

Supporting information:

Discovery of phosphoric acid mono-{2-[(E/Z)-4-(3,3-dimethyl-butyrylamino)-3,5-difluoro-benzoylimino]-thiazol-3-ylmethyl} ester (Lu AA47070): A phosphonooxymethylene prodrug of a potent and selective hA_{2A} receptor antagonist

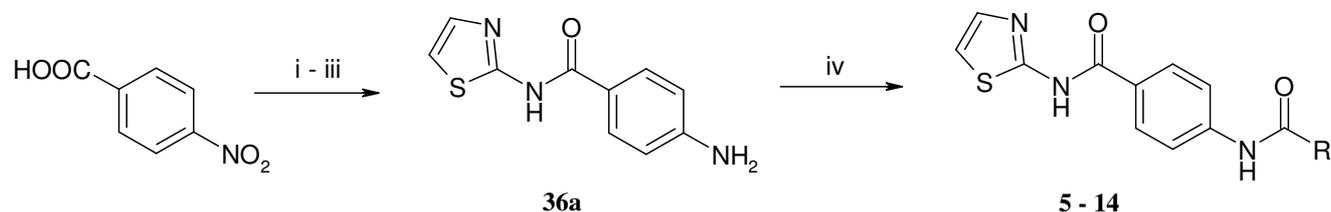
Anette G. Sams, Gitte K. Mikkelsen, Mogens Larsen, Morten Langgård, Mark E. Howell, Tenna J. Schrøder, Lise T. Brennum, Lars Torup, Erling B. Jørgensen, Christoffer Bundgaard, Mads Kreilgård, and Benny Bang-Andersen

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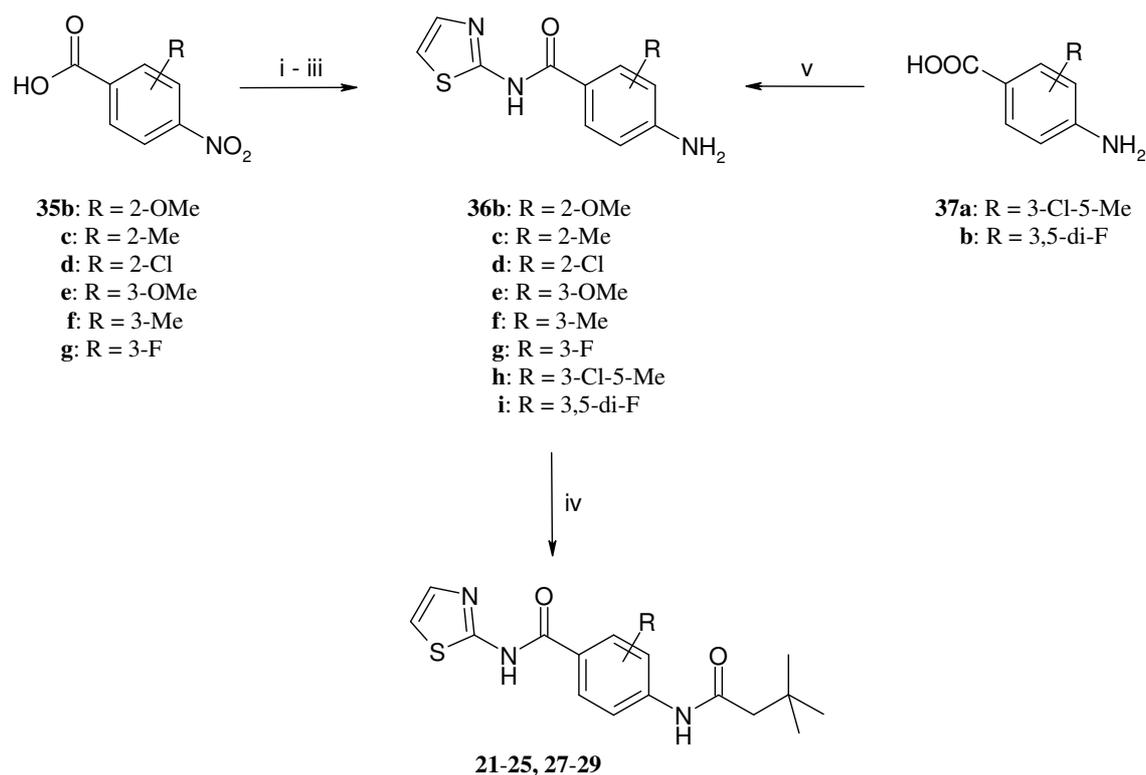
1. Schematic overviews of synthetic procedures towards compounds 5-30

SCHEME A: Synthesis of compounds 5-14



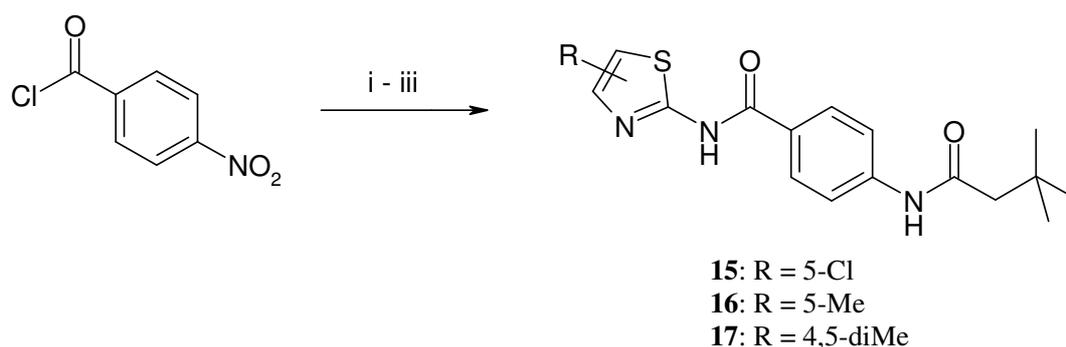
Reagents and conditions: (i) $(\text{COCl})_2$, 1,2-DCE, DMF; (ii) 2-aminothiazole, pyridine, 1,2-DCE, 50 °C, 67%; (iii) Pd(C), H_2 , 92%; (iv) RCOCl , pyridine, 1,2-DCE, 50-69%.

SCHEME B: General synthetic methods towards compounds 21-25, 27-29



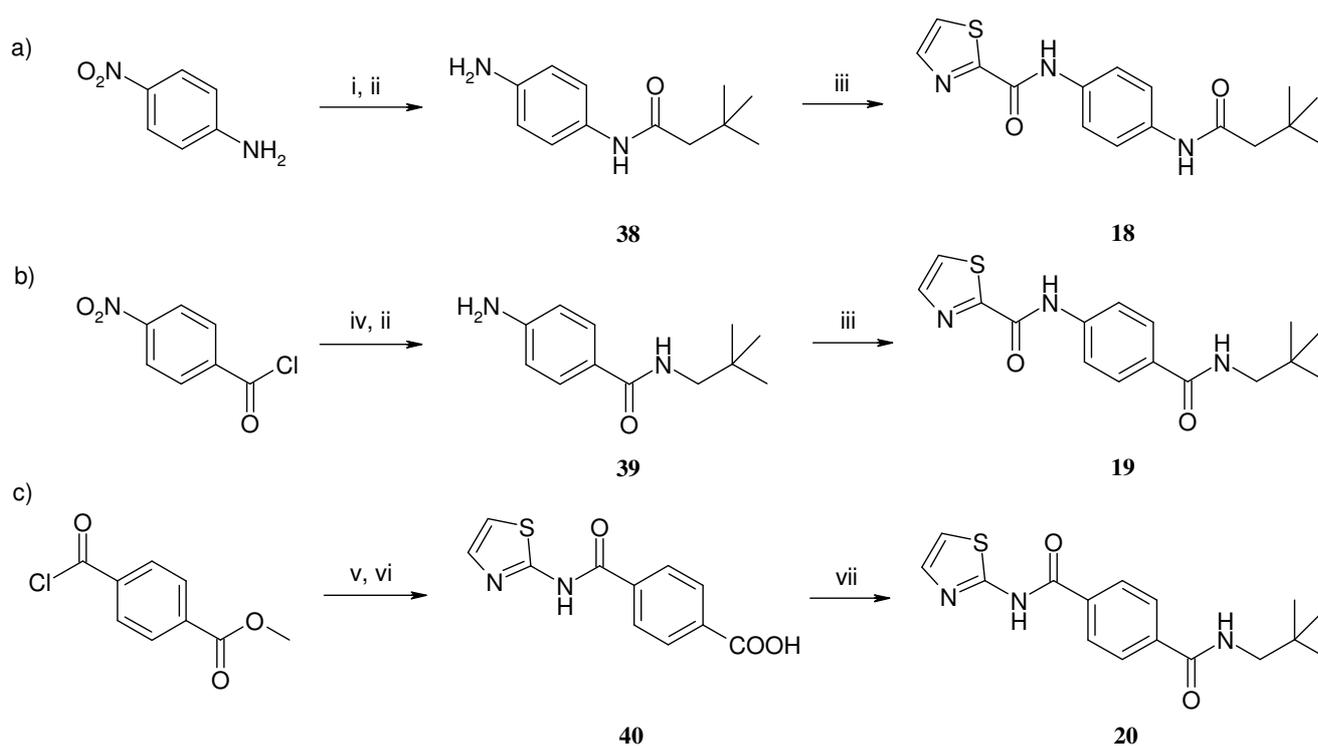
Reagents and conditions: (i) $(\text{COCl})_2$, 1,2-DCE, DMF; (ii) 2-aminothiazole, pyridine, 1,2-DCE, 54-65%; (iii) Pd(C), H_2 , 49-80%; (iv) $\text{Me}_3\text{CCH}_2\text{COCl}$, pyridine, 1,2-DCE, 8-80%; (v) 2-aminothiazole, EDC, HOBT, DIPEA, DMF, 60 °C, 18-62%.

SCHEME C: Preparation of 15-17



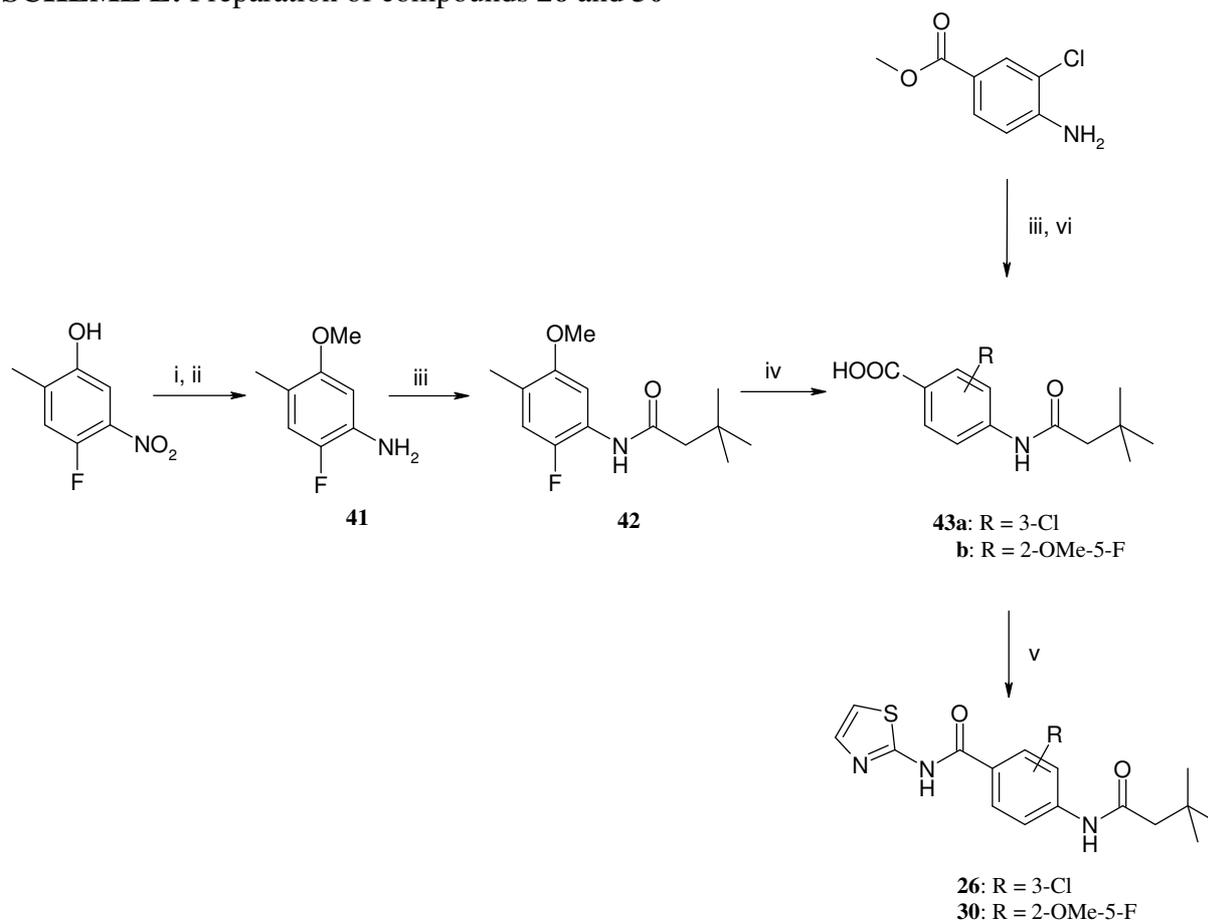
Reagents and conditions: (i) 5-chloro-2-aminothiazole or 5-methyl-2-aminothiazole or 4,5-dimethyl-2-aminothiazole, pyridine, 1,2-DCE, 60 °C; (ii) Zn, AcOH, MeOH, reflux, 33-43%; (iii) 3,3-dimethylbutyrylchloride, pyridine, 1,2-DCE, 15-20%.

SCHEME D: Preparation of 18-20



^a Reagents and conditions: (i) 3,3-dimethyl-butyl chloride, pyridine, 1,2-DCE, 40°C, 66%; (ii) Zn, 2M HCl, EtOH, 40°C, 56-63%; (iii) 2-carboxy-thiazole, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), DIPEA, DMF; (iv) 2,2-dimethyl-propylamine, pyridine, 1,2-DCE, 75%; (v) 2-amino-thiazole, pyridine, 1,2-DCE, 50 °C, 66%; (vi) 2M NaOH, THF, 70%; (vii) 2,2-dimethyl-propylamine, EDC, DIPEA, 1,2-DCE, 16%.

SCHEME E: Preparation of compounds 26 and 30



Reagents and conditions: (i) MeI, K_2CO_3 , acetone, reflux, 85%; (ii) Pd(C), H_2 , 100%; (iii) Me_3CCH_2COCl , pyridine, 1,2-DCE, 62-98%; (iv) $KMnO_4$, pyridine/ H_2O , 90 °C, 40%; (v) 2-aminothiazole, EDC, HOBT, DIPEA, DMF, 25-40%; (vi) 2M NaOH (aq.), MeOH, 40 °C, 90%.

2. Synthetic procedures and analytical data for compounds 5-30

General procedure for the parallel synthesis of 5-14, 21-25, 27-29:

4-Butyrylamino-*N*-thiazol-2-yl-benzamide (10):

0.2 mL of a 0.43 M stock solution of butanoic acid in DMF containing 6 mmol DIPEA per mmol butanoic acid was mixed with 0.1 mL of a 0.86 M stock solution of *O*-(7-azabenzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) in DMF. The mixture was allowed to react for 10 min. at ambient temperature, and then 0.1 mL of a 0.43 M stock solution of 4-amino-*N*-thiazol-2-yl-benzamide in DMF was added. The resulting mixture was incubated for 18 h at ambient temperature. Purification was performed by preparative HPLC-MS.

¹H NMR (D₆-DMSO): 0.92 (t, 3H); 1.63 (m, 2H); 2.34 (t, 2H); 7.26 (d, 1H); 7.55 (d, 1H); 7.74 (d, 2H); 8.06 (d, 2H); 10.20 (s, 1H); 12.47 (br s, 1H).

The following compounds were prepared analogously:

4-Propionylamino-*N*-thiazol-2-yl-benzamide (11):

¹H NMR (D₆-DMSO): 1.13 (d, 6H); 2.64 (h, 1H); 7.26 (d, 1H); 7.56 (d, 1H); 7.76 (d, 2H); 8.07 (d, 2H); 10.17 (s, 1H); 12.48 (br, 1H).

4-Isobutyrylamino-*N*-thiazol-2-yl-benzamide (12):

¹H NMR (D₆-DMSO): 1.10 (t, 3H); 2.38 (q, 2H); 7.27 (d, 1H); 7.56 (d, 1H); 7.75 (d, 2H); 8.07 (d, 2H); 10.21 (s, 1H); 12.44 (br, 1H).

4-(3-Methyl-butyrylamino)-*N*-thiazol-2-yl-benzamide (13):

¹H NMR (D₆-DMSO): 0.95 (d, 6H); 2.10 (h, 1H); 2.41 (d, 2H); 7.26 (d, 1H); 7.55 (d, 1H); 7.75 (m, 2H); 8.06 (m, 2H); 10.19 (s, 1H); 12.49 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-*N*-thiazol-2-yl-benzamide (14):

Yield: 0.5 g (69%)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.24 (s, 2H); 7.26 (d, 1H); 7.55 (d, 1H); 7.75 (d, 2H); 8.06 (d, 2H); 10.11 (br, 1H); 12.45 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-2-methoxy-*N*-thiazol-2-yl-benzamide (21):

Yield: 0.53 g (77%)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.25 (s, 2H); 3.96 (s, 3H); 7.30 (d, 1H); 7.33 (dd, 1H); 7.56 (d, 1H); 7.66 (d, 1H); 7.81 (d, 1H); 10.26 (s, 1H); 11.54 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-2-methyl-*N*-thiazol-2-yl-benzamide (22):

Yield: 0.39 g (55%)

¹H NMR (D₆-DMSO): 1.03 (s, 9H); 2.21 (s, 2H); 2.40 (s, 3H); 7.26 (d, 1H); 7.52-7.55 (4H); 9.99 (s, 1H); 12.38 (s, 1H).

2-Chloro-4-(3,3-dimethyl-butyrylamino)-*N*-thiazol-2-yl-benzamide (23):

Yield: 0.07 g (35%)

¹H NMR (D₆-DMSO): 1.03 (s, 9H); 2.23 (s, 2H); 7.30 (d, 1H); 7.54 (d, 1H); 7.55-7.61 (2H); 7.92 (d, 1H); 10.91 (s, 1H); 12.58 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-3-methoxy-*N*-thiazol-2-yl-benzamide (24):

Yield: 0.275 g (33%)

¹H NMR (D₆-DMSO): 1.03 (s, 9H); 2.35 (s, 2H); 3.95 (s, 3H); 7.27 (d, 1H); 7.56 (d, 1H); 7.72 (dd, 1H); 7.80 (d, 1H); 8.20 (d, 1H); 9.17 (s, 1H); 12.58 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-3-methyl-*N*-thiazol-2-yl-benzamide (25):

Yield: 0.065 g (20%)

¹H NMR (D₆-DMSO): 1.06 (s, 9H); 2.29 (s, 2H); 2.30 (s, 3H); 7.27 (d, 1H); 7.55 (d, 1H); 7.68 (d, 1H); 7.90 (dd, 1H); 7.98 (d, 1H); 9.29 (s, 1H); 12.49 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-3-fluoro-*N*-thiazol-2-yl-benzamide (27):

Yield: 1.14 g (81%)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.34 (s, 2H); 7.27 (d, 1H); 7.56 (d, 1H); 7.94 (dd, 1H); 7.99 (dd, 1H); 8.14 (t, 1H); 9.87 (s, 1H); 12.66 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-3,5-difluoro-N-thiazol-2-yl-benzamide (28):

Yield: 0.075 g (12%)

¹H NMR (D₆-DMSO): 1.05 (s, 9H); 2.27 (s, 2H); 7.32 (d, 1H); 7.59 (d, 1H); 7.90 (d, 2H); 9.83 (s, 1H); 12.82 (br, 1H).

3-Chloro-4-(3,3-dimethyl-butyrylamino)-5-methyl-N-thiazol-2-yl-benzamide (29):

Yield: 0.03 g (8%)

¹H NMR (D₆-DMSO): 1.08 (s, 9H); 2.26 (s, 2H); 2.28 (s, 3H); 7.30 (d, 1H); 7.58 (d, 1H); 7.97 (d, 1H); 8.07 (d, 1H); 9.67 (s, 1H); 12.70 (br, 1H).

N-(5-Chloro-thiazol-2-yl)-4-(3,3-dimethyl-butyrylamino)-benzamide (15):

4-Nitrobenzoic acid (7.3 g, 44 mmol) was suspended in 150 mL 1,2-DCE and 5 mL DMF under an argon atmosphere, and oxalylchloride (2M in dichloromethane) (31 mL, 32 mmol) was added slowly to the stirred suspension. After stirring at room temperature for 1 h, the solvent was removed by evaporation under reduced pressure, and the reaction mixture was re-dissolved in 200 mL 1,2-DCE. A suspension of 5-chloro-2-amino thiazole (4 g, 30 mmol) and pyridine (4.5 mL, 58 mmol) in 150 mL 1,2-DCE was added portion wise and the reaction mixture was stirred at 60 °C overnight. The reaction mixture was cooled and filtered. The filtrate was washed with water and 1,2-DCE, dried *in vacuo* and re-crystallized from EtOH/H₂O. Then it was suspended in 40 mL MeOH and 50 mL glacial acetic acid was added followed by Zn powder (3 g). The mixture was stirred at 72 °C for 48 h, filtered and the solvent was removed. The crude product was taken up in 2M HCl (aq.) and precipitated by addition of NaOH 2M to pH ca. 6. The solids were collected by filtration and re-crystallized from MeOH/H₂O. The obtained residue (0.68 g, 2.4 mmol) was suspended in 20 mL 1,2-DCE and pyridine (0.225 mL, 2.8 mmol) and 3,3-dimethyl-butyryl chloride (0.39 mL, 2.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature over night and then the solvent was removed by evaporation. The residue was re-crystallized from EtOH/H₂O.

Yield: 0.77 g (5% overall)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.24 (s, 2H); 7.60 (s, 1H); 7.75 (d, 2H); 8.06 (d, 2H); 10.15 (s, 1H); 12.73 (br s, 1H).

The following were prepared similarly:

4-(3,3-Dimethyl-butyrylamino)-N-(5-methyl-thiazol-2-yl)-benzamide (16):

Yield: 0.038 g, (8% overall)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.23 (s, 2H); 2.38 (s, 3H); 7.21 (s, 1H); 7.23 (d, 2H); 8.04 (d, 2H); 10.11 (s, 1H); 12.29 (br s, 1H).

4-(3,3-Dimethyl-butyrylamino)-N-(4,5-dimethyl-thiazol-2-yl)-benzamide (17):

Yield: 0.06 g (7% overall)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.20 (s, 3H); 2.23 (s, 2H); 2.27 (s, 3H); 7.72 (d, 2H); 8.03 (d, 2H); 10.12 (s, 1H); 12.26 (br s, 1H).

Preparation of 18 and 19 :

0.7 M stock solutions in DMF were prepared from 2-carboxy-thiazole (A) and HATU (B)

0.2 M stock solutions in DMF were prepared from **38** (C) and **39** (D)

Thiazole-2-carboxylic acid [4-(3,3-dimethyl-butyrylamino)-phenyl]-amide (18):

0.15 mL each of (A) and (B) was combined and added 0.055 mL DIPEA. The mixture was incubated for 10 min. then 0.2 mL (C) was added. Gently shaken at room temperature for 18 h. Purification was done by preparative HPLC with MS-detection.

Thiazole-2-carboxylic acid [4-(2,2-dimethyl-propylcarbonyl)-phenyl]-amide (19):

0.15 mL each of (A) and (B) was combined and added 0.055 mL DIPEA. The mixture was incubated for 10 min. then 0.2 mL (D) was added. Gently shaken at room temperature for 18 h. Purification was done by preparative HPLC with MS-detection.

***N*-(2,2-Dimethyl-propyl)-*N'*-thiazol-2-yl-terephthalamide (20):**

To a solution of **40** (0.5 g, 2 mmol) in 10 mL 1,2-DCE and 0.5 mL DMF was added EDC (0.38 g, 2 mmol), 2,2-dimethyl-propylamine (0.28 mL, 2.4 mmol) and DIPEA (0.5 mL, 3 mmol). The reaction mixture was stirred overnight at room temperature, and then HCl (2M, aq.) (1.2 mL, 2.4 mmol) was added along with 3 mL H₂O. The reaction mixture was filtered, the precipitate re-dissolved in ethyl acetate and washed with 2M NaOH, dried over MgSO₄, filtered and evaporated.

Yield: 0.1 g (16%)

¹H NMR (D₆-DMSO): 0.92 (s, 9H); 3.13 (d, 2H); 7.30 (d, 1H); 7.58 (d, 1H); 7.98 (d, 2H); 8.16 (d, 2H); 8.52 (t, 1H); 12.76 (br s, 1H).

3-Chloro-4-(3,3-dimethyl-butyrylamino)-*N*-thiazol-2-yl-benzamide (26):

Compound **43a** (1.35 g, 5 mmol) was suspended in 40 mL 1,2-DCE and added 0.5 mL DMF, then oxalylchloride (2M in dichloromethane) (3.5 mL, 7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then the solvents were evaporated and the residue re-suspended in 30 mL 1,2-DCE and added pyridine (0.4 mL, 5 mmol) and a suspension of 2-aminothiazole (0.4g, 4 mmol) in 10 mL 1,2-DCE. The reaction mixture was stirred at 50 °C overnight and the solvent was evaporated. The residue was taken up in 150 mL ethyl acetate and NaHCO₃ (sat). The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried on MgSO₄, filtered and evaporated to yield the product as a solid, which was re-crystallized from EtOH/H₂O.

Yield: 0.42 g (30%)

¹H NMR (D₆-DMSO): 1.05 (s, 9H); 2.37 (s, 2H); 7.29 (d, 1H); 7.57 (d, 1H); 7.98 (d, 1H); 8.04 (dd, 1H); 8.24 (d, 1H); 9.54 (s, 1H); 12.69 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-5-fluoro-2-methoxy-*N*-thiazol-2-yl-benzamide (30):

Compound **43b** (1.13 g, 4 mmol), DIPEA (1.3 mL, 8 mmol), EDC (0.76 g, 4 mmol), HOBt (0.54 g, 4 mmol) and 2-aminothiazol (0.4 g, 4 mmol) was suspended 30 mL 1,2-DCE. The reaction mixture was stirred at room temperature for 48 h, and then 20 mL ethyl acetate and 20 mL 1M HCl was added and the reaction mixture was stirred. This led to precipitation of the product as a solid which was recovered by filtration and re-crystallized from EtOH/H₂O.

Yield: 0.58 g (40%)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.36 (s, 2H); 3.92 (s, 3H); 7.30 (d, 1H); 7.53 (d, 1H); 7.64 (d, 1H); 7.99 (d, 1H); 9.88 (s, 1H); 11.66 (s, 1H).

General procedure for the preparation of intermediates 36a-i:

4-Amino-*N*-thiazol-2-yl-benzamide (36a):

4-Nitrobenzoic acid (13.8 g, 83 mmol) was suspended in 500 mL 1,2-DCE and 5 mL DMF under an argon atmosphere, and oxalylchloride (2M in dichloromethane) (62 mL, 124 mmol) was added slowly to the stirred suspension. After stirring at room temperature for 1 h, the solvent was removed by evaporation under reduced pressure, and the reaction

mixture was re-dissolved in 400 mL 1,2-DCE. A suspension of 2-amino-thiazole (8.3 g, 83 mmol) and pyridine (6.7 mL, 83 mmol) in 100 mL 1,2-DCE was added portion wise and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was cooled and filtered. The filtrate was washed with 1,2-DCE and dried *in vacuo*, then it was suspended in 400 mL abs. EtOH and 200 mL ethyl acetate and 50 mL glacial acetic acid was added followed by 10% Pd/C (0.5 g). The mixture was hydrogenated for 72 h at 3 bar H₂, filtered and the solvent was removed. The crude product was added NaHCO₃ (sat.) and ethyl acetate, the remaining solids (pure product) were collected by filtration and dried *in vacuo*. The liquid phases were separated, the organics were washed with brine, dried over MgSO₄, filtered and evaporated to yield a solid. The solid fractions were pure product and were combined and used without further purification.

Yield: 14.5 g (80%)

¹H NMR (D₆-DMSO): 5.93 (s, 2H); 6.50 (d, 2H); 7.18 (d, 1H); 7.49 (d, 1H); 7.84 (d, 2H); 12.05 (br s, 1H).

4-Amino-2-methoxy-N-thiazol-2-yl-benzamide (36b):

Yield: 13.9 g (53%)

¹H NMR (D₆-DMSO): 3.45 (s, 3H); 6.15 (s, 2H); 6.25-6.35 (2H); 7.20 (d, 1H); 7.46 (d, 1H); 7.71 (d, 1H); 10.97 (s, 1H).

4-Amino-2-methyl-N-thiazol-2-yl-benzamide (36c):

Yield: 1.3 g (58%)

¹H NMR (D₆-DMSO): 2.35 (s, 3H); 5.66 (br s, 2H); 6.36-6.46 (2H); 7.17 (d, 1H); 7.42 (d, 1H); 7.48 (d, 1H).

4-Amino-2-chloro-N-thiazol-2-yl-benzamide (36d):

Yield: 0.94 g (46%)

¹H NMR (D₆-DMSO): 5.95 (s, 2H); 6.52 (m, 1H); 6.65 (d, 1H); 7.23 (d, 1H); 7.36 (d, 1H); 7.50 (d, 1H); 12.18 (s, 1H).

4-Amino-3-methoxy-N-thiazol-2-yl-benzamide (36e):

Yield: 6.5 g (17%)

¹H NMR (D₆-DMSO): 3.85 (s, 3H); 5.59 (s, 2H); 6.67 (d, 1H); 7.19 (d, 1H); 7.48-7.65 (3H); 12.17 (br s, 1H).

4-Amino-3-methyl-N-thiazol-2-yl-benzamide (36f):

Yield: 6 g (72%)

¹H NMR (D₆-DMSO): 2.09 (s, 3H); 5.71 (s, 2H); 6.63 (d, 1H); 7.17 (d, 1H); 7.39 (d, 1H); 7.69-7.81 (m, 2H); 11.96 (br s, 1H).

4-Amino-3-fluoro-N-thiazol-2-yl-benzamide (36g):

Yield: 5.9 g (30%)

¹H NMR (D₆-DMSO): 6.00 (s, 2H); 6.80 (t, 1H); 7.21 (d, 1H); 7.51 (d, 1H); 7.74 (m, 1H); 7.81 (m, 1H); 12.19 (s, 1H).

4-Amino-3-chloro-5-methyl-N-thiazol-2-yl-benzamide (36h):

4-Amino-3-chloro-5-methylbenzoic acid (2.8 g, 15 mmol) was dissolved in 8 mL DMF and 80 mL 1,2-DCE, and DIPEA (2.5 mL, 15 mmol), EDC (2.85 g, 15 mmol) HOBt (2 g, 15 mmol) and 2-aminothiazol (1.5 g, 15 mmol) was added. The reaction mixture was stirred at 60 °C for 48 h, the solvent was evaporated and the residue was taken up in ethyl acetate and brine. The phases were separated and the organic phase was washed twice with brine and then with ammonium chloride (sat.). The organics were dried on MgSO₄, filtered and evaporated. Purified by flash chromatography on silica.

Yield: 0.72 g (18%)

¹H NMR (D₆-DMSO): 2.20 (s, 3H); 5.87 (br s, 2H); 7.21 (d, 1H); 7.52 (d, 1H); 7.79 (d, 1H); 7.97 (d, 1H); 12.22 (br, 1H).

4-Amino-3,5-di-fluoro-N-thiazol-2-yl-benzamide (36i):

Prepared as described above for **36h**.

Yield: 0.5 g (25%)

¹H NMR (D₆-DMSO): 6.14 (s, 2H); 7.25 (d, 1H); 7.55 (d, 1H); 7.77 (d, 2H); 12.38 (s, 1H).

***N*-(4-Amino-phenyl)-3,3-dimethyl-butylamide (38):**

A solution of 4-nitroaniline (0.96 g, 7 mmol) and pyridine (0.54 mL, 9 mmol) in 40 mL 1,2-DCE was slowly added 3,3-dimethyl-butyl chloride (1.17 mL, 9 mmol), and the reaction mixture was stirred at 40 °C overnight. The crude mixture was extracted with 1M HCl twice. The phases were separated and the organic phase was dried on MgSO₄, filtered and evaporated. The residue was dissolved in 60 mL EtOH and Zn (5g) added followed by 30 mL 2M HCl. The reaction mixture was stirred overnight at 40 °C, then it was cooled and filtered, and the organic solvent was evaporated. The aqueous phase was basicified with 2M NaOH. The formed precipitate was collected by filtration, washed with water and dried *in vacuo*.

Yield: 0.6 g (42%)

¹H NMR (D₆-DMSO): 1.00 (s, 9H); 2.09 (s, 2H); 4.81 (s, 2H); 6.48 (m, 2H); 7.19 (m, 2H); 9.32 (s, 1H).

4-Amino-*N*-(2,2-dimethyl-propyl)-benzamide (39):

A suspension of 4-nitro-benzoic acid chloride (1 g, 5.4 mmol) and pyridine (0.53 mL, 6.5 mmol) in 10 mL 1,2-DCE was added 2,2-dimethyl-propylamine (0.75 mL, 6.5 mmol) and the reaction mixture was stirred at room temperature for 3 h. Then 1 mL 2M HCl was added, and the crude mixture was washed with H₂O and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried on MgSO₄, filtered and evaporated. The obtained solid was recrystallized from EtOH/H₂O and dried. The residue was dissolved in 20 mL EtOH and Zn (5g) added together with 30 mL 2M HCl. The reaction mixture was stirred at 40 °C for 2 h, then the organic solvent was evaporated and the aqueous phase was basicified with 2M NaOH. The formed precipitate was collected by filtration, washed with water and dried *in vacuo*.

Yield: 0.62 g (56%)

¹H NMR (D₆-DMSO): 0.87 (s, 9H); 3.05 (d, 2H); 5.55 (s, 2H); 6.53 (m, 2H); 7.58 (m, 2H); 7.83 (t, 1H).

***N*-Thiazol-2-yl-terephthalamic acid (40):**

2-Aminothiazole (2.1 g, 21 mmol) and pyridine (1.7 mL, 21 mmol) were suspended in 100 mL 1,2-DCE, and a suspension of 4-chlorocarbonyl-benzoic acid methyl ester (5 g, 25 mmol) in 300 mL 1,2-DCE was added portionwise. Stirred at 50 °C overnight, then the solvent was removed under reduced pressure. The remaining solids were re-suspended in ethyl acetate and NaHCO₃ (sat.) and then filtered, washed with ethyl acetate and dried *in vacuo*. The residue was dissolved in 100 mL THF and 100 mL 2M NaOH and stirred at room temperature for 4 h. The organic solvent was removed by evaporation under reduced pressure and the aqueous phase acidified with 2M HCl. The precipitated product was removed by filtration, washed with water and dried *in vacuo*.

Yield: 2.9 g (56%)

¹H NMR (D₆-DMSO): 7.33 (d, 1H); 7.59 (d, 1H); 8.07 (d, 2H); 8.19 (d, 2H); 13.08 (br, 1H).

2-Fluoro-5-methoxy-4-methyl-phenylamine (41):

4-Fluoro-2-methyl-5-nitro-phenol (11.3 g, 66 mmol) was dissolved in 200 mL acetone and K₂CO₃ (10.8 g, 80 mmol) and MeI (8.2 mL, 132 mmol) was added. The reaction mixture was refluxed for 1½ h. It was then cooled filtered and evaporated. The residue was partitioned between ethyl acetate and water, and the organic phase was washed with water, then dried on MgSO₄, filtered and evaporated. The obtained crude product was re-crystallized from EtOH/H₂O and dried. The product was dissolved in 150 mL EtOH and 5

mL glacial acetic acid, and hydrogenated in the presence of ca. 0.5 g 10% Pd/C. The catalyst was filtered off through a pad of celite, and the solvent removed by evaporation, to give a deep red oil, which solidified on standing.

Yield: 8.7 g (85%)

¹H NMR (D₆-DMSO): 1.98 (s, 3H); 3.67 (s, 3H); 4.87 (br s, 2H); 6.37 (d, 1H); 6.75 (d, 1H).

***N*-(2-Fluoro-5-methoxy-4-methyl-phenyl)-3,3-dimethyl-butyramide (42):**

Compound **41** (4.65 g, 30 mmol) and pyridine (7.25 mL, 90 mmol) was dissolved in 50 mL 1,2-DCE and 3,3-dimethyl-butyryl chloride (5 mL, 36 mmol) was added drop wise. The reaction mixture was stirred at room temperature for 3h, then water and 2M HCl was added to the mixture, the phases were separated, and the organic phase was dried on MgSO₄, filtered and evaporated to a dark brown oil, which solidified on standing. Re-crystallised from EtOH/H₂O.

Yield: 4.7 g (62%)

¹H NMR (D₆-DMSO): 1.02 (s, 9H); 2.10 (s, 3H); 2.24 (s, 2H); 3.73 (s, 3H); 7.03 (d, 1H); 7.39 (d, 1H); 9.46 (br s, 1H).

3-Chloro-4-(3,3-dimethyl-butyrylamino)-benzoic acid (43a):

4-Amino-3-chloro-benzoic acid methyl ester (0.95 g, 5 mmol) and pyridine (0.53 mL, 6.5 mmol) was dissolved in 20 mL 1,2-DCE, and 3,3-dimethyl-butyryl chloride (0.9 mL, 6.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, then the solvent was evaporated and the residue was taken up in ethyl acetate and 2M HCl. The phases were separated and the organic phase was washed with NaHCO₃ (sat.) and H₂O, then dried on MgSO₄, filtered and evaporated. The residue was dissolved in 20 mL MeOH and 20 mL 2M NaOH. The mixture was stirred at 40 °C for 18 h, then the solvent was reduced *in vacuo*, and the aqueous phase was acidified with 2M HCl to precipitate the product. The product was recovered by filtration, washed with water and dried.

Yield: 1.28 g (95%)

¹H NMR (D₆-DMSO): 1.04 (s, 9H); 2.35 (s, 2H); 7.87 (d, 1H); 7.94-7.96 (2H); 9.54 (s, 1H); 13.33 (br, 1H).

4-(3,3-Dimethyl-butyrylamino)-5-fluoro-2-methoxy-benzoic acid (43b):

Compound **42** (2.53 g, 10 mmol) was dissolved in 50 mL pyridine/H₂O (1:1) and KMnO₄ (6.8 g, 35 mmol) was added portion wise. The reaction mixture was stirred at 90°C for 18 h, then it was cooled and diluted with water, filtered, and acidified with 2M HCl, then extracted with ethyl acetate. The organic phase was extracted with 2M NaOH, and the aqueous phase acidified to precipitate the product in a pure form.

Yield: 1.13g (40%)

¹H NMR (D₆-DMSO): 1.02 (s, 9H); 2.34 (s, 2H); 3.77 (s, 3H); 5.52 (d, 1H); 7.89 (d, 1H); 9.79 (br s, 1H); 12.63 (br, 1H).

3. Table of analytical details of 5-9 and 18,19 incl. hA_{2A} affinity data:

Compound	Purity, UV (%)	mw	m/z (MH ⁺)	hA _{2A} K _i nM	hA _{2A} %inhib. @10 μM
5	97.2	323.4	324.1	360	
6	96.2	353.4	354.1	530	
7	97.8	357.8	357.9	290	
8	99.0	337.4	338.3	310	
9	98.9	337.4	338.3	370	
18	100.0	317.4	318.0		18
19	100.0	317.4	318.0		-1

4. Broad screen profiling of compound 28

Compound **28** was tested at MDS Pharma Services against 60 different targets in radio ligand binding assay. At all targets except adenosine A_{2A} and A₁ receptors **28** (10000 nM) displayed less than 50 % inhibition of binding.

Target, Ligand, Species, Origin and % inhibition of binding at 10000 nM of **28** in a Lead Profiling screen at MDS pharmanervices.

Species: H=Human; R=Rat, M=Mouse; SH=Syrian hamster; RB=Rabbit.

Target	Ligand	Species	Origin	% Inhibition at 10000 nM
				Cpd. 28
Adenosine A ₁	[³ H]DPCPX	H	recombinant	93
Adenosine A _{2A}	[³ H]CGS-21680	H	recombinant	94
Adenosine A ₃	[¹²⁵ I]AB-MECA	H	recombinant	37
Adrenergic α _{1A}	[³ H]Prazosin	R	submaxillary gland	11
Adrenergic α _{1B}	[³ H]Prazosin	R	liver	-10
Adrenergic α _{1D}	[³ H]Prazosin	H	recombinant	2
Adrenergic α _{2A}	[³ H]MK-912	H	recombinant	-3
Adrenergic β ₁	[¹²⁵ I]Cyanopindolol	H	recombinant	0
Adrenergic β ₂	[³ H]CGP-12177	H	recombinant	9
Bradykinin B ₁	[³ H](Des-Arg10)-Kallidin	H	IMR-90 cells	-5
Bradykinin B ₂	[³ H]Bradykinin	H	recombinant	7
Calcium Channel L-Type: Benzothiazepine	[³ H]Diltiazem	R	brain	6
Calcium Channel L-Type: Dihydropyridine	[³ H]Nitrendipine	R	cerebral cortex	4
Calcium Channel N-Type	[¹²⁵ I]w-Conotoxin GVIA	R	brain frontal lobe	5
Dopamine D ₁	[³ H]SCH-23390	H	recombinant	10
Dopamine D _{2S}	[³ H]Spiperone	H	recombinant	-13

Target	Ligand	Species	Origin	% Inhibition at 10000 nM
				Cpd. 28
Dopamine D ₃	[³ H]Spiperone	H	recombinant	12
Dopamine D _{4.2}	[³ H]Spiperone	H	recombinant	0
	[¹²⁵ I]Endothelin-1	H	recombinant	2
Endothelin ET _B	[¹²⁵ I]Endothelin-1	H	recombinant	0
Epidermal Growth Factor (EGF)	[¹²⁵ I]Epidermal Growth Factor (EGF) (Murine)	H	A431 cells	-5
Estrogen ER α	[³ H]Estradiol	H	recombinant	17
GABA _A : Agonist Site	[³ H]Muscimol	R	brain (minus cerebellum)	4
GABAA: Benzodiazepine: Central	[³ H]Flunitrazepam	R	brain (minus cerebellum)	-5
GABA _B : Non-Selective	[³ H]CGP-54626	R	brain	9
GABA _{B1A}	[³ H]CGP-54626	H	recombinant	
Glucocorticoid	[³ H]Dexamethasone	H	HeLa S3 cells	-1
Glutamate: Kainate	[³ H]Kainic acid	R	brain (minus cerebellum)	-14
Glutamate: NMDA: Agonism	[³ H]CGP-39653	R	cerebral cortex	-6
Glutamate: NMDA: Glycine	[³ H]MDL105519	R	cerebral cortex	-12
Glutamate: NMDA: Phencyclidine	[³ H]TCP	R	cerebral cortex	-4
Growth Hormone Secretagogue (GHS, Ghrelin)	[¹²⁵ I]Ghrelin	H	recombinant	6
Histamine H ₁	[³ H]Pyrilamine	H	recombinant	-11
Histamine H ₂	[¹²⁵ I]Aminopotentidine	H	recombinant	-9

Target	Ligand	Species	Origin	% Inhibition at 10000 nM
				Cpd. 28
Histamine H ₃	[³ H]R(-)- α -Methylhistamine (RAMH)	H	recombinant	16
Imidazoline I ₂ : Central	[³ H]Idazoxan	R	cerebral cortex	1
Interleukin IL-1	[¹²⁵ I]Interleukin-1 α (IL-1 α)	M	3T3 cells	-6
Leukotriene , Cysteinyl CysLT ₁	[³ H]Leukotriene D ₄	H	recombinant	-20
Muscarinic M ₁	[³ H]Methylscopolamine	H	Recombinant Sf9 cells	-11
Muscarinic M ₂	[³ H]N-Methylscopolamine	H	recombinant	-13
Muscarinic M ₃	[³ H]N-Methylscopolamine	H	recombinant	-1
Neuropeptide Y ₁	[¹²⁵ I]Peptide YY	H	SK-N-MC cells	-1
Neuropeptide Y ₂	[¹²⁵ I]Peptide YY	H	KAN-TS neuroblastoma cells	5
Nicotinic Acetylcholine	[¹²⁵ I]Epibatidine	H	IMR-32 cells	-11
Opiate δ (OP1: DOP)	[³ H]Naltrindole	H	recombinant	-11
Opiate κ (OP2: KOP)	[³ H]Diprenorphine	H	recombinant	0
Opiate μ (OP3: MOP)	[³ H]Diprenorphine	H	recombinant	-3
Phorbol Ester	[³ H]PDBu	M	brain	5
Platelet Activating Factor (PAF)	[³ H]PAF	H	platelets	4
Potassium Channel [K _{ATP}]	[³ H]Glyburide	SH	pancreatic beta cells HIT-T15	0
Potassium Channel [Herg]	[³ H]Astemizol	H	recombinant	15

Target	Ligand	Species	Origin	% Inhibition at 10000 nM
				Cpd. 28
Purinergic P _{2X}	[³ H]α, β-Methylene ATP	RB	urinary bladder	-1
Purinergic P _{2Y}	[³⁵ S]ATP-αS	R	brain	-1
Serotonin 5-HT _{1A}	[³ H]8-OH-DPAT	H	recombinant	24
Serotonin 5-HT ₃	[³ H]GR-65630	H	recombinant	13
Sigma σ ₁	[³ H]Haloperidol	H	Jurkat cells	10
Sigma σ ₂	[³ H]Ifenprodil	R	brain	4
Sodium Channel: Site 2	[³ H]Batrachotoxin in A 20-α-Benzoate	R	brain	3
Tachykinin NK ₁	[³ H]SR-140333	H	recombinant	-17
Testosterone	[³ H]Mibolerone	R	recombinant	6
Thyroid Hormone	[¹²⁵ I]Triiodothyronine	R	liver	
Transporter: Dopamine (DAT)	[¹²⁵ I]RTI-55	H	recombinant	-10
Transporter: GABA	[³ H]GABA	R	cerebral cortex	-2
Transporter: Norepinephrine (NET)	[¹²⁵ I]RTI-55	H	recombinant	8
Transporter: Serotonin (5-Hydroxytryptamine) (SERT)	[¹²⁵ I]RTI-55	H	recombinant	26

5. Kinetic data for chemical hydrolysis $t_{1/2}$ of 32

32 hydrolyses to release **28** as a pseudo first order reaction at constant pH. Accelerated stability measurements were performed at 48 °C in a range of buffers with constant ionic strength. The rate constants and half-lives are listed below.

Rate constants and half-life as a function of pH at 48 °C for the pseudo first order reaction of hydrolysis of 32

pH	k_1 (h^{-1})	$t_{1/2}$ (h)
1.1	0.000658	1053
3.9	0.000820	845
4.9	0.000434	1597
7.0	nd ^a	>1600
8.3	nd ^a	>1600

^a The formation of **28** was extremely slow compared to pH 4.9.

nd: not determined