 (d, *J* = 7.0 Hz, 2H), 4.53 (s, 2H), 4.10

(d,  $J = 5.5$  Hz, 2H), 1.35 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  172.3, 166.5, 165.5, 163.6, 160.1, 153.4, 147.7, 134.8, 131.7, 130.4, 129.3, 127.8, 118.0, 116.6, 114.3, 81.5, 63.4, 30.2, 14.6 ppm. HPLC: 12.75 min.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-(trifluoromethoxy)phenyl)pyrimidine-5-carbonitrile 30.** Reagent: **21, 93**. Yield: 24%.  $^1\text{H}$  NMR (DMSO)  $\delta$  8.22 (br s, 2H), 7.95 (d,  $J = 8.8$  Hz, 2H), 7.93 (s, 1H), 7.70 (d,  $J = 8.8$ , 2H), 7.57 (d,  $J = 9.2$  Hz, 2H), 7.57 (d,  $J = 8.4$  Hz, 2H), 4.64 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  166.4, 166.1, 160.0, 157.6, 152.9, 150.0, 135.3, 133.5, 132.1, 131.4, 129.8, 128.3, 121.6, 119.4, 115.6, 93.8, 86.5, 29.7 ppm. HPLC: 12.83 min.

**4-Amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(4-(dimethylamino)phenyl)pyrimidine-5-carbonitrile 31.** Reagent: **22, 93**. Yield: 34%.  $^1\text{H}$  NMR (DMSO)  $\delta$  7.94 (d,  $J = 8.0$  Hz, 2H), 7.87 (d,  $J = 8.4$ , 2H), 7.71 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 2H), 6.75 (d,  $J = 8.3$  Hz, 2H), 4.53 (s, 2H), 2.99 (s, 6H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  171.8, 166.1, 165.5, 163.9, 153.7, 152.3, 134.8, 131.8, 130.0, 129.3, 127.8, 122.0, 117.8, 117.3, 111.1, 79.8, 39.7, 30.1 ppm. HPLC: 11.91 min.

**4-amino-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)-6-(p-tolyl)pyrimidine-5-carbonitrile 32.** Reagent: **23, 93**. Yield: 34%.  $^1\text{H}$  NMR (DMSO)  $\delta$  7.93 (d,  $J = 8.4$  Hz, 2H), 7.76 (d,  $J = 8.0$ , 2H), 7.74 (s, 1H), 7.56 (d,  $J = 8.4$  Hz, 2H), 7.33 (d,  $J = 8.4$  Hz, 2H), 4.53 (s, 2H), 2.38 (s, 3H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  172.5, 167.3, 165.5, 163.5, 153.4, 141.2, 134.8, 133.1, 131.7, 129.3, 129.1, 128.5, 127.8, 118.1, 116.4, 82.2, 30.2, 21.1 ppm. HPLC: 12.62 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)thio)pyrimidine-5-carbonitrile 33.** Reagents: **14, 93**. Yield 11%.  $^1\text{H}$  NMR (DMSO)  $\delta$  7.94 (s, 2H), 7.73 (s, 1H), 7.56 (s, 2H), 7.47 (s, 1H), 7.40 (s, 1H), 7.07 (s, 1H), 6.13 (s, 2H), 4.54 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  166.8, 163.9, 153.8, 150.3, 147.9, 135.2, 132.2, 130.1, 129.8, 128.2, 124.1, 118.5, 116.9, 109.0, 108.7, 102.3, 102.2, 30.6 ppm. HPLC: 12.27 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(((2-(4-chlorophenyl)oxazol-4-yl)methyl)thio)pyrimidine-5-carbonitrile 34.** Reagents: **14, 106**. Yield 20%.  $^1\text{H}$  NMR (DMSO)  $\delta$  8.22 (s, 1H), 7.97 (d,  $J = 4.4$  Hz, 2H), 7.60 (d,  $J = 8.8$  Hz, 2H), 7.48 (dd,  $J = 4.0, 1.6$  Hz, 1H), 7.43 (d,  $J = 1.6$  Hz, 1H), 7.08 (d,  $J = 4$  Hz, 1H), 6.15 (s, 2H), 4.35 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  172.2, 166.4, 163.5, 159.6, 149.8, 147.4, 138.3, 137.6, 135.3, 129.6, 129.3, 127.7, 125.5, 123.6, 116.4, 108.6, 108.2, 101.9, 81.9, 25.8 ppm. HPLC: 11.81 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(((2-(4-fluorophenyl)oxazol-4-yl)methyl)thio)pyrimidine-5-carbonitrile 35.** Reagents: **14, 107**. Yield 50%.  $^1\text{H}$  NMR (DMSO)  $\delta$  8.17 (s, 1H), 8.01 (dd,  $J = 8.0, 5.6$  Hz, 2H), 7.48 (d,  $J = 8.0$  Hz, 1H), 7.42 (s, 1H), 7.39 (t,  $J = 8.8$  Hz, 2H), 7.08 (d,  $J = 8.0$  Hz, 1H), 6.13 (s, 2H), 4.31 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  172.2, 166.5, 164.6, 163.5, 162.2, 159.7, 149.8, 147.5, 138.1, 137.4, 129.6, 128.5, 128.4, 123.6, 116.4, 116.2, 108.6, 108.2, 101.9, 81.9, 25.9 ppm. HPLC: 11.16 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-(((2-(3-fluorophenyl)oxazol-4-yl)methyl)thio)pyrimidine-5-carbonitrile 36.** Reagents: **14, 108**. Yield 35%.  $^1\text{H}$  NMR (DMSO)  $\delta$  8.22 (s, 1H), 7.81 (d,  $J = 8.0$  Hz, 1H), 7.71 (d,  $J = 9.2$  Hz, 1H), 7.61 (m, 1H), 7.48 (dd,  $J = 8.0, 2.0$  Hz, 1H), 7.42 (d,  $J = 1.6$  Hz, 1H), 7.40 (dt,  $J = 8.8, 2.4$  Hz, 1H), 7.08 (d,  $J = 8.0$  Hz, 1H), 6.13 (s, 2H), 4.32 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  172.2, 166.5, 163.5, 161.1, 159.3, 149.8, 147.5, 138.4, 137.9, 131.6, 131.5, 129.6, 128.8, 128.7, 123.7, 122.1, 117.7, 117.5, 116.5, 112.7, 112.4, 108.6, 108.2, 101.9, 81.9, 25.8 ppm. HPLC: 11.25 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-fluorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 37.** Reagents: **14, 95.** yield 38%. <sup>1</sup>H NMR (DMSO) δ 7.96 (s, 2H), 7.69 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.13 (s, 2H), 4.53 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.4, 166.4, 165.7, 164.4, 163.5, 161.9, 153.2, 149.8, 147.5, 129.7, 129.6, 129.5, 128.5, 128.3, 120.7, 119.7, 117.5, 116.5, 116.4, 116.3, 116.2, 116.1, 107.9, 101.9, 101.6, 81.9, 30.2. HPLC: 11.59 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(3-fluorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 38.** Reagents: **14, 97.** Yield 32%. <sup>1</sup>H NMR (DMSO) δ 7.75–7.74 (m, 2H), 7.71 (d, *J* = 9.6 Hz 1H), 7.57–7.51 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.34–7.31 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.13 (s, 2H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.4, 165.3, 163.7, 163.5, 161.2, 153.5, 149.9, 147.5, 135.0, 131.5, 131.4, 129.7, 123.7, 122.3, 118.4, 117.2, 116.9, 116.5, 112.6, 112.4, 108.6, 108.2, 101.9, 81.9, 30.2 ppm. HPLC: 12.26 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-*p*-tolylthiazol-4-yl)methylthio) pyrimidine-5-carbonitrile 39.** Reagents: **17, 100.** Yield 49%. <sup>1</sup>H NMR (DMSO) δ 7.78 (br s, 2H), 7.63 (br s, 1H), 7.47 (br s, 1H), 7.41 (br s, 1H), 7.26 (br s, 2H), 7.05 (br s, 1H), 6.12 (s, 2H), 4.53 (s, 2H), 2.32 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.4, 167.0, 166.3, 163.5, 152.9, 149.8, 147.4, 140.1, 130.3, 129.7, 125.9, 123.6, 116.8, 116.5, 108.6, 108.2, 101.8, 81.9, 30.3, 20.9 ppm. HPLC: 12.31 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-methoxyphenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 40.** Reagents: **14, 101.** Yield 61%. <sup>1</sup>H NMR (DMSO) δ 8.12 (br s, 2H), 7.85 (s, 1H), 7.83 (s, 1H), 7.58 (s, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 7.41 (s, 1H), 7.04 (br s, 3H), 6.13 (s, 2H), 4.51 (s, 2H), 3.81 (s, 3H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.4, 166.8, 166.4, 163.5, 160.8, 152.8, 149.8, 147.4, 129.7, 127.6, 125.7, 123.6, 116.5, 116.3, 114.5, 108.6, 108.2, 101.8, 81.9, 55.4, 30.3 ppm. HPLC: 11.48 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(benzo[d][1,3]dioxol-5-yl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 41.** Reagents: **14, 105.** Yield 61%. <sup>1</sup>H NMR (DMSO) δ 8.07 (br s, 2H), 7.58 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 3H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.12 (s, 2H), 6.10 (s, 2H), 4.50 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.4, 166.6, 166.3, 163.5, 152.8, 149.8, 149.0, 148.0, 147.4, 129.6, 127.3, 123.6, 120.7, 116.6, 116.5, 108.8, 108.5, 108.1, 105.9, 101.8, 101.7, 81.8, 30.2 ppm. HPLC: 11.42 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-bromophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 42.** Reagents: **14, 103.** Yield 54%. <sup>1</sup>H NMR (DMSO) δ 8.14 (br s, 2H), 7.85 (s, 1H), 7.83 (s, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.66 (s, 1H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.40 (s, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 2H), 4.53 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.4, 165.6, 163.5, 153.4, 149.8, 147.4, 132.1, 132.0, 129.6, 127.9, 123.6, 123.5, 117.9, 116.4, 108.5, 108.2, 101.8, 81.9, 30.1 ppm. HPLC: 12.58 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-iodophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 43.** Reagents: **14, 104.** Yield 27%. <sup>1</sup>H NMR (DMSO) δ 7.86 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.70 (s, 1H), 7.68 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.53 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.4, 165.9, 163.5, 153.4, 149.8, 147.4, 138.0, 132.3, 129.6, 129.1, 127.8, 123.6, 117.9, 116.4, 108.5, 108.2, 101.8, 97.0, 81.9, 30.2 ppm. HPLC: 12.75 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(3-chlorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 44.** Reagents: **14, 96.** Yield 28%. <sup>1</sup>H NMR (DMSO) δ 7.93 (s, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.76 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 12.0 Hz, 1H), 7.40 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 165.0, 163.5, 153.5, 149.8, 147.4, 134.7, 133.9, 131.2, 129.9, 129.6, 125.3, 124.8, 123.6, 118.4, 116.5, 108.6, 108.2, 101.8, 81.9, 30.1 ppm. HPLC: 11.68 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(3,4-dichlorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 45.** Reagents: **14, 102.** Yield 58%. <sup>1</sup>H NMR (DMSO) δ 8.06 (br s, 1H), 7.83 (br s, 1H), 7.77 (br s, 1H), 7.71 (br s, 1H), 7.47 (br s, 1H), 7.38 (br s, 1H), 7.04 (br s, 1H), 6.11 (s, 2H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.2, 166.3, 163.9, 163.5, 153.6, 149.8, 147.4, 133.2, 132.6, 131.4, 129.6, 127.3, 126.1, 123.6, 118.8, 116.4, 108.5, 108.1, 101.8, 81.9, 30.1 ppm. HPLC: 13.08 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(2-chlorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 46.** Reagents: **14, 98.** Yield 56%. <sup>1</sup>H NMR (DMSO) δ 8.17–8.15 (m, 1H), 7.86 (s, 1H), 7.64–7.62 (m, 1H), 7.50–7.45 (m, 3H), 7.39 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.57 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 174.6, 172.3, 166.4, 163.5, 162.0, 152.2, 149.8, 147.4, 131.1, 131.0, 130.7, 130.6, 129.6, 127.7, 123.6, 119.3, 116.5, 108.5, 108.2, 101.8, 81.9, 30.1 ppm. HPLC: 11.96 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(2-fluorophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 47.** Reagents: **14, 99.** Yield 50%. <sup>1</sup>H NMR (DMSO) δ 8.22 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.83 (s, 1H), 7.56–7.50 (m, 1H), 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43–7.34 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.12 (s, 2H), 4.57 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.4, 163.5, 160.5, 159.1, 158.0, 152.4, 149.8, 147.4, 131.9, 131.8, 129.7, 128.3, 125.2, 123.6, 120.5, 120.4, 118.9, 118.8, 116.5, 116.4, 108.6, 101.8, 81.9, 30.1 ppm. HPLC: 11.58 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-trifluoromethylphenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 48.** Reagents: **14, 108.** Yield: 22%. <sup>1</sup>H NMR (DMSO) δ 8.12 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.4, 2H), 7.82 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 2H), 4.56 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.3, 166.5, 165.1, 163.6, 153.9, 149.9, 147.5, 136.4, 129.7, 126.8, 126.3, 123.7, 119.0, 116.5, 108.6, 108.2, 101.9, 82.7, 81.9, 30.2 ppm. HPLC: 11.23 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-(4-nitrophenyl)thiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 49.** Reagents: **14, 111.** Yield: 29%. <sup>1</sup>H NMR (DMSO) δ 8.36 (d, *J* = 9.2 Hz, 2H), 8.34 (s, 1H), 8.20 (d, *J* = 9.2, 2H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 2H), 4.35 (s, 2H) ppm. <sup>13</sup>C NMR: δ 167.0, 164.0, 159.3, 150.2, 148.8, 147.9, 139.6, 139.4, 132.5, 130.1, 127.5, 125.0, 124.1, 116.9, 109.0, 108.7, 102.3, 82.4, 26.6 ppm. HPLC: 11.08 min.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-phenylthiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 50.** Reagents: **14, 94.** Yield 20%. <sup>1</sup>H NMR (DMSO) δ 7.92–7.89 (m, 2H), 7.68 (s, 1H), 7.49–7.46 (m, 4H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.12 (s, 2H), 4.54 (s, 2H) ppm. <sup>13</sup>C NMR (DMSO) δ 172.4, 166.9, 166.4, 163.5, 153.2, 149.9, 147.5, 132.9, 130.3, 129.7, 129.3, 126.1, 123.7, 117.5, 116.5, 108.6, 108.2, 101.9, 81.9, 30.3 ppm. LCMS: [M+H]<sup>+</sup> calc: 446.08, found: 446.13.

**4-Amino-6-(benzo[d][1,3]dioxol-5-yl)-2-((2-cyclohexylthiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 51.** Reagents: **14, 109.** Yield 15%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H),

7.04 (s, 1H), 6.91 (d,  $J = 8.0$  Hz, 1H), 6.05 (s, 2H), 5.85 (br s, 2H), 4.52 (s, 2H), 3.02 (t,  $J = 8.0$  Hz, 1H), 2.14 (s, 1H), 2.11 (s, 1H), 1.85 (s, 1H), 1.82 (s, 1H), 1.75 (d,  $J = 8.4$  Hz, 1H), 1.54–1.22 (m, 5H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.5, 174.1, 166.3, 163.8, 151.4, 150.7, 148.2, 129.7, 124.1, 116.7, 114.5, 109.1, 108.4, 101.9, 82.6, 42.8, 33.9, 31.2, 26.2, 25.9 ppm. HPLC: 11.56 min.

**4-Amino-6-(benzo[*d*][1,3]dioxol-5-yl)-2-((2-morpholinothiazol-4-yl)methylthio)pyrimidine-5-carbonitrile 52.** Reagents: **14**, **112**. Yield: 48%.  $^1\text{H}$  NMR (DMSO)  $\delta$  7.48 (dd,  $J = 8.0, 1.6$  Hz, 1H), 7.40 (d,  $J = 1.2$  Hz, 1H), 7.09 (d,  $J = 8.4$  Hz, 1H), 6.80 (s, 1H), 6.14 (s, 2H), 4.27 (s, 2H), 3.70 (t,  $J = 4.4$  Hz, 4H), 3.35–3.32 (m, 4H+ $\text{H}_2\text{O}$ ) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  174.6, 172.6, 171, 166.3, 163.5, 149.8, 148.2, 147.5, 129.7, 123.6, 116.5, 108.6, 108.2, 105.1, 101.9, 81.8, 65.4, 48.1, 30.8, 14.1 ppm. HPLC: 8.00 min.

**4-Amino-6-(benzo[*d*][1,3]dioxol-5-yl)-2-(thiazol-4-ylmethylthio)pyrimidine-5-carbonitrile 53.** Reagents: **14**, 4-(Chloromethyl)-1,3-thiazole hydrochloride (2 equivalents of base used). Yield 53%.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  9.05 (d,  $J = 2.0$  Hz, 1H), 7.94 (d,  $J = 1.2$  Hz, 1H), 7.46 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.37 (d,  $J = 1.2$  Hz, 2H), 7.08 (d,  $J = 8.0$  Hz, 1H), 6.13 (s, 2H), 4.53 (s, 2H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  172.4, 166.4, 163.5, 154.2, 152.6, 149.8, 147.4, 129.7, 123.7, 116.9, 116.5, 108.6, 108.2, 101.9, 81.9, 29.9 ppm. LCMS:  $[\text{M}+\text{H}]^+$  calc: 370.05, found: 370.07.

**2-(((1H-Imidazol-4-yl)methyl)thio)-4-amino-6-(benzo[*d*][1,3]dioxol-5-yl)pyrimidine-5-carbonitrile 54.** Reagents : **14**, 4-(chloromethyl)-1H-imidazole hydrochloride (2 equivalents of base used). Yield 54%.  $^1\text{H}$  NMR (MeOD)  $\delta$  7.67 (s, 1H), 7.50 (d,  $J = 8.0$  Hz, 1H), 7.36 (s, 1H), 7.07 (s, 1H), 6.93 (d,  $J = 8.0$  Hz, 1H), 6.04 (s, 2H), 4.38 (s, 2H) ppm.  $^{13}\text{C}$  NMR (DMSO)  $\delta$  173.4, 166.8, 163.9, 150.2, 147.9, 135.6, 134.0, 130.2, 124.1, 117.5, 117.0, 109.0, 108.7, 102.3, 82.2, 27.8 ppm. HPLC : 11.92 min. HRMS : ESI+H calc. 353.0742 found 353.0814.

## Biology

**Single-point [ $^{35}\text{S}$ ]GTP $\gamma\text{S}$  assay results for compounds 26, 28, 34–39, 41, 44, 46–49, 51 and 54.**  $E_{\text{max}}$  (%) determined at a concentration of  $100 \times K_i$  of ligand ( $n = 2$ ); CPA is the reference agonist, with  $E_{\text{max}}(\text{CPA}) = 100\%$ .

| Cpd       | $E_{\text{max}}$ (%) | Cpd       | $E_{\text{max}}$ (%) | Cpd       | $E_{\text{max}}$ (%) |
|-----------|----------------------|-----------|----------------------|-----------|----------------------|
| <b>26</b> | 37                   | <b>38</b> | 42                   | <b>48</b> | 50                   |
| <b>28</b> | 39                   | <b>39</b> | 52                   | <b>49</b> | 32                   |
| <b>34</b> | 57                   | <b>41</b> | 49                   | <b>51</b> | 41                   |
| <b>35</b> | 68                   | <b>44</b> | 54                   | <b>54</b> | 59                   |
| <b>36</b> | 42                   | <b>46</b> | 39                   |           |                      |
| <b>37</b> | 51                   | <b>47</b> | 42                   |           |                      |