Table 17

BB-17	Name	Amino-(hetero)arene reactant B	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-17-1	5-Methoxycarbonylamino-2-methyl-oxazole-4-carboxylic acid ethyl ester	5-Amino-2-methyl-1,3-oxazole-4-carboxylic acid ethyl ester	0.56 (II)	229.13	10.12 (s, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.67 (s, 3 H), 2.39 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H)

Synthesis of building blocks BB-20

To a soln. of bromides C (1 eq) in DMSO (2.5 mL/mmol) was added NaN_3 (1.5 eq) at RT. The rxn mixture was stirred at RT for 5h (see Table 18~~Error! Reference source not found.~~) and quenched with H_2O. It was extracted with EtOAc and the combined org. phases were dried over $MgSO_4$ and concentrated in vacuo.

Table 18

BB-20	Name	Bromo-(hetero)arene reactant C	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-20-1	5-Azido-2-methyl-thiazole-4-carbaldehyde	5-Bromo-2-methylthiazole-4-carbaldehyde	0.56 (II)	169.04

Synthesis of building blocks BB-18

A 2.4 M soln. of $LiAlH_4$ in THF (1 eq) was diluted with anh. THF (2 mL/mmol) and cooled to -10°C. A soln. of ethyl ester BB-17 (1 eq, see Table 19) in anh. THF (2 mL/mmol) was added dropwise at -10°C. The rxn mixture was allowed to warm from -10°C to 5°C over 1h and quenched successively at 0°C with ice water, with a 2M aq. soln. of NaOH and with ice water. The suspension was diluted with THF, stirred for 30 min at RT, filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table 19

BB-18	Name	Reactant BB-17	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-18-1	(4-Hydroxymethyl-2-methyl-oxazol-5-yl)-carbamic acid methyl ester	BB-17-1	0.37 (II)	187.14	9.47 (s, 1 H), 4.92 (t, *J* = 5.6 Hz, 1 H), 4.16 (d, *J* = 5.7 Hz, 2 H), 3.65 (s, 3 H), 2.32 (s, 3 H)

Synthesis of building blocks BB-19

To a soln. of alcohol BB-18 (1 eq, see Table 20) in anh. DCM (10 mL/mmol) was added portionwise MnO_2 (9 eq) at RT and the rxn mixture was stirred at 45°C for 4h. It was filtered over a pad of celite and the filtrate was washed with a sat. aq. soln. of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo.

Table 20

BB-19	Name	Reactant BB-18	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) *δ*:
BB-19-1	(4-Formyl-2-methyl-oxazol-5-yl)-carbamic acid methyl ester	BB-18-1	0.44 (II)	185.17	11.10 (s, 1 H), 9.81 (s, 1 H), 3.74 (s, 3 H), 2.39 (s, 3 H)

Synthesis of building blocks BB-21

To a soln. of amines D (1 eq, see Table ~~20~~21) and TEA (3 eq) in THF (10 mL/mmol) was added Boc_2O (1.1 eq) at 0°C. The rxn mixture was stirred at 0°C for 10 min and at RT for 18h. It was partitioned between DCM and H_2O and the aq. phase was extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

Table ~~20~~21

BB-21	Name	Amino-(hetero)arene reactant D	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) *δ*:
BB-21-1	(5-Carbamoyl-1H-[1,2,3]triazol-4-yl)-carbamic acid *tert*-butyl ester	4-Amino-1H-1,2,3-triazole-5-carboxamide	0.59 (II)	no	14.70 (s br, 1 H), 9.03 (s, 1 H), 7.88 (s, 1 H), 7.56 (s, 1 H), 1.48 (s, 9 H)

Synthesis of building blocks BB-22

NaH (3 eq, as a 60% dispersion in mineral oil) was added portionwise at 0°C to a soln. or suspension of intermediate BB-21 (1 eq) in THF (10 mL/mmol). The suspension was stirred at RT for 20 min and MeI (1.1 eq) was added at 0°C. The rxn mixture was stirred at 0°C for 10 min and at RT for 48h (see Table ~~21~~22). When necessary to reach completion of the rxn, extra amounts of NaH (1 eq) and/or MeI (0.3 eq) were needed. The rxn mixture was quenched with half sat. aq. soln. of $NaHCO_3$ at 0°C and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by precipitation of the impurities from a soln. of the crude in DCM/MeOH and addition of Et_2O.

Table 2122

BB-22	Name	Reactant BB-21	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-22-1	(5-Carbamoyl-2-methyl-2H-[1,2,3]triazol-4-yl)-carbamic acid *tert*-butyl ester	BB-21-1	0.61 (II)	242.19	8.89 (s, 1 H), 7.84 (s, 1 H), 7.60 (s, 1 H), 4.10 (s, 3 H), 1.44 (s, 9 H)

Synthesis of building blocks BB-23

To a stirred soln. of amide intermediate BB-22 (1 eq) in DCM (10 mL/mmol) was added portionwise Burgess'reagent (3 eq) under argon. The rxn mixture was stirred at RT for 18h (see Table 2223) and partitioned between DCM and H_2O. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 2223

BB-23	Name	Reactant BB-22	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-23-1	(5-Cyano-2-methyl-2H-[1,2,3]triazol-4-yl)-carbamic acid *tert*-butyl ester	BB-22-1	0.74 (II)	224.12	10.38 (s, 1 H), 4.16 (s, 3 H), 1.48 (s, 9 H)

Synthesis of building blocks BB-24

Nitrile BB-23 (1 eq) was dissolved in a 7M soln. of NH_3 in MeOH (7 mL/mmol). The flask was evacuated and refilled with nitrogen. Raney nickel (0.1 eq) was added at 0°C and the temperature was allowed to reach RT. The flask was evacuated and refilled with hydrogen. The suspension was stirred under a hydrogen atmosphere at RT for 4h (see Table 2324) and filtered over a pad of Celite. The cake was washed with MeOH and the filtrate was concentrated in vacuo.

Table 2324

BB-24	Name	Reactant BB-23	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-24-1	(5-Aminomethyl-2-methyl-2H-[1,2,3]triazol-4-yl)-carbamic acid *tert*-butyl ester	BB-23-1	0.45 (II)	228.17	9.07 (s br, 1 H), 3.99 (s, 3 H), 3.58 (s, 2 H), 1.43 (s, 9 H)

Synthesis of building blocks BB-25

Method A (pentafluorophenyl ester)

A soln. of the appropriate alcohol (1 eq) and bis(pentafluorophenyl)carbonate (1.2 eq) in MeCN (0.55 mL/mmol) was cooled to 0°C and Et_3N (3.2 eq) was added dropwise. The rxn mixture was allowed to reach RT and stirred for 18h (see Table ~~24~~25). The mixture was concentrated in vacuo and the residue was purified by CC using DCM/MeOH and/or by prep. LC-MS using method 3.

Method B (Cyclisation)

A soln. of the appropriate hydrazide (1 eq) and CDI (1.5 eq) in anh. Dioxane (4.2 mL/mmol) was heated to 85°C and stirred for 18h. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and H_2O. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~24~~25

BB-25	Name	Method Reactant alcohol/hydrazide	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-25-1	Carbonic acid oxetan-3-yl ester pentafluorophenyl ester	A 3-Hydroxy oxetane	0.86 (II)	no io	5.65 (m, 1 H), 4.87 (m, 2 H), 4.65 (ddd, J_1 = 0.9 Hz, J_2 = 4.7 Hz, J_3 = 8.1 Hz, 2 H)
BB-25-2	Carbonic acid pentafluorophenyl ester 3-trifluoromethyl-oxetan-3-yl ester	Prepared according to Med. Chem. Commun., 2013, 4, 95-100	0.95 (II)	no io	5.18 (d, J = 8.7 Hz, 2 H), 4.87 (d, J = 9.6 Hz, 2 H)
BB-25-3	Carbonic acid 3-methyl-oxetan-3-yl ester pentafluorophenyl ester	A 3-Methyloxetan-3-ol	0.90 (II)	no io	4.77 (d, J = 7.7 Hz, 2 H), 4.54 (d, J = 8.2 Hz, 2 H), 1.76 (s, 3 H)
BB-25-4	5-Isopropyl-3H-[1,3,4]oxadiazol-2-one	B Isobutyric acid hydrazide	0.49 (II)	130.49	12.05 (s br, 1 H), 2.81-2.91 (m, 1 H), 1.19 (d, J = 6.9 Hz, 6 H)

Synthesis of building blocks BB-26

Method A (SEM protection)

To a suspension of the appropriate ketone (1 eq) and SEM-Cl (1.3 eq) in DCM (3.5 mL/mmol) was added dropwise DIPEA (1.5 eq) at 0°C. The rxn mixture was stirred at 0°C for 1.5 h and quenched with a sat. aq. soln. of $NaHCO_3$. It

was extracted with DCM, the org. phase was washed with a sat. aq. soln. of $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (THP protection)

To a suspension of the appropriate ketone (1 eq) in DCM (1.6 mL/mmol) was added TsOH (0.1 eq) and 3,4-dihydro-2H-pyran (1.3 eq). The rxn mixture was stirred at RT for 1.5 h and quenched with a sat. aq. soln. of $NaHCO_3$. It was extracted with DCM, the org. phase was washed with a sat. aq. soln. of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~25~~26

BB-26	Name	Method Reactant ketone	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$	^{1}H NMR (500 MHz, DMSO-d6) δ:
BB-26-1	1-(1-Methyl-4-nitro-1H-pyrazol-3-yl)-ethanone	*commercially available*			
BB-26-2	1-[4-Nitro-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-ethanone	A 1-(4-Nitro-1H-pyrazol-5-yl)ethanone	1.05 (I)	no io	8.41 (s, 1 H), 5.48 (s, 2 H), 3.55 (m, 2 H), 2.65 (s, 3 H), 0.85 (m, 2 H), -0.03 (m, 9 H)
BB-26-3	1-[4-Nitro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-3-yl]-ethanone		1.01 (I)	286.25	
BB-26-4	1-[4-Nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethanone	B 1-(4-Nitro-1H-pyrazol-5-yl)ethanone	0.80 (I)	240.22	

Building blocks BB-28

Table ~~26~~27

BB-28	Name	
BB-28-1	3-Amino-1-methyl-1H-pyrazole-4-carbonitrile	*commercially available*

Synthesis of building blocks BB-29

To a mixture of the appropriate amine E (1 eq), the appropriate halide (1.05 to 1.2 eq) and sodium *tert*-butoxide (2 eq) in toluene (3 mL/mmol) under N_2, was added BINAP (0.2 eq) and $Pd_2(dba)_3$ (0.1 eq). The rxn mixture was flushed with

N_2, heated to a given temperature in a sealed vial and stirred for a given time (see Table ~~27~~28). It was partitioned between

water and EtOAc and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 2728

BB-29	Name	Reactant amine E	Reactant halide	T[°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-29-1	8-(2-Fluoro-6-methyl-phenyl)-1,4-dioxa-8-aza-spiro[4.5]decane	1,4-Dioxa-8-azaspiro[4.5]decane	2-Bromo-3-fluorotoluene	100 18	1.01 (I)	252.19
BB-29-2	8-(2-Methoxy-4-methyl-pyridin-3-yl)-1,4-dioxa-8-aza-spiro[4.5]decane	1,4-Dioxa-8-azaspiro[4.5]decane	3-Bromo-2-methoxy-4-methylpyridine	100 20	0.81 (I)	265.19
BB-29-3	8-(2-Fluoro-6-methyl-phenyl)-1,4-dioxa-8-aza-spiro[4.6]undecane	1,4-Dioxa-8-aza spiro[4.6]undecane	2-Bromo-3-fluorotoluene	100 2.5	1.03 (I)	266.30
BB-29-4	7-(2-Fluoro-6-methyl-phenyl)-1,4-dioxa-7-aza-spiro[4.5]decane	1,4-Dioxa-7-azaspiro[4.5]decane	2-Bromo-3-fluorotoluene	100 6	1.00 (I)	252.29
BB-29-5	8-(2-Methoxy-4-trifluoromethyl-pyridin-3-yl)-1,4-dioxa-8-aza-spiro[4.5]decane	1,4-Dioxa-8-azaspiro[4.5]decane	3-Bromo-2-methoxy-4-trifluoromethyl-pyridine	100 18	1.03 (I)	319.16
BB-29-6	8-(4-Chloro-2-methoxy-pyridin-3-yl)-1,4-dioxa-8-aza-spiro[4.5]decane	1,4-Dioxa-8-azaspiro[4.5]decane	3-Bromo-4-chloro-2-methoxy pyridine	80 6	0.96 (I)	285.12

Synthesis of building blocks BB-30

Step A: Aromatic nucleophilic substitution

To a soln. of the appropriate amine F (1 eq) and the appropriate halide (1.1 eq) in a given solvent (0.9 to 1.5 mL/mmol) was added K_2CO_3 (2 eq) and the mixture was heated to a given temperature and stirred for 18h (see Table 2829). It was quenched with water and extracted with DCM or EtOAc. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Table ~~28~~29

BB-30A	Name	Reactant amine F	Reactant halide	Solvent T[°C]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-30-1A	[1-(2-Fluoro-6-formyl-phenyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester	4-(Boc-amino) piperidine	2,3-Difluoro benzaldehyde	DMSO 100	0.93 (II)	323.20
BB-30-2A	[1-(2-Fluoro-6-formyl-phenyl)-4-methyl-piperidin-4-yl]-carbamic acid *tert*-butyl ester	4-(Boc-amino)-4-methyl piperidine	2,3-Difluoro benzaldehyde	DMA 120	1.05 (I)	337.15
BB-30-3A	[1-(2-Fluoro-6-formyl-phenyl)-3-methyl-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	3-(Boc-amino)-3-methylpyrrolidine	2,3-Difluoro benzaldehyde	DMA 120	1.03 (I)	323.17
BB-30-4A	[(R)-1-(2-Fluoro-6-formyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	(R)-3-(Boc-amino)pyrrolidine	2,3-Difluoro benzaldehyde	DMSO 100	0.98 (I)	309.19
BB-30-6A	[1-(2-Fluoro-6-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	4-(Boc-amino) piperidine	2,3-Difluoronitrobenzene	DMA 80	1.05 (I)	340.22
BB-30-7A	(4'-Formyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-carbamic acid tert-butyl ester	4-(Boc-amino) piperidine	3-fluoro-2-methoxypyridine-4-carbaldehyde	DMA 120	0.95 (I)	336.21

Step B:

Method A: Reduction

A suspension of intermediate BB-30A (1 eq) in anh. MeOH (2 mL/mmol) was cooled to 0°C and $NaBH_4$ (1.2 to 1.3 eq) was added portionwise at 0°C (see Table ~~29~~30). The rxn mixture was stirred for 1h at 0°C to reach completion. It was carefully quenched by dropwise addition of water at 0°C and extracted with EtOAc. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo.

Method B: Hydrogenation

Intermediate BB-30A (1 eq) was dissolved in EtOH (5 mL/mmol). The flask was evacuated three times and refilled with nitrogen. Wet Pd/C (0.05 eq) was added and the flask was evacuated three times and refilled with hydrogen. The suspension was stirred under an atmospheric pressure of hydrogen for 3h and filtered over a pad of Celite. The cake was washed with EtOAc and MeOH and the filtrate was concentrated in vacuo.

Table ~~29~~30

BB-30B	Name	Method Reactant BB-32A	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-30-1B	[1-(2-Fluoro-6-hydroxymethyl-phenyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester	A BB-30-1A	0.82 (II)	325.24
BB-30-2B	[1-(2-Fluoro-6-hydroxymethyl-phenyl)-4-methyl-piperidin-4-yl]-carbamic acid *tert*-butyl ester	A BB-30-2A	0.86 (I)	339.23
BB-30-3B	[1-(2-Fluoro-6-hydroxymethyl-phenyl)-3-methyl-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	A BB-30-3A	0.82 (I)	325.22
BB-30-4B	[(R)-1-(2-Fluoro-6-hydroxymethyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	A BB-30-4A	0.82 (I)	311.23
BB-30-6B	[1-(2-Amino-6-fluoro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	B BB-30-6A	0.88 (I)	310.28

Step C:

Method A: Acetylation

A soln. of intermediate BB-30B (1 eq) and TEA (1.5 eq) in DCM (0.5 to 5 mL/mmol) was cooled to 0°C and AcCl (1.5 eq) was added dropwise at 0°C (see Table ~~30~~31). The rxn mixture was stirred for 1h at 0°C to reach completion. It was diluted with DCM and washed with a 10% aq. soln. of citric acid, with a sat. aq. soln. of $NaHCO_3$ and with brine. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B: Sandmeyer rxn (bromination)

To a soln. of intermediate BB-30B (1 eq) in MeCN (5 mL/mmol) was added dropwise at 0°C tetrafluoroboric acid as diethyl ether complex (1.2 eq). The soln. was stirred for 5 min at 0°C and tert-butyl nitrite (1.2 eq) was added dropwise. The rxn mixture was added dropwise at 0°C to a suspension of copper(I) bromide (1.5 eq) and copper(II) bromide (3 eq) in H_2O (3.1 mL/mmol). The resulting soln. was stirred for 18h allowing the temperature to reach RT. It was

partitionned between EtOAc and a sat. soln. of NH_4Cl. The org. phase was washed with a sat. soln. of NH_4Cl and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 3031

BB-30C	Name	Method Reactant BB-30B	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-30-1C	Acetic acid 2-(4-*tert*-butoxycarbonylamino-piperidin-1-yl)-3-fluoro-benzyl ester	A BB-30-1B	0.97 (II)	367.25
BB-30-2C	Acetic acid 2-(4-*tert*-butoxycarbonylamino-4-methyl-piperidin-1-yl)-3-fluoro-benzyl ester	A BB-30-2B	1.09 (I)	381.22
BB-30-3C	Acetic acid 2-(3-*tert*-butoxycarbonylamino-3-methyl-pyrrolidin-1-yl)-3-fluoro-benzyl ester	A BB-30-3B	1.06 (I)	367.22
BB-30-4C	Acetic acid 2-((R)-3-*tert*-butoxycarbonylamino-pyrrolidin-1-yl)-3-fluoro-benzyl ester	A BB-30-4B	1.02 (I)	353.14
BB-30-6C	[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	B BB-30-6B	1.13 (I)	373.15

Final step:

Method A: hydrogenation (using BB-30C) Intermediate BB-30C (1 eq) was dissolved in a mixture of MeOH (6 mL/mmol) and EtOAc (2 mL/mmol) and the flask was evacuated three times and refilled with nitrogen (see Table 3132). Wet Pd/C (0.08 eq) was added and the flask was evacuated three times and refilled with hydrogen. The suspension was hydrogenated under atmospheric pressure for 3h and filtered over a pad of Celite. The cake was washed with EtOAc and MeOH and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B: fluorination (using BB-30A)

To a soln. of intermediate BB-30A (1 eq) in DCM (6 to 58 mL/mmol) was added dropwise a 50% soln. of bis(2-methoxyethyl)aminosulfur trifluoride (2 to 2.75 eq). The soln. was stirred for 4 to 18h at RT (see Table 3132), quenched at 0°C with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method C: Sandmeyer rxn (chlorination using BB-30B)

To a soln. of intermediate BB-30B (1 eq) in MeCN (5 mL/mmol) was added dropwise at 0°C tetrafluoroboric acid as diethyl ether complex (1.2 eq). The soln. was stirred for 5 min at 0°C and tert-butyl nitrite (1.2 eq) was added dropwise.

The rxn mixture was added dropwise at 0°C to a suspension of copper(I) chloride (1.5 eq) and copper(II) chloride (3 eq) in H_2O (3.1 mL/mmol). The resulting soln. was stirred for 18h allowing the temperature to reach RT. It was partitionned between EtOAc and a sat. soln. of NH_4Cl. The org. phase was washed with a sat. soln. of NH_4Cl and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method D: Kumada rxn (using BB-30C)

To a mixture of intermediate BB-30C (1 eq) and di-μ-iodobis(tri-t-butylphosphino)dipalladium(I) in toluene (3.8 mL/mmol) was added dropwise under argon a 1M soln. of cyclopropylmagnesium bromide in 2-methyltetrahydrofuran (4 eq). The rxn mixture was stirred at RT for a given time (see Table ~~31~~32). When necessary, an extra amount of a 1M soln. of cyclopropylmagnesium bromide in 2-methyltetrahydrofuran (2 eq) was added. The rxn mixture was quenched with H_2O and extracted with EtOAc. The org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and when necessary, an additional purification by prep. LC-MS using method 1 was performed.

Table ~~31~~32

BB-30	Name	Method Reactant BB-30C, BB-30-B or BB-30A	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-30-1	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester	A BB-30-1C	1.00 (II)	309.16
BB-30-2	[1-(2-Fluoro-6-methyl-phenyl)-4-methyl-piperidin-4-yl]-carbamic acid *tert*-butyl ester	A BB-30-2C	1.12 (I)	323.24
BB-30-3	[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	A BB-30-3C	1.02 (I)	309.24
BB-30-4	[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester	A BB-30-4C	0.99 (I)	295.29
BB-30-6	[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	B BB-30-1A	1.09 (I)	345.43
BB-30-7	[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	C BB-30-6B	1.10 (I)	329.16

BB-30-8	[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester	D BB-30-6C	1.14 (I)	335.26
BB-30-9	(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-carbamic acid tert-butyl ester	B BB-30-7A	1.09 (I)	358.21

Synthesis of building blocks BB-31

To a mixture of the appropriate amine G (1 eq), the appropriate halide (1.5 eq) and sodium *tert*-butoxide (2 eq) in toluene (3.5 mL/mmol) under N_2, was added BINAP (0.2 eq) and $Pd_2(dba)_3$ (0.1 eq) (see Table ~~32~~33). The rxn mixture was flushed with N_2, heated to 110°C in a sealed vial and stirred for 1h. It was partitioned between water and DCM and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~32~~33

BB-31	Name	Reactant amine G	Reactant halide	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-31-1	3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(2-fluoro-6-methyl-phenyl)-azetidine	3-[(*tert*-Butyl dimethylsilanyl)oxy] azetidine	2-Bromo-3-fluorotoluene	1.21 (I)	296.28

Synthesis of building blocks BB-32

To a soln. of intermediate BB-31 (1 eq) in THF (3 mL/mmol) was added dropwise at 0°C a 1M soln. of TBAF (2 eq) in THF. The rxn mixture was stirred for 30 min at 0°C (see Table ~~33~~34) and partitioned between DCM and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table ~~33~~34

BB-32	Name	Reactant BB-31	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-32-1	1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-ol	BB-31-1	0.60 (I)	182.35

Synthesis of building blocks BB-33

To a soln. of intermediate BB-32 (1 eq), TEA (2 eq) and catalytic amount of DMAP (0.25 eq) in DCM (5 mL/mmol) was added at 0°C *p*-toluenesulfonyl chloride (1.3 eq). The rxn mixture was allowed to warm to RT and stirred for 2h (see Table ~~34~~35). When necessary to reach completion of the rxn, an extra amount of *p*-toluenesulfonyl chloride (0.3 eq) was added. It was partitioned between water and DCM and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM.

Table ~~34~~35

BB-33	Name	Reactant BB-32	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
BB-33-1	Toluene-4-sulfonic acid 1-(2-fluoro-6-methyl-phenyl)-azetidin-3-yl ester	BB-32-2	1.08 (I)	336.15

Building blocks BB-34

BB-34	Name	
BB-34-1	3-amino-4-bromopyrazole	*commercially available*
BB-34-2	4-Bromo-1-methyl-1H-pyrazol-3-ylamine	

Synthesis of intermediates of formula A-1

Method A ($NaBH(OAc)_3$ / THF)

To a soln. of aldehyde BB-4 (1 eq) and amine BB-7 (1 to 1.15 eq) in THF (4 to 8 mL/mmol) were added AcOH (1.5 eq) and the rxn mixture was stirred for 20 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~35~~36). When necessary to reach completion of the rxn, an extra portion of $NaBH(OAc)_3$ (1 eq) was added at RT. It was partitioned between EtOAc and a sat. aq. soln. of $NaHCO_3$. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc/MeOH.

Method B ($NaBH_4$ / TFE)

A soln. of aldehyde BB-4 (1 eq) and amine BB-7 (1 to 1.1 eq) in TFE (2 mL/mmol) was stirred for 10 min at 40°C and cooled to 0°C. $NaBH_4$ (1.2 eq) was added portionwise and the rxn mixture was stirred at 40°C for a given time (see Table ~~35~~36). It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~35~~36

A-1	Name	Reactant BB-4	Reactant BB-7	Method time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
A-1-1A	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[4-nitro-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-ylmethyl]-amine	BB-4-1A	BB-7-1	A 18	0.95 (I)	464.26
A-1-1B	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[4-nitro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-3-ylmethyl]-amine	BB-4-1B	BB-7-1	A 18	0.93 (I)	464.29
A-1-2	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[3-nitro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-ylmethyl]-amine	BB-4-2	BB-7-1	A 2	0.94 (I)	464.25
A-1-3	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-(1-methyl-4-nitro-1H-pyrazol-3-ylmethyl)-amine	BB-4-3	BB-7-1	A 1	0.69 (II)	348.21
A-1-4	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[5-nitro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-ylmethyl]-amine	BB-4-4	BB-7-1	B 1	0.85 (II)	464.22
A-1-5	(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-[3-nitro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-ylmethyl]-amine	BB-4-2	BB-7-2	A 24	0.93 (I)	477.23
A-1-6	(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-[4-nitro-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-ylmethyl]-amine	BB-4-1A	BB-7-2	A 24	0.93 (I)	477.25

A-1-7	[1-(2-Fluoro-6-methyl-phenyl)-4-methyl-piperidin-4-yl]-(1-methyl-3-nitro-1H-pyrazol-4-ylmethyl)-amine	BB-4-5	BB-7-3	A 18	0.76 (I)	362.21
A-1-8	[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-yl]-(1-methyl-3-nitro-1H-pyrazol-4-ylmethyl)-amine	BB-4-5	BB-7-4	A 18	0.77 (I)	348.21

Synthesis of intermediates of formula A-2

Method A (Nitro reduction from A-1)

To a soln. of intermediate A-1 (1 eq) in EtOH (3.5 to 7.4 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.02 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table ~~36~~37). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc or DCM/MeOH.

Method B1 (Reductive amination from BB-5 and BB-8 using $NaBH(OAc)_3$)

To a soln. of amine BB-5 (1 eq) and ketone BB-8 (1.05 to 1.2 eq) in THF (4 mL/mmol) was added AcOH (1.5 eq) and the rxn mixture was stirred for 5 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~36~~37). It was acidified with a 1M aq. soln. of HCl until pH~3-4 and extracted with DCM. The aq. phase was basified with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc/MeOH.

Method B2 (Reductive amination from BB-5 and BB-8 using $NaBH_4$)

A soln. of amine BB-5 (1 eq) and ketone BB-8 (1.05 eq) in MeOH (4 mL/mmol) was stirred for 18h at RT. $NaBH_4$ (1.6 eq) was added portionwise at 0°C and the rxn mixture was stirred at RT for a given time (see Table ~~36~~37). It was quenched with H_2O at 0°C, basified with a 1M aq. soln. of NaOH and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using EtOAc/MeOH.

Method C (Reductive amination from BB-6 and BB-7)

To a soln. of aldehyde BB-6 (1 eq) and amine BB-7 (1.1 eq) in THF (4 mL/mmol) was added AcOH (1.5 eq) and the rxn mixture was stirred for 5 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~36~~37). It was acidified with a 10% aq. soln. of citric acid and extracted with DCM. The aq. phase was basified with a 1M aq. soln. of NaOH and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by prep. LC-MS using method 7.

Method D (Reductive amination from BB-7 and BB-20)

A soln. of aldehyde BB-20 (1 eq) in TFE (2 mL/mmol) was stirred at 35°C for 5 min. Amine BB-7 (1 eq) was added and the rxn mixture stirred at 35°C for 5 min. $NaBH_4$ (1.2 eq) was added portionwise and the rxn mixture was stirred at

-35°C for a given time (see Table ~~36~~37). It was quenched with H_2O, basified with a 1M aq. soln. of NaOH and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo.

Method E (Boc cleavage from A-4)

To a soln. of intermediate A-4 (1 eq) in DCM (5 mL/mmol) was added TFA (1.5 to 2 mL/mmol) at 0°C and the rxn mixture was stirred at RT for a given time (see Table ~~36~~37). It was cooled to 0°C, quenched with a 1M aq. soln. of NaOH until pH reached 12 to 13 and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

Method F (Nucleophilic substitution of BB-5 on BB-33)

A soln. of intermediate BB-33 (1 eq) and amine BB-5 (3 eq) in MeCN (5.7 mL/mmol) was heated at 110°C under microwave irradiation for a given time (see Table ~~36~~37) and filtered. The filtrate was purified by prep. LC-MS using method 12.

Table ~~36~~37

A-2	Name	Reactant A-1, BB-5, BB-6, BB-20 or A-4	Reactant BB-8, BB-7 or BB-33	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
A-2-1A	[4-Amino-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-ylmethyl]-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	A-1-1A	-	A RT 3	0.85 (I)	433.86
A-2-1B	[4-Amino-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-3-ylmethyl]-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	A-1-1B	-	A RT 2	0.81 (I)	433.80
A-2-2	[3-Amino-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-ylmethyl]-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	A-1-2	-	A RT 18	0.85 (I)	434.10
A-2-3	(4-Amino-1-methyl-1H-pyrazol-3-ylmethyl)-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	A-1-3	-	A RT 2	0.56 (II)	318.13

A-2-12	[3-Amino-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrazol-4-ylmethyl]-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amine	A-1-5	-	A RT 5	0.79 (I)	447.31
A-2-13	[4-Amino-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-ylmethyl]-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amine	A-1-6	-	A RT 2.5	0.80 (I)	447.30
A-2-14	(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-[1-(2-fluoro-6-methyl-phenyl)-4-methyl-piperidin-4-yl]-amine	A-1-7	-	A RT 4	0.67 (I)	332.27
A-2-15	(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-[1-(2-fluoro-6-methyl-phenyl)-azepan-4-yl]-amine	BB-5-1	BB-8-3	B RT 18	0.69 (I)	332.25
A-2-16	4-{[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-ylamino]-methyl}-1-methyl-1H-pyrazol-3-ylamine	A-1-8	-	A RT 2	0.66 (I)	318.22
A-2-17	(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-[1-(2-fluoro-6-methyl-phenyl)-piperidin-3-yl]-amine	BB-5-1	BB-8-4	B RT 20	0.64 (I)	318.22
A-2-18	4-{[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-ylamino]-methyl}-1-methyl-1H-pyrazol-3-ylamine	BB-5-	BB-33-1	F 110 1	0.57 (I)	290.04

Synthesis of intermediates of formula A-3

Method A1 (or A2, respectively) (Cyclisation from A-2)

To a soln. of intermediate A-2 (1 eq) in MeCN (or DCM, respectively) (3.7 to 10 mL/mmol) was added CDI (or DSC, respectively) (1.2 to 2 eq) and the rxn mixture was stirred at a given temperature for a given time (see Table ~~37~~38).

When necessary to reach completion of the rxn an extra amount of CDI (0.5 to 1 eq) was added. The solvent was evaporated

off and the residue was partitioned between EtOAc or DCM and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc or DCM/MeOH, by precipitation from DCM/MeOH/Et_2O or MeCN or by prep. LC-MS using method 12.

Method B (Cyclisation from D-1)

A soln. of intermediate D-1 (1 eq) in DMF (8 mL/mmol) was heated at 120°C under microwave irradiation for a given time (see Table ~~37~~38) and partitioned between EtOAc and H_2O. The org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~37~~38

A-3	Name	Reactant A-2 or D-1	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
A-3-1A	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	A-2-1A	A1 RT 0.5	1.15 (I)	460.16
A-3-1B	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	A-2-1B	A1 RT 0.8	1.13 (I)	460.28
A-3-2	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-2	A1 RT 1.5	1.16 (I)	460.26
A-3-3	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	A-2-3	A1 RT 18	0.85 (II)	344.10
A-3-4	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trimethylsilanyl-ethoxymethyl)-1,3,6,7-tetrahydro-purin-2-one	A-2-4	A1 RT 18	1.07 (II)	460.24
A-3-5	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-5	A1 RT 1.5	0.93 (II)	344.18

A-3-15	5-[1-(2-Fluoro-6-methyl-phenyl)-4-methyl-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-14	A1 RT 18	1.02 (I)	358.22
A-3-16	5-[1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-15	A1 RT 2	1.03 (I)	358.21
A-3-17	5-[1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-16	A1 RT 0.5	0.94 (I)	344.18
A-3-18	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-3-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-17	A1 RT 1	0.99 (I)	344.16
A-3-19	5-[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	A-2-18	A2 45 18	0.61 (I)	316.17

Synthesis of intermediates of formula A-4

To a soln. of amine BB-24 (1 eq) and ketone BB-8 (1.1 to 1.2 eq) in THF (10 mL/mmol) was added AcOH (1.5 eq) and the rxn mixture was stirred for 5 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~38~~39). It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc/MeOH.

Table ~~38~~39

A-4	Name	Reactant BB-24	Reactant BB-8	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
A-4-1	(5-{[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-ylamino]-methyl}-2-methyl-2H-[1,2,3]triazol-4-yl)-carbamic acid *tert*-butyl ester	BB-24-1	BB-8-1	2	0.80 (II)	419.19

A-4-2	{5-[(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylamino)-methyl]-2-methyl-2H-[1,2,3]triazol-4-yl}-carbamic acid *tert*-butyl ester	BB-24-1	BB-8-2	1.5	0.78 (I)	432.29

Synthesis of intermediates of formula B-1

To a suspension of intermediate A-2 (1 eq) in anh. THF (3 mL/mmol) was added TEA (3 eq). The rxn mixture was cooled to 0°C and Boc_2O (1.1 eq) was added. It was stirred for 10 min at 0°C and at RT for a given time (see Table 3940) and was partitioned between EtOAc and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using DCM/MeOH or Hept/EtOAc.

Table 3940

B-1	Name	Reactant A-2	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
B-1-1	(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester	A-2-5	RT 18	0.91 (II)	418.08

Synthesis of intermediates of formula B-2

Method A ($NaBH(OAc)_4$ / AcOH / THF)

To a soln. of amine B-1 (1 eq) and aldehyde BB-12 (1.2 eq) in THF (4 to 5 mL/mmol) was added AcOH (1.5 eq) and the rxn mixture was stirred for 5 min at RT. $NaBH(OAc)_3$ (1.5 to 2 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table 4041). When necessary to reach completion of the rxn an extra amount of $NaBH(OAc)_3$ (0.2 to 1 eq) was added. The rxn mixture was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc/MeOH.

Method B ($NaBH_4$ / TFE)

A soln. of amine B-1 (1 eq) and aldehyde BB-12 (1 eq) in TFE (2 mL/mmol) was stirred for 10 min at 35°C and cooled to 0°C. $NaBH_4$ (1.2 eq) was added portionwise and the rxn mixture was stirred for a given time at a given temperature (see Table 4041). When necessary to reach completion of the rxn an extra amount of aldehyde BB-12 (1 eq) was added. It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 4041

B-2	Name	Reactant B-1	Reactant BB-12	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
B-2-1	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-methyl-3-[(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1H-pyrazol-4-ylmethyl}-carbamic acid *tert*-butyl ester	B-1-1	BB-12-1	A RT 48	1.03 (II)	577.03
B-2-2	{3-[(6-Chloro-3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1-methyl-1H-pyrazol-4-ylmethyl}-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester	B-1-1	BB-12-2	A RT 48	1.08 (II)	611.06
B-2-3	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[3-(2-fluoro-6-trifluoromethyl-benzylamino)-1-methyl-1H-pyrazol-4-ylmethyl]-carbamic acid *tert*-butyl ester	B-1-1	BB-12-3	B 35 4	1.09 (II)	594.02

Synthesis of intermediates of formula B-3

To a soln. of intermediate B-2 (1 eq) in DCM (4 to 16.5 mL/mmol) was added TFA (1 to 3.2 mL/mmol) and the rxn mixture was stirred at RT for a given time (see Table 4142). It was quenched with a 2M aq. soln. of NaOH until pH 12-13 and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using DCM/MeOH.

Table 4142

B-3	Name	Reactant B-2	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
B-3-1	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-methyl-3-[(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1H-pyrazol-4-ylmethyl}-amine	B-2-1	RT 4	0.77 (II)	477.10

B-3-2	{3-[(6-Chloro-3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1-methyl-1H-pyrazol-4-ylmethyl}-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	B-2-2	RT 3.5	0.82 (II)	511.08
B-3-3	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[3-(2-fluoro-6-trifluoromethyl-benzylamino)-1-methyl-1H-pyrazol-4-ylmethyl]-amine	B-2-3	RT 1	0.82 (II)	494.10

Synthesis of intermediates of formula C-1

Method A ($NaBH(OAc)_4$ / AcOH / THF)

To a soln. of amine BB-5 (1 eq) and ketone BB-13 (1.1 to 1.2 eq) in THF (4 mL/mmol) was added AcOH (1.5 eq) and the rxn mixture was stirred for 5 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~42~~43). It was quenched with a 1M aq. soln. of NaOH until pH 10 and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using EtOAc/MeOH.

Method B ($NaBH_4$ / TFE)

A soln. of aldehyde BB-14 (1 eq) and amine BB-15 (1.1 eq) in TFE (2 mL/mmol) was stirred for 5 min at 40°C and cooled to 0°C. $NaBH_4$ (1.2 eq) was added portionwise and the rxn mixture was stirred for a given time at a given temperature (see Table ~~42~~43). It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc.

Method C (nitro reduction from C-4)

To a soln. of intermediate C-4 (1 eq) in EtOH (4.5 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.02 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table ~~42~~43). It was filtered over a pad of celite and the filtrate was concentrated in vacuo.

Table ~~42~~43

C-1	Name	Reactant BB-5 or BB-14	Reactant BB-13 or BB-15	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
C-1-1	3-[(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-amino]-pyrrolidine-1-carboxylic acid *tert*-butyl ester	BB-5-1	BB-13-1	A RT 18	0.49 (II)	296.16

C-1-2	4-[(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester	BB-5-1	BB-13-2	A RT 1	0.51 (II)	310.13
C-1-3	4-[(3-Amino-1-methyl-1H-pyrazol-4-ylmethyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester	BB-14-1	BB-15-1	B 40 1	0.53 (II)	324.19
C-1-4	4-[(4-Amino-1-methyl-1H-pyrazol-3-ylmethyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester	C-4-1		C RT 4.5	0.48 (I)	310.28

Synthesis of intermediates of formula C-2

To a soln. of intermediate C-1 (1 eq) in MeCN (3.7 mL/mmol) was added CDI (1.2 to 2 eq) and the rxn mixture was stirred at a given temperature for a given time (see Table ~~43~~44). The solvent was evaporated off and the residue was partitioned between DCM and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc or triturated in MeCN and the solid was filtered.

Table ~~43~~44

C-2	Name	Reactant C-1	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
C-2-1	3-(2-Methyl-6-oxo-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester	C-1-1	RT 0.5	0.73 (II)	321.98
C-2-2	4-(2-Methyl-6-oxo-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl)-piperidine-1-carboxylic acid *tert*-butyl ester	C-1-2	RT 0.7	0.75 (II)	336.14
C-2-3	4-(2-Methyl-6-oxo-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl)-azepane-1-carboxylic acid *tert*-butyl ester	C-1-3	RT 18	0.77 (II)	350.24

C-2-4	4-(2-Methyl-5-oxo-2,4,5,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-6-yl)-piperidine-1-carboxylic acid tert-butyl ester	C-1-4	RT 0.5	0.75 (I)	336.38

Synthesis of intermediates of formula C-3

To a soln. of intermediate Ii (1 eq) in DCM (4 to 10 mL/mmol) was added TFA (1 to 1.6 mL/mmol) at 0°C and the rxn mixture was stirred at RT for a given time (see Table 4445). It was cooled to 0°C, quenched with a 32% aq. soln. of NaOH until pH reached 12 to 13 and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

Table 4445

C-3	Name	Reactant Ii	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
C-3-1	2-Methyl-5-pyrrolidin-3-yl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ii-1	RT 18	0.64 (II)	380.17
C-3-2	2-Methyl-5-piperidin-4-yl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ii-2	RT 0.75	0.62 (II)	394.08
C-3-3	5-Azepan-4-yl-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ii-3	RT 0.5	0.64 (II)	408.22
C-3-4	2-Methyl-6-piperidin-4-yl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	Ii-4	RT 1.5	0.67 (I)	394.22
C-3-5	2-Methyl-5-piperidin-4-yl-7-[1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ii-5	RT 1	0.69 (I)	408.29
C-3-6	7-(2-Cyclopropyl-benzyl)-2-methyl-5-piperidin-4-yl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ii-6	RT 1	0.67 (I)	366.28

Synthesis of intermediates of formula C-4

A soln. of aldehyde BB-4 (1 eq) and amine BB-15 (1.1 eq) in MeOH (4 mL/mmol) was stirred for 1.5 h at RT and cooled to 0°C. $NaBH_4$ (1.6 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table ~~45~~46). It was quenched with a 1M aq. soln. of NaOH and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~45~~46

C-4	Name	Reactant BB-4	Reactant BB-15	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
C-4-1	4-[(1-Methyl-4-nitro-1H-pyrazol-3-ylmethyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester	BB-4-3	BB-15-2	0.5	0.61 (I)	340.39

Synthesis of intermediates of formula D-1

To a soln. of aldehyde BB-19 (1 eq) and amine BB-7 (1.4 eq) in THF (10 mL/mmol) was added AcOH (1.5 eq) followed by $NaBH(OAc)_3$ (1.5 eq). The rxn mixture was stirred at RT for a given time (see ~~Table).~~Table 47). It was quenched with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Table ~~46~~47

D-1	Name	Aldehyde BB-19	Amine BB-7	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
D-1-1	(4-{[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-ylamino]-methyl}-2-methyl-oxazol-5-yl)-carbamic acid methyl ester	BB-19-1	BB-7-1	18	0.70 (II)	377.27

Synthesis of intermediates of formula E-1

Method A ($NaBH(OAc)_3$ / THF)

To a soln. of ketone BB-26 (1 eq) and amine BB-7 (1 eq) in THF (8 mL/mmol) were added AcOH (1.5 eq) and the rxn mixture was stirred for 20 min at RT. $NaBH(OAc)_3$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table 48). When necessary to reach completion of the rxn, an extra amount of $NaBH(OAc)_3$ (1 eq) was added at RT. It was partitioned between EtOAc and a sat. aq. soln. of $NaHCO_3$. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B ($Ti(OiPr)_4$ / $NaBH_4$)

A suspension of ketone BB-26 (1 eq) and amine BB-7 (1.05 eq) in titanium (IV) isopropoxide (3 eq) was stirred at RT for 18h. The rxn mixture was cooled to -10°C and EtOH (1 mL/mmol), THF (1 mL/mmol) and $NaBH_4$ (3 eq) were sequentially added. The mixture was allowed to reach RT for 1h and further stirred at RT for a given time (see ~~Table~~ ~~).~~ Table 48). It was quenched with water at 0°C and filtered. The filtrate was extracted with EtOAc and the combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

Method C ($NaBH_4$ / TFE)

A soln. of ketone BB-26 (1 eq) and amine BB-7 (1.1 eq) in TFE (2 mL/mmol) was stirred for 1 to 2.5 h at RT and cooled to 0°C. $NaBH_4$ (1.5 to 2 eq) was added portionwise and the rxn mixture was stirred for 20 min at 0°C and for a given time at RT (see Table 48). It was quenched at 0°C with a sat. aq. soln. of $NaHCO_3$ and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~47~~48

E-1	Name	Reactant BB-26	Reactant BB-7	Method time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-1-1	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-[1-(1-methyl-4-nitro-1H-pyrazol-3-yl)-ethyl]-amine	BB-26-1	BB-7-1	A 144	0.77 (I)	362.23
E-1-2	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-[4-nitro-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-ethyl}-amine	BB-26-2	BB-7-1	B 2	1.01 (I)	478.18
E-1-3	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethyl}-amine	BB-26-4	BB-7-1	C 0.5	0.87 (I)	432.24
E-1-4	(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-{1-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethyl}-amine	BB-26-4	BB-7-2	C 2.5	0.80 (I)	445.23

E-1-5	[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-{1-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethyl}-amine	BB-26-4	BB-7-8	C 0	0.85 (I)	452.22
E-1-6	[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-{1-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethyl}-amine	BB-26-4	BB-7-7	C 0	0.86 (I)	468.25

Synthesis of intermediates of formula E-2

Method A: hydrogenation

To a soln. of intermediate E-1 (1 eq) in EtOH (7 to 7.5 mL/mmol) was added 10% Pd/C moistened with ~50% water (0.02 eq) and the rxn mixture was hydrogenated under atmospheric pressure for a given time (see Table 49). It was filtered over a pad of celite and the filtrate was concentrated in vacuo. When necessary, the crude was purified by prep. LC-MS using method 5.

Method B: reduction

To a soln. of intermediate E-1 (1 eq) in MeOH (9 mL/mmol) was added $CoCl_2$ (1.5 eq) and the rxn mixture was stirred for 5 min at RT and cooled to 0°C. $NaBH_4$ (5 eq) was added portionwise and the mixture was stirred for 15 min at 0°C (see Table 49). It was quenched at 0°C with water and MeOH was evaporated off. The residue was partitioned between EtOAc and water and the aq. phase was further extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo.

Table 4849

E-2	Name	Reactant E-1	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-2-1	[1-(4-Amino-1-methyl-1H-pyrazol-3-yl)-ethyl]-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	E-1-1	4	0.59 (I)	332.28
E-2-2	{1-[4-Amino-2-(2-trimethylsilanyl-ethoxymethyl)-2H-pyrazol-3-yl]-ethyl}-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	E-1-2	24	0.92 (I)	448.25
E-2-3	{1-[4-Amino-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-ethyl}-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	E-1-3	A 2	0.71 (I)	402.09

E-3-5	6-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-methyl-2-(tetrahydro-pyran-2-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	E-2-5	RT 1.5	1.02 (I)	448.22
E-3-6	6-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-7-methyl-2-(tetrahydro-pyran-2-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one	E-2-6	RT 1.5	1.02 (I)	464.27

Synthesis of intermediates of formula E-4

To a soln. of amine BB-28 (1 eq) and aldehyde or ketone BB-12 (2 eq) in THF (2.6 mL/mmol) were added AcOH (1.5 eq) and the rxn mixture was stirred for 18h at RT. $NaBH_4$ (1.5 eq) was added portionwise and the rxn mixture was stirred at RT for a given time (see Table 51). It was partitioned between EtOAc and a sat. aq. soln. of $NaHCO_3$. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table 4951

E-4	Name	Reactant BB-28	Reactant BB-12	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-4-1	1-Methyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazole-4-carbonitrile	BB-28-1	BB-12-4	2	0.90 (I)	281.20

Synthesis of intermediates of formula E-5

Method A (Grignard addition using nitriles E-4)

To a stirred soln. of nitrile E-4 (1 eq) in THF (6 mL/mmol) under argon was added dropwise at 0°C a 3M soln. of R^4MgBr in Et_2O (6 eq). The rxn mixture was allowed to reach RT and stirred at a given temperature for a given time (see Table 52). When necessary to reach completion of the rxn, extra amounts of a 3M soln. of R^4MgBr in Et_2O (2 eq) were added. The mixture was cooled to 0°C, quenched with a sat. aq. soln. of NH_4Cl and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (Heck rxn using bromides E-7 or E-8)

A mixture of bromide E-7 or E-8 (1 eq), K_2CO_3 (1.2 eq), $Pd(OAc)_2$ (0.03 eq) and 1,3-bis(diphenylphosphino)propane (0.06 eq) in a mixture of DMF (2.5 mL/mmol) and H_2O (0.6 mL/mmol) was flushed with Ar and butyl vinyl ether (5 eq) was added dropwise at RT. The rxn mixture was heated at a given temperature for a given time (see Table 52). After cooling to RT, a 1M aq. solution of HCl (2 mL/mmol) was added and the mixture was stirred for 1h at RT. It was

neutralised with a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~50~~52

E-5	Name	Reactant E-4, E-7 or E-8	Reactant R^4MgBr or vinyl ether	MethodT [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-5-1	1-[1-Methyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-4-1	MeMgBr, as a 3M soln. in Et_2O	A 80 3	0.91 (I)	298.22
E-5-2	1-[1-(Tetrahydro-pyran-2-yl)-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-8-1	Butyl vinyl ether	B 105 18	1.01 (I)	368.24
E-5-3	1-[3-(2-Cyclopropyl-benzylamino)-1-methyl-1H-pyrazol-4-yl]-ethanone	E-7-2	Butyl vinyl ether	B 100 3	0.89 (I)	270.35
E-5-4	1-[3-(2-Cyclopropyl-benzylamino)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-ethanone	E-8-2	Butyl vinyl ether	B 100 2	1.00 (I)	340.24
E-5-5	1-{1-Methyl-3-[(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-1H-pyrazol-4-yl}-ethanone	E-7-4	Butyl vinyl ether	B 100 18	0.76 (I)	299.22

Synthesis of intermediates of formula E-6

Method A

A suspension of ketone E-5 or E-10 (1 eq) and amine BB-7 (1.1 to 1.2 eq) in titanium (IV) isopropoxide (3 to 5 eq) was stirred at RT for 18h. The rxn mixture was cooled to 0°C and EtOH (1 to 2.5 mL/mmol), THF (1 mL/mmol) and $NaBH_4$ (3 eq) were sequentially added. The mixture was stirred at RT for a given time (see Table 53), quenched with water at 0°C and when necessary filtered over a pad of celite. It was extracted with EtOAc and the combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B

To a mixture of ketone E-5 or E-10 (1 eq) and amine BB-7 (1.1 to 1.2 eq) in THF (3 mL/mmol) was added titanium (IV) isopropoxide (3 to 4.4 eq) and the soln. was stirred at RT for 18h. It was cooled to 0°C and MeOH (6 mL/mmol) and $NaBH_4$ (1.3 to 2 eq) were sequentially added. After stirring for a given time at RT (see Table 53), it was quenched with water and a 1M soln. of NaOH and extracted with EtOAc. When necessary a filtration over a pad of celite was performed. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 5 or 8.

Table 5153

E-6	Name	Reactant E-5 or E-10	Reactant BB-7	Method time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-6-1	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-[1-methyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethyl}-amine	E-5-1	BB-7-1	1	0.89 (I)	490.28
E-6-2	[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-{1-[1-(tetrahydro-pyran-2-yl)-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethyl}-amine	E-5-2	BB-7-1	A 18	0.96 (I)	560.38
E-6-3	{1-[1-Cyclopropyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethyl}-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-amine	E-10-1	BB-7-1	A 1	0.98 (I)	516.39
E-6-4	{1-[1-Cyclopropyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethyl}-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-amine	E-10-1	BB-7-7	A 0.5	0.93 (I)	552.33
E-6-5	[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-{1-[1-methyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethyl}-amine	E-5-1	BB-7-7	A 0.5	0.92 (I)	526.38

Synthesis of intermediates of formula E-7

Method A

A soln. of amine BB-34 (1 eq) and aldehyde or ketone BB-12 (1.05 to 1.1 eq) in MeOH (2 to 4 mL/mmol) was stirred for 1h at RT. $NaBH_4$ (1.6 to 2 eq) was added portionwise at 0°C and the rxn mixture was stirred at a given temperature for a given time (see **Table** ~~52~~54). It was quenched with H_2O at 0°C and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using EtOAc/MeOH.

Method B

A soln. of amine BB-34 (1 eq), aldehyde or ketone BB-12 (1.1 eq) and AcOH (1.1 eq) in MeOH (1.5 mL/mmol) was stirred under Ar for 1h at RT. Molybdenum(VI) dichloride dioxide (0.05 eq) in MeOH (1.5 mL/mmol) was added at RT followed by phenylsilane (1.5 eq). The rxn mixture was stirred at a given temperature for a given time (see **Table** ~~52~~54) and quenched with a sat. soln. of $NaHCO_3$. It was extracted with DCM and the combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using EtOAc/MeOH.

Table ~~52~~54

E-7	Name	Reactant BB-34	Reactant BB-12	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-7-1	(4-Bromo-1H-pyrazol-3-yl)-(2-trifluoromethyl-benzyl)-amine	BB-34-1	BB-12-4	A 0 1.5	0.91 (I)	320.02
E-7-2	(4-Bromo-1-methyl-1H-pyrazol-3-yl)-(2-cyclopropyl-benzyl)-amine	BB-34-2	BB-12-5	A RT 2.5	0.97 (I)	305.85
E-7-3	(4-Bromo-1H-pyrazol-3-yl)-(2-cyclopropyl-benzyl)-amine	BB-34-1	BB-12-5	A RT 1	0.89 (I)	292.18
E-7-4	(4-Bromo-1-methyl-1H-pyrazol-3-yl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine	BB-34-2	BB-12-1	B RT 18	0.87 (I)	335.08

Synthesis of intermediates of formula E-8

To a suspension or solution of the intermediate E-7 (1 eq) in DCM (2 to 4 mL/mmol) was added TsOH (0.1 eq) and 3,4-dihydro-2H-pyran (1.3 eq). The rxn mixture was stirred at a given temperature for a given time (see Table ~~53~~55) and quenched with a sat. aq. soln. of $NaHCO_3$. It was extracted with DCM, the org. phase was washed with a sat. aq. soln. of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~53~~55

E-8	Name	Reactant E-7	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-8-1	[4-Bromo-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-(2-trifluoromethyl-benzyl)-amine	E-7-1	50 20	1.08 (I)	404.09
E-8-2	[4-Bromo-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-(2-cyclopropyl-benzyl)-amine	E-7-3	45 18	1.06 (I)	376.17

Synthesis of intermediates of formula E-9

To a soln. of THP-protected intermediate E-5 (1 eq) in DCM (2 mL/mmol) was added dropwise TFA (1.5 mL/mmol). The soln. was stirred at RT for a given time (see Table ~~54~~56), quenched at 0°C with a 1M aq. soln. of NaOH until pH 10-11 and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~54~~56

E-9	Name	Reactant E-5	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
E-9-1	1-[3-(2-Trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-5-2	RT 1	0.82 (I)	284.16
E-9-2	1-[3-(2-Cyclopropyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-5-4	RT 72	0.82 (I)	256.33

Synthesis of intermediates of formula E-10

A mixture of intermediates E-9 (1 eq), boron species BB-10 (2 eq), Na_2CO_3 (2 eq), 2,2'-bipyridyl (1 eq) and $Cu(OAc)_2$ (1 eq) in toluene (10 to 12 mL/mmol) was flushed with N_2 and heated at a given temperature for a given time (see Table ~~55~~57). It was partitioned between EtOAc or DCM and a sat. aq. soln. of $NaHCO_3$ and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~55~~57

E-10	Name	Reactant E-9	Reactant BB-10	T [°C] time [h]	t_R [min] (LC/MS-method)	MS-data m/z $[M+H]^+$

E-10-1	1-[1-Cyclopropyl-3-(2-trifluoromethyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-9-1	Cyclopropyl boronic acid	70 2.5	0.97 (I)	324.22
E-10-2	1-[1-Cyclopropyl-3-(2-cyclopropyl-benzylamino)-1H-pyrazol-4-yl]-ethanone	E-9-2	Cyclopropyl boronic acid	80 2	0.95 (I)	296.33

Synthesis of compounds of formula Ia

Method A1 (Alkylation of A-3 or E-3: NaH/THF)

To a soln. of intermediate A-3 or E-3 (1 eq) in a mixture of anh. THF (3 to 7.3 mL/mmol) and anh. DMF (0 to 0.7 mL/mmol) was added NaH (1.5 to 10 eq, as a 60% dispersion in mineral oil) at 0°C. The suspension was stirred for 10 min and halide BB-9 (1.1 to 1.5 eq) was added at 0°C. The rxn mixture was stirred at a given temperature for a given time under possible microwave irradiation (see

Table 58). When necessary to reach completion of the rxn an extra amount of NaH (0.5 eq, as a 60% dispersion in mineral oil) and/or halide BB-9 (0.5 eq) was added. The mixture was quenched with water or a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 1, 2 or 5.

Method A2 (Alkylation of A-3 or E-3 using NaH/THF followed by saponification)

Similar to method A1 except that the rxn mixture was quenched with a 2M aq. soln. of NaOH and stirred ON at RT before the extraction with EtOAc.

Method B (Mitsunobu with A-3 or E-3)

To a soln. or suspension of intermediate A-3 or E-3 (1 eq) and alcohol BB-9 (1.1 to 6 eq) in toluene (3.4 to 24 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (1.1 to 2 eq) under argon. The rxn mixture was heated to a given temperature and stirred for a given time (see

Table 58). When necessary to reach completion of the rxn, extra amounts of a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (0.2 eq) were sequentially added under argon. It was quenched with water or a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc or DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using methods 2, 3, 4 or 5 was performed.

Method C (Cyclisation from B-3)

To a suspension of intermediate B-3 (1 eq) in MeCN (5.1 to 11.2 mL/mmol) was added CDI (5 to 7 eq) and the rxn mixture was stirred at a given temperature for a given time (see

Table 58). The solvent was evaporated off and the residue was partitioned between EtOAc and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc/MeOH.

Method D (Alkylation of A-3: K_2CO_3/DMF)

To a stirred soln. of intermediate A-3 (1 eq) in DMF (3.9 to 4.7 mL/mmol) was added K_2CO_3 (1.5 to 3 eq) followed by the appropriate halide BB-9 (1.3 to 1.5 eq). The rxn mixture was stirred at a given temperature for a given time (see Table 58). When necessary to reach completion of the rxn, extra amounts of halide BB-9 (1 eq) were added at RT. It was partitioned between EtOAc and H_2O. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH.

Method E (Cyclisation from E-6)

To a suspension of diamine E-6 (1 eq) in MeCN (or DCM, respectively) (8 to 12.7 mL/mmol) was added DSC (or CDT, respectively) (1.2 to 1.3 eq) and optionally Et_3N (3 eq) at RT. The rxn mixture was stirred at a given temperature for a given time (see Table 58) and partitioned between EtOAc or DCM and a 1M soln. of NaOH or a sat. soln. of $NaHCO_3$. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 4, 5, 8 or 10.

Table ~~56~~58

Ia	Name	Reactant A-3, B-3, E-3 or E-6	Reactant BB-9	Method T [°C] time [h]	t_R [min] (LC/MS-method)	MS-data m/z $[M+H]^+$
Ia-1A	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 1)	A-3-1A	BB-9-1	A1 RT 66	1.30 (I)	618.26
Ia-1B	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 195)	A-3-1B	BB-9-1	A1 RT 2	1.29 (I)	618.28
Ia-2	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 5)	A-3-2	BB-9-1	A1 RT 24	1.31 (I)	618.38

Ia-89	5-[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	E-6-35	-	E RT 1.5	1.22 (I)	552.28

Synthesis of compounds of formula Ib and Ic

Method A (complete SEM cleavage)

Step A (TFA treatment):

To a soln. of SEM-protected intermediate Ia (1 eq) in DCM (2 to 4 mL/mmol) was added dropwise TFA (4 to 6 mL/mmol). The soln. was stirred at RT for a given time (see Table 59), quenched at 0°C with a 32% or 1M aq. soln. of NaOH until pH 7-8 and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo.

Step B (additional treatment):

The crude was dissolved in THF (5 to 10 mL/mmol) and treated with ethylenediamine (3 eq) for 30 min to 1h at 60°C. The rxn mixture was partitioned between DCM and water and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc.

Method B (partial SEM cleavage with O-alkylation)

Step A (TFA treatment):

To a soln. of SEM-protected intermediate Ia (1 eq) in DCM (2 mL/mmol) was added dropwise TFA (4 mL/mmol). The soln. was stirred at RT for a given time (see Table 59), quenched at 0°C with a 32% aq. soln. of NaOH until pH 7-8 and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo.

Step B (treatment with alcohol):

The crude was dissolved in EtOH or MeOH (5 mL/mmol) and treated with a 4M soln. of HCl in dioxane (5 mL/mmol) for 30 min at 70°C. The rxn mixture was basified with a 1M aq. soln. of NaOH until pH 8-9 and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method C (Bn cleavage)

To a soln. of Bn-protected intermediate Ia (1 eq) in EtOH (9.8 mL/mmol) was added ammonium formate (4 eq). The flask was evacuated three times and refilled with nitrogen. 10% Pd/C moistened with ~50% water (0.1 eq) was added and the flask was evacuated and refilled with hydrogen. The rxn mixture was hydrogenated under atmospheric pressure at a given temperature for a given time (see Table 59). When necessary to reach completion of the rxn, extra amounts of ammonium formate (4 eq) and/or 10% Pd/C moistened with ~50% water (0.1 eq) were added. The rxn mixture was filtered over a pad of celite and the filtrate was concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method D (THP cleavage)

To a soln. of THP-protected intermediate Ia (1 eq) in DCM (4 to 5 mL/mmol) was added dropwise TFA (2 to 4 mL/mmol). The soln. was stirred at RT for a given time (see Table 59), quenched at 0°C with a 1M aq. soln. of NaOH until pH 10-11 and extracted with DCM. The combined org. phases were dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 2, 5 or 11.

Table ~~57~~59

Ib or Ic	Name	Reactant Ia	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
Ib-1	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one or 6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 2)	Ia-1A or Ia-1B	A RT 2	1.15 (I)	488.22
Ib-2	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 6)	Ia-2	A RT 2.5	1.14 (I)	488.24
Ic-1	2-Ethoxymethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 7)	Ia-2	B (EtOH) RT 1	1.08 (II)	546.02
Ib-3	1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-1,3,6,9-tetrahydro-purin-2-one (Example 14)	Ia-5	A (only step A) RT 4.5	0.91 (II)	488.11

Ib-20	7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ia-82	D RT 3	1.12 (I)	523.30
Ib-21	5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ia-83	D RT 6	1.15 (I)	494.22

Synthesis of compounds of formula Ic, Id and Ie

Method A (methylation using silver carbonate)

To a suspension of intermediate Ib (1 eq) and silver carbonate (1.2 eq) in toluene (6 mL/mmol) was added MeI (5 eq) and the rxn mixture was stirred at 85°C for a given time (see Table 60). It was filtered and the filtrate was concentrated in vacuo. The crude was purified by CC using DCM/MeOH. When necessary, an additional purification by prep. LC-MS using methods 1, 3 or 4 was performed.

Method B (alkylation using NaH and halide or aziridine)

Method B1: A soln. or suspension of intermediate Ib (1 eq) in anh. THF (6 to 10 mL/mmol) was added dropwise at 0°C to a suspension of NaH (2.2 to 4 eq, as a 60% dispersion in mineral oil) in anh. THF (4 to 6 mL/mmol).

Method B2: NaH (4 eq, as a 60% dispersion in mineral oil) was added portionwise at 0°C to a soln. or suspension of intermediate Ib (1 eq) in THF (10 to 13 mL/mmol).

Common following procedure: The suspension was stirred for 10 to 30 min at RT, cooled to 0°C and halide or aziridine BB-10 (1.2 to 3 eq) was added. The rxn mixture was stirred at a given temperature for a given time (see Table 60). When necessary to reach completion of the rxn, extra amounts of NaH (1 to 2 eq) and/or halide or aziridine BB-10 (1 eq) were added. The rxn mixture was quenched with H_2O at 0°C and extracted with EtOAc or DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH.

Method C (alkylation using Mitsunobu conditions)

To a soln. or suspension of intermediate Ib (1 eq) and alcohol BB-10 (1.5 to 2 eq) in toluene (6 to 12 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to a given temperature and stirred for a given time (see Table 60). It was quenched with water and extracted with EtOAc or DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using methods 2, 4, 5, 8 or 10 was performed.

Method D (methylation using DBU)

To a soln. of intermediate Ib (1 eq) and DBU (1.2 eq) in anh. DMF (4 mL/mmol) was added MeI (1.3 eq). The rxn mixture was stirred at RT for a given time (see Table 60) and evaporated under reduced pressure. The residue was purified by prep. LC-MS using methods 2, 4 and/or 5.

Method E (alkylation using K_2CO_3 and halide or epoxide)

A mixture of compound Ib (1 eq), K_2CO_3 (1.5 to 5 eq) and epoxide or halide BB-10 (2 to 5 eq) in DMF (5 to 8.5 mL/mmol) was heated to a given temperature and stirred for a given time (see Table 60). When necessary to reach completion of the rxn an extra amount of epoxide or halide BB-10 (1 eq) was added and the rxn mixture was further stirred for 2h at 120°C. It was partitioned between EtOAc and H_2O and the org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method F (1,4-nucleophilic addition using K_2CO_3)

A mixture of compound Ib (1 eq), α,β-unsaturated carbonyl reagent BB-10 (2 eq), K_2CO_3 (1.5 eq) and TEA (3 eq) in THF (10 mL/mmol) was heated to 60°C and stirred for a given time (see Table 60). It was partitioned between DCM and H_2O and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method G (1,4-nucleophilic addition using CsF)

To a soln. of compound Ib (1 eq) in DMF (10 mL/mmol) was added nitroalkene BB-10 (1 eq) and CsF (1.2 eq) at 0°C. The rxn mixture was stirred for 30 min at 0°C and at RT for a given time (see Table 60). Consecutive additions of BB-10 (1 eq) and CsF (1 eq) at 0°C were necessary to allow the rxn to proceed. It was partitioned between EtOAc and H_2O and the org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by prep LC-MS using method 4.

Method H (alkoxycarbonylation/alkylcarbamylation)

A soln. of compound Ib (1 eq) and TEA (3 eq) in DCM (8.1 mL/mmol) was cooled to 0°C and chloroformate or isocyanate BB-10 (2 eq) was added dropwise at 0°C. The rxn mixture was allowed to slowly reach RT and stirred for a given time (see Table 60). It was diluted with DCM and washed with a sat. aq. soln. of $NaHCO_3$ and with brine. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method I (urea formation)

A soln. of compound Ib (1 eq) and TEA (3 eq) in THF (10 mL/mmol) was treated with CDI (1.2 eq) and the rxn mixture was stirred at RT for 15 min. Amine BB-10 (3 to 5 eq) was added at RT and the mixture was stirred at a given temperature for a given time (see Table 60). The rxn mixture was partitioned between DCM and a half sat. aq. soln. of $NaHCO_3$ and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method J1 (Chan-Lam rxn 1)

A mixture of compound Ib (1 eq), boron species BB-10 (2 eq), Na_2CO_3 (2 eq), 2,2'-bipyridyl (1 eq) and $Cu(OAc)_2$ (1 eq) in toluene (10 to 12 mL/mmol) was flushed with N_2 and heated at a given temperature for a given time (see Table 60 ~~).~~). When necessary to reach completion of the rxn an extra amount of boron species BB-10 (2 eq) was added. It was

partitioned between EtOAc or DCM and a sat. aq. soln. of $NaHCO_3$ and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH and/or by prep. HPLC using method 3 or 5.

Method J2 (Chan-Lam rxn 2)

A suspension of 2,2'-bipyridyl (1 eq) and $Cu(OAc)_2$ (1 eq) in trifluorobenzene (3 mL/mmol) was heated to 70°C and stirred for 30 min. It was added at RT to a mixture of compound Ib (1 eq), boron species BB-10 (2 eq) and Na_2CO_3 (2 eq) in trifluoromethylbenzene (1.5 mL/mmol). The rxn mixture was heated to 110°C and stirred for a given time (see Table 60). It was diluted with EtOAc and washed with a 10% soln. of citric acid. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by prep. LC-MS using method 4.

Method K (alkylation using Cs_2CO_3 and tosylate)

A mixture of compound Ib (1 eq), tosylate BB-10 (1.05 to 1.5 eq) and Cs_2CO_3 (2 to 2.3 eq) in DMA (5 to 7 mL/mmol) was heated at a given temperature for a given time (see Table 60). It was partitioned between EtOAc and water and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or/and by prep. LC-MS using method 4 or 5.

Table 60

Ic/Id/Ie	Name	Reactant Ib	Reactant BB-10	Method T [°C] time [h]	t_R [min] (LC/MS-method)	MS-data m/z $[M+H]^+$
Ic-2	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 3)	Ib-1	MeI	A 85 0.25	1.08 (II)	502.27
Id-1	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-1-methyl-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 4)				1.07 (II)	502.70
Ic-3	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 8)	Ib-2	MeI	B1 RT 1.5	1.22 (I)	502.16

If-30	(S)-2-(Azetidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 122)	Ic-33	-	H RT 5	0.91 (I)	557.19
If-31	(R)-2-(Azetidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 130)	Ic-34	-	H RT 4	0.91 (I)	557.14
If-32	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-methyl-propenyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 153)	Ic-9	-	J 50 0.5	1.32 (I)	542.18
If-33	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-methyl-allyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 154)				1.28 (I)	542.17
If-34	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-oxo-azetidin-3-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 157)	Ic-42	-	K 0 72	1.11 (I)	557.13
If-35	6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-isopropyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 191)	Ic-74	-	L RT 18	1.22 (I)	530.05

Synthesis of compounds of formula Ig

Method A (carboxylic ester reduction)

To a soln. of methyl ester If (1 eq) in anh. EtOH (23 mL/mmol) was added $CaCl_2$ (0.3 eq) and the rxn mixture was cooled to -10°C. $NaBH_4$ (4 eq) was added portionwise and the mixture was stirred for 15 min at -10°C and at a given temperature for a given time (see Table 62). When necessary to reach completion of the rxn, a further amount of $NaBH_4$ (4 eq) was added. It was quenched at 0°C with water and EtOH was evaporated off. The residue was partitioned

between DCM and water and the aq. phase was further extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (acylation/alkoxycarbonylation/dialkylcarbamylation/alkylsulfonylation/dialkylsulfamylation)

A soln. of amine If (1 eq) and TEA (1.5 to 6 eq) in DCM (0.5 to 36 mL/mmol) (or DMF, respectively) was cooled to 0°C and halide BB-25 (1.1 to 2 eq) (or pentafluorophenylcarbonate BB-25, respectively) was added dropwise at 0°C (or at RT, respectively). The rxn mixture was allowed to slowly reach RT and stirred for a given time (or stirred at a given temperature for a given time, respectively) (see Table 62). It was diluted with DCM and washed with a 10% aq. soln. of citric acid when suitable, with a sat. aq. soln. of $NaHCO_3$ and with brine. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH and/or by prep. LC-MS using methods 3 or 8.

Method C (Boc protection)

To a soln. of amine If (1 eq) in anh. THF (2 mL/mmol) was added TEA (3 eq). The rxn mixture was cooled to 0°C and Boc_2O (1.5 eq) was added. It was stirred for 5 min at 0°C and at RT for a given time (see Table 62) and was partitioned between DCM and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. When necessary, the crude was purified by CC using Hept/EtOAc.

Method D (nitrile reduction)

Nitrile If (1 eq) was suspended in a 7M soln. of NH_3 in MeOH (40 mL/mmol). The flask was evacuated and refilled with nitrogen. Raney nickel (0.1 eq) was added at 0°C and the temperature was allowed to reach RT. The flask was evacuated and refilled with hydrogen. The suspension was stirred under a hydrogen atmosphere at RT for a given time (see Table 62) and filtered over a pad of Celite. The cake was washed with MeOH and the filtrate was concentrated in vacuo.

Method E

Step A: Mitsunobu

To a suspension of alcohol If (1 eq) and phtalimide (1.5 eq) in toluene (16 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to 110°C and stirred for 18h. It was quenched with water and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or DCM/MeOH.

Step B: phtalimide cleavage

A soln. of the crude from previous step (1 eq) was dissolved in EtOH (35 mL/mmol) and treated with hydrazine hydrate (20 eq). The rxn mixture was heated to 80°C and stirred for a given time (see Table 62). It was basified with a 1M aq. soln. of NaOH and partitioned between DCM and H_2O. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH.

Method F (reductive amination)

To a stirred soln. of amine If (1 eq) in a mixture of DCM (10 mL/mmol) and MeOH (15 mL/mmol) or in THF (7 to 8.5 mL/mmol) was added successively AcOH (1.2 to 1.5 eq), the appropriate aldehyde BB-25 (1.3 to 2 eq) and

$NaBH(OAc)_3$ (1.5 to 2 eq). The rxn mixture was stirred at RT for a given time (see Table 62) and the volatiles were evaporated in vacuo. The residue was partitioned between DCM and a sat. aq. soln. of $NaHCO_3$. The org. phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method G (alkylation)

To a soln. of amine If (1 eq) in DMF (10 mL/mmol) was added the appropriate halide BB-25 (3 eq), DIPEA (2 eq) and KI (0.05 eq). The rxn mixture was heated at 150°C under microwave irradiation for a given time (see Table 62) and partitioned between EtOAc and H_2O. The org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method H (urea formation)

A soln. of amine If (1 eq) and TEA (4 eq) in THF (12 mL/mmol) was treated with CDI (1.5 eq) and the rxn mixture was stirred at RT for 15 min. Amine BB-25 (1.5 eq) was added at RT and the mixture was stirred at a given temperature for a given time (see Table 62). When necessary to reach completion of the rxn, extra amounts of amine (1 to 10 eq) were added. The rxn mixture was partitioned between DCM and H_2O and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using DCM/MeOH and/or by prep. LC-MS using method 4.

Method I (PyBOP activated SNAr)

Compound If (1 eq), heteroarene BB-25 (1.5 eq) and DIPEA (2 eq) were dissolved in anh. DMF (5 mL/mmol) and the mixture was stirred for 5 min at RT. PyBOP (1.6 eq) was added portionwise and the rxn mixture was further stirred at RT for a given time (see Table 62). It was partitioned between EtOAc and a 5% aq. soln. of $KHSO_4$ and the org. phase was washed with a sat. aq. soln. of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method J (SNAr)

To a soln. of compound If (1 eq) in DMSO (5 mL/mmol) was added DIPEA (3 eq) and halo-heteroarene BB-25 (1.2 eq). The rxn mixture was stirred at RT for a given time (see Table 62) and partitioned between EtOAc and a 5% aq. soln. of $KHSO_4$. The org. phase was washed with a 5% aq. soln. of $KHSO_4$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method K (hydrogenation)

Compound of formula If (1 eq) was dissolved in EtOH (10 mL/mmol). The flask was evacuated three times and refilled with nitrogen. Wet Pd/C (0.02 eq) was added and the flask was evacuated three times and refilled with hydrogen. The suspension was stirred under an atmospheric pressure of hydrogen for a given time (see Table 62) and filtered over a pad of Celite. The cake was washed with MeOH and the filtrate was concentrated in vacuo.

Synthesis of compounds of formula Ih

Method A (deuteration)

Compound of formula Ia (1 eq) was dissolved in a mixture of CD_3OD (12 mL/mmol) and EtOAc (4 mL/mmol). The flask was evacuated three times and refilled with nitrogen. Wet Pd/C (0.1 eq) was added and the flask was evacuated three times and refilled with deuterium. The suspension was stirred under an atmospheric pressure of deuterium for a given time (see Table 63) and filtered over a pad of Celite. The cake was washed with EtOAc and the filtrate was concentrated in vacuo. The crude was purified by prep. LC-MS using method 4.

Method B (substitution with F)

A suspension of compound Ia (1 eq) and dry CsF (6 eq) in anh. DMSO (5.4 mL/mmol) was heated to a given temperature under argon and stirred for a given time (see Table 63). The rxn mixture was partitioned between EtOAc and H_2O and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method C (Suzuki coupling)

A mixture of compound Ia (1 eq), boron species (1.1 eq), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.03 eq) and K_2CO_3 (2 eq) in dioxane (13.6 mL/mmol) was flushed with N_2 and heated at a given temperature for a given time (see Table 63). It was partitioned between EtOAc and a sat. aq. soln. of $NaHCO_3$ and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc/MeOH.

Method D (substitution with OMe)

A suspension of compound Ia (1 eq) in MeOH (6 mL) was treated with a 25% soln. of NaOMe in MeOH (6 eq). The rxn mixture was heated to a given temperature for a given time (see Table 63) and partitioned between DCM and water. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method E (substitution with amine)

A soln. of compound Ia (1 eq) in MeOH (9 mL/mmol) was treated with the appropriate amine (21 eq, pure or as soln.). The rxn mixture was heated at 150°C under microwave irradiation for a given time (see Table 63) and partitioned between DCM and H_2O. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method F (phenol alkylation using NaH as base)

To a soln. of compound Ia (1 eq) in anh. THF (9.7 mL/mmol) was added NaH (5 eq, as a 60% dispersion in mineral oil) at 0°C. The suspension was stirred for 10 min and the appropriate halide (1.1 to 1.5 eq) was added at 0°C. The rxn mixture was stirred at a given temperature for a given time (see Table 63). When necessary to reach completion of the rxn, extra amounts of NaH (5 eq, as a 60% dispersion in mineral oil) and/or halide BB-9 (3 eq) were added. The mixture was quenched with water at 0°C and extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or by prep. LC-MS using method 11.

Method G (phenol alkylation using K_2CO_3 as base)

To a stirred suspension of compound Ia (1 eq) in DMF (8.5 mL/mmol) was added K_2CO_3 (3 eq) followed by the appropriate halide (5 eq). The rxn mixture was stirred at a given temperature under microwave irradiation for a given time (see Table 63). It was partitioned between EtOAc and H_2O and the org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method H (phenol alkylation using Mitsunobu conditions)

To a soln. of compound Ia (1 eq) and alcohol (3 eq) in toluene (8 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (1.5 eq) under argon. The rxn mixture was heated to 110°C and stirred for a given time (see Table 63). It was quenched with water and extracted with DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc and/or by prep. LC-MS using method 11.

Table 63

Ih	Name	Reactant Ia	Amine/ halide/ alcohol/ boron reagent	Method T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
Ih-1	5-(1-(2-fluoro-6-methylphenyl)piperidin-4-yl)-2-methyl-7-(3-trifluoromethyl-[6-^{2}H]pyridine-2-yl-methyl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-d]pyrimidin-6-one (Example 23)	Ia-9	-	A RT 48	1.00 (II)	504.12
Ih-2	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(6-fluoro-3-trifluoromethyl-pyridin-2-ylmethyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 36)	Ia-9	-	B 100 3	1.03	521.11
Ih-3	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(6-methyl-3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 37)	Ia-9	Trimethyl boroxine	C 100 2	1.03 (II)	517.13

To a suspension or soln. of intermediate C-2 (1 eq) in a mixture of anh. THF (3 to 3.6 mL/mmol) and anh. DMF (0.1 to 0.25 mL/mmol) was added NaH (2 eq, as a 60% dispersion in mineral oil) at 0°C. The suspension was stirred for 10 min at 0°C and BB-9 (1.2 to 1.5 eq) was added at 0°C. The rxn mixture was stirred at a given temperature for a given time (see Table 64), quenched at 0°C with a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc or DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Method B (Mitsunobu)

To a soln. or suspension of intermediate C-2 (1 eq) and alcohol BB-9 (1.1 to 1.3 eq) in toluene (7 mL/mmol) was added a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (2 eq) under argon. The rxn mixture was heated to a given temperature and stirred for a given time (see Table 64). When necessary to reach completion of the rxn, extra amounts of a 1M soln. of (tributylphosphoranylidene)acetonitrile in toluene (0.2 eq) were sequentially added under argon. It was quenched with water or a sat. aq. soln. of $NaHCO_3$ and extracted with EtOAc or DCM. The combined org. phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using methods 2, 3, 4 or 5 was performed.

Table 64

Ii	Name	Reactant C-2	Reactant BB-9	MethodT [°C] time [h]	t_R [min] (LC/MS-method)	MS-data m/z $[M+H]^+$
Ii-1	3-[2-Methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester	C-2-1	BB-9-1	A RT 18	0.94 (II)	480.08
Ii-2	4-[2-Methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-piperidine-1-carboxylic acid *tert*-butyl ester	C-2-2	BB-9-1	A RT 18	0.97 (II)	494.09
Ii-3	4-[2-Methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-azepane-1-carboxylic acid *tert*-butyl ester	C-2-3	BB-9-1	A RT 18	0.98 (II)	508.19

Ii-4	4-[2-Methyl-5-oxo-4-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-6-yl]-piperidine-1-carboxylic acid tert-butyl ester	C-2-4	BB-9-1	A RT 2	1.07 (I)	494.21
Ii-5	4-{2-Methyl-6-oxo-7-[1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl}-piperidine-1-carboxylic acid tert-butyl ester	C-2-2	BB-9-15	B 110 24	1.07 (I)	508.26
Ii-6	4-[7-(2-Cyclopropyl-benzyl)-2-methyl-6-oxo-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-piperidine-1-carboxylic acid tert-butyl ester	C-2-2	BB-9-9	B 110 1.5	1.05 (I)	466.03

Synthesis of compounds of formula Ij

Method A (Buchwald coupling)

To a mixture of intermediate C-3 (1 eq), halo-(hetero)arene BB-16 (1.1 to 2 eq) and sodium *tert*-butoxide (2 to 2.3 eq) in toluene (3 to 7.8 mL/mmol) under N_2, was added BINAP (0.2 to 0.3 eq) and $Pd_2(dba)_3$ (0.1 to 0.15 eq). The rxn mixture was flushed with N_2, heated under stirring at a given temperature for a given time (see Table 65). It was partitioned between water and EtOAc or DCM and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc or DCM/MeOH. When necessary, an additional purification by prep. LC-MS using methods 1, 3, 4, 5, 6 or 10 was performed.

Method B (aromatic nucleophilic substitution)

To a soln. of intermediate C-3 (1 eq) and halo-(hetero)arene BB-16 (1.2 to 2 eq) in DMSO (1.5 to 4.5 mL/mmol) was added K_2CO_3 or CsF (2 eq) and the mixture was heated to a given temperature and stirred for a given time under possible microwave irradiation (see Table 65). It was partitioned between EtOAc and H_2O. The org. phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc. When necessary, an additional purification by prep. LC-MS using method 1 was performed.

Table ~~58~~65

Ij	**Name**	**Reactant C-3**	**Reactant BB-16**	**Method T [°C] time [h]**	**t_R [min] (LC/MS-method)**	**MS-data m/z $[M+H]^+$**

Ij-40	6-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 302)	C-3-4	BB-16-24	A 100 4	1.21 (I)	522.27
Ij-41	5-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 303)	C-3-2	BB-16-28	A 100 4	1.21 (I)	528.35
Ij-42	6-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one (Example 304)	C-3-4	BB-16-28	A 100 2.5	1.22 (I)	528.32
Ij-43	7-(2-Cyclopropyl-benzyl)-5-[1-(2-cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 307)	C-3-6	BB-16-28	A 100 3	1.21 (I)	500.36
Ij-44	7-(2-Cyclopropyl-benzyl)-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 308)	C-3-6	BB-16-27	A 100 3	1.17 (I)	510.36

Method D (multistep)

Step A: Aromatic nucleophilic susbtitution

To a soln. of amine C-3 (1 eq) and halide BB-16 (2 eq) in DMSO (3.4 mL/mmol) was added CsF (2 eq). The rxn mixture was heated at a given temperature for a given time under possible microwave irradiation (see Table 66) and was partitioned between EtOAc and water. The org. phase was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc.

Table ~~59~~66

Ij-A	Name	Reactant C-3	Reactant BB-16	T [°C] time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
Ij-17A	1,3-Dimethyl-5-{4-[2-methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-piperidin-1-yl}-1H-pyrazole-4-carbaldehyde	C-3-2	BB-16-17	150 3 microwave	1.01 (I)	516.21

Step B: Decarbonylation

To a soln. of Ij-A (1 eq) in MeOH (8 mL/mmol) was added toluene-4-sulfonic acid monohydrate (0.25 eq) and the rxn mixture was heated at 120°C under microwave condition for a given time (see Table 67). It was concentrated in vacuo and partitioned between EtOAc and a sat. aq. soln. of $NaHCO_3$. The org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc/MeOH.

Table ~~60~~67

Ij-B	Name	Reactant Ij-A	time [h]	t_R [min] (LC/MS-method)	MS-data m/z $[M+H]^+$
Ij-17B	5-[1-(2,5-Dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one	Ij-17A	9	0.86 (I)	488.21

Step C: Chlorination

To a soln. of Ij-B (1 eq) in THF (5 mL/mmol) was added NCS (1.4 eq) and the rxn mixture was stirred at RT for a given time (see Table 68). It was partitioned between EtOAc and water and the org. phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by CC using Hept/EtOAc. When necessary an additional purification by prep. LC-MS using method 5 was performed.

Table ~~61~~68

Ij	Name	Reactant Ij-B	time [h]	t_R [min] (LC/MS method)	MS-data m/z $[M+H]^+$
Ij-17	5-[1-(4-Chloro-2,5-dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Example 238)	Ij-17B	0.5	1.11 (I)	522.17

Chiral separation of compounds of formula Ia, Ic or Ij

Racemates of formula Ia, Ic or Ij were separated into the respective enantiomers using preparative chiral HPLC or SFC (equipped with a given column and eluting with given parameters (see Table 69), detection: UV 210 nm).

Both enantiomers were characterized by analytical chiral HPLC or SFC (equipped with a given Daicel column and eluting with given parameters (see Table 69), detection: UV 210 to 280 nm).

The absolute configuration for the molecule Ik-70 (Example 324, enantiomer B) was assessed by single crystal X-ray diffraction (suitable crystal obtained from iPrOH) and proved to be in absolute (R)-configuration. Consequently, the absolute configuration for the molecule Ik-69 (Example 323, enantiomer A) was assigned (S). In analogy, for all example compounds wherein **R^4** represents methyl listed in Table 69 below, the enantiomer showing higher activity in the in vitro biological assay disclosed below may be assumed to have the absolute (S)-configuration.

Table ~~62~~69

Ik	**Name**	**Racemate Ia, Ic or Ij**	**Column Eluent Flow (preparative)**	**Column Eluent Flow (analytical)**	**t_R [min] chiral HPLC**
Ik-1	5-[(R)- or (S)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Enantiomer A) (Example 57)	Ij-5	ChiralCel OD-H 20x250 mm, 5 µm Hept/(EtOH+0.1% DEA) 70/30 16 mL/min	ChiralCel OD-H 4.6x250 mm, 5 µm (Hept+0.05% DEA)/(EtOH+0.05% DEA) 70/30 0.8 mL/min	5.97
Ik-2	5-[(S)- or (R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Enantiomer B) (Example 58)				8.36
Ik-3	5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-((S)- or (R)-2-fluoro-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one (Enantiomer B) (Example 185)	Ic-71	ChiralPak ID 20x250 mm, 5 µm Hept/(EtOH+0.1% DEA) 90/10 16 mL/min	ChiralPak ID 4.6x250 mm, 5 µm (Hept+0.02% DEA)/(EtOH+0.02% DEA) 90/10	12.8

II. Biological Assays

In vitro assay

Adherent cells (CHO-K1 C5AR1 beta-arrestin cell line, DiscoverX, CA USA) are washed with PBS, detached by incubation with Dissociation Buffer (Gibco Cat# 13151-014, 2 ml per 165 cm2 dish) for 3 minutes, then washed with 10 ml PBS (without Mg++ and Ca++) and counted. 7'500 cells/384-well are seeded out in 384-well plates (Cell culture plate MTP384 white Polystyrene, Corning, Cat# 3570) in 20 μl/well Cell plating medium (F12 HAMs/10% FCS/1% P/S) and incubated at 37°C / 5% CO2 / 24h.

5 μl Antagonist at 6-fold end concentration or DMSO control is added to assay medium and subsequently 5 μl 1 - 10 nM C5a agonist at 6 fold end concentration. Cells are centrifuged for 1 min at 1000 rpm and incubated for 1.5 hour in at 37°C. Plates are equilibrated at room temperature for several minutes before adding 12 μl/well Detection Reagent (PathHunter Detection Kit, DiscoverX, Cat# 93-0001). Plates are centrifuged for 1 min at 1000 rpm and incubated for 45 minutes at RT before being measured on a Fluostar Optima, BMG Labtech. IC_{50} values are calculated from a serial dilution range of antagonist using inhouse software and given in nmol/l.

The calculated IC_{50} values may fluctuate depending on the daily cellular assay performance. Fluctuations of this kind are known to those skilled in the art. Average IC_{50} values from several measurements are given as geometric mean values.

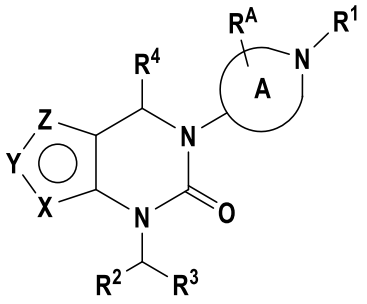
Antagonistic activities of exemplified compounds are displayed in Table 70.

Table 70: list of examples and their antagonistic activities

Example Number	Compound N°	C5aR IC_{50} (nM)	**Example Number**	Compound N°	C5aR IC_{50} (nM)	**Example Number**	Compound N°	C5aR IC_{50} (nM)
1	Ia-1A	85	**130**	If-31	390	**259**	Ia-42	49
2	Ib-1	10	**131**	Ig-25	100	**260**	Ia-43	40
3	Ic-2	36	**132**	Ig-26	8	**261**	Ik-25	580
4	Id-1	293	**133**	Ig-27	22	**262**	Ik-26	472
5	Ia-2	16	**134**	Ig-28	13	**263**	Ik-27	21
6	Ib-2	9	**135**	Ig-29	17	**264**	Ia-45	216
7	Ic-1	16	**136**	Ig-30	163	**265**	Ik-29	12
8	Ic-3	14	**137**	Ig-31	81	**266**	Ik-30	356
9	Ic-4	8	**138**	Ia-16	11	**267**	Ia-46	201
10	Ie-1	341	**139**	Ig-32	18	**268**	Ia-47	72
11	Ia-3	603	**140**	Ig-33	18	**269**	Ia-48	193
12	Ia-4	226	**141**	Ig-34	21	**270**	Ij-23	54
13	Ia-5	28	**142**	Ig-35	32	**271**	Ij-24	51
14	Ib-3	466	**143**	Ig-36	17	**272**	Ij-25	18

Claims

1. A compound of formula (I)



Formula (I)

wherein

- **Y** represents N**R**^{5}; and **X** and **Z** independently represent N or CH;
- **Y** represents C**R**^{6}; one of **X** and **Z** represents N**R**^{7}, O or S, and the other of **X** and **Z** represents N; or
- **Y** represents N; one of **X** and **Z** represents N**R**^{8}, and the other of **X** and **Z** represents N or CH;

ring A represents a saturated 4- to 7-membered mono-cyclic carbocyclic ring containing the ring nitrogen atom to which **R**^{1} is attached, wherein said **ring A** is optionally mono-substituted with **R**^{A}; wherein **R**^{A} represents (C_{1-4})alkyl;

R^{1} represents phenyl; 5-membered heteroaryl, or 6-membered heteroaryl wherein said phenyl, 5-membered heteroaryl or 6-membered heteroaryl independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; cyano; or (C_{3-6})cycloalkyl;

R^{2} represents phenyl, 5-membered heteroaryl, or 6-membered heteroaryl; wherein said phenyl, 5-membered heteroaryl, or 6-membered heteroaryl independently is mono-, or di-, or tri-substituted, wherein the substituents are independently selected from

- (C_{1-4})alkyl;
- (C_{1-4})alkoxy;
- (C_{1-3})fluoroalkyl;
- (C_{1-3})fluoroalkoxy;
- halogen;
- (C_{3-6})cycloalkyl-**X**^{21}-, wherein **X**^{21} represents a direct bond, -O-, or -(C_{1-3})alkylene-O-, and wherein the (C_{3-6})cycloalkyl optionally contains one ring oxygen atom; or
- **R**^{21a}**R**^{21b}N-, wherein **R**^{21a} and **R**^{21b} independently represent hydrogen or (C_{1-4})alkyl;

R^{3} represents hydrogen or (C_{1-3})alkyl;

R^{4} represents hydrogen, or (C_{1-4})alkyl;

R^{5} represents

- hydrogen;

- (C_{1-4})alkyl;
- (C_{1-4})alkyl which is mono-substituted with hydroxy, (C_{1-4})alkoxy, cyano, or $R^{N1}R^{N2}N$-, wherein
  - R^{N1} and R^{N2} together with the nitrogen atom form a 4- to 6-membered saturated ring optionally containing one further ring heteroatom selected from O and N; wherein said ring is optionally mono-substituted with (C_{1-4})alkyl, or (C_{1-4})alkoxy;
  - R^{N1} and R^{N2} are independently selected from hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, or (C_{1-4})alkoxy-(C_{2-4})alkylene;
  - R^{N1} represents (C_{1-4})alkyl-C(O)-; and R^{N2} represents hydrogen, or (C_{1-4})alkyl; or
  - R^{N1} represents phenylsulfonyl-, wherein the phenyl is optionally substituted by one to three substituents independently selected from (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, cyano, or nitro; and R^{N2} represents hydrogen, or (C_{1-4})alkyl;
- (C_{2-4})alkyl which is di- or tri-substituted, wherein the substituents are independently selected from hydroxy, (C_{1-4})alkoxy, or $R^{N1}R^{N2}N$-, wherein
  - R^{N1} and R^{N2} together with the nitrogen atom form a 4- to 6-membered saturated ring; or
  - R^{N1} and R^{N2} are independently selected from hydrogen, or (C_{1-4})alkyl;
- (C_{2-4})fluoroalkyl;
- $(CH_3)_3Si$-$(CH_2)_2$-O-(C_{1-4})alkylene-;
- (C_{2-5})alkynyl;
- (C_{2-5})alkenyl;
- $R^{N3}R^{N4}N$-C(O)-(C_{0-4})alkylene-, wherein R^{N3} and R^{N4} independently are hydrogen or (C_{1-4})alkyl;
- (C_{1-4})alkoxy-C(O)-(C_{0-4})alkylene-;
- (C_{1-4})alkoxy-C(O)-(C_{2-4})alkylene-, wherein the (C_{2-4})alkylene is mono-substituted by $R^{N5}R^{N6}N$-, wherein R^{N5} and R^{N6} independently are hydrogen or (C_{1-4})alkyl
- (C_{1-4})alkoxy-C(O)-(C_{2-4})alkylene-, wherein the (C_{2-4})alkylene is substituted by one to three halogen;
- (C_{1-4})alkoxy-C(O)-NH-(C_{2-4})alkylene-, wherein the (C_{2-4})alkylene- is optionally substituted by one to three halogen;
- (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, wherein the cycloalkyl is optionally substituted by one or two substituents independently selected from fluoro, (C_{1-4})alkyl, nitro, or (C_{1-4})alkoxy-C(O)-NH-; or
- ring^B-$\mathbf{X}^B$-; wherein $\mathbf{X}^B$ is a direct bond, or (C_{1-4})alkylene-; and wherein ring^B is a 4- to 6-membered saturated heterocyclyl containing one or two ring heteratom independently selected from O, S, and N$\mathbf{R}^B$, wherein said ring^B is attached to $\mathbf{X}^B$ at a ring carbon atom;
  wherein said ring^B is optionally substituted by one or two substituents independently selected from oxo, hydroxy, fluoro, (C_{1-4})alkyl or (C_{1-4})alkoxy; and wherein
  $\mathbf{R}^B$ independently represents
  - hydrogen;
  - (C_{1-4})alkyl;

- (C_{2-4})fluoroalkyl;
- (C_{1-4})alkyl-C(O)-;
- (C_{1-4})alkoxy-C(O)-;
- (C_{1-4})alkyl-SO_2-;
- $R^{N7}R^{N8}N$-SO_2- wherein R^{N7} and R^{N8} are independently hydrogen or (C_{1-4})alkyl;
- $R^{N9}R^{N10}N$-C(O)- wherein R^{N9} and R^{N10} are independently hydrogen or (C_{1-4})alkyl;
- $Ring^C$-O-C(O)-, and wherein $ring^C$ is (C_{3-6})cycloalkyl optionally containing one ring oxygen atom, wherein $ring^C$ is optionally substituted with one R^C, wherein R^C is (C_{1-4})alkyl or (C_{1-4})fluoroalkyl; or
- $Ring^D$, wherein $ring^D$ is a 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from O, N or S, wherein $ring^D$ is unsubstituted or mono-substituted with R^D, wherein R^D is (C_{1-4})alkyl or (C_{1-4})fluoroalkyl;

R^6 represents

- hydrogen;
- (C_{1-4})alkyl;
- (C_{1-4})fluoroalkyl; or
- (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, wherein the cycloalkyl is optionally substituted by one to three substituents independently selected from halogen or (C_{1-4})alkyl;

R^7 represents

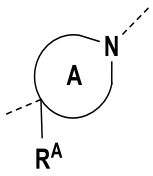
- hydrogen;
- (C_{1-4})alkyl; or
- $(CH_3)_3Si$-$(CH_2)_2$-O-(C_{1-4})alkylene-; and

R^8 represents

- hydrogen;
- (C_{1-4})alkyl;
- (C_{2-4})fluoroalkyl;
- (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, wherein the cycloalkyl is optionally substituted by one to three substituents independently selected from halogen or (C_{1-4})alkyl;
- (C_{1-4})alkoxy-C(O)-(C_{1-4})alkylene-; or
- $(CH_3)_3Si$-$(CH_2)_2$-O-(C_{1-4})alkylene-;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1; wherein ring **A** represents a fragment



wherein said ring **A** is selected from azetidin-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,4-diyl, piperidin-1,3-yl, and azepan-1,4-diyl; and wherein said ring **A** is substituted with $\mathbf{R^1}$ on the ring nitrogen atom, and optionally substituted, on the ring carbon atom linked to the rest of the molecule, with $\mathbf{R^A}$, wherein $\mathbf{R^A}$ is (C_{1-4})alkyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claims 1 or 2; wherein

Y represents N$\mathbf{R^5}$; one of **X** and **Z** represents N, and the other of **X** and **Z** represents N or CH;

or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3; wherein $\mathbf{R^1}$ represents

- phenyl which is mono- or di-substituted, wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituents are independently selected from (C_{1-4})alkyl; (C_{1-4})alkoxy; halogen; cyano; and (C_{1-3})fluoroalkyl; or
- pyridinyl which is di-substituted, wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule, wherein the substituents are independently selected from (C_{1-4})alkyl; (C_{1-4})alkoxy; halogen; and (C_{1-3})fluoroalkyl;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 3; wherein $\mathbf{R^1}$ represents phenyl which is mono-, or di-substituted; wherein at least one substituent is attached in *ortho* position with regard to the point of attachment of the rest of the molecule;

- wherein said *ortho*-substituent is (C_{1-4})alkyl); (C_{1-4})alkoxy; halogen; or (C_{1-3})fluoroalkyl;
- and, if present, the remaining substituent independently is methyl; methoxy; halogen; or cyano;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 3; wherein $\mathbf{R^1}$ is 2-chloro-6-methyl-phenyl, 2-fluoro-6-methyl-phenyl, 2,6-dimethyl-phenyl, 2-methoxy-6-methyl-phenyl, 2-fluoro-6-cyano-phenyl, 2-fluoro-6-trifluoromethyl-phenyl, 2-fluoro-6-trifluoromethoxy-phenyl, 4-chloro-2,5-dimethyl-2H-pyrazol-3-yl, 2,5-dimethyl-4-cyano-pyrazol-3-yl, 3-fluoro-pyridin-2-yl, 3-methoxy-pyridin-2-yl, 2-methoxy-4-methyl-pyridin-3-yl, 2-fluoro-4-methyl-pyridin-3-yl, 2-methyl-4-fluoro-pyridin-3-yl~~2-methyl-4-fluoro-~~, 2-cyano-4-methyl-pyridin-3-yl, 2,4-dimethoxy-pyridin-3-yl, 4-methoxy-6-methyl-pyrimidin-5-yl, 4,6-dimethoxy-pyrimidin-5-yl, 2,6-difluorophenyl, 2-chloro-6-fluoro-phenyl, 2-bromo-6-fluoro-phenyl, 2-fluoro-6-difluoromethyl-phenyl, 2-fluoro-6-cyclopropyl-phenyl, 2-methoxy-4-chloro-pyridin-3-yl, 2-methoxy-4-difluoromethyl-pyridin-3-yl, or 2-methoxy-4-trifluoromethyl-pyridin-3-yl;

or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6; wherein **R^2** represents phenyl, 5-membered heteroaryl; or 6-membered heteroaryl; wherein said phenyl, 5-membered heteroaryl, or 6-membered heteroaryl, independently is mono-, or di-, or tri-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; (C_{3-6})cycloalkyl-**X^{21}**-, wherein **X^{21}** represents a direct bond, -O-, or -(C_{1-3})alkylene-O-, and wherein the (C_{3-6})cycloalkyl contains one optional ring oxygen atom; and **$R^{21a}R^{21b}$**N-, wherein **R^{21a}** and **R^{21b}** independently represent hydrogen or (C_{1-4})alkyl;
or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 6; wherein **R^2** represents

- phenyl; wherein said phenyl is mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4})alkyl; (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; (C_{1-3})fluoroalkoxy; halogen; and (C_{3-6})cycloalkyl-**X^{21}**-, wherein **X^{21}** represents a direct bond, -O-, or -(C_{1-3})alkylene-O-, and wherein the (C_{3-6})cycloalkyl contains one optional ring oxygen atom; or
- 6-membered heteroaryl containing one or two nitrogen atoms; wherein said 6-membered heteroaryl independently is mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4})alkoxy; (C_{1-3})fluoroalkyl; halogen; and (C_{3-6})cycloalkyl-**X^{21}**-, wherein **X^{21}** represents a direct bond, -O-, or -(C_{1-3})alkylene-O-, and wherein the (C_{3-6})cycloalkyl contains one optional ring oxygen atom;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 6; wherein **R^2** represents 2-chloro-phenyl, 2-cyclopropyl-phenyl, 2-isopropyl-phenyl, 2-ethoxy-phenyl, 2-trifluoromethyl-phenyl, 2-isopropoxy-phenyl, 2-cyclopropoxy-phenyl, 2-(oxetan-3-yloxy)-phenyl, 2-cyclopropylmethoxy-phenyl, 2-fluoro-6-trifluoromethyl-phenyl, 2-bromo-6-trifluoromethyl-phenyl, 2-trifluoromethoxy-phenyl, 2,4-difluoro-6-isopropoxy-phenyl, 4-isopropyl-pyrimid-5-yl, 3-trifluoromethyl-pyrazin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-methyl-3-trifluoromethyl-pyridin-2-yl, 6-chloro-3-trifluoromethyl-pyridin-2-yl, 6-fluoro-3-trifluoromethyl-pyridin-2-yl, 6-methylamino-3-trifluoromethyl-pyridin-2-yl, 6-methoxy-3-trifluoromethyl-pyridin-2-yl, 6-dimethylamino-3-trifluoromethyl-pyridin-2-yl, 4-trifluoromethyl-pyridin-3-yl or 2-methyl-4-trifluoromethyl-thiazol-5-yl;

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9; wherein **R^5** represents

- hydrogen;
- (C_{1-4})alkyl;
- (C_{1-4})alkyl which is mono-substituted with (C_{1-4})alkoxy, or cyano;
- (C_{2-4})alkyl which is mono-substituted with hydroxy or $R^{N1}R^{N2}$N-, wherein
  - R^{N1} and R^{N2} together with the nitrogen atom form a 4- to 6-membered saturated ring optionally containing one further ring heteroatom selected from O and N; wherein said ring is optionally mono-substituted with (C_{1-4})alkyl, or (C_{1-4})alkoxy;
  - R^{N1} and R^{N2} are independently selected from hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, or (C_{1-4})alkoxy-(C_{2-4})alkylene;

- R^{N1} represents (C_{1-4})alkyl-C(O)-; and R^{N2} represents hydrogen, or (C_{1-4})alkyl; or
- R^{N1} represents phenylsulfonyl-, wherein the phenyl is optionally substituted by one to three substituents independently selected from (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, cyano, or nitro; and R^{N2} represents hydrogen, or (C_{1-4})alkyl;

- (C_{3-4})alkyl which is di-substituted, wherein the substituents are independently selected from hydroxy, (C_{1-4})alkoxy, or $R^{N11}R^{N12}N$-, wherein R^{N11} and R^{N12} are independently selected from hydrogen, or (C_{1-4})alkyl;
- (C_{2-4})fluoroalkyl;
- (C_{2-5})alkenyl;
- (C_{1-4})alkoxy-C(O)-(C_{1-4})alkylene-;
- (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, wherein the cycloalkyl is optionally substituted by one or two substituents independently selected from fluoro, methyl, nitro, or (C_{1-4})alkoxy-C(O)-NH-;
- $ring^{B1}$-$\mathbf{X^{B1}}$-; wherein $\mathbf{X^{B1}}$ is a direct bond, or (C_{1-4})alkylene-; and wherein $ring^{B1}$ is a 4- to 6-membered saturated heterocyclyl containing one ring heteratom which is O, wherein said $ring^{B1}$ is attached to $\mathbf{X^{B1}}$ at a ring carbon atom; wherein said $ring^{B1}$ is optionally substituted by one substituent selected from hydroxy, fluoro, (C_{1-4})alkyl, or (C_{1-4})alkoxy; or
- $ring^{B2}$-$\mathbf{X^{B2}}$-; wherein $\mathbf{X^{B2}}$ is a direct bond, or (C_{1-4})alkylene-; and wherein $ring^{B2}$ is a 4- to 6-membered saturated heterocyclyl containing one ring heteratom which is N$\mathbf{R^B}$, wherein said $ring^{B2}$ is attached to $\mathbf{X^{B2}}$ at a ring carbon atom; wherein said $ring^{B2}$ is optionally substituted by one oxo substituent, or by one or two fluoro substituents; and wherein

$\mathbf{R^B}$ independently represents

- hydrogen;
- (C_{1-4})alkyl;
- (C_{2-4})fluoroalkyl;
- (C_{1-4})alkyl-C(O)-;
- (C_{1-4})alkoxy-C(O)-;
- (C_{1-4})alkyl-SO_2-;
- $R^{N7}R^{N8}N$-SO_2- wherein R^{N7} and R^{N8} are independently hydrogen or (C_{1-4})alkyl;
- $R^{N9}R^{N10}N$-C(O)- wherein R^{N9} and R^{N10} are independently hydrogen or (C_{1-4})alkyl;
- $Ring^{C}$-O-C(O)-, and wherein $ring^{C}$ is (C_{3-6})cycloalkyl optionally containing one ring oxygen atom, wherein $ring^{C}$ is optionally substituted with one R^{C}, wherein R^{C} is (C_{1-4})alkyl or (C_{1-4})fluoroalkyl; or
- $Ring^{D}$, wherein $ring^{D}$ is a 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from O, N or S, wherein $ring^{D}$ is unsubstituted or mono-substituted with R^{D}, wherein R^{D} is (C_{1-4})alkyl or (C_{1-4})fluoroalkyl;

or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of claims 1 to 9; wherein $\mathbf{R^5}$ represents

- hydrogen;
- (C_{1-4})alkyl;
- (C_{1-4})alkyl which is mono-substituted with (C_{1-4})alkoxy, or cyano;
- (C_{2-4})alkyl which is mono-substituted with hydroxy;
- (C_{2-4})fluoroalkyl;
- (C_{2-5})alkenyl;
- (C_{1-4})alkoxy-C(O)-(C_{1-4})alkylene-;
- (C_{3-6})cycloalkyl-(C_{0-4})alkylene-, wherein the cycloalkyl is optionally substituted by one or two substituents independently selected from fluoro, and methyl;
- $ring^{B1}$-$\mathbf{X^{B1}}$-; wherein $\mathbf{X^{B1}}$ is a direct bond or methylene; and wherein $ring^{B1}$ is a 4- to 6-membered saturated heterocyclyl containing one ring heteratom which is O, wherein said $ring^{B1}$ is attached to $\mathbf{X^{B1}}$ at a ring carbon atom; wherein said $ring^{B1}$ is optionally substituted by one substituent selected from hydroxy, fluoro, or (C_{1-4})alkyl;
- $ring^{B2}$-$\mathbf{X^{B2}}$-; wherein $\mathbf{X^{B2}}$ is a direct bond, or methylene; and wherein $ring^{B2}$ is a 4- to 6-membered saturated heterocyclyl containing one ring heteratom which is N$\mathbf{R^B}$, wherein said $ring^{B}$ is attached to $\mathbf{X^{B2}}$ at a ring carbon atom; wherein said $ring^{B2}$ is optionally substituted by one oxo substituent, or by two fluoro substituents; and wherein

  $\mathbf{R^B}$ independently represents

  - hydrogen;
  - (C_{2-4})fluoroalkyl;
  - (C_{1-4})alkoxy-C(O)-;
  - $Ring^{C}$-O-C(O)-, and wherein $ring^{C}$ is (C_{3-6})cycloalkyl optionally containing one ring oxygen atom, wherein $ring^{C}$ is optionally substituted with one methyl; or
  - $Ring^{D}$, wherein $ring^{D}$ is a 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from O, N or S, wherein $ring^{D}$ is unsubstituted or mono-substituted with R^D, wherein R^D is (C_{1-4})alkyl or (C_{1-4})fluoroalkyl;

or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 11; wherein $\mathbf{R^4}$ represents hydrogen or methyl;
or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 1, wherein the compound is:
6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;
6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(4-trifluoromethyl-pyridin-3-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

[6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-5-oxo-4-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-2-yl]-acetic acid methyl ester;

2-Cyclopropyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-fluoro-2-methyl-propyl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-Cyclopropylmethyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(1-methyl-cyclopropylmethyl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-Ethyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-tert-Butyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(1-Fluoro-cyclopropylmethyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-isopropyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-isopropenyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,7-dimethyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(1-Fluoro-cyclopropylmethyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-Cyclopropyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(2,2-Difluoro-propyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-(1-Fluoro-cyclopropylmethyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

2-Cyclopropyl-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

4-(2-Cyclopropyl-benzyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-isopropyl-benzyl)-2-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-Cyclopropyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-Cyclopropyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Ethoxymethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[$^{2}H_3$]methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-acetic acid methyl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-hydroxy-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropoxy-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(1-(2-fluoro-6-methylphenyl)piperidin-4-yl)-2-methyl-7-(3-trifluoromethyl-[6-^{2}H]pyridine-2-yl-methyl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-d]pyrimidin-6-one;

[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-acetonitrile;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-hydroxy-2-methyl-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2-Amino-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-2-methyl-propionic acid methyl ester;

2-(2,2-Diethoxy-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-acetamide;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-N,N-dimethyl-acetamide;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-2-methyl-propionic acid methyl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-hydroxy-1,1-dimethyl-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-hydroxy-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[2-(3-methoxy-azetidin-1-yl)-ethyl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(6-Chloro-3-trifluoromethyl-pyridin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(6-fluoro-3-trifluoromethyl-pyridin-2-ylmethyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(6-methyl-3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(6-methoxy-3-trifluoromethyl-pyridin-2-ylmethyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(3-hydroxy-2-methyl-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2,3-Dihydroxy-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-((R)-2-hydroxy-3-methoxy-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Chloro-3-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-propionic acid methyl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-2-methyl-propionitrile;

2-(3-Amino-2-methyl-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-((S)-2-hydroxy-3-methoxy-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2,6-Dimethyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Methoxy-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-Fluoro-2-{4-[2-methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-piperidin-1-yl}-benzonitrile;

7-(6-Dimethylamino-3-trifluoromethyl-pyridin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(6-methylamino-3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(2'-Fluoro-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Dimethylamino-3-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-propionic acid methyl ester;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2-Dimethylamino-3-hydroxy-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-methylamino-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2-Dimethylamino-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-fluoro-6-trifluoromethyl-benzyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-pyrrolidin-1-yl-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-piperidin-1-yl-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-morpholin-4-yl-ethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[2-(4-methyl-piperazin-1-yl)-ethyl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

N-{2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-ethyl}-acetamide;

{2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-ethyl}-carbamic acid tert-butyl ester;

2-Methyl-5-(3'-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2-Cyclopropylamino-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[2-(isopropyl-methyl-amino)-ethyl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[2-(Cyclopropyl-methyl-amino)-ethyl]-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-{2-[(2-methoxy-ethyl)-methyl-amino]-ethyl}-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-propionamide;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-oxetan-3-yl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-propionitrile;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-nitro-cyclohexyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

{2,2,2-Trifluoro-1-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-1-methyl-ethyl}-carbamic acid tert-butyl ester;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-isobutyramide;

4'-Methyl-4-[2-methyl-6-oxo-7-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-2'-carbonitrile;

5-(4'-Fluoro-2'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-2-methyl-propionitrile;

2-(2-Amino-1,1-dimethyl-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid tert-butyl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester;

5-(2',4'-Dimethoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;

{2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-cyclopentyl}-carbamic acid tert-butyl ester;

4-Chloro-N-{2-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-1,1-dimethyl-ethyl}-benzenesulfonamide;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(1-isobutyl-azetidin-3-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[1-(2,2-Difluoro-ethyl)-azetidin-3-yl]-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[1-(2-Fluoro-ethyl)-azetidin-3-yl]-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-4,4-Difluoro-2-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;

(S)-4,4-Difluoro-2-[5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;

N-{2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-1,1-dimethyl-ethyl}-2-nitro-benzenesulfonamide;

2-((R)-4,4-Difluoro-pyrrolidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-((S)-4,4-Difluoro-pyrrolidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Acetyl-pyrrolidin-3-yl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Acetyl-azetidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Acetyl-pyrrolidin-2-ylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid methyl ester;

(S)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid tert-butyl ester;

(S)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid methyl ester;

(S)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid ethyl ester;

(S)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid isopropyl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid ethyl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid isopropyl ester;

(R)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid tert-butyl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(1-isobutyryl-azetidin-3-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid isobutyl ester;

(R)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid methyl ester;

(R)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid ethyl ester;

(R)-2-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-ylmethyl]-azetidine-1-carboxylic acid isopropyl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(1-methanesulfonyl-azetidin-3-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-sulfonic acid dimethylamide;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid oxetan-3-yl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid 3-trifluoromethyl-oxetan-3-yl ester;

3-[5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-2-yl]-azetidine-1-carboxylic acid 3-methyl-oxetan-3-yl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[1-(5-methyl-[1,3,4]oxadiazol-2-yl)-azetidin-3-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[1-(5-isopropyl-[1,3,4]oxadiazol-2-yl)-azetidin-3-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2-[1-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-azetidin-3-yl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidine-2-carboxylic acid isopropyl ester;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-6-oxo-7-(2-trifluoromethyl-benzyl)-4,5,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidine-2-carboxylic acid dimethylamide;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-methyl-propenyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-methyl-allyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-isobutyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-[2-([$^{2}H_{3}$]methyl)[1,1,2,3,3,3-$^{2}H_{6}$]propyl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-oxo-azetidin-3-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(1-methyl-cyclopropylmethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2,2-Difluoro-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1,1-Dimethyl-prop-2-ynyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-isopropyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-([1,1,1,2,3,3,3-$^{2}H_{7}$]propan-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-([1,1,1,3,3,3-$^{2}H_{6}$]propan-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(3-fluoro-oxetan-3-ylmethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Cyclopropylmethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(3-methyl-oxetan-3-ylmethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Fluoro-cyclopropylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(2-fluoro-2-methyl-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Ethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-[1,1,2,2,2-$^{2}H_{5}$]Ethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one ;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-(3-hydroxy-oxetan-3-ylmethyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2,2-Difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-tert-Butyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Cyclopropyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-((S)-2-fluoro-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-((R)-2-fluoro-propyl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-((S)-2,2-Difluoro-1-methyl-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-((R)-2,2-Difluoro-1-methyl-ethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-((R)-2,2-Difluoro-cyclopropylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-((S)-2,2-Difluoro-cyclopropylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2,2-Difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Fluoro-cyclopropylmethyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(1-Fluoro-cyclopropylmethyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-(2,2-Difluoro-propyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Cyclopropyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Cyclopropyl-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Bromo-6-trifluoromethyl-benzyl)-2-cyclopropyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Bromo-6-trifluoromethyl-benzyl)-2-(2,2-difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-4-methyl-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(S)-1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(R)-1-(2-Fluoro-6-methyl-phenyl)-azepan-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-Methoxymethyl-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-isopropyl-benzyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethoxy-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Chloro-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(4-Chloro-2,5-dimethyl-2H-pyrazol-3-yl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-trifluoromethyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-trifluoromethoxy-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Chloro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-[(R)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropylmethoxy-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(4-isopropyl-pyrimidin-5-ylmethyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-7-[2-(oxetan-3-yloxy)-benzyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-isopropoxy-benzyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Ethoxy-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Isopropyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Cyclopropyl-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(4-isopropoxy-pyridazin-3-ylmethyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(R)-1-(2-Fluoro-6-methyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(R)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(S)-1-(2,6-Dimethyl-phenyl)-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(R)-1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(S)-1-(2-Fluoro-6-methyl-phenyl)-3-methyl-pyrrolidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[(R)-1-(2-Fluoro-6-methyl-phenyl)-piperidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-azetidin-3-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d]pyrimidin-5-one;

6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d]pyrimidin-5-one;

6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,6,7-tetrahydro-[1,2,3]triazolo[4,5-d]pyrimidin-5-one;

1-Cyclopropylmethyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-1,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

1-Cyclopropyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

1-Cyclopropylmethyl-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-1-(1-methyl-cyclopropylmethyl)-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-1-(2-fluoro-2-methyl-propyl)-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

1-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-1-(2,2-Difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(2-trifluoromethyl-benzyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-(2-trifluoromethyl-benzyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-(3-trifluoromethyl-pyridin-2-ylmethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-3-(2-trifluoromethyl-benzyl)-1,3,6,7-tetrahydro-purin-2-one;

1-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-3-(2-trifluoromethyl-benzyl)-7-(2-trimethylsilanyl-ethoxymethyl)-1,3,6,7-tetrahydro-purin-2-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-6,7-dihydro-4H-oxazolo[5,4-d]pyrimidin-5-one; or

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-6,7-dihydro-4H-thiazolo[5,4-d]pyrimidin-5-one;

or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 1, wherein the compound is:

6-[1-(2-Fluoro-6-trifluoromethoxy-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-trifluoromethyl-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2-fluoro-6-trifluoromethoxy-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

2-{4-[7-(2-Cyclopropyl-benzyl)-2-methyl-6-oxo-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl]-piperidin-1-yl}-3-fluoro-benzonitrile;

7-(2-Cyclopropyl-benzyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2,6-difluoro-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-[(R)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2-methyl-7-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

3-Fluoro-2-(4-{2-methyl-6-oxo-7-[(R)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl}-piperidin-1-yl)-benzonitrile;

3-Fluoro-2-(4-{2-methyl-6-oxo-7-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,6,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-5-yl}-piperidin-1-yl)-benzonitrile;

5-[1-(2,6-Difluoro-phenyl)-piperidin-4-yl]-2-methyl-7-[(S)-1-(2-trifluoromethyl-phenyl)-ethyl]-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

6-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

5-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

6-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2-cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

4-(2-Cyclopropyl-benzyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2-(tetrahydro-pyran-2-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

4-(2-Cyclopropyl-benzyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-2-(tetrahydro-pyran-2-yl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-4-(2-Cyclopropyl-benzyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-4-(2-Cyclopropyl-benzyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-4-(2-Cyclopropyl-benzyl)-2-(2,2-difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-4-(2-Cyclopropyl-benzyl)-2-(2,2-difluoro-propyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-Cyclopropyl-4-(2-cyclopropyl-benzyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-Cyclopropyl-4-(2-cyclopropyl-benzyl)-6-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-Cyclopropyl-4-(2-cyclopropyl-benzyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-Cyclopropyl-4-(2-cyclopropyl-benzyl)-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

6-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-methyl-2-(tetrahydro-pyran-2-yl)-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-Cyclopropyl-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-Cyclopropyl-6-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-6-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,7-dimethyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-(2,2-Difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-(2,2-Difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-2-(tetrahydro-pyran-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-[1-(2-cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-6-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-6-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-2-Cyclopropyl-6-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(S)-2-Cyclopropyl-6-[1-(2-difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-7-methyl-4-(2-trifluoromethyl-benzyl)-2,4,6,7-tetrahydro-pyrazolo[4,3-d]pyrimidin-5-one;

(R)-5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Cyclopropyl-6-fluoro-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-7-(2-cyclopropyl-benzyl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-7-(2-cyclopropyl-benzyl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-2-(tetrahydro-pyran-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-2-(tetrahydro-pyran-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2-(tetrahydro-pyran-2-yl)-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Difluoromethyl-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(4'-Difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Fluoro-6-methyl-phenyl)-piperidin-4-yl]-2,4-dimethyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(2'-Methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(3-trifluoromethyl-pyridin-2-ylmethyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-2-cyclopropyl-4-methyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(2'-Methoxy-4'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(2'-Methoxy-4'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2-(tetrahydro-pyran-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-4-methyl-2-(tetrahydro-pyran-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-[1-(2-Chloro-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-7-(2-Cyclopropyl-benzyl)-5-(2'-methoxy-4'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-7-(2-Cyclopropyl-benzyl)-5-(2'-methoxy-4'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(4'-Chloro-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(4'-Chloro-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-2,4-dimethyl-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-5-(4'-Chloro-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-5-(4'-Chloro-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(S)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-(2'-methoxy-4'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

(R)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;
(S)-2-Cyclopropyl-7-(2-cyclopropyl-benzyl)-5-(4'-difluoromethyl-2'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-4-methyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;
(R)-5-[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one; or
(S)-5-[1-(2-Bromo-6-fluoro-phenyl)-piperidin-4-yl]-7-(2-cyclopropyl-benzyl)-2,4-dimethyl-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1, wherein the compound is 2-(2,2-Difluoro-propyl)-5-[1-(2-fluoro-6-methyl-phenyl)-piperidin-4-yl]-7-(2-trifluoromethyl-benzyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidin-6-one;

or a pharmaceutically acceptable salt thereof.

~~15~~16. A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 1 to ~~14~~15, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

~~16~~17. A compound according to any one of claims 1 to ~~14~~15, or a pharmaceutically acceptable salt thereof, for use as a medicament.

~~17~~18. Use of a~~A~~ compound according to any one of claims 1 to ~~14~~15, or a pharmaceutically acceptable salt thereof, ~~for use in~~in the preparation of a medicament for the prevention or treatment of vasculitic diseases or disorders, inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders, neurodegenerative diseases or disorders, complement related inflammatory diseases or disorders, bullous diseases or disorders, diseases or disorders related to ischemia and/or ischemic reperfusion injury, inflammatory bowel diseases or disorders, autoimmune diseases or disorders, or cancer.

~~18~~19. ~~A~~ Use of a compound according to any one of claims 1 to ~~14~~15, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; the prevention or treatment of increased leukocyte and platelet activation ~~(~~and infiltration to tissues thereof~~)~~; the prevention or treatment of pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; the prevention or treatment of pathologic sequelae associated with insulin-dependent diabetes mellitus; the prevention of / the reduction of the risk of myocardial infarction or thrombosis; prevention or treatment of edema or increased capillary permeability; or the prevention of / the reduction of coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia.

~~19. Use of a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of vasculitic diseases or disorders; inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders;~~

neurodegenerative diseases or disorders; complement related inflammatory diseases or disorders; bullous diseases or disorders; diseases or disorders related to ischemia and/or ischemic reperfusion injury; inflammatory bowel diseases or disorders; autoimmune diseases or disorders; cancer; deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; pathologic sequelae associated with insulin-dependent diabetes mellitus; the risk of myocardial infarction or thrombosis; edema or increased capillary permeability; or coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia.

20. A method of treatment of vasculitic diseases or disorders; inflammatory diseases or disorders involving intravascular microvesicle release, immune complex (IC) diseases or disorders; neurodegenerative diseases or disorders; complement related inflammatory diseases or disorders; bullous diseases or disorders; diseases or disorders related to ischemia and/or ischemic reperfusion injury; inflammatory bowel diseases or disorders; autoimmune diseases or disorders; cancer; deleterious consequences of contact sensitivity and inflammation caused by contact with artificial surfaces; increased leukocyte and platelet activation (and infiltration to tissues thereof); pathologic sequelae associated to an intoxication or an injury such as a trauma, an hemorrhage, a shock, or surgery including transplantation; pathologic sequelae associated with insulin-dependent diabetes mellitus; the risk of myocardial infarction or thrombosis; edema or increased capillary permeability; or coronary endothelial dysfunction induced by cardiopulmonary bypass and/or cardioplegia; comprising administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof.