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(54) Title: MODULATORS OF ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTORS AND THERAPEUTIC USES THEREOF

(57) Abstract: Compounds with α7 nicotinic acetylcholine receptor (α7 nAChR) agonistic activity, processes for their preparation, pharmaceutical compositions containing the same and the use thereof for the treatment of neurological and psychiatric diseases.

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MODULATORS OF ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTORS AND THERAPEUTIC USES THEREOF

The present invention relates to compounds with α7 nicotinic acetylcholine receptor (α7 nAChR) agonistic activity, processes for their preparation, pharmaceutical compositions containing the same and the use thereof for the treatment of neurological and psychiatric diseases.

Background of the invention

A number of recent observations point to a potential neuroprotective effect of nicotine in a variety of neurodegeneration models in animals and in cultured cells, involving excitotoxic insults (1-5), trophic deprivation (6), ischemia (7), trauma (8), Aß-mediated neuronal death (9-11) and protein-aggregation mediated neuronal degeneration (9;12). In many instances where nicotine displays a neuroprotective effect, a direct involvement of receptors comprising the α7 subtype has been invoked (7;11-15) suggesting that activation of α7 subtype-containing nicotinic acetylcholine receptors may be instrumental in mediating the neuroprotective effects of nicotine. The available data suggest that the α7 nicotinic acetylcholine receptor represents a valid molecular target for the development of agonists/positive modulators active as neuroprotective molecules. Indeed, α7 nicotinic receptor agonists have already been identified and evaluated as possible leads for the development of neuroprotective drugs (16-20). Involvement of α7 nicotinic acetylcholine receptor in inflammatory processes has also recently been described (21). Thus, the development of novel modulators of this receptor should lead to novel treatments of neurological, psychiatric and inflammatory diseases.

Known prior art

Different compounds carrying an aryl/heteroaryl- ureido or carbamoyl moiety and a basic nitrogen and exhibiting nicotinic and muscarinic

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acetylcholine receptor affinity or claimed for use in Alzheimer disease were found to be described: fused pyridazine derivatives (WO03070707); methods for treating an inflammatory condition (US2004127536); aza-bicyclic *N*-biarylamides (WO03078431); heterocyclic urea derivatives (WO0266468); spirocyclic piperidines (WO2004004714); phenyl-substituted indoles and indazoles (WO0174773); phenyl-subsituted imidazopyridines (WO0174815);

Heterocyclic compounds carrying a basic nitrogen and hexibiting various types of biological activity were found to be described: anti herpes virus compounds (US6288091); 2H-phthalazin-1-one derivatives (WO00044726); 1,4-dihydro-2(2H)isoquinolines (DE2406490); pyridine compounds (JP06016638); piperidine amides (WO0198268); 8-amino-aryl-substituted imidazopyrazines as kinase inhibitors (US2005009832);

Heterocyclic compounds were also disclosed in Heterocycles (1997), 45(4), 723-734: 1-[ω[(arylamino)carbonyl]alkyl]-4-(benzocycloalkyl)piperazines.

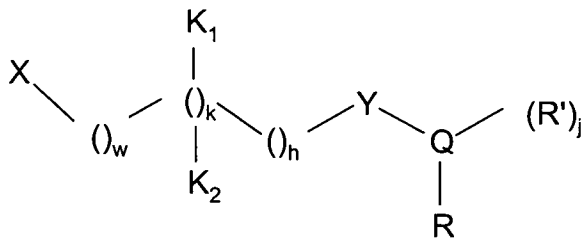
These referenced compounds are readily distinguishable structurally from those herein disclosed by either the functionalities, attachment chain or substitution pattern; these prior documents fail to disclose or suggest the unique combination of structural fragments which embody the novel ω-aminoalkylureas or carboxamides having activity on the nicotinic alpha7 receptor herein disclosed.

Summary of the invention

The invention provides novel compounds acting as full or partial agonists at the α7 nicotinic acetylcholine receptor (α7 nAChR), pharmaceutical compositions containing the same compounds and the use thereof for the treatment of diseases that may benefit from the activation of the alpha 7 nicotinic acetylcholine receptor such as neurological and psychiatric disorders, in particular Alzheimer's disease and schizophrenia.

Description of the invention

This invention provides compounds of formula (I)



(I)

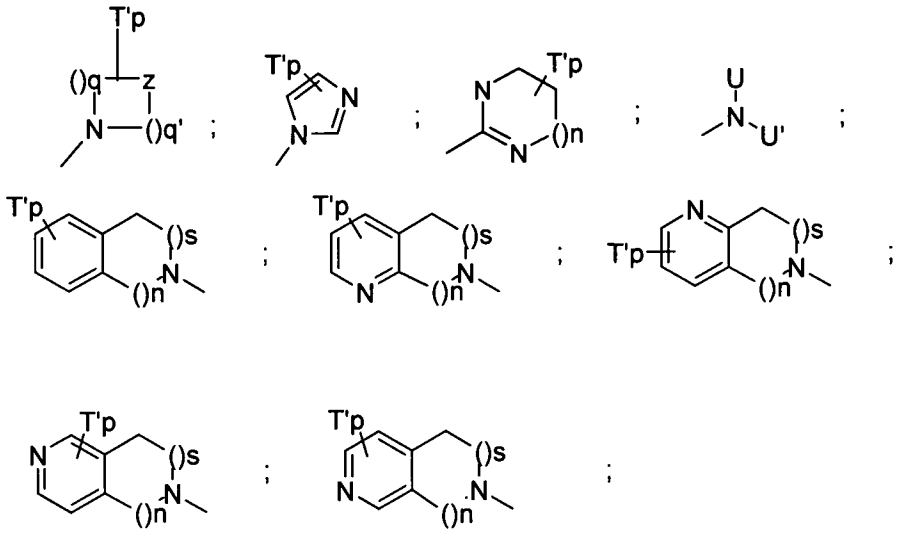
wherein

w, h and k are, independently from one another, 0,1,2, or 3 with the condition that $3 \leq w + h + k \leq 5$;

K1 and K2, which are bound to either the same or a different carbon atom where k>1, represent independently from one another hydrogen; halogen; (C_1-C_5) alkyl, alkoxy, fluoroalkyl, alkylene, fluoroalkylene; hydroxyalkyl; or K1 and K2 taken together may form an alkylidene or a fluoroalkylidene group; or K1 and K2, taken together with the carbon atom to which they are attached, form a (C_3-C_6) cycloalkyl group; or when k is ≥2, two $()_k$ carbon atoms may form an unsaturated bond; or when w is 1, 2, or 3, and k is 1, K1 and K2 taken together with the carbon atom to which they are attached may form an oxo group;

j is 0, 1 or 2;

X is a group of formula



Z is CH_2, N, O, S, S(=O), or $S(=O)_2$;

p is 0, 1, 2 or 3;

n is 0, 1 or 2;

s is 1 or 2;

q and q' are, independently from one another, integers from 1 to 4;

T' represent, independently from one another, hydroxy; mercapto; amino; cyano; nitro; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; or, when p is 2 or 3, two T' form a 5- to 8-membered ring with spiro or fused junction;

U and U' represent, independently from one another, hydrogen; cyano; hydroxy; amino; a mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino group; a linear or branched (C_1-C_6) alkoxy group; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with hydroxy, mercapto, amino, cyano, nitro, oxo, trihalomethyl, trihalomethoxy, carbamoyl,

sulphamoyl, linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl, mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl, (C_5-C_{10}) aryl- or heteroarylsulphonylamino, (C_1-C_3) alkylsulphonylamino, (C_5-C_{10}) aryl- or heteroarylsulphonyl, (C_1-C_3) alkylsulphonyl, mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl, mono- or di- (C_1-C_3) alkylsulphamoyl, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain bearing a 5- to 10-membered aryl or heteroaryl group optionally substituted with one or more groups independently selected from hydroxy, mercapto, amino, cyano, nitro, trihalomethyl, trihalomethoxy, linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxyxcarbonyl, alkylcarbonylamino, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino, linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl, carbamoyl, (C_5-C_{10}) aryl- or heteroarylsulphonylamino, (C_1-C_3) alkylsulphonylamino, mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl, (C_1-C_3) alkylsulphamoyl, sulphamoyl, mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl, a 5 to 10 membered aromatic or heteroaromatic ring optionally substituted with one or more groups independently selected from hydroxy; halogen; mercapto; amino; cyano; nitro; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl-, alkoxyxcarbonyl, alkylcarbonylamino; mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-

(C_1-C_6) alkyl; carbamoyl; (C_5-C_{10}) aryl- or heteroarylsulphonylamino; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl; mono- or di- (C_1-C_3) alkylsulphamoyl; sulphamoyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl;

-Y-Q- is –C(=O)NH-Q- or -NH-C(=O)-NH-Q;

Q is a 5 to 10-membered aromatic or heteroaromatic ring;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino, mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl; mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, (C_1-C_6) alkylthio-(C_1-C_6) alkyl;

R' represent, independently from one another when j = 2, halogen; hydroxy; mercapto; cyano; nitro; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy, hydroxyalkyl, mercaptoalkyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, (C_1-C_6) alkylthio-(C_1-C_6) alkyl,

provided that when k is zero and the sum of w and h is 4, T' is mercapto; amino; trihaloalkyl; hydroxyalkyl; (C1-C6) aminoalkyl; mercaptoalkyl; alkylthio; alkoxycarbonyl; alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; mono- or di- (C_1-C_3) alkylaminosulphonyl, or $j \neq 0$;

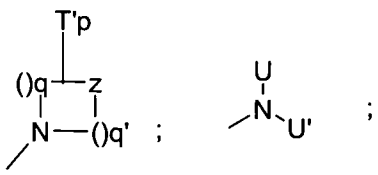
and that when j is zero, and the sum of w, h and k is 4, then K1 and K2 are not both hydrogen;

and with the exclusion of the following compounds:

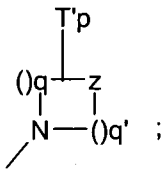
1--[4-(2-Amino-thiazol-5-yl)-phenyl]-3-(3-imidazol-1-yl-propyl)-urea;1-(Biphenyl-4-yl)-3-(5-(spiro(indane-1,4'-piperidine-10-yl)-pentyl)-urea; 1-(Biphenyl-4-yl)-3-(4-(spiro(indane-1,4'-piperidine-10-yl)-butyl)-urea;3-{4-[3-(3-Morpholin-4-yl-propyl)-ureido]-phenyl}-1H-indazole-5-carboxylic acid amide;3-{4-[3-(3-Piperidin-1-yl-propyl)-ureido]-phenyl}-1H-indazole-5-carboxylic acid amide;1-[4-(8-Methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-morpholin-4-yl-propyl)-urea

1-[4-(8-Cyclopropylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-pyrrolidin-1-yl-propyl)-urea;1-(2-Hydroxy-3-morpholin-4-yl-propyl)-3-[4-(8-methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-urea;1-[4-(8-Cyclopropylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-morpholin-4-yl-propyl)-urea;1-[4-(8-Methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-pyrrolidin-1-yl-propyl)-urea; N-Biphenyl-4-yl-4-piperazin-1-yl-butyramide

Within compounds of formula I above described, most preferred compounds are those in which X is

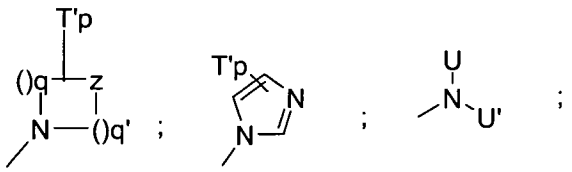


More preferred group compounds are those for which X is



In one embodiment, this invention provides compounds hereafter referred to as G1, in which:

X is:



z is selected from CH_2, N, O;

T' represent, independently from one another when p is greater than 1, hydroxy; amino; cyano; nitro; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; or when p is 2 or 3, two T' substituents form a 5- to 8-membered ring with spiro or fused junction;

U and U' represent, independently from one another, hydrogen; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with hydroxy, oxo, trihalomethyl, trihalomethoxy, carbamoyl, sulphamoyl, pyridyl, linear, branched or cyclic (C_1-C_3) alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, mono- or di-, linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl, (C_1-C_3) alkylsulphonylamino, (C_1-C_3)

alkylsulphonyl, mono- or di- (C_1-C_3) alkylsulphamoyl, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino;

Q is a 6 to 10-membered aromatic or heteroaromatic ring;

R represents a 5 to 10-membered aromatic or heteroaromatic ring optionally substituted with one or more groups independently selected from: halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl; mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl;

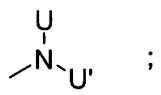
R' represent, independently from one another when j = 2, halogen; hydroxy; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy, hydroxyalkyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphonyl; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl, mono- or di- (C_1-C_3) alkylamino-(C_1-C_3) alkyl, (C_1-C_3) alkylthio-(C_1-C_3) alkyl;

In one aspect of this invention, G1 provides a group of compounds hereafter referred to as G1a wherein w + h + k = 4.

Within G1a, a particular embodiment provides compounds in which

k is 0;

X is a group of formula:



;

U and U' represent, independently from one another, hydrogen; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with trihalomethyl, trihalomethoxy, carbamoyl, sulphamoyl, pyridyl;

-Y- is a group –C(=O)NH- or -NH-C(=O)NH-;

j is 0, or 1;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

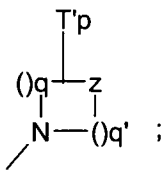
R' represents halogen; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy.

In another embodiment, this invention provides a group of compounds hereafter referred to as G2 in which:

w + h + k = 4

K1 and K2 represent, independently from one another hydrogen; halogen; (C_1-C_3) alkyl, alkoxy;

X is a group of formula:



;

z is CH_2, N, O;

p is 0 or 1;

T' represents linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

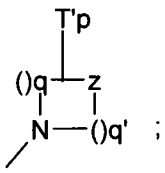
R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl; mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl;

R' represent, independently of one another when j = 2, halogen; hydroxy; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl, mono- or di- (C_1-C_3) alkylamino-(C_1-C_3) alkyl, (C_1-C_3) alkylthio-(C_1-C_3) alkyl;

Within G2, a particular embodiment defines a group of compounds hereafter referred to as G3 in which:

K1 and K2 represent, independently from one another hydrogen; halogen; (C_1-C_3) alkyl;

X is a group of formula:



;

z is CH_2, N;

q and q' are, independently from one another, integers from 1 to 3;

T' represents linear, branched or cyclic (C_1-C_3) alkyl, alkylcarbonyl;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

R' represents, independently from one another when j = 2, halogen; trihalomethyl; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy.

In one aspect, G3 provides a subset of compounds hereafter referred to as G4a in which -Y- is a group –C(=O)NH-.

Within G4a, a particular embodiment is that in which:

Q is a phenyl or pyridyl ring;

j is 1 or 2;

R represents a phenyl, pyridyl, or pyrazolyl ring, optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl.

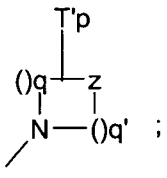
In another aspect, G3 provides a subset of compounds hereafter referred to as G4b where:

-Y- is a group -NH-C(=O)-NH-.

Within G4b, a particular embodiment is that in which:

K1 and K2 represent, independently from one another hydrogen; halogen; (C_1-C_3) alkyl;

X is a group of formula:



;

z is CH_2, N;

p is 0 or 1;

q and q' are, independently from one another, integers from 1 to 3;

T' represents linear, branched or cyclic (C_1-C_3) alkyl, alkylcarbonyl;

-Y- is a group -NH-C(=O)-NH-;

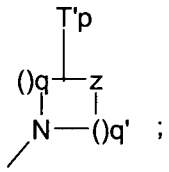
Q is a phenyl or pyridyl;

R represents a phenyl, pyridyl or pyrazole ring, optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

Under yet another aspect of invention, G1 also provides a group of compounds hereafter referred to as G5, wherein

w+ h+ k= 3;

X is



;

Within G5, one embodiment provides a group of compounds hereafter referred to as G5a in which:

q and q' are, independently from one another, integers from 1 to 3;

T' represent, independently from one another when p is greater than 1, hydroxy; cyano; oxo; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl; (C_1-C_3)

alkylsulphonylamino; mono- or di- (C_1-C_3) alkylsulphamoyl; (C_1-C_3) sulphonyl;

-Y- is a group -NH-C(=O)-NH-;

R represents a 5 to 6-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; cyano; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphonyl; mono- or di- linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl;

R' represents, independently of one another when j = 2, halogen; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy.

Within G5a, a particular embodiment is represented by compounds in which

k is 0;

p is 0, or 1;

T' represents, independently from one another when p is greater than 1, linear, branched or cyclic (C_1-C_3) alkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

-Y- is a group -NH-C(=O)-NH-;

Q is a phenyl or pyridyl;

j is 0 or 1;

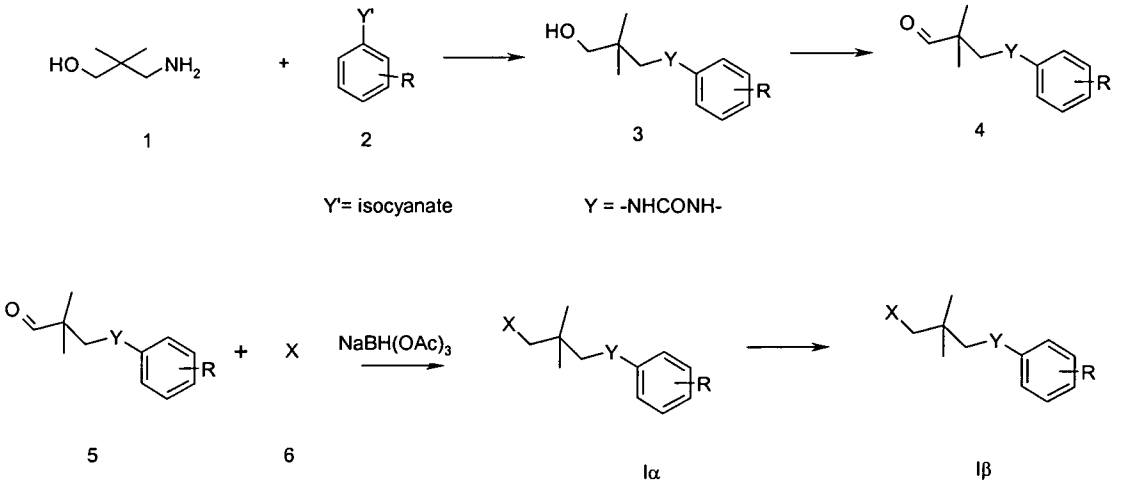
R represents a phenyl or pyridyl ring optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_6) alkyl, alkoxy; linear, branched, or cyclic (C_1-C_3)

alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

R' represents halogen.

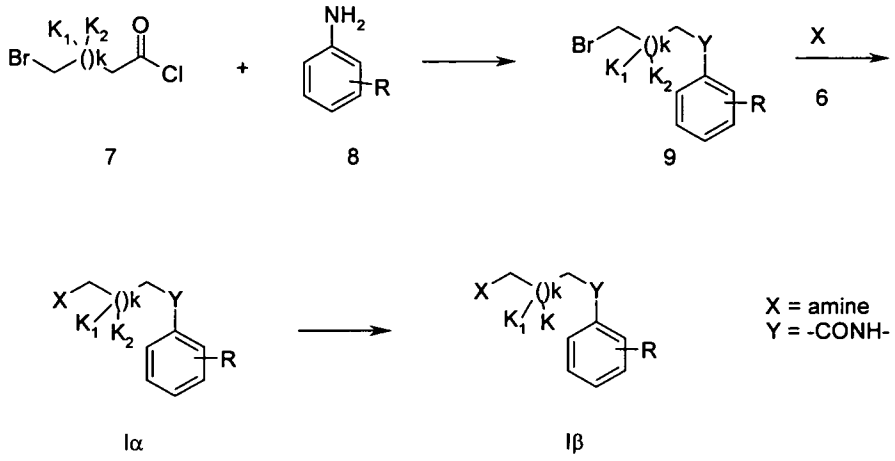
The compounds of the invention can be prepared through a number of synthetic routes amongst which the ones illustrated in Schemes 1-5 below:

a) Scheme 1



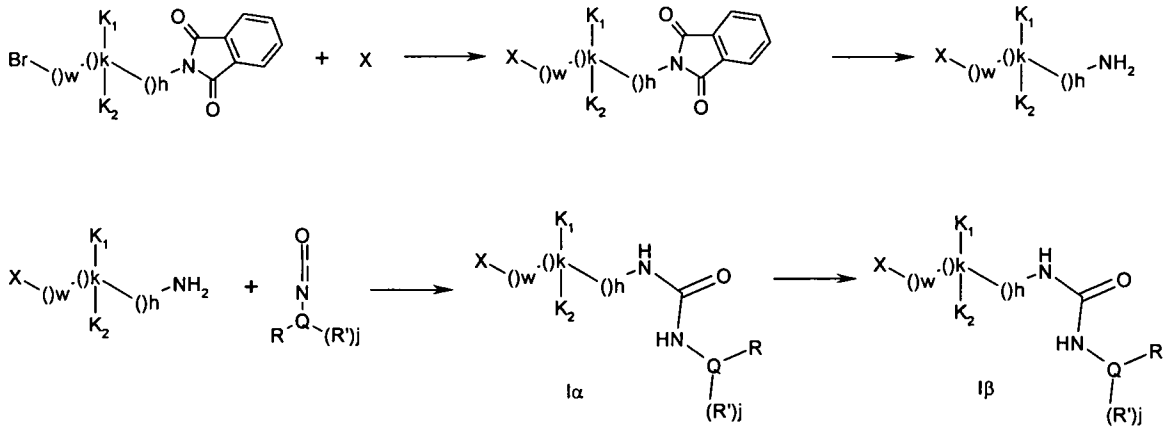
According to Scheme 1, an aminoalcohol, for example 3-amino-2,2-dimethyl-propan-1-ol when k = 1 and K1 = K2 = $-CH_3$, is reacted with for example an isocyanate or a carbamoyl chloride, hereby exemplified by an arylisocyanate, in an organic solvent such as for example dichloromethane, tetrahydrofuran, dimethylformamide or mixtures thereof, until the reaction is complete. The hydroxyurea 3 then oxidised under standard conditions (for example Swern oxidation) and the obtained aldehyde 4 is then reacted with a suitably substituted amine 6 under standard reductive alkylation conditions - for example with sodium triacetoxyborohydride - to afford compound Iα. In the case of R being a halogen or a boronic acid ester, Iα can be further processed – for example via a cross-coupling reaction, for example under the conditions of the Suzuki coupling, with a boronic acid or an aryl or heteroaryl halide - to yield compounds Iβ.

b) Scheme 2



According to Scheme 2 an ω-haloalkanoyl chloride is reacted with an (hetero)aromatic amine 8 in the presence of an organic base to afford an ω-haloalkanoic acid amide 9. This species is reacted with an amine 6 to displace the halogen and afford compounds Iα. In the case of R being a halogen or a boronic acid ester, Iα can be further processed - for example via a cross-coupling reaction, for example under the conditions of the Suzuki coupling, with a boronic acid or an aryl or heteroaryl halide - to yield compounds Iβ.

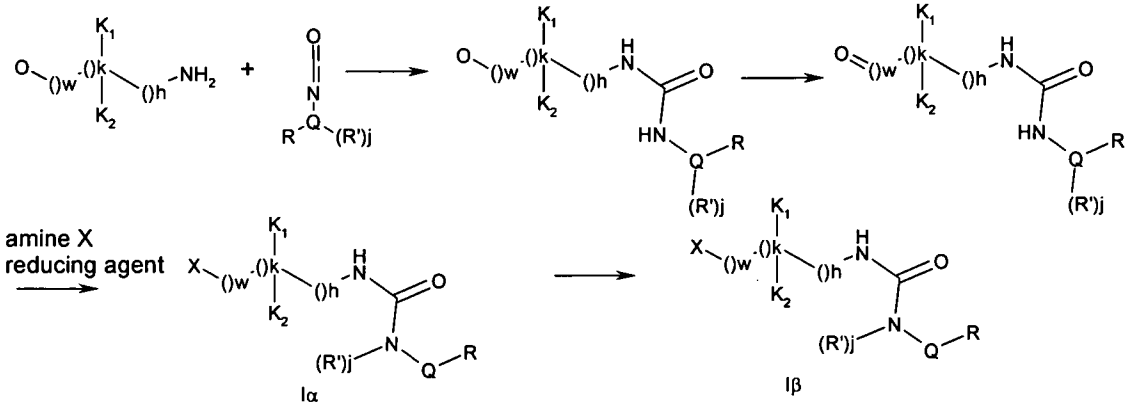
c) Scheme 3



According to Scheme 3, a suitably activated ω-haloalkylphthalimide, is reacted with an amine X in an organic solvent such as for example but not limited to 2-butanone or dimethylformamide in the presence of a base such as

for example triethylamine or potassium carbonate. For example, a mixture of amine (or its hydrochloride salt) and ω-haloalkylphthalimide are refluxed in methylethyl ketone in the presence of alkaline carbonate until the reaction is complete, then the reaction mixture is cooled, the insoluble materials removed by filtration, the filtrate washed with chloroform or dichloromethane, and the filtrate and washings concentrated to dryness. In the following step, the ω-aminoalkylphthalimide is converted into a ω-diamine, for example by refluxing a mixture of the ω-aminoalkylphthalimide and hydrazine hydrate in ethanol. The ω-diamine is reacted with an activated species such as for example an isocyanate or a carbamoyl chloride in an organic solvent such as dichloromethane, tetrahydrofuran, dimethylformamide or mixtures thereof, to give compounds of formula Iα In the case of R being a halogen, a boronic acid or a boronic ester, Iα can be further processed - for example via a cross-coupling reaction, for example under the conditions of the Suzuki coupling, with a boronic acid or an aryl or heteroaryl halide - to yield compounds of formula I.

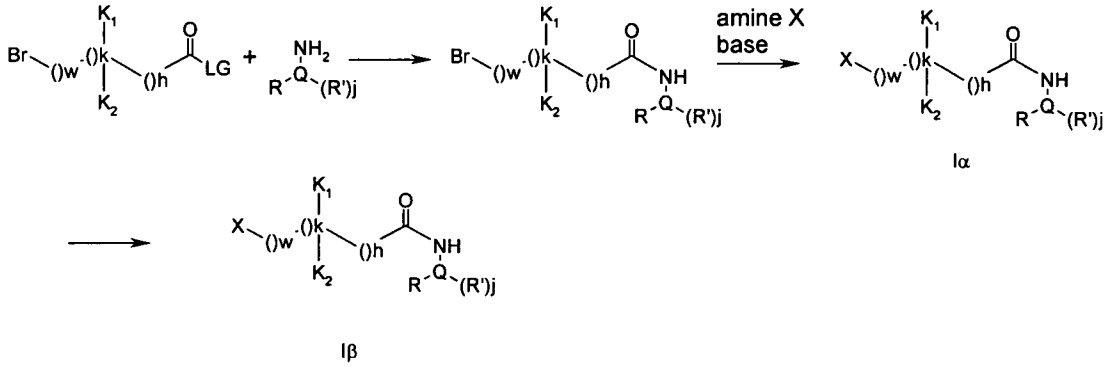
d) Scheme 4



According to Scheme 4, a suitable aldehyde precursor, for example an aminoalcohol, for example aminopropanol when k = 1 and K1 = K2 = H, is reacted with for example an isocyanate or a carbamoyl chloride, hereby exemplified by an arylisocyanate, in an organic solvent such as for example

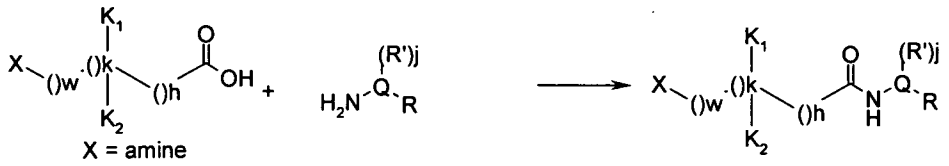
dichloromethane, tetrahydrofuran, dimethylformamide or mixtures thereof, until the reaction is complete. The aldehyde precursor thus obtained is then converted to the aldehyde, for example oxidised under standard conditions (for example Swern oxidation) in the case of an alcohol, and the aldehyde is then reacted with a suitably substituted amine X under standard reductive alkylation conditions - for example with sodium triacetoxyborohydride - to afford compounds Iα. In the case of R being a halogen, a boronic acid or a boronic acid ester, Iα can be further processed – for example via a cross-coupling reaction, for example under the conditions of the Suzuki coupling, with a boronic acid or an aryl or heteroaryl halide - to yield compounds of formula I.

e) Scheme 5



According to Scheme 5 a suitably activated ω-haloalkanoic acid (for example where the moiety C(=O)-LG represents an acyl chloride or activated ester or imidazolide) is reacted with an (hetero)aromatic amine in the presence of an organic base to afford an ω-haloalkanoic acid amide. This species is further reacted with an amine X to displace the ω-halogen atom and afford compounds of formula Iα. In the case of R being a halogen, a boronic acid or a boronic acid ester, Iα can be further processed - for example via a cross-coupling reaction, for example under the conditions of the Suzuki coupling, with a boronic acid or an aryl or heteroaryl halide - to yield compounds of formula I.

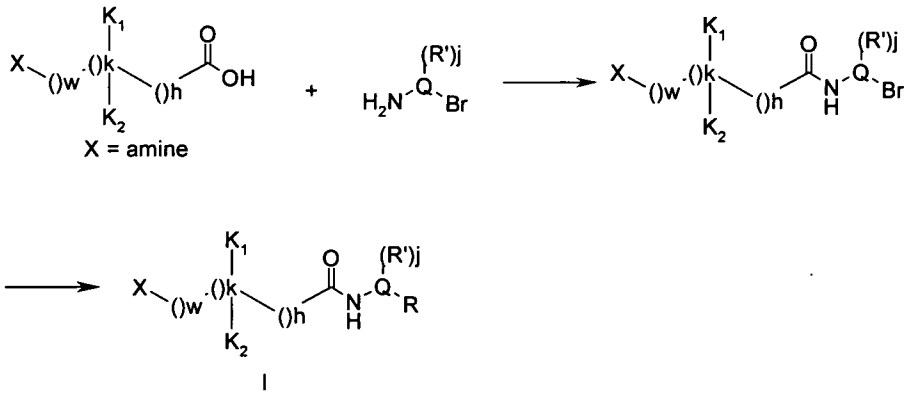
f) Scheme 6



I

According to Scheme 6, an ω-aminoalkanoic acid is suitably activated using an agent such for example but not limited to as 1,1'-carbonyldiimidazole in a solvent such as for example dichloromethane, dimethylformamide or mixtures thereof and reacted with a suitable heterocyclic amine to afford subject matter compounds of formula I.

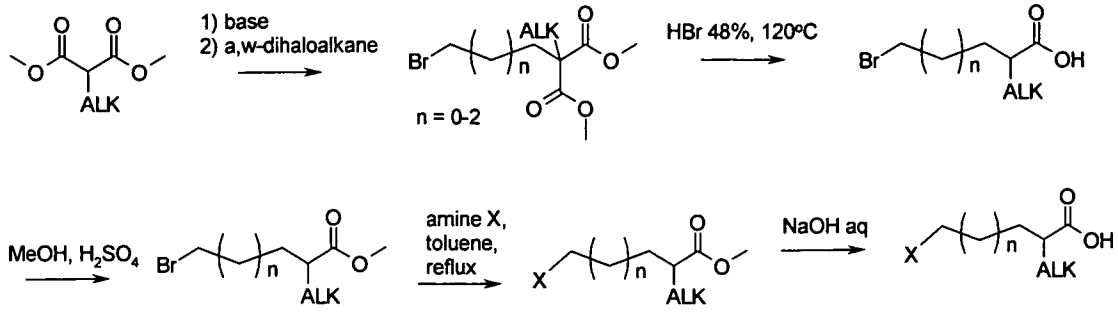
g) Scheme 7



I

According to Scheme 7, an ω-aminoalkanoic acid is suitably activated using an agent such for example but not limited to as 1,1'-carbonyldiimidazole in a solvent such as for example dichloromethane, dimethylformamide or mixtures thereof and reacted with a suitable bromoaryl or heteroaryl amine to afford bromoaryl or heteroaryl amides, which are then reacted further under cross-coupling conditions, for example Suzuki conditions, to afford subject matter compounds of formula I.

Scheme 8 shows one possible route towards the synthesis of chain-substituted acids, precursors to compounds of Formula I



According to Scheme 8, an alkyl-substituted malonic acid diester it treated with base, such as for example but not limited to sodium hydride in a solvent such as tetrahydrofurane or dimethylformamide and reacted with an α,ω-dihaloalkane. The disubstituted malonic acid diester thus obtained is hydrolysed and mono-decarboxylated by treatement with a strong acid, such as for example hydrobromic acid. Esterification is then carried out, for example by treatement with methanol and a catalytic amount of acid. Substitution of the ω-halogen may be accomplished by the use of a suitable amine heating in a solvent like toluene, but not limited to this solvent. Finally, hydrolysis of the ester function with an aqueous base affords intermediates which can be activated as described to afford compounds of Formula I.

The compounds in this invention can in general be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry. In general, the amides can be prepared through a base-catalysed nucleophilic addition between the appropriate carboxylic acid with an appropriately selected amine or via a nucleophilic substitution reaction wherein the appropriate amine reacts with either the selected acyl halide, anhydride or ester to yield the required amine. When coupling the acids to the amines, standard chemical coupling reagents such as carbonyldiimidazole (CDI), 1,3-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) can be used in the presence or absence of hydroxybenzotriazole (HOBt). In an alternative procedure the carboxylic acids are converted into the corresponding acyl

halides by reaction with, for example, thionyl chloride or oxalyl chloride. Subsequently, the acid halide is added to the appropriately selected amine to yield the amide using art-known reaction procedures such as the Schotten-Baumann method.

The carboxylic acids and the amines are readily available, or may be prepared using methods that are well known in the art. Many compounds are commercially available, for example, from Aldrich Chemicals, or when the compounds are not commercially available, they may be readily prepared from available precursors using straightforward transformations that are well known in the art. For example the carboxylic acids can be prepared by hydrolysis of nitriles, carbonation of organometallic compounds or oxidation of primary alcoholds or aldehydes. In particular branched alkyl nitriles are prepared from the corresponding alkyl acetonitriles by conversion to the dialkyl or spiroalkyl derivative using e.g. sodium hexamethyldisilazane and methyl iodide or dibromobutane, followed by hydrolysis under acidic or basic conditions to the desired carboxylic acid. Appropriate acids and bases in the hydrolysis are for example H2SO4 and KOH. The hydrolysis reaction can be conveniently performed using microwave heating.

The compounds of formula I, their optical isomers or diastereomers can be purified or separated according to well-known procedures, including but not limited to chromatography with a chiral matrix and fractional crystallisation.

The pharmacological activity of a representative group of compounds of formula I was demonstrated in an *in vitro* assay utilising cells stably transfected with the alpha 7 nicotinic acetylcholine receptor and cells expressing the alpha 1 and alpha 3 nicotinic acetylcholine receptors and 5HT3 receptor as controls for selectivity. According to a further aspect, the invention is therefore directed to a method of treating neurological and

psychiatric disorders, which comprises administering to a subject, preferably a human subject in need thereof, an effective amount of a compound of formula I. Neurological and psychiatric disorders that may benefit from the treatment with the invention compounds include but are not limited to senile dementia, attention deficit disorders, Alzheimer's disease and schizophrenia. In general, the compounds of formula I can be used for treating any disease condition, disorder or dysfunction that may benefit from the activation of the alpha 7 nicotinic acetylcholine receptor, including but not limited to Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, memory or learning deficit, panic disorders, cognitive disorders, depression, sepsis and arthritis.

The dosage of the compounds for use in therapy may vary depending upon, for example, the administration route, the nature and severity of the disease. In general, an acceptable pharmacological effect in humans may be obtained with daily dosages ranging from 0.01 to 200 mg/kg.

In yet a further aspect, the invention refers to a pharmaceutical composition containing one or more compounds of formula I, in association with pharmaceutically acceptable carriers and excipients. The pharmaceutical compositions can be in the form of solid, semi-solid or liquid preparations, preferably in form of solutions, suspensions, powders, granules, tablets, capsules, syrups, suppositories, aerosols or controlled delivery systems. The compositions can be administered by a variety of routes, including oral, transdermal, subcutaneous, intravenous, intramuscular, rectal and intranasal, and are preferably formulated in unit dosage form, each dosage containing from about 1 to about 1000 mg, preferably from 1 to 600 mg of the active ingredient. The compounds of the invention can be in the form of free bases or as acid addition salts, preferably salts with pharmaceutically acceptable acids. The invention also includes separated isomers and diastereomers of

compounds I, or mixtures thereof (e.g. racemic mixtures). The principles and methods for the preparation of pharmaceutical compositions are described for example in Remington's Pharmaceutical Science, Mack Publishing Company, Easton (PA).

Experimental Procedures - Synthesis of compounds

General

Unless otherwise specified all nuclear magnetic resonance spectra were recorded using a Varian Mercury Plus 400 MHz spectrometer equipped with a PFG ATB Broadband probe.

HPLC-MS analyses were performed with a Waters 2795 separation module equipped with a Waters Micromass ZQ (ES ionisation) and Waters PDA 2996, using a Waters XTerra MS C18 3.5μm 2.1x50mm column.

Preparative HLPC was run using a Waters 2767 system with a binary Gradient Module Waters 2525 pump and coupled to a Waters Micromass ZQ (ES) or Waters 2487 DAD, using a Supelco Discovery HS C18 5.0 μm 10 x 21.2 mm column.

Gradients were run using 0.1% formic acid/water and 0.1% formic acid/acetonitrile with gradient 5/95 to 95/5 in the run time indicated.

All column chromatography was performed following the method of Still, C.; J. Org Chem 43, 2923 (1978). All TLC analyses were performed on silica gel (Merck 60 F254) and spots revealed by UV visualisation at 254 nm and KMnO4 or ninhydrin stain.

When specified for array synthesis, heating was performed on a Buchi Syncore® system.

All microwave reactions were performed in a CEM Discover oven.

Abbreviations used throughout the Experimental Procedures

CDI	*N,N'*-carbonyldiimidazole
DCM	Dichloromethane
DCE	1,2-dichloroethane
DMEA	*N,N*-dimethylethylamine
DMF	*N,N*-dimethylformamide
DMSO, dmso	Dimethylsulphoxide
DAM	*N,N*-dimethylacetamide
SCX	strong cation exchanger
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
LC-MS, LCMS	Liquid chromatography - mass spectrometry
HPLC	High performance liquid chromatography

General procedure for aminoalkylamine synthesis - phthalimide route

N-(3-Bromopropyl)phthalimide (1 eq) was added to a suspension of amine (1 eq), sodium iodide (0.5 eq) and potassium carbonate (1.1 eq) in 2-butanone (*ca.* 20 volumes with respect to phthalimide weight). The resulting suspension was stirred for 18h at 85°C, then the reaction was filtered and the solvent removed by vacuum distillation; the resulting oil was washed with water and recovered with DCM. The solvent was removed under reduced pressure to yield the amino-phthalimide products pure enough to be used in the next step without further purification.

The phthalimides thus obtained (1 eq) were dissolved in EtOH (*ca.* 7-10 volumes with respect to phthalimide weight) and hydrazine monohydrate (2 eq) was added dropwise. The mixture was heated at 80°C for 4 h, after which the reaction was acidified with 37% HCl and the solid which precipitated was removed by filtration. The solution was concentrated under vacuum and taken up with 1N HCl. Any residual 2,3-dihydro-phthalazine-1,4-

dione was removed by filtration. The aqueous solution was evaporated under vacuum to recover pure product.

In case of acid sensitive derivatives the reaction mixture was filtered and washed with EtOH, concentrated under vacuum and taken up with toluene and DCM to remove excess 2,3-dihydro-phthalazine-1,4-dione. Solvent removal under reduced pressure afforded the pure product.

1-[4-(3-Amino-propyl)-piperazin-1-yl]-ethanone

2-[3-(4-Acetyl-piperazin-1-yl)-propyl]-isoindole-1,3-dione (5.0 g, 16 mmol) was dissolved in EtOH (50 mL) and hydrazine monohydrate (1.5 mL, 32 mmol) was added. The mixture was heated at 80°C for 1 hour.

1-(4-Bromo-phenyl)-3-(3-piperidin-1-yl-propyl)-urea

a) 2-(3-Piperidin-1-yl-propyl)-isoindole-1,3-dione

N-(3-Bromopropyl)phthalimide (5.36 g, 20 mmol) was added to a suspension of piperidine (1.98 mL, 20 mmol), sodium iodide (3.9 g, 26 mmol) and potassium carbonate (4.15 g, 21 mmol) in 2-butanone (100 mL). The resulting suspension was stirred for 24 hour at 90°C.

The reaction was filtered to remove inorganic salts and the solvent removed by vacuum distillation; the resulting oil was washed with water and recovered with DCM. The solvent was removed under reduced pressure to afford 4.39 g of desired product as a white solid (yield: 81%).

C16H20N2O2 Mass (calculated) [272.35],; found $[M+H^+]$=273

^{1}H-NMR (400 MHz, CDCl3) 1.25-1.47(6H, m), 1.76-1.92 (2H, m), 2.14-2.42 (6H, m), 3.63-3.68 (2H, m), 7.63-7.73 (2H, m), 7.76-7.86 (2H, m).

b) 3-Piperidin-1-yl-propylamine hydrochloride

2-(3-Piperidin-1-yl-propyl)-isoindole-1,3-dione (7.5 g, 18.34 mmol) was dissolved in EtOH (45 mL) and hydrazine monohydrate (1.78 mL, 34.5 mmol) was added. The mixture was heated at 80°C for 1 hour. The reaction was then cooled and acidified with 5 mL of 37% HCl and

2,3-dihydro-phthalazine-1,4-dione was removed by filtration. The solution was concentrated under vacuum, 10 mL of 1N HCl were added and the mixture was filtered again to remove the residual 2,3-dihydro-phthalazine-1,4-dione. The aqueous solution was evaporated under vacuum and 3.0 g (yield 48%) of pure product were recovered.

C8H18N2 Mass (calculated) [142.25]; (found) $[M+H^+]=143$

NMR (400 MHz, dmso-d6): 1.25-1.45 (2 H, m), 1.57-1.92 (4 H, m), 1.93-2.17 (2H, m), 4.05-5.37 (4H, m).

General procedure for urea synthesis

To a cooled solution of amine (1 eq) in dichloromethane an equimolar amount of an aryl or heteroaryl isocyanate was added. In the case of the amine being in the form of a hydrochloride or *bis*-hydrochloride salt, equimolar amounts of TEA were added to free-base the amine.

The mixture was left stirring at 0°C for 1-4 hours. The *p*-bromophenyl ureas generally precipitated out of solution as white solids, were recovered by filtration and if necessary purified further by washing with Et_2O or by flash chromatography. The *m*-bromophenylureas were isolated by solvent removal under reduced pressure and purified by crystallisation from an mixture of AcOEt: Et_2O.

Alternatively, to a solution of aniline in DCM (0.32 mmol/mL) cooled at 0°C, triphosgene (1 eq) was added under N_2 flux; a white precipitate formed and NEt_3 (1.1 eq) was added and the mixture generally became a yellow solution. After 30 minutes the amine was added and the reaction was left stirring at 0°C for 2 hours, when LC-MS generally showed complete conversion. If a precipitate was present it was filtered affording the urea product, otherwise the solution was washed with NaOH 10% solution and the organic phase concentrated under reduced pressure. The crude was then purified by crystallization from Et_2O.

1-(4-Bromo-phenyl)-3-(3-piperidin-1-yl-propyl)-urea

To a cooled solution of 3-piperidin-1-yl-propylamine dihydrochloride (0.96 g, 4 mmol) in dichloromethane (20 mL) TEA was added (1.11 mL, 8 mmol).

p-Bromophenylisocyanate (0.78 g, 4 mmol) was then added and the mixture was stirred at 0°C until a white solid precipitated out of solution after 2 hours. The white solid was filtered off and washed with Et_2O to give 1.4 g of pure title compound.

C15H22BrN3OMass (calculated) [340.27]; (found) [$M+H^+$]=340-342

Lc Rt (10 min method)= 2.69, 92%

NMR (400 MHz, dmso-d6): 1.26-1.63 (8H, m); 2.14-2.36 (4H, m); 2.45-2.51 (2H, m, under DMSO); 3.00-3.13 (2H, m); 6.11-6.26 (1H, m), 7.33 (4H, s), 8.52-8.66(1H,s).

1-(2-Chloro-4-Bromo-phenyl)-3-(4-piperidin-1-yl-butyl)-urea

Prepared via the general procedure for urea synthesis (via isocyanate)

Yield: 76%

NMR (400 MHz, dmso-d6): 1.27-1.52 (10H, m), 2.14-2.37 (6H, m), 3.03-3.4 (2H, m), 7.04 (1H, t), 7.40 (1H, dd), 7.60 (1H, d), 8.50 (1H, s), 8.12 (1H, d).

1-(2-Fluoro-4-Bromo-phenyl)-3-(4-piperidin-1-yl-butyl)-urea

Prepared via the general procedure for urea synthesis (via isocyanate)

Yield: 88%

NMR (400 MHz, dmso-d6): 1.22-1.50 (10H, m), 2.12-2.37 (6H, m), 3.00-3.13(2H, m), 6.62 (1H, t), 7.25 (1H, d), 7.47 (1H, dd), 8.10 (1H, t), 8.33 (1H, s).

1-(2,6 difluoro-4-Bromo-phenyl)-3-(4-piperidin-1-yl-butyl)-urea

Prepared via the general procedure for urea synthesis (via isocyanate)

Yield: 67%

C16H22BrF2N3O Mass (calculated) 390; (found) [M+H$^+$]= 390-392

Lc Rt= 2.04 (100%), 10'

NMR (400 MHz, dmso-d6): 1.31-1.51 (10H, m), 2.17-2.37 (6H, m), 2.98-3.09 (2H, m), 6.36 (1H, t), 7.44 (1H, d), 7.82 (1H, s).

1-(2-Fluoro-4-Bromo-phenyl)-3-(3-piperidin-1-yl-propyl)-urea

Prepared via the general procedure for urea synthesis (via isocyanate)

Yield: 86%

C15H21BrFN3O Mass (calculated) 358; (found) [M+H$^+$]= 358-360

Lc Rt= 2.18 (100%), 10'

NMR (400 MHz, dmso-d6): 1.31-1.40 (2H, m), 1.41-1.49 (4H, m), 1.50-1.57 (2H, m), 2.17-2.35 (6H, m), 3.07 (2H, q, J=5.8Hz), 6.59 (1H, t), 7.25 (1H, dt), 7.46 (1H, dd), 8.08 (1H, t), 8.34 (1H, s).

1-(2-Chloro-4-Bromo-phenyl)-3-(3-piperidin-1-yl-propyl)-urea

Prepared via the general procedure for urea synthesis (via isocyanate)

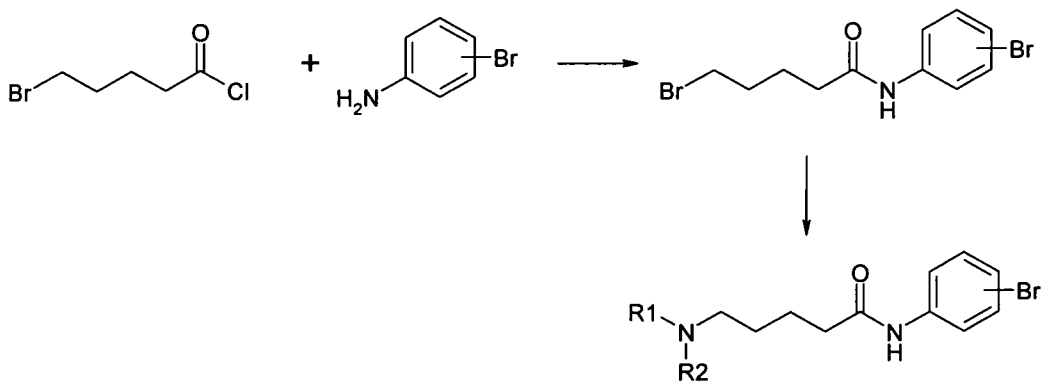
Yield: 78%

C15H21BrClN3O Mass (calculated) 374; (found) [M+H$^+$]= 374-376

Lc Rt= 2.46 (98%), 10'

NMR (400 MHz, dmso-d6): 1.30-1.39 (2H, m),1.42-1.49 (4H, m), 1.50-1.60 (2H, m), 2.16-2.37 (6H, m), 3.08 (2H, q, J=4.7), 7.01(1H, t), 7.40 (1H, dd), 7.62 (1H, d), 8.48 (1H, s), 8.11 (1H, d).

General procedure for amide synthesis from ω-haloalkanoyl chlorides



One-pot with low molar excess of amine R1R2NH

In a round-bottom 2-neck flask, triethylamine (1 eq) was added to a solution of aryl or heteroaryl amine (1 eq) in a volume of DCE such as to obtain a 1.2 M solution of amine; 5-bromovaleryl chloride (0.95 eq) was then added dropwise as a solution in 1.2 M solution in DCE and the reaction was stirred at room temperature for 1 hour 30 minutes. A 1.8 M solution of amine R1R2NH (3 eq) and triethylamine (1 eq) in DCE were then added and the reaction mixture strirred at 55°C for a time between 4 and 16 h, until LCMS monitoring showed reaction completion. After this period the reaction mixture was partitioned between water and DCM; the organic layer was washed with saturated NaCl and dried over Na_2SO_4. The crude amides obtained after solvent evaporation at reduced pressure were purified by trituration from Et_2O or by flash chromatography.

One-pot with high molar excess of amine R1R2NH

Alternatively, a solution of aniline (1 eq) and triethylamine (1 eq) in dichloromethane (0.2 mmol/mL) was cooled at 0°C under nitrogen atmosphere. 5-Bromo-pentanoyl chloride (1 eq) in dichloromethane (0.3 mmol/mL) was slowly added. The mixture was stirred at room temperature for 1.5 hours, after which the amine R1R2NH (5 eq) and triethylamine (1 eq) were added at once and the reaction was stirred at room temperature for further 40 hours. The organic solution was washed with brine, dried and the solvent removed. The product were triturated by hexane/diethyl ether 1/1 or purified by flash chromatography.

One-pot, high molar excess of amine R1R2NH - array method

To a solution of aniline (1 eq for each molar equivalent of amine R1R2NH used) and triethylamine (1 eq for each molar equivalent of amine R1R2NH used) in dichloromethane (0.3 mmol/mL for each amine R1R2NH used) 5-bromo-pentanoyl chloride (1 eq for each molar equivalent of amine

R1R2NH used) was slowly added and the mixture stirred at room temperature for 2 hours. The solution was then split in as many aliquotes as many amines used in the array and each portion added to a vial containing an amine R1R2NH (5 eq) and triethylamine (1 eq). The reactions were then shaken at room temperature for 40 hours. The organic solutions were washed with brine, collected, dried (Na_2SO_4) and the solvent evaporated. The products were purified by preparative HPLC.

Two steps, using an equimolar amount of amine R1R2NH

5-Bromopentanoic acid-(4-bromophenyl)-amide

4-Bromo-aniline (6 g, 0.035 mol) and 0.035 mol of NEt_3 (4.87 mL) were dissolved in 120 mL of dichloromethane and cooled at 0°C.

To this solution, 0.038 mol of 5-bromovaleryl chloride (5.4 mL) were slowly added and the resulting mixture was stirred for 1 h at 0°C.

When all the starting material was consumed (as monitored by LCMS) the solution was washed with 50 mL of Na_2CO_3 0.4 M and the organic layer was recovered by extraction and drying over Na_2SO_4. The solvent was removed under reduced pressure giving 10 g of the title compound as a white solid (yield 86%).

C11H13Br2NO Mass (calculated) [335]; (found) [$M+H^+$]=335

Lc Rt = 2.64, 100% (5 min method)

NMR (400 MHz, CDCl3) 1.70-2.00 (4H, m), 2.35-2.45 (2H, m), 3.38-3.48 (2H, m), 7.30-7.50 (4H, m).

1 eq of the thus prepared alkylating agent was dissolved in butanone (5-10 mL/mmol substrate) and to this 1 eq of NaI and 1.1 eq of the amine R1R2NH were added. The mixture was stirred at 70°C or 24 hours. The mixture was cooled. When the products precipitated as salts, they were taken into water, free-based by addition of NaOH 10% to pH = 10 and extracted with dichloromethane. In the case where no product precipitation occurred, the

solvent was removed under reduced pressure, the crude was taken into dichloromethane and extracted after adjusting the pH to 10 with NaOH 10%. If necessary, the products were further purified by flash chromatography

5-Azepan-1-yl-pentanoic acid (4-bromo-3-fluoro-phenyl)-amide

Following the general procedure for amide synthesis, 3-fluoro-4-bromoaniline (66 mg, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol) were dissolved in DCE (0.5 mL) and 5-bromovaleryl chloride (66 mg, 0.33 mmol) in DCE (0.5 mL) was added dropwise. After 1.5 hours, azepane (118 mg, 0.105 mmol) and triethylamine (35 mg, 0.35 mmol) in DCE (0.5 mL) were added and the reaction mixture heated at 55°C for 4 hours. Work-up followed by prep HPLC afforded the title compound (87 mg, 77%) as the formate salt.

C17H24BrFN2O Mass (calculated) [371.30]; (found) $[M+H^+]$=371.33/373.35.

LC Rt=2.23, 100% (10 min method)

NMR (400 MHz, $CDCl_3$): 1.7 (4H, s); 1.88-1.84 (8H, m); 2.44 (2H, mt); 2.98 (2H, m); 3.15 (4H, bs); 7.27 (1H, m); 7.4 (1H, dd, J=8.8,7.6); 7.80 (1H, dd, J=10.8, 2.4); 8.63 (1H, **H**COOH,s); 9.8 (1H, bs).

5-Azepan-1-yl-pentanoic acid (4-bromo-3-trifluoromethyl-phenyl)-amide

Following the general procedure, 4-bromo-3-trifluoromethyl-aniline (82 mg, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol) were dissolved in DCE (0.5 mL) and 5-bromovaleryl chloride (66 mg, 0.33 mmol) in DCE (0.5 mL) was added dropwise. After 1h 30 min, azepane (118 mg, 0.105 mmol) and triethylamine (35 mg, 0.35 mmol) in DCE (0.5 mL) were added, and the reaction mixture heated at 55°C for 4 hours. Work-up followed by prep HPLC afforded the title compound (29 mg, 20%) as its formate salt.

C18H24BrF3N2O Mass (calculated) [421.30]; (found) $[M+H^+]$=421.29/423.29.

LC Rt=2.52, 98% (10 min method)

5-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pentanoic acid (3-bromo-phenyl)-amide

Prepared according to the general procedure for amide synthesis and purified by preparative HPLC to afford 106 mg (47%) of the title compound as the formate salt.

$C_{19}H_{24}N_3OBr$. HCO_2H Mass (calculated) [390.33-46.03]; found $[M+H^+]$=390.23,

Lc Rt=1.73, 100%

NMR (400 MHz, CD_3OD): 1.73-1.89 (4H, m); 2.46-2.50 (2H, m); 2.91 (3H, s); 3.19-3.27 (4H, m); 3.49-3.55 (2H, m); 7.19-7.24 (2H, m), 7.31 (1H, br dd, J=5.2 Hz, 6.8 Hz); 7.38 (1H, ddd, J=6.8 Hz, 1.6 Hz, 2.0 Hz); 7.80 (1H, ddd, J=8.0 Hz, 7.6 Hz, 1.6 Hz); 7.91 (1H, s); 8.46 (1H, s); 8.51 (1H, br d, J=4.8 Hz).

5-(Methyl-pentyl-amino)-pentanoic acid (4-bromo-phenyl)-amide

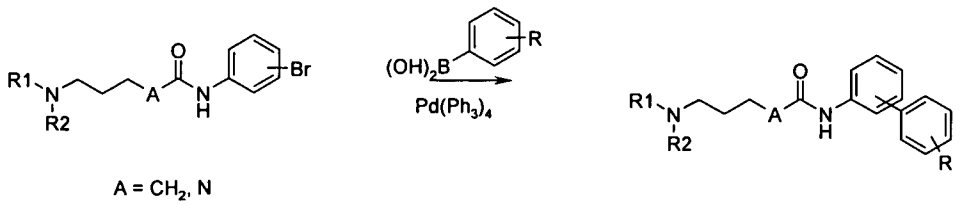
Prepared according to the general procedure for amide synthesis and purified by preparative HPLC to afford 123 mg (60%) of the title compound as the formate salt.

$C_{17}H_{27}N_2Obr$ HCO_2H Mass (calculated) [355.32-46.03]; found $[M+H^+]$=355.27,

Lc Rt=1.98, 100%

NMR (400 MHz, CD_3OD): 0.95 (3H, t, J=6.8 Hz); 1.32-1.44 (4H, m); 1.67-1.81 (6H, m); 2.43-2.49 (2H, m); 2.81 (3H, s); 3.04-3.13 (4H, m); 7.42-7.45 (2H, m), 7.49-7.52 (2H, m),.8.51 (1H, s).

General procedure for cross-coupling reaction with boronic acids



Thermal conditions on ureas (A = N)

To a degassed solution of aryl or heteroaryl bromide prepared following the general procedure for urea synthesis described above (1 eq), the appropriate boronic acid (1.3 eq) was added dissolved in 40 volumes (*i.e.* 1 mL/g substrate) of acetonitrile/0.4N aqueous Na_2CO_3 (1/1), $Pd[(PPh_3)]_4$ (10% mol). The solution was refluxed overnight under nitrogen either in a round-bottom flask or in a glass test tube in a Buchi SynCore® apparatus.

The acetonitrile phase was separated and the desired products purified over a SCX or silica column. Fractions containing the desired product were combined and dried under reduced pressure.

Microwave conditions on ureas (A = N)

To a degassed solution of bromide prepared following the general procedure for urea synthesis (1 eq), the appropriate boronic acid (1 eq) and Na_2CO_3 (3 eq) in 20 volumes (*i.e.* 1 mL/g substrate) of acetonitrile/water (1/1), $Pd[(PPh_3)]_4$ (10% mol) were added.

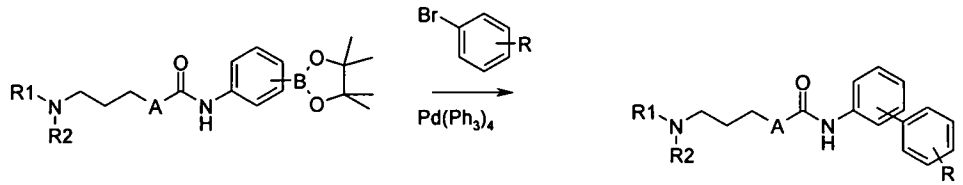
The solution was irradiated in a microwave oven using the following parameters: power: 200 watt; ramp time: 1 min; hold time: 20:00 min; temperature: 90°C; pressure: 200 psi. The acetonitrile phase was separated, the solvent was removed under reduced pressure and the crude material purified using SCX column (eluting with a gradient of DCM/MeOH, MeOH, NH_3/MeOH). The fractions containing product were combined and dried under reduced pressure.

Microwave conditions on amides (A = CH_2)

To a degassed mixture of 5-alkyl-pentanoic acid aryl-amide (0.1 g, 1 eq) aryl boronic acid (1.1 eq) in acetonitrile/sodium carbonate 0.4M solution 1/1 (4 mL), a catalytic amount of $Pd[(PPh_3)]_4$ (5 mmol%) was added. The reaction mixture was heated at 90°C for 20 minutes under microwave irradiation (150 Watt, pressure max) and then again other 20 minutes. The

organic layer was separated and concentrated, and further purified by SCX column and/or by preparative HPLC. The solvent was removed under reduced pressure to afford the corresponding product.

General procedure for cross-coupling reaction with aryl/heteroaryl bromides



A = CH_2, N

To a degassed mixture of ω-aminoalkanoic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (0.16 g, 0.4 mmol,1 eq) (prepared following the general procedures described above) and an aryl/heteroaryl bromide (0.4 mmol, 1 eq) in acetonitrile/sodium carbonate 0.4M solution 1/1 (8 mL) a catalytic amount of $Pd[(PPh_3)]_4$ (5 mmol %) was added. The reaction mixture was stirred at 90°C for 18 hours under N_2 and monitored for formation of the product by LCMS. The organic layer was separated and filtered on a Celite® pad and the solvent removed under reduced pressure. The crude was purified by preparative HPLC or flash chromatography.

General method for the synthesis of 1-(4-aryl-phenyl)-3-(4-aminoalkyl-butyl)-ureas via reductive amination and cross-coupling

a) 1-(4-Bromo-phenyl)-3-(4,4-diethoxy-butyl)-urea

A solution of 4-aminobutyraldehyde diethyl acetal (0.88 mL, 5 mmol) in dry DCM (10 mL) was added over 30' to a solution of 4-bromophenylisocyanate (1 g, 5 mmol, 1 eq) in dry DCM (25 mL) cooled to 0°C (ice/water bath) under N_2; after 1 hour a thick white precipitate of the urea formed. The solid was recovered by filtration and washing with Et_2O (3 X 20 mL) to yield 1-(4-bromo-phenyl)-3-(4,4-diethoxy-butyl)-urea in essentially quantitative yield (1.78 g).

C15H23BrN2O3 Mass (calculated) [359.27]; (found) [M+Na+]=381.11/383.25

LC Rt=3.54, 100% (10 min method)

NMR (400 MHz, dmso-d6): 1.08 (6H, t, *J*=5.85 Hz); 1.42 (2H, m); 1.50 (2H, m); 3.06 (2H, m); 3.41 (2H, q); 3.54 (2H, q); 4.45 (1H, t); 6.19 (1H, t); 7.37 (4H, s); 8.54 (1H, s).

b) 1-(4-Bromo-phenyl)-3-(4-aminoalkyl-butyl)-ureas

1-(4-Bromo-phenyl)-3-(4,4-diethoxy-butyl)-urea (0.72 g, 2 mmol, 1 eq) was dissolved in dry DCM (10 mL) at room temperature and Montomorrilonite K-5 (0.145 g) was added. The reaction was stirred at room temperature for 2 hours, when LC-MS showed complete conversion into the aldehyde.

The reaction mixture was filtered to remove all solids and the amine (6 mmol, 3 eq) was added, followed by $NaBH(OAc)_3$ (4 mmol, 2 eq). The reaction was stirred at room temperature for 24 hrs.

Upon reaction completion (as monitored by LC-MS), the solvent was removed under reduced pressure and the resulting residue was purified by SCX column, eluting with DCM:MeOH 1:1 and then 2M NH_3 in MeOH.

c) 1-(4-aryl-phenyl)-3-(4-aminoalkyl-butyl)-ureas

To a degassed mixture of 1-(4-bromo-phenyl)-3-(4-aminoalkyl-butyl)-ureas (0.11 g, 1 eq) and a substituted benzeneboronic acid or pinacolboronate ester (1.5 eq) in acetonitrile/sodium carbonate 0.4M solution 1/1 (3 mL) a catalytic amount of $Pd[(PPh_3)]_4$ (5 mmol %) was added. The reaction mixture was heated at 90°C for 10 minutes under microwave irradiation (150 Watt) and then again other 10 minutes, if needed. The organic layer was separated and purified by SCX column or by prep HPLC (standard acidic conditions).

1-Methyl-4-piperidin-1-yl-butylamine

a) N-Boc-5-methyl-2-pyrrolidinone

A solution of di-tert-butyl carbonate (12.1 g; 55.5 mmol) in acetonitrile

(20 mL) was added dropwise to a solution of 5-methyl-2-pyrrolidinone (5.0 g; 50 mmol) and 4-dimethylamino-pyridine (0.31 g; 5 mol%) in acetonitrile (50 mL) at RT. The mixture was stirred for 7 hrs. The solvent evaporated and the obtained crude dissolved in ethyl acetate and washed with $NaHCO_3$ sat. solution. The organic layer was collected and dried (Na_2SO_4) and evaporation of the solvent gave the clean product.

9.41 g; 90%

$C_{10}H_{17}NO_3$ calculated 199; found 126/144

Lc Rt (5 min)= 1.73, 99%

NMR (400 MHz, dmso-d6): 1.22 (3H, d, J= 6.4 Hz); 1.43 (9H, s); 1.50-1.57 (1H, m); 2.04-2.14 (1H, m); 2.26 (1H, ddd, J= 3.2 Hz, 9.2 Hz, 17.2 Hz); 2.56 (1H, ddd, J= 9.2 Hz, 10.42 Hz, 17.2 Hz); 4.07-4.15 (1H, m).

b) (1-Methyl-4-oxo-4-piperidin-1-yl-butyl)-carbamic acid tert-butyl ester

N-Boc-5-methyl-2-pyrrolidinone (0.7 g; 3.52 mmol) and piperidine (1.55 g; 18.2 mmol, 1.8 mL) were mixed and heated at 150°C by MW irradiation for 40 minutes. The mixture was diluted with dichloromethane and the solution washed trice with HCl 1.0 M solution. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by flash chromatography (cyclohexane: ethyl acetate).

0.522 g; 73%

$C_{15}H_{28}N_2O_3$ calculated 284; found 285

Lc Rt (3 min)= 1.31, 99%

NMR (400 MHz, dmso-d6): 0.99 (3H, d, J= 6.8 Hz); 1.35 (9H, s); 1.36-1.40 (2H, m); 1.43-1.48 (2H, m); 1.50-1.58 (4H, m); 2.15-2.30 (2H, m); 3.30-3.46 (5H, m); 6.63 (1H, d, J= 8.8 Hz).

c) 4-Amino-1-piperidin-1-yl-pentan-1-one

(1-Methyl-4-oxo-4-piperidin-1-yl-butyl)-carbamic acid tert-butyl ester

(3.50 g; 12.3 mmol) was dissolved in CH_2Cl_2 (40 mL) at 0°C and HCl 37% solution (6 mL) were slowly added. After 15 minutes the ice bath was removed and the mixture stirred at RT for 4 hrs. NaOH 2N solution was slowly added to reach pH>8 and the organic layer collected, dried and the solvent evaporated.

2.0 g; 88%

$C_{10}H_{20}N_2O$ calculated 184; found 185

Lc Rt (5 min)= 0.35, 100%

NMR (400 MHz, dmso-d6): 0.95 (3H, d, J= 6.4 Hz); 1.32-1.57 (8H, m); 2.20-2.36 (2H, m); 2.68-2.76 (1H, m); 3.21 (4H, br m).

d) 1-Methyl-4-piperidin-1-yl-butylamine

4-Amino-1-piperidin-1-yl-pentan-1-one (2.0 g, 10.9 mmol) was dissolved in THF (50 mL) at 0°C and a solution of lithium aluminum hydride 1.0 M in THF (22 mL, 22 mmol) was slowly added. The mixture was stirred at 0°C for 30 min, then 4 hrs at RT. Water (0.8 mL) was added to the solution and the solvent evaporated. The residue was treated with ether and NaOH 15% solution. The organic layer was collected and dried. Evaporation of the solvent gave a product clean enough to be used without further purification.

1,21 g; 65%

$C_{10}H_{22}N_2$ calculated 170; found 171

Lc Rt (5 min)= 0.35, 100%

NMR (400 MHz, dmso-d6): 0.89 (3H, d, J= 6.4 Hz); 1.10-1.17 (2H, m); 1.30-1.37 (4H, m); 1.39-1.45 (6H, m); 2.10-2.14 (2H, m); 2.23 (4H, br m); 2.65-2.69 (1H, m).

2,2-Difluoro-4-piperidin-1-yl-butylamine

a) 3,3-Difluoro-succinamic acid

To a solution of 2,2-Difluoro-succinic acid (2.0 g, 13 mmol) in 20 mL of iPrOAc, Trifluoroacetic anhydride (2.2 mL, 15.6 mmol) was added in one

portion.

The solution was stirred under N_2 atmosphere at 50°C for 1 hour. The formation of the 2,2-Difluoro-succinic anhydride was confirmed by LCMS after quenching of a little part with methanol [$C_5H_6F_2O_4$ calculated 168; found M- 167; Lc Rt (5 min)= 1.05].

The solution was then cooled at room temperature and added dropwise to NH_3 in methanol (7N, 15 mL, 105 mmol) under N_2 atmosphere maintaining the temperature below 20°C.

The solvent was then evaporated and the residue dissolved in a small amount of water basified with Na_2CO_3 (pH 8-9). The aqueous phase was washed with EtOAc, acidified with HCl 6N to pH 1 and the product extracted several time with Et_2O and $CHCl_3$.

The organic layers were collected and dried. Evaporation of the solvent gave 0.877 g of crude product used without further purification.

Yield: 45%

$C_4H_5F_2NO_3$ calculated 153; found M- 152

Lc Rt (5 min)= 0.32

NMR (400 MHz, dmso-d6): 3.16 (2H, t, J = 15.4); 7.86 (1H, s); 8.09 (1H, s); 12.90 (1H, s).

b) 2,2-Difluoro-4-oxo-4-piperidin-1-yl-butyramide

3,3-Difluoro-succinamic acid (0.18 g, 1.2 mmol) was dissolved in 10 mL of acetonitrile and the mixture was cooled at 0°C under N_2 atmosphere. N,N-dicyclohexylcarbodiimide (0.266 g, 1.3 mmol) was added and the mixture was stirred again at 0°C for further 10 minutes. 1-Hydroxybenzotriazole hydrate (0.308 g, *ca.* 2 mmol) was then added and the ice bath removed.

After 20 minutes at RT Piperidine (0.115 mL, 1.2 mmol) was added and the reaction was stirred at RT overnight.

The solvent was evaporated and the residue dissolved in Dichloromethane. The organic phase was washed with HCl 0.16 N and then with water.

The organic solvent was then evaporated and the residue purified by SiO_2 column (eluant: EtOAc:DCM 9:1).

0.113 g of pure product were obtained.

Yield: 43%

$C_9H_{14}F_2N_2O_2$ calculated 220; found M+ 221

Lc Rt (5 min)= 1.16

NMR (400 MHz, dmso-d6): 1.35-1.57 (6H, m); 3.25-3.36 (6H, m); 7.71 (1H, s); 7.92 (1H, s).

c) 2,2-Difluoro-4-piperidin-1-yl-butylamine

To solution of 2,2-Difluoro-4-oxo-4-piperidin-1-yl-butyramide (0.323 g, 1.5 mmol) in 10 mL of dry THF was slowly added lithium aluminum hydride solution 1.0 M in THF (5.88 mL, 5.9 mmol) under Nitrogen atmosphere at 0°C. The mixture was stirred for 3 days at RT. The excess of hydride was then quenched with water and the solvent removed. The residue was then diluted with methanol and filtered on Celite®. The solution was purified by SCX column and the obtained oil was used without further purification.

0.169 g of product were obtained.

Yield: 59%

$C_9H_{18}F_2N_2$ calculated 192; found M+ 193

Lc Rt (5 min)= 0.19

^{19}F-HNMR (400 MHz, dmso-d6): -106.16 (quint.)

2,2-Dimethyl-4-piperidin-1-yl-butylamine

a) 2,2-Dimethyl-4-oxo-4-piperidin-1-yl-butyric acid

To solution of 2,2-dimethylsuccinic anhydride (1.0 g, 7.8 mmol) and

triethylamine (0.79 g, 078 mmol) in CH_2Cl_2 (40 mL) was slowly added a solution of piperidine (0.66 g, 7.8 mmol) in CH_2Cl_2 (10 mL) at RT. The mixture was stirred for 4 hrs. NaOH 1.0M solution was added and the aqueous layer collected and subsequently acidified to pH 4 using HCl 2.0 M solution. Extraction with $CHCl_3$ and evaporation of the solvent gave a crude product clean enough to be used without further purification.

1.63 g; 98%

$C_{11}H_{19}NO_3$ calculated 213; found M+ 214/M- 212

Lc Rt (5 min)= 1.56

NMR (400 MHz, dmso-d6): 1.10 (6H, s); 1.32-1.37 (2H, m); 1.40-1.44 (2H, m); 1.50-1.55 (2H, m); 2.50 (2H, s); 3.31-3.35 (4H, m); 11.7 (1H, br s).

b) 2,2-Dimethyl-4-oxo-4-piperidin-1-yl-butyramide

To a solution of 2,2-dimethyl-4-oxo-4-piperidin-1-yl-butyric acid (2.0 g, 9.4 mmol) in CH_2Cl_2 (40 mL) was slowly added oxalyl chloride (2.98 g, 23.5 mmol) under nitrogen atmosphere at RT. The mixture was stirred for 3 hrs. After evaporation of the solvent and the excess of oxalyl chloride, the obtained crude product was dissolved in CH_2Cl_2 (20 mL) and added to a solution of ammonia 0.5 M in dioxane (200 mL). After addition of $NaHCO_3$ sat. solution, the organic layer was extracted twice, collected and dried. Evaporation of the solvent gave a crude product purified by flash chromatography (CH_2Cl_2/CH_3OH=96/4).

0.93 g; 46%

$C_{11}H_{20}N_2O_2$ calculated 212; found M+ 213

Lc Rt (5 min)= 1.32

NMR (400 MHz, CD_3OD): 1.27 (6H, s); 1.48-1.54 (2H, m); 1.56-1.61 (2H, m); 1.63-1.69 (2H, m); 2.64 (2H, s); 3.45-3.49 (4H, m).

c) 2,2-Dimethyl-4-piperidin-1-yl-butylamine

To solution of 2,2-dimethyl-4-oxo-4-piperidin-1-yl-butyramide (2.0 g,

9.43 mmol) in THF was slowly added lithium aluminum hydride solution 1.0 M in THF (28.3 mL) at 0°C under nitrogen atmosphere. The mixture was stirred for 6 hrs. Water (1.0 mL) was added to the solution and the solvent evaporated. The residue was treated with ether and NaOH 1.0 M solution, the organic layers collected and dried. Evaporation of the solvent gave 1.4 g of crude product used without further purification.

1.40 g; 80%

$C_{11}H_{24}N_2$ calculated 185; found M+ 186

Lc Rt (10 min)= 0.21

NMR (400 MHz, dmso-d6): 0.75 (6H, s); 1.26-1.29 (2H, m); 1.32-1.36 (2H, m); 1.41-1.47 (4H, m); 2.13-2.17 (2H, m); 2.25 (4H, br m); 2.26 (2H, br s).

4-Piperidin-1-yl-pentylamine

a) 2-(4-Bromo-pentyl)-isoindole-1,3-dione

1,4-Dibromo-pentane (2.9 g, 15,7 mmol) was added to a solution of potassium phthalimide in 2-butanone at RT and the mixture stirred at RT 24 hrs, then 10 hrs at 50°C. After cooling the solvent was evaporated and the crude purified by flash chromatography (cyclohexane/ethyl acetate).

4.0 g; 86%

NMR (400 MHz, Acetone): 1.68 (3H, d, J= 6.8 Hz); 1.80-1.93 (4H, m); 3.69 (2H, m); 4.26-4.34 (1H, tq, J= 6.8 Hz, 4.8 Hz); 7.85 (4H, br m).

b) 2-(4-Piperidin-1-yl-pentyl)-isoindole-1,3-dione

A mixture of 2-(4-bromo-pentyl)-isoindole-1,3-dione (0.3 g, 1 mmol), piperidine (0.1 mL, 1 mmol) and potassium carbonate (0.14 g, 1 mmol) in DMF (3 mL) were mixed in a pressure tube at 80°C for 6 hrs. After filtration the solvent was evaporated and the obtained residue purified by flash chromatography (hexane/ethyl acetate).

0.19 g; 62%

NMR (400 MHz, dmso-d6): 0.82 (3H, d, J= 6.4 Hz); 1.30-1.45 (8H, m); 1.53-1.62 (2H, m); 2.20-2.25 (2H, m); 2.35-2.40 (2H, m); 2.52-2.55 (1H, m); 3.54 (2H, m); 7.80-7.86 (4H, br m).

c) 4-Piperidin-1-yl-pentylamine

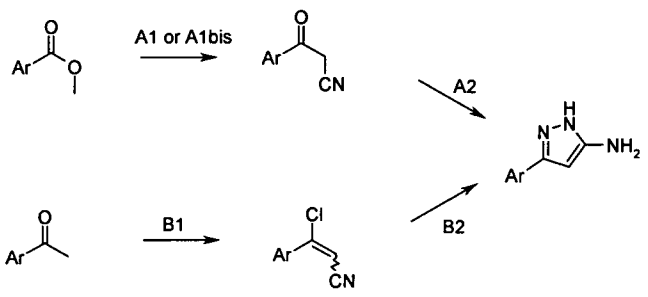
2-(4-Piperidin-1-yl-pentyl)-isoindole-1,3-dione (0.19 g, 0.63 mmol) was dissolved in ethanol. After addition of hydrazine hydrate (0.06 g, 1.27 mmol) the mixture was stirred at reflux for 6 hrs and then left at RT overnight. After filtration of the solid, the organic solution was concentrated in vacuum and the obtained crude product purified by scx-column.

0.05 g; 46%

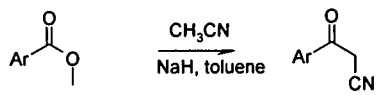
NMR (400 MHz, dmso-d6): 0.84 (3H, d, J= 6.4 Hz); 1.28-1.46 (10H, m); 2.25-2.30 (2H, m); 2.37-2.51 (5H, m).

General 3-amino-5-aryl/heteroaryl pyrazole synthesis

The 3-amino-5-aryl/heteroaryl pirazoles used in the Examples were eithere commercially available os synthesised using the routes shown in the Scheme below:



General procedure for aryl/heteroaryl β-ketonitrile synthesis (A1):



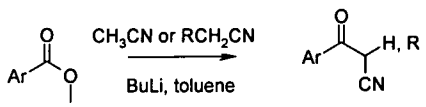
To a solution of an aryl or heteroaryl methyl carboxylate (6.5 mmol) in dry toluene (6 mL) under N_2, NaH (50-60% dispersion in mineral oil, 624 mg, 13 mmol) was carefully added. The mixture was heated at 80°C and then dry CH_3CN was added dropwise(1.6 mL, 30.8 mmol). The reaction was heated for

18 hours and generally the product precipitated from the reaction mixture as Na salt.

The reaction was then allowed to cool down to room temperature and the solid formed was filtered and then dissolved in water. The solution was then acidified with 2N HCl solution and at pH between 2-6 (depending on the ring substitution on the aryl/heteroaryl system) the product precipitated and was filtered off. If no precipitation occurred, the product was extracted with DCM.

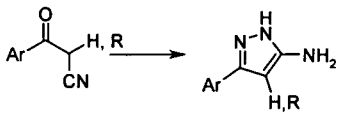
After work-up, the products were generally used in the following step without further purification. The general yield was between 40 and 80%.

General procedure for aryl/heteroaryl β-ketonitrile synthesis (route A1bis):



To a solution of dry alkanenitrile in toluene (1 mmol/mL, 5 eq.) cooled down to -78°C under nitrogen, a solution of *n*-butyllithium in *n*-hexane (1.6 N, 3.5 eq) was added dropwise. The mixture was left stirring at -78°C for 20 minutes and then a solution of the aryl or heteroaryl methyl carboxylate in toluene (0.75 mmol/mL, 1 eq.) was added and the reaction allowed to reach room temperature. Upon reaction completion, after about 20 minutes, the mixture was cooled down to 0°C and HCl 2N was added to pH 2. The organic phase was recovered, dried over Na_2SO_4 and concentrated under reduced pressure, affording the title product which was generally used without further purification.

General procedure for aryl aminopyrazole synthesis (route A2):



To a solution of the β-ketonitrile (7.5 mmoL), in absolute EtOH (15 mL) hydrazine monohydrate (0.44 mL, 9.0 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with water.

The organic phase was concentrated under reduced pressure to give a crude product that was purified by SiO_2 column or by precipitation from Et_2O.

Yields were generally between 65 and 90%.

5-(1H-Indol-5-yl)-2H-pyrazol-3-ylamine

a) 1-Triisopropylsilanyl-1H-indole-5-carboxylic acid methyl ester

To a solution of 1g of methyl indole-5-carboxylate (5.7 mmol) in 10 mL of dry DMF 273 mg of NaH (mineral oil dispersion 50-60%, 5.7 mmol) were added and the mixture cooled to 0°C. Triisopropylchlorosilane (1.06 g, 5.7mmol) were added drop wise and after 1 hour LC-MS showed complete conversion of the starting material to the title product. The mixture was diluted with 30 mL of DCM and washed with saturated Na2CO3. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified with SiO_2 column eluting with *n*-hexane. The title compound was obtained (500 mg, yield 26%).

$C_{19}H_{29}NO_2Si$

Mass (calculated) [331]; (found) $[M+H^+]$=332

LC Rt=3.39, 100% (5 min method)

^{1}H-NMR: (dmso-d_6): 1.06 (d, 18H, J=7.52), 1.75 (quin, 3H, J=7.52), 6.75 (m, 1H), 7.48 (m, 1H), 7.60 (m, 1H), 7.72 (m, 1H), 8.25 (s, 1H).

b) 3-Oxo-3-(1-triisopropylsilanyl-1H-indol-5-yl)-propionitrile

To a solution of 393 µL of anhydrous CH_3CN (7.5 mmol) in 6 mL of dry toluene cooled down to -78°C, 5.35 mLof butyllithium in hexane solution (1.6 N) were added dropwise. The mixture was left stirring at -78°C for

20 minutes and then a solution of 500 mg of 1-triisopropylsilanyl-1H-indole-5-carboxylic acid methyl ester (1.5 mmol) in 2 mL of dry toluene were added and the reaction allowed to reach room temperature. Upon reaction completion after about 20 minutes the mixture was cooled down to 0°C and HCl 2N was added to pH 2. The organic phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure, affording 490 mg of title product which was used in the next step without further purification (yield = 96%).

$C_{20}H_{28}N_2OSi$

Mass (calculated) [340]; (found) $[M+H^+]$=341 $[M-H^+]$=339

LC Rt=3.10, 89% (5 min method)

^{1}H-NMR: (dmso-d_6): 1.06 (18H,d, J=7.52), 1.76 (3H,quin, J=7.52), 4.76 (1H, d), 7.78-7.81 (1H, m), 7.48-7.52 (1H, m), 7.60-7.73 (2H, m), 8.25 (s, 1H).

c) 5-(1H-Indol-5-yl)-2H-pyrazol-3-ylamine

To a solution of 3-Oxo-3-(1-triisopropylsilanyl-1H-indol-5-yl)-propionitrile (490 mg, 1.44 mmol) in 15 mL of absolute EtOH, 720 µL of hydrazine monohydrate (14.4 mmol) were added and the reaction refluxed for 18 hours. LC-MS showed complete conversion to the aminopyrazole and also silyl deprotection. The mixture was concentrated under reduced pressure, and purified with SiO2 column (eluent gradient from 100% DCM to DCM:MeOH 9:1) to afford the title compounds (120mg, yield: 41%).

$C_{11}H_{10}N_4$

Mass (calculated) [198]; (found) $[M+H^+]$=199

LC Rt=0.84, 100% (3 min method)

5-Pyridin-3-yl-2H-pyrazol-3-ylamine

a) 3-Oxo-3-pyridin-3-yl-propionitrile

The product was prepared according to the general procedure for aminopyrazole synthesis (route A1).

^{1}H-NMR (400 MHz, MeOH-d_4): 9.07 (1H, d), 8.81 (2H, dd), 8.26 (1H,

dt), 7.59 (1H, dd), 4.79 (2H, s).

b) 5-Pyridin-3-yl-2H-pyrazol-3-ylamine

The product was prepared according to general procedure for aminopyrazole synthesis (route A2).

The crude product was purified with SiO2 column (5 g) with gradient elution from 100% DCM to DCM-NH3 (2N MeOH solution) 95:5. The title product (371 mg, 68% yield) was obtained.

^{1}H-NMR (400 MHz, MeOH-d_4): 8.82 (1H, d), 8.41 (1H, dd), 7.98 (1H, dt), 7.37 (1H, dd), 5.82 (2H, s)

3-Imidazo[1,2-a]pyridin-6-yl-3-oxo-propionitrile

The product was obtained starting from imidazo[1,2-a]pyridine-6-carboxylic acid methyl ester according to general procedure A1

Yield 39%

C10H7N3O Mass (calculated) [185]; (found) [M+H+]=186 [M-H]=184

LC Rt=0.23, 100% (3 min method)

1H-NMR: (dmso-d6): 4.72 (2H,s), 7.61-7.65 (2H, m), 7.70 (1H, m), 8.07 (1H, s), 9.40 (s, 1H).

5-Imidazo[1,2-a]pyridin-6-yl-1H-pyrazol-3-ylamine

The title compound was synthesized according to general procedure A2 starting 3-imidazo[1,2-a]pyridin-6-yl-3-oxo-propionitrile

Yield: 84%

C10H9N5 Mass (calculated) [199]; (found) [M+1]= 200

LCMS, (5min method, RT=0.21 min,

NMR (1H, 400MHz, MeOH-d_4) 3,34 (s, 2H), 5,90 (br s, 1H), 7,57 (s, 1H), 7,63 (br s, 1H), 7,86 (s, 1H), 8,73 (s, 1H).

5-(3-Fluoro-phenyl)-1H-pyrazol-3-yl-amine

a) 3-(3-Fluoro-phenyl)-3-oxo-proprionitrile

The product was prepared according to a modification of general route

A1. To a solution of methyl-3-fluorobenzoate (3 g, 18 mmol) in dry toluene (25 mL) under N_2, NaH (50-60% dispersion in mineral oil, 1.44 g, 36 mmol) was carefully added.

The mixture was heated at 90°C and then dry CH_3CN was added dropwise (4.45 mL, 85.2 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as its sodium salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered, then redissolved in water, and the solution was acidified with 2N HCl to pH 5-6, upon which precipitation was observed. Filtration of the solid from the aqueous solution afforded 2.12 g of the title compound (72% yield) which was used directly in the following step.

b) 5-(3-Fluoro-phenyl)-1H-pyrazol-3-yl-amine

The product was prepared according to a slight modification of route A2. To a solution of 3-(3-fluoro-phenyl)-3-oxo-propionitrile (1.92 g, 11.77 mmoL) in absolute EtOH (32 mL) hydrazine monohydrate (0.685 mL, 14.12 mmol) was added and the reaction was heated at reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude was treated with ether and filtered to give 1.71 g of title compound were recovered (82% yield).

$C_9H_8FN_3$

Mass (calculated) [177]; (found) $[M+H^+]$ =190

LC Rt = 1.13, 69% (5 min method)

5-Pyridin-4-yl-1H-pyrazol-3-ylamine

3-Oxo-3-pyridin-4-yl-propionitrile

The product was prepared according to a modification of route A1. To a solution of 3 g (22 mmol) of isonicotinic acid methyl ester in dry toluene (30 mL) under N_2, NaH (50-60% dispersion in mineral oil, 1.75 g, 44 mmol) was carefully added.

The mixture was heated at 90°C and then dry CH_3CN was added dropwise (5.39 mL, 103 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as the sodium salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered, then it was dissolved in water and the solution was acidified with 6N HCl solution to pH 5-6 and the product extracted with DCM. The pH of the aqueous phase was adjusted again to 4-5 and another extraction with DCM afforded more product.

The organic phases were combined, dried and evaporated. The product was used directly in the following step. Yield of crude product: 58%.

b) 5-Pyridin-4-yl-1H-pyrazol-3-ylamine

The product was prepared according to a modification of route A2. To a solution of 3-oxo-3-pyridin-4-yl-propionitrile (1.86 g, 12.74 mmoL) in absolute EtOH (35 mL) hydrazine monohydrate (0.74 mL, 15.29 mmol) was added and the reaction was heated at reflux for 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude product obtained was washed with ether to afford the title compound (yield: 39%).

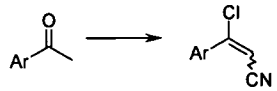
$C_8H_8N_4$

Mass (calculated) [160]; (found) $[M+H^+]$ =161

LC Rt = 0.23, 100% (5 min method)

^{1}H-NMR (400 MHz, dmso-d6): 5.02 (2H, s); 5.85 (1H, s); 7.59 (2H, d, J=6 Hz); 8.50 (2H, d, J=6 Hz); 11.93 (1H, s).

Chlorocynnamonitrile synthesis (route B1)

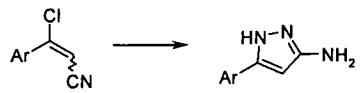


$POCl_3$ (2 eq with respect to the aryl/heteroaryl acetophenone) were added dropwise to 4 molar equivalents of anhydrous DMF cooled down to 0°C, at such

a rate that the temperature did not exceed 10°C. The acetophenone (1 eq) was then added dropwise and the reaction was allowed to reach room temperature.

The reaction was then stirred for further 30' and then 0.4 mmol of hydroxylamine hydrochloride were added. The reaction was then heated up to 50°C, after which heating was removed and additional 4 eq. of hydroxylamine hydrochloride were added portionwise (at such a rate that the temperature never exceeded 120°C). The reaction was then stirred until the temperature of the mixture spontaneously decreased to 25°C. Water (100 mL) were then added and the mixture was extracted with diethyl ether. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used for the next step without further purification.

Aryl aminopyrazole synthesis (route B2)



To a solution of the chlorocynnamonitrile (0.5 mmol/mL, 1 eq) in absolute EtOH 2 eq of hydrazine monohydrate were added and the reaction was heated at reflux for 4 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated with Et_2O, allowing to recover the title compound which was generally used without further purification.

5-(3-Bromo-phenyl)-2H-pyrazol-3-ylamine

a) 3-(3-Bromo-phenyl)-3-chloro-acrylonitrile

To 30.9 mL of dry DMF (400 mmol) cooled down to 0°C 18.3 mL of $POCl_3$ (200 mmol) were added dropwise so that the temperature was always under 10°C. To the mixture 19.9 g (100 mmol) of 1-(3-bromophenyl)ethanone were added dropwise and the reaction was allowed to reach room temperature.

When the addition was complete the reaction was stirred for further 30 minutes and then 2.7 g (40 mmol) of hydroxylamine hydrochloride were

added and the reaction heated up to 50°C. The heating was then removed and other 27 g (400 mmol) of hydroxylamine hydrochloride were added portionwise (so that the temperature did never exceed120°C).

After the last addition the reaction was left stirring until the temperature of the mixture spontaneously decreased to 25°C. Water (100 mL) was then added and the mixture was extracted with diethyl ether. The organic phase was dried over Na_2SO_4 andconcentrated under reduced pressure.

The crude product was used for the next step without further purification.

C_9H_5BrClN

^{1}H-NMR (400 MHz, dmso-d_6): 7.03 (s, 1H), 7.44-7.54 m, 1H), 7.72-7.84 (m, 2H), 8.00 (br s, 1H).

Yield 68%

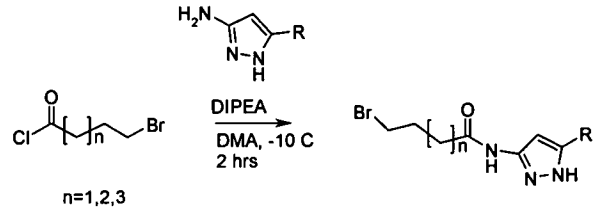
b) 5-(3-Bromo-phenyl)-2H-pyrazol-3-ylamine

To a solution of 3-(3-bromo-phenyl)-3-chloro-acrylonitrile (10 mmoL), in absolute EtOH (20 mL) hydrazine monohydrate (1 mL, 20 mmol) was added and the reaction was heated at reflux for 4 hrs. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated with Et_2O, allowing to recover 1.8 g of the title compound as pure product (yield 54%).

$C_9H_8BrN_3$

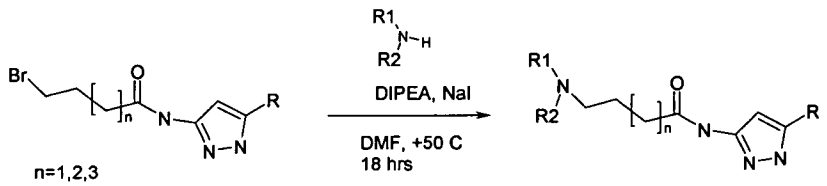
^{1}H-NMR(400 MHz, dmso-d_6): 4.58, 5.03 (1H, 2 tautomeric peaks),5.64, 5.84 (1H, 2 tautomeric peaks), 7.28 (1H, s), 7.35 (1H, s), 7.53-7.65 (1H, m), 7.77 (1H, s), 11.56, 11.97 (1H, 2 tautomeric peaks).

General method for the synthesis of ω-bromo-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides



A solution of ω-bromoalkanoyl chloride (15.7 mmol, 1 eq) in dry DMA (35 mL) was cooled to -10°C (ice/water bath) under N_2; a solution of 5-aryl/heteroaryl-1H-pyrazol-3-ylamine (15.7 mmol, 1 eq) and diisopropylethylamine (15.7 mmol, 1 eq) in dry DMA (15 mL) is added over 30'. After 2 hrs at -10°C, completion of the reaction as monitored by LC-MS was generally observed (acylation on the pyrazole ring is also detected). The reaction is then quenched by addition of H_2O (ca. 50 mL); the thick white precipitate formed upon addition of water was recovered by filtration. Washing with Et_2O (3 X 10 mL) usually efficiently removed the byproduct of acylation on the pyrazole ring.

General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides

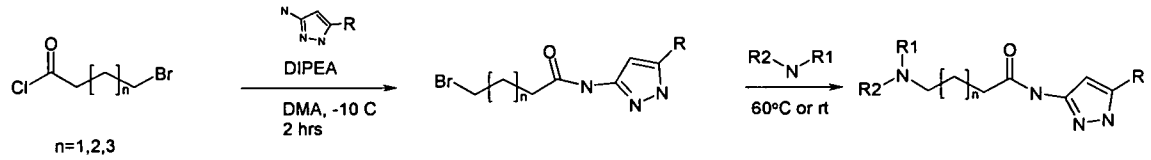


ω-Bromo-alkanoic acid [5-aryl-1H-pyrazol-3-yl]-amide (0.6 mmol, 1 eq) is dissolved in DMF (4 mL), sodium iodide (0.6 mmol, 1.0 eq) is added followed by the secondary amine (1.5 mmol, 2.5 eq) and diisopropylethylamine (0.6 mmol, 1 eq). The reaction is then stirred under N_2 at + 50°C for 18 hrs.

Upon reaction completion (as monitored by LC-MS), the solvent is removed at reduced pressure and the resulting oily residue is dissolved in DCM (20 mL),

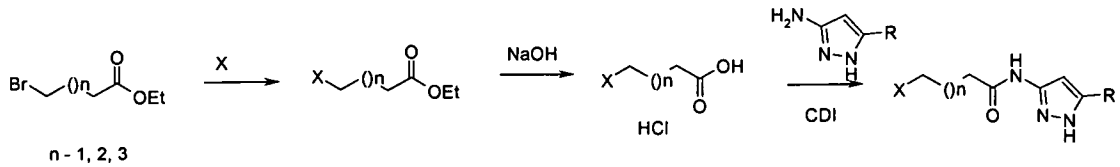
washed with sat. Na_2CO_3 (2 X 20 mL) and sat. NaCl (2 X 20 mL); the organic layer is dried over Na_2SO_4 and the solvent removed under reduced pressure. The title compounds were purified either by silica column or preparative HPLC.

General synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides: acylation-nucleophilic substitution



To a solution of ω -bromoalkanoyl chloride (0.94 mmol, 1eq) in DMA (1mL) cooled at 0°C is added a solution of 3-amino-5-aryl/heteroarylpyrazole (0.94 mmol, 1eq) and diisopropylethylamine (1.88 mmol, 2 eq) in DMA (2 mL) and the reaction is stirred for 1 hour at 0°C. The secondary amine (2.35 mmol, 2.5 eq) and NaI (0.94mmol, 1 eq) are then added. For 3-carbon chain derivatives the reaction was generally complete after 2 hours at room temperature. For 4-carbon chain derivatives the reaction mixture was generally heated at 60°C for 24-48 hours. Upon complete conversion of the bromo-intermediate (as monitored by LC-MS), the solvent was removed under reduced pressure. The residue was taken up in DCM (2 mL) and washed with Na_2CO_3 saturated water solution. The organic phase was concentrated under reduced pressure and the crude products were either recrystallised from CH_3CN, or purified by SiO_2 column (gradient from 100%DCM to DCM-NH3MeOH 2N solution 8:2) or by preparative HPLC (standard acidic conditions).

General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route



To a solution of amine X (65 mmol) in toluene (15 mL) ethyl ω -bromoalkanoate (26 mmol) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool to room temperature and any solid present was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give the ω-aminoester which was used in the next step without further purification.

To a suspension of crude ethyl ω-aminoalkanoate from the previous step (about 25 mmol) in 15 mL of water, NaOH (1.4 g, 25 mmol) was added and the mixture was heated at reflux for 16 hours. The reaction was then allowed to cool down to room temperature, the solution was acidified at 0°C with HCl 6N and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. Evaporation of the solvent under reduced pressure afforded the ω-aminoacid as a white solid. To a suspension of ω-aminoacid (7.93 mmol) in 12,2-dichloroethane (20 mL), *N,N'*-carbonyldiimidazole (1.2 g, 7.4 mmol) was added and the mixture was stirred at room temperature for 2 hours (when all the aminoacid was activated complete dissolution of the suspension was generally observed). The 3-amino-5-aryl/heteroarylpyrazole (5.29 mmol) was then added and the reaction was stirred for further 10 hours. Upon reaction completion (as monitored by LC-MS) if the formation of two isomers was observed, the mixture was heated at 50°C until the conversion of the less stable isomer to the title compound was observed (as monitored by LC-MS). The solvent was washed with sat. Na_2CO_3 solution, extracted and removed under reduced pressure. The crude products were either recrystallised from CH_3CN, or purified by SiO_2 column or by preparative HPLC.

Example 1

5-Azepan-1-yl-pentanoic acid (2-chloro-2',3'-difluoro-biphenyl-4-yl)-amide

a) 5-Azepan-1-yl-pentanoic acid (4-bromo-3-chloro-phenyl)-amide

Following the general procedure, 4-bromo-3-chloroaniline (72 mg, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol) were dissolved in DCE (0.5 mL) and 5-bromovaleryl chloride (66 mg, 0.33 mmol) in DCE (0.5 mL) was added dropwise. After 1h 30 min, azepane (118 mg, 0.105 mmol) and triethylamine (35 mg, 0.35 mmol) in DCE (0.5 mL) was added and the reaction mixture heated at +55°C for 4 hours. Work-up followed by preparative HPLC afforded the title compound (23 mg, 17%) as formate.

C17H24BrClN2O Mass (calculated) [387.75]; (found) [$M+H^+$]=389.28.

LC Rt=2.34, 100% (10 min method)

b) 5-Azepan-1-yl-pentanoic acid (2-chloro-2',3'-difluoro-biphenyl-4-yl)-amide

Following the general procedure for cross-coupling under microwave conditions, 5-azepan-1-yl-pentanoic acid (4-bromo-3-chloro-phenyl)-amide (70 mg, 0.18 mmol) and 2,3-difluorophenyl boronic acid (31 mg, 0.2 mmol) were dissolved in acetonitrile/0.4 M Na_2CO_3 1/1 (1.5 mL each) and $Pd[P(Ph)_3]_4$ (11 mg, 0.01 mmol) was added. After irradiating for 20 minutes, preparative HPLC purification afforded the title compound (23 mg, 27%) as the corresponding formate, as a white solid.

C23H27ClF2N2O Mass (calculated) [420.93]; (found) [$M+H^+$]=421.38

LC Rt= 2.04, 100% (10 min method)

NMR (400 MHz, $CDCl_3$): 1.63 (4H, s); 1.80 (8H, m); 2.43 (2H, m); 2.94 (2H, m); 3.1 (4H, bs); 6.96 (1H, m); 7.05-7.02 (2H, m); 7.11 (1H, d, J=8); 7.16 (1H, d, J=8.4); 7.53 (1H, d, J=8.4); 7.9 (1H, s); 8.56(1H, s, **H**COOH); 9.68 (1H, s, NH).

Example 2

4'-{5-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pentanoylamino}-biphenyl-3-carboxylic acid amide

Prepared according to the general procedure for amide synthesis followed by the general procedure for cross-coupling under microwave irradiation to give 0.07 g of title compound (62%).

$C_{26}H_{30}N_4O_2$. Mass (calculated) [430.55]; (found) [$M+H^+$]=431.42

Lc Rt=1.59, 100%

NMR (400 MHz, dmso-d6): 1.37-1.45 (2H, m); 1.51-1.59 (2H, m); 2.17 (3H, s); 2.28-2.36 (4H, m); 2.62-2.66 (2H, m), 2.81-2.85 (2H, m); 7.14 (1H, br dd, J=7.6 Hz, 4.8 Hz); 7.24 (1H, d, J=8.0 Hz); 7.40 (1H, br s); 7.48 (1H, dd, J=8 Hz, 7.6 Hz); 7.61-7.7.0 (5H, m); 7.78 (2H, m); 8.06 (1H, s); 8.11 (1H, s); 9.96 (1H, s).

Example 3

1-(2, 2'-Dimethoxy-biphenyl-4-yl)-3-(4-piperidin-1-yl-butyl)-urea

1-(4-Bromo-3-methoxy-phenyl)-3-(4-piperidin-1-yl-butyl)-urea (prepared according to the general procedure for urea synthesis, reaction with isocyanate) was weighed into a microwave vessel (100 mg, 0.26 mmol) and dissolved in acetonitrile (1 mL). To this, 2-methoxyphenylboronic acid (47 mg, 0.312 mmol) was added, along with tetrakis(triphenylphosphine)palladium (20 mg, 0.017 mmol) and a solution of sodium carbonate (1 mL, 0.4 M). The reaction mix was then exposed to microwave irradiation at psi 250, at 90°C for 20 minutes. On reaction completion by LCMS, the separated organic phase was removed from the reaction mix and passed through a plug of Celite®. The collected crude was loaded onto an SCX column, eluting the desired compound with a solution of ammonia in methanol (20% ammonia). Fractions containing the desired compound were combined and dried affording the titled compound (30 mg,

0.073 mmol, 28% yield).

C24H33N3O3 Mass (calculated) [411.55]; (found) [M+H$^+$] =412

LC Rt=2.03, 98% (10 min method)

NMR (400 MHz, $CDCl_3$): 1.57-1.67 (11H, m); 2.42-2.50 (5H, m); 3.29 (2H, m); 3.77 (6H, s); 5.85 (1H, s); 6.61 (1H, s); 6.75-6.77 (1H, d); 6.95-7.00 (2H, m); 7.15 (1H, d); 7.21-7.22 (1H, m) 7.23-7.33 (2H, m)

Example 4

5-Imidazol-1-yl-pentanoic acid (3'-acetylamino-biphenyl-4-yl)-amide

a) 5-Bromopentanoic acid-(4-bromophenyl)-amide

4-Bromo-aniline (6 g, 0.035 mol) and 0.035 mol of NEt_3 (4.87 mL) were dissolved in 120 mL of dichloromethane and cooled at 0°C.

To this solution, 0.038 mol of 5-bromovaleryl chloride (5.4 mL) were slowly added and the resulting mixture was stirred for 1 h at 0°C.

When all the starting material was consumed (monitoring by LCMS) the solution was washed with 50 mL of Na_2CO_3 0.4 M and the organic layer was recovered by extraction and drying over Na_2SO_4. The solvent was removed under reduced pressure giving 10 g of the title compound as a white solid (yield 86%).

C11H13Br2NO Mass (calculated) [335]; (found) [M+H$^+$]=335

Lc Rt = 2.64, 100% (5 min method)

NMR (400 MHz, CDCl3) 1.70-2.00 (4H, m), 2.35-2.45 (2H, m), 3.38-3.48 (2H, m), 7.30-7.50 (4H, m).

b) 5-Imidazolyl acid-(4-bromophenyl)-amide

400 mg (1.19 mmol) of 5-bromopentanoic acid-(4-bromophenyl)-amide and 800 mg of imidazole (11.7 mmol) were suspended in 2 mL of a mixture of Toluene: EtOH 1:1. The reaction mixture was heated at 160°C for 10 minutes under microwave conditions. The solvent was removed under reduced pressure and the crude mixture dissolved in DCM (10 mL) and washed twice with 1M

NaOH. The solution was dried over Na_2SO_4, filtered and the solvent removed to give the desired product as a white powder (240 mg yield 62%).

NMR (400 MHz, dmso-d6): 7.65 (1H, s), 7.56-7.52 (2H, m), 7.46-7.42 (2H, m), 7.42 (1H, m), 6.87 (1H, m), 3.95 (2H, t, J = 12 Hz), 2.30 (2H, t, J = 7.2 Hz), 1.75-1.68 (2H, m), 1.55-1.45 (2H, m).

c) 5-Imidazol-1-yl-pentanoic acid (3'-acetylamino-biphenyl-4-yl)-amide

A mixture of 1 mL of 0.4 M solution of Na_2CO_3 and 1 mL of DMF was added to a microwave tube containing 5-imidazolyl acid-(4-bromophenyl)-amide (100 mg, 0.31 mmol), 3-acetoamidophenyl boronic acid (83.4 mg, 0.46 mmol) and $[Pd(PPh_3)_4]$ (16 mg, 0.03 mmol). The reaction mixture was heated at 90°C for 20 minutes under microwave conditions. The mixture was diluted with MeOH and the solution passed through a plug of Celite®. The solvent was removed under reduced pressure and the crude mixture dissolved in DCM and washed with 1M NaOH. The organic phase was dried over MgSO4, filtered and the solvent removed under reduced pressure. Purification by SCX and after by crystallization from EtOAC/Et_2O gave 43 mg of pure product (yield 37%).

C22H24N4O2 Mass (calculated) [376]; (found) $[M+H^+]$= 377

Lc Rt 2.11 (10 min)

Purity 98%

NMR (400 MHz, dmso-d6): 10.03 (1H, s), 8.85 (1H, d, J = 2.0 Hz), 8.50 (1H, dd, J= 4.8 Hz, 1.6 Hz), 8.03 (1H, m), 7.67 (4H, m), 7.63 (1H, s), 7.44 (1H, m), 6.87 (1H, m), 3.98 (2H, t, J = 7.2 Hz), 2.34 (2H, t, J= 7.2 Hz), 1.74 (2H, m), 1.53 (2H, m).

Example 5

1-(2,2'-Difluoro-biphenyl-4-yl)-3-(4-piperidin-1-yl-butyl)-urea

a) 1-(4-Bromo-3-fluoro-phenyl)-3-(4-piperidin-1-yl-butyl)-urea

Prepared via the general procedure for urea synthesis (triphosgene

activation of aniline).

Yield: 71%

C16H23BrFN3O Mass (calculated) 372; (found) [M+H$^+$]= 372-374

Lc Rt= 2.26 (100%), 10'

NMR (400 MHz, dmso-d6): 128-1.56 (10H, m), 2.16-2.38 (6H, m), 3.00-3.15 (2H, m), 6.30 (1H, t), 6.99 (1H, dd), 7.46 (1H, t), 7.59 (1H, dd), 8.81 (1H, s).

b) 1-(2,2'-Difluoro-biphenyl-4-yl)-3-(4-piperidin-1-yl-butyl)-urea

To a degassed solution of 1-(4-bromo-3-fluoro-phenyl)-3-(4-piperidin-1-yl-butyl)-urea (100 mg, 0.26 mmol) in DME/H_2O (1.8 mL/0.3 mL) 2-fluorophenyl boronic acid (55 mg, 0.39 mmol), Na_2CO_3 (55 mg, 0.52 mmol), $Pd(OAc)_2$ (6 mg, 10% mol) and tri-o-tolylphosphine (34 mg, 20% mol), were added. The solution was irradiated under microwave conditions for 20 minutes with power 200W.

The organic phase was diluted with 1 mL of AcOEt and separated

The crude was purified with prep-HPLC (36 mg, 40% yield).

Molecular formula: C22H27F2N3O

Mass (calculated) [387]; (found) [M+H$^+$]=388

Lc Rt (10 min method)= 399, 97%

^{1}H-NMR (400MHz, d_6-DMSO): 1.27-1.54 (10H, m), 2.25-2.44 (6H, m), 2.94-3.13 (2H, m), 6.33-6.45 (1H, m), 7.09-7.14 (1H, m), 7.21-7.30 (3H, m), 7.34-7.45 (2H, m), 7.48-7.55 (1H, m), 8.16 (1H, s), 8.85 (1H, s).

Example 6

3'-Fluoro-4'-[3-(4-piperidin-1-yl-butyl)-ureido]-biphenyl-3-carboxylic acid amide)

a) 1-(2-Fluoro-4-bromo-phenyl)-3-(4-piperidin-1-yl-butyl)-urea

Prepared via the general procedure for urea synthesis (isocyanate)

Yield:88%

NMR (400 MHz, dmso-d6): 1.22-1.50 (10H, m), 2.12-2.37 (6H, m), 3.00-3.13(2H, m), 6.62 (1H, t), 7.25 (1H, d), 7.47 (1H, dd), 8.10 (1H, t), 8.33 (1H, s)

b) 3'-Fluoro-4'-[3-(4-piperidin-1-yl-butyl)-ureido]-biphenyl-3-carboxylic acid amide

To a degassed solution of 1-(2-fluoro-4-bromo-phenyl)-3-(3-piperidin-1-yl-propyl)-urea (100 mg, 0.27 mmol), the 3-benzamide-phenylboronic acid (66 mg,0.44 mmol) and Na_2CO_3 (3 eq) in 20 volumes (weight/vol) of acetonitrile/water (1/1), $Pd[(PPh_3)]_4$ (10% mol) were added.

The solution was irradiated in a microwave oven using the following parameters:

power: 200 watt; ramp time: 1 min; hold time: 20:00 min; temperature: 90°C; pressure: 200 psi.

The acetonitrile phase was separated, the solvent was removed under reduced pressure and the crude material purified using SCX column (eluting with a gradient of DCM/MeOH, MeOH, NH_3/MeOH). The fractions containing the desired product were combined and dried under reduced pressure, and then further purified by preparative HPLC (yield 15%).

Molecular formula: C22H27F2N3O

Mass (calculated) [387]; (found) $[M+H^+]$=388

Lc Rt (10 min method)= 399, 97%

^{1}H-NMR (400MHz, CD3OD): 1.40-1.67 (10H, m), 2.26-2.58 (6H, m), 3.21-3.27 (2H, m), 7.13-7.20 (1H, m), 7.21-7.28 (1H, m), 7.30-7.39 (1H, m), 7.40-7.51 (2H, m), 7.56 (1H, s,), 8.11-8.16 (1H, m).

Example 7

4'-{5-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-pentanoylamino}-biphenyl-3-carboxylic acid amide

Prepared according to the general method for amide coupling (one-pot,

excess amine followed by the general method for cross-coupling with boronic acids, microwave conditions) to give 0.07 g (yield = 62%) of title compound.

$C_{26}H_{30}N_4O_2$. Mass (calculated) [430.55]; (found) [$M+H^+$]=431.42

Lc Rt=1.59, 100%

NMR (400 MHz, dmso-d6): 1.37-1.45 (2H, m); 1.51-1.59 (2H, m); 2.17 (3H, s); 2.28-2.36 (4H, m); 2.62-2.66 (2H, m), 2.81-2.85 (2H, m); 7.14 (1H, br dd, J=7.6 Hz, 4.8 Hz); 7.24 (1H, d, J=8.0 Hz); 7.40 (1H, br s); 7.48 (1H, dd, J=8 Hz, 7.6 Hz); 7.61-7.7.0 (5H, m); 7.78 (2H, m); 8.06 (1H, s); 8.11 (1H, s); 9.96 (1H, s).

Example 8

1-(4'-Methoxy-biphenyl-4-yl)-3-(1-methyl-4-piperidin-1-yl-butyl)-urea

a) 1-(4-Bromo-phenyl)-3-(1-methyl-4-piperidin-1-yl-butyl)-urea

To a solution of 1-methyl-4-piperidin-1-yl-butylamine (1.07 g, 6.3 mmol) in CH_2Cl_2 (15 mL) at 0°C was slowly added a solution of 4-bromophenyl isocyanate (1.25 g, 6.3 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred 30 min at 0C, then 3 hrs at RT. The solvent was evaporated and the residue purified by SCX column. The obtained solid was washed with ether.

1.57 g; 68%

$C_{17}H_{26}BrN_3O$ calculated 368; found 368/370

Lc Rt (5 min)= 1.35, 100%

NMR (400 MHz, dmso-d6): 1.02 (3H, d, J= 6.8 Hz); 1.30-1.45 (5H, m); 2.13-2.17 (5H, m); 2.13-2.17 (2H, m); 2.23 (4H, br m); 3.57-3.64 (1H, m); 5.97 (1H, J= 8 Hz); 7.29-7.34 (4H, m); 8.36 (1H, s).

b) 1-(4'-Methoxy-biphenyl-4-yl)-3-(1-methyl-4-piperidin-1-yl-butyl)-urea

To a degassed mixture of 1-(4-bromo-phenyl)-3-(1-methyl-4-piperidin-1-yl-butyl)-urea (0.3 g, 0.81 mmol) and 4-methoxyphenylboronic acid (186 mg, 1.22 mmol) in acetonitrile/sodium carbonate 0.4M solution 1/1

(8 mL) a catalytic amount of $Pd[(PPh_3)]_4$ (47 mg, 5 mmol %) was added. The reaction mixture was heated at 90°C for 20 minutes under microwave condition. After addition of ethyl acetate (1 mL), the organic layer was separated and purified by scx columns.

0.27 g; 84%

$C_{17}H_{26}BrN_3O$ calculated 395; found 396

Lc Rt (10 min)= 2.23, 100%

NMR (400 MHz, dmso-d6): 1.05 (3H, d, J= 6.4 Hz); 1.33-1.47 (10H, m); 2.06-2.18 (2H, m); 2.26 (4H, br m); 3.61-3.67 (1H, m); 3.75 (3H, s); 5.95 (1H, J= 8 Hz); 6.95-6.97 (2H, m); 7.39-7.46 (4H, m); 7.50-7.52 (2H, m); 8.30 (1H, s).

Example 9

1-(2,2-Dimethyl-4-piperidin-1-yl-butyl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-urea

a) 1-(4-Bromo-phenyl)-3-(2,2-dimethyl-4-piperidin-1-yl-butyl)-urea

To a solution of 2,2-dimethyl-4-piperidin-1-yl-butylamine (1.4 g, 7.6 mmol) in CH_2Cl_2 (20 mL) at 0°C was slowly added a solution of 4-bromophenyl isocyanate (1.5 g, 7.6 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred 20 min at 0°C, then 4 hrs at RT. The solvent was evaporated and the residue treated with ether and the solid separated. The solution was purified by SCX column. The obtained solid was used without further purification.

0.825 g (28%)

$C_{18}H_{28}BrN_3O$ calculated 382; found M+ 382/384

Lc Rt (5 min)= 1.39

NMR (400 MHz, dmso-d6): 0.80 (6H, s); 1.28-1.34 (4H, m); 1.41-1.46 (4H, m); 2.17-2.21 (2H, m); 2.28 (4H, br m); 2.90 (2H, d, J= 6Hz); 6.15 (1H, t, J= 6 Hz); 7.33-7.35 (4H, m); 8.51 (1H, s).

b) 1-(2,2-Dimethyl-4-piperidin-1-yl-butyl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-urea

To a degassed mixture of 1-(4-bromo-phenyl)-3-(2,2-dimethyl-4-piperidin-1-yl-butyl)-urea (0.11 g, 0.29 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-4-yl)-1H-pyrazole (90 mg, 0.43 mmol) in acetonitrile/sodium carbonate 0.4M solution 1/1 (4 mL) a catalytic amount of $Pd[(PPh_3)]_4$ (17 mg, 5 mmol %) was added. The reaction mixture was heated at 90°C for 20 minutes under microwave condition. After addition of ethyl acetate (1 mL), the organic layer was separated and purified by scx columns followed by preparative HPLC.

0.067 g; 61%

$C_{22}H_{33}N_5O$ calculated 383; found M+ 384

Lc Rt (10 min)= 1.61

NMR (400 MHz, dmso-d6): 0.82 (6H, s); 1.35-1.40 (4H, m); 1.48-1.54 (4H, m); 2.40-2.44 (2H, m); 2.46-2.50 (4H, br m); 2.91 (2H, d, J= 6Hz); 3.81 (3H, s); 6.32 (1H, t, J= 6 Hz); 7.33-7.39 (4H, m); 7.72 (1H, s); 7.97 (1H, s); 8.23 (1H, s); 8.56 (1H, s).

Example 10

1-(4-Piperidin-1-yl-pentyl)-3-(4-pyridin-3-yl-phenyl)-urea

a) 1-(4-Bromo-phenyl)-3-(4-piperidin-1-yl-pentyl)-urea

To a solution of 4-piperidin-1-yl-pentylamine (0.20 g, 1.18 mmol) in CH_2Cl_2 (4 mL) at 0°C was slowly added a solution of 4-bromophenyl isocyanate (0.23 g, 1.18 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred 5 min at 0°C, then 1 hrs at RT. The solvent was evaporated and the residue used without further purification.

0.39 g; 90%

NMR (400 MHz, CD_3OD): 0.96 (3H, d, J= 6.4 Hz); 1.25-1.59 (10H, m); 2.46-2.55 (5H, m); 3.11 (2H, t, J= 6.8 Hz); 7.25-7.28 (2H, m); 7.32-7.36 (2H, m).

b) 1-(4-Piperidin-1-yl-pentyl)-3-(4-pyridin-3-yl-phenyl)-urea

To a degassed mixture of 1-(4-bromo-phenyl)-3-(4-piperidin-1-yl-pentyl)-urea (130 mg, 0.35 mmol) and pyridine-3-boronic acid (65 mg, 0.53 mmol) in acetonitrile/sodium carbonate 0.4M solution 1/1 (4 mL) a catalytic amount of $Pd[(PPh_3)]_4$ (17 mg, 5 mmol %) was added. The reaction mixture was heated at 90°C for 10 minutes under microwave condition. After addition of ethyl acetate (1 mL), the organic layer was separated and purified by scx columns followed by preparative HPLC.

0.025 g; 19%

$C_{22}H_{30}N_4O$ calculated 366; found 367

Lc Rt (10 min)= 0.24-0.81

NMR (400 MHz, dmso-d6): 0.82 (6H, d, J= 6.8); 1.24-1.55 (10H, m); 2.46-2.68 (5H, m); 3.05-3.09 (2H, m); 6.38 (1H, t, J= 5.6 Hz); 7.41 (1H, ddd, J= 8.0 Hz, 4.8 Hz, 0.8 Hz); 7.49-7.52 (2H, m); 7.57-7.60 (2H, m); 7.99 (1H, ddd, J= 8.0 Hz, 2.0 Hz, 1.6 Hz); 8.21 (1H, s); 8.47 (1H, dd, J= 4.8 Hz, 1.6 Hz); 8.74 (1H, s); 8.82 (1H, dd, J= 2.0 Hz, 0.8 Hz).

Example 11

1-[4-(1-Methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(3,3,3-trifluoro-propylamino)-butyl]-urea

a) 1-(4-Bromo-phenyl)-3-[4-(3,3,3-trifluoro-propylamino)-butyl]-urea

1-(4--Bromo-phenyl)-3-(4,4-diethoxy-butyl)-urea (0.72 g, 2 mmol, 1 eq) was dissolved in dry DCM (10 mL) at room temperature and Montomorrilonite K-5 (0.145 g) is added. The reaction was stirred ar room temperature for 2 hours, when LC-MS shows complete conversion into the aldehyde. The reaction mixture was filtered to remove all solids and trifluopropylamine.HCl (0.9 g, 6 mmol, 3 eq) and diisoproylethylamine (1.05 mL, 6 mmol, 3 eq) were added, followed by $NaBH(OAc)_3$ (1.2 g, 4 mmol, 2 eq,). The reaction was stirred at rt for 24 hrs. Upon reaction

completion (as monitored by LC-MS), the solvent was removed under reduced pressure and the resulting residue was purified by SCX column, eluting with DCM:MeOH 1:1 and then 2M NH3 in MeOH. 1-(4-Bromo-phenyl)-3-[4-(3,3,3-trifluoropropylamino)-butyl]-urea was obtained (0.33 g, 40% yield).

C14H19BrF3N3O Mass (calculated) [382.23]; (found) [M+H$^+$]=381.25 (ESI-)

LC Rt=0.63, 90% (10 min method)

b) 1-[4-(1-Methyl-1H-pyrazol-4-yl)-phenyl]-3-[4-(3,3,3-trifluoro-propylamino)-butyl]-urea

To a degassed solution of 1-(4-Bromo-phenyl)-3-[4-(3,3,3-trifluoropropylamino)-butyl]-urea (0.11 g, 0.3 mmol), 31-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (0.0.94 g, 0.45 mmol) in 3 mL Acetonitrile/ 0.4 M Na_2CO_3 (50/50) Pd[(PPh_3)]$_4$ (0.02 mmol) were added. The solution was irradiated under the microwave conditions described above. The acetonitrile layer was separated and filtered on a Celite® pad. The solution was dried and the product purified by preparative HPLC to yield 20 mg of the title compound as formate salt (0.048 mmol, 16% yield).

C18H24F3N5O Mass (calculated) [383.42]; (found) [M+H$^+$]= 384.21

Lc Rt= 1.48 (100%)

NMR (400 MHz, dmso-d6): 1.31 (4H, m); 2.43-2.30 (2H, m); 2.57-2.55 (2H, m); 2.75 (2H, m); 3.05 (2H, m); 3.81 (3H, s); 6.17 (1H, bs); 7.38-7.32 (4H, m); 7.72 (1H, s); 7.97 (1H, s); 8.18 (1H, s, **H**COOH); 8.43 (1H, s).

Example 12

4'-(5-Azepan-1-yl-pentanoylamino)-2'-chloro-biphenyl-3-carboxylic acid amide

a) 5-Azepan-1-yl-pentanoic acid (4-bromo-3-chloro-phenyl)-amide

4-bromo-3-chloroaniline (0.72 g, 3.5 mmol), triethylamine (0.48 mL, 3.35 mmol) and 5-bromovaleryl chloride (0.44 mL, 3.32 mmol) are reacted for

2 hrs at rt in DCE (12 mL): after this time, azepane (1.18 mL, 10.3 mmol) and more triethylamine (0.48 mL, 3.35 mmol) are added and the reaction stirred for +55°C for 4 h. After reaction completion and work-up, the title compound is clean enough (92% purity) for the following step (1.3 g, quant yield).

C17H24BrClN2O Mass (calculated) [387.75]; (found) [M+H$^+$]= 387.32/389.28

Lc Rt= 2.83 (92%), 10'

b) 4'-(5-Azepan-1-yl-pentanoylamino)-2'-chloro-biphenyl-3-carboxylic acid amide

5-Azepan-1-yl-pentanoic acid (4-bromo-3-chloro-phenyl)-amide (0.07 g, 0.18 mmol) and benzamide-3-boronic acid (0.044 g, 0.27 mmol) are reacted in acetonitrile/sodium carbonate 0.4M solution 1/1 (3 mL) with a catalytic amount of $Pd[(PPh_3)]_4$ (5 mmol %).

The title compound is obtained as free base after purification by SCX column (0.045 g, 0.11 mmol, 60% yield)

C24H30ClN3O2 Mass (calculated) [472.98]; (found) [M+H$^+$]= 428.46

Lc Rt= 2.04 (100%), 10'

NMR (400 MHz, $CDCl_3$): 1.68-1.55 (8H, m); 1.77 (4H, m); 2.41 (2H, m;, 2.58 (2H, m); 2.67 (2H, m); 2.72 (2H, m); 7.27 (1H, s); 7.49 (2H, m); 7.59 (1H, s); 7.8 (2H, m); 7.85 (1H, s); 8.16 (1H, bs).

Example 13

5-Azepan-1-yl-pentanoic acid (2-fluoro-2'-methoxy-biphenyl-4-yl)-amide

a) 5-Azepan-1-yl-pentanoic acid (4-bromo-3-fluoro-phenyl)-amide

4-Bromo-3-fluoroaniline (0.66 g, 3.5 mmol), triethylamine (0.48 mL, 3.35 mmol) and 5-bromovaleryl chloride (0.44 mL, 3.32 mmol) are reacted for 2 hrs at rt in DCE (12 mL): after this time, azepane (1.18 mL, 10.3 mmol) and more triethylamine (0.48 mL, 3.35 mmol) are added and the reaction stirred

for +55°C for 4 h. After reaction completion and work-up, the title compound is clean enough (90% purity) for the following step (1.29 g, quant yield).

C17H24BrFN2O Mass (calculated) [371.30]; (found) [M+H$^+$]= 371.33/373.35

Lc Rt= 2.23 (90%), 10'

b) 5-Azepan-1-yl-pentanoic acid (2-fluoro-2'-methoxy-biphenyl-4-yl)-amide

5-Azepan-1-yl-pentanoic acid (4-bromo-3-fluoro-phenyl)-amide (0.093 g, 0.25 mmol) and 2-methoxyphenyl-boronic acid (0.057 g, 0.37 mmol) are reacted in acetonitrile/sodium carbonate 0.4M solution 1/1 (4 mL) with a catalytic amount of $Pd[(PPh_3)]_4$ (5 mmol %).

The title compound is obtained as formate salt after purification by preparative HPLC (0.025 g, 0.06 mmol, 13% yield).

C24H31FN2O2 Mass (calculated) [398.53]; (found) [M+H$^+$]= 399.18

Lc Rt= 2.98 (98%), 10'

NMR (400 MHz, CD_3OD): 1.83-1.72 (8H, m); 1.9 (4H, m); 2.5 (2H, m); 3.18 (2H, m); 3.37 (4H, m); 3.77 (3H, s); 6.99 (1H, m); 7.06 (1H, bs); 7.21 (1H, m); 7.25 (2H, m); 7.35 (1H, m); 7.57 (1H, m); 8.49 (1H, s, **H**COOH).

Example 14

1-(2,2-Difluoro-4-piperidin-1-yl-butyl)-3-(4'-methoxy-biphenyl-4-yl)-urea

a) 1-(4-Bromo-phenyl)-3-(2,2-difluoro-4-piperidin-1-yl-butyl)-urea

To a solution of 2,2-difluoro-4-piperidin-1-yl-butylamine (0.149 g, 0.78 mmol) in CH2Cl2 (4 mL) at 0°C a solution of 4-bromophenyl isocyanate (0.153 g, 0.78 mmol) in CH2Cl2 (1 mL) was slowly added. The mixture was stirred at 0°C for 30 min, then at room temperature until the reactants were all consumed. The solution was purified by SCX column. The oil obtained was used without further purification (0.218 g).

Yield: 72%

C16H22BrF2N3O calculated 390; found M+ 390/392

Lc Rt (5 min)= 1.34

1H-NMR (400 MHz, dmso-d6): 1.43-1.57 (8H, m); 2.02-2.53 (8H, m); 7.22-7.43 (6H, m).

b) 1-(2,2-Difluoro-4-piperidin-1-yl-butyl)-3-(4'-methoxy-biphenyl-4-yl)-urea

To a degassed mixture of 1-(4-bromo-phenyl)-3-(2,2-difluoro-4-piperidin-1-yl-butyl)-urea (0.109 g, 0.28 mmol), 4-methoxyphenylboronic (0.051 g, 0.34 mmol) and Na2CO3 (0.042 g, 0.40 mmol) in DME (1.3 mL) and water (0.2 mL) tri-o-tolylphosphine (0.017 g, 20 mmol%) and Pd(OAc)2 (0.003 g, 5% mmol) were added. The reaction mixture was heated at 90°C for 10 minutes under microwave conditions. After addition of ethyl acetate (1 mL), the organic layer was separated and purified by scx columns followed by SiO2 column (gradient from 100%DCM to DCM-NH3 in MeOH 2N solution 9:1) to give 0.010 g of product.

Yield: 9%

C23H29F2N3O2 calculated 417; found M+ 418/M- 416

Lc Rt (10 min)= 2.23, 100%

NMR (400 MHz, dmso-d6): 1.47-1.62 (6H, m); 2.09-2.22 (2H, m); 2.46-2.62 (6H, m); 3.64 (2H, t, J=14); 3.81 (3H, s); 6.96 (2H, d, J=8.8); 7.40 (2H, d, J=6.8), 7.47-7.51 (4H, m).

19F-HNMR (400 MHz, dmso-d6): -118.90 (quint.)

Example 15

5-Piperidin-1-yl-pentanoic acid [5-(4-methoxy-phenyl)-4-methyl-2H-pyrazol-3-yl]-amide

a) 3-(4-Methoxy-phenyl)-2-methyl-3-oxo-propionitrile

The product was prepared according to the general procedure for

aminopyrazole synthesis (route A1).

The crude product was purified with SiO2 column (10 g) with gradient elution from 100% Hexane to Hexane-AcOEt 7:3. to give 1.43 g of pure product (yield 31%).

^{1}H-NMR (400 MHz, MeOH-d_4): 7.97 (2H, d), 6.98 (1H, d), 4.31 (1H, q, J = 7.3 Hz), 3.89 (3H, s), 1.63 (3H, d, J = 7.3 Hz).

b) 5-(4-Methoxy-phenyl)-4-methyl-2H-pyrazol-3-ylamine

The product was prepared according to the general procedure for aminopyrazole synthesis (route A2)

The crude product was purified with SiO2 column (10 g) with gradient elution from 100% DCM to DCM-MeOH 8:2. 1.0 g of pure product were obtained (yield 65%).

^{1}H-NMR (400 MHz, CDCl3): 7.37 (2H, d), 6.97 (2H, d), 3.84 (3H, s), 2.03 (3H, s).

c) 5-Piperidin-1-yl-pentanoic acid [5-(4-methoxy-phenyl)-4-methyl-2H-pyrazol-3-yl]-amide

The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides.

The crude product was purified with SiO2 column (2 g) with gradient elution from 100% DCM to DCM-NH3 (2N MeOH solution) 95:5.

The obtained crude was then purified again by prep-HPLC to give 54 mg of pure product (yield 7%).

$C_{21}H_{30}N_4O_2$

Mass (calculated) [370]; (found) [$M+H^+$] =371

LC Rt=1.61, 100% (10 min method)

^{1}H-NMR (400 MHz, dmso-d_6): 9.57 (1H, s), 8.12 (1H, s), 7.47 (2H, d), 7.02 (2H, d), 3.78 (3H, s), 2.41 (4H, broad), 2.37 (2H, m), 2.29 (2H, t), 1.91

(3H, s), 1.57 (2H, m), 1.50 (6H, m), 1.38 (2H, m).

Example 16

N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

a) 4-Piperidin-1-yl-butyric acid ethyl ester

To a solution of piperidine (5.4 g, 65 mmol) in toluene (15 mL) ethyl 4-bromobutyrate (3.8 mL, 26 mmol) was added and the reaction mixture was refluxed for 10 hours. The mixture was allowed to cool down to room temperature and the white solid present (piperidium bromide) was filtered off and washed with ether. The filtrate was concentrated under reduced pressure to give the title product which was used in the next step without further purification.

$C_{11}H_{21}NO_2$

Mass (calculated) [199]; (found) $[M+H^+]$ =200

LC Rt = 0.2, 100% (5 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.22-1.25 (3H, m), 1.46-1.47 (2H, m), 1.57-1.63 (4H, m), 1.78-1.84 (2H, m), 2.30-2.35 (4H, m), 2.42 (4H, m, broad), 4.08-4.14 (2H, m).

b) 4-Piperidin-1-yl-butyric acid

To a suspension of crude 4-piperidin-1-yl-butyric acid ethyl ester from the previous step (about 25 mmol) in 15 mL of water, NaOH (1.4 g, 25 mmol) was added and the mixture was heated at reflux for 16 hours. The reaction was then allowed to cool down to room temperature, the solution was acidified at 0°C with HCl 6N and concentrated under reduced pressure. The residue was treated with EtOH and the sodium chloride which precipitated was filtered off. Evaporation of the solvent under reduced pressure afforded 2.8 g of the title compound as a white solid in 58% overall yield of steps a) and b).

$C_9H_{17}NO_2$

Mass (calculated) [171]; (found) $[M+H^+]$ =172

LC Rt = 0.23, 100% (5 min method)

^{1}H-NMR (400 MHz, dmso-d_6): 1.44-1.51 (2H, m); 1.64-1.80 (6H, m); 2.22-2.25 (2H, m); 2.75-2.78 (2H, m, broad); 2.91-2.94 (2H, m, broad); 3.30-3.40 (2H, m).

c) N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

To a suspension of 4-piperidin-1-yl-butyric acid (1.32 g, 7.93 mmol) in 12,2-dichloroethane (20 mL), *N,N'*-carbonyldiimidazole (1.2 g, 7.4 mmol) was added and the mixture was stirred at room temperature for 2 hours (when all the aminoacid was activated complete dissolution of the suspension was generally observed). 3-Amino-5-(4-methoxyphenyl)pyrazole (1 g, 5.29 mmol) was then added and the reaction was stirred for further 10 hours. Upon reaction completion (as monitored by LC-MS) the formation of two isomers was observed, and the mixture was heated at 50°C until the conversion of the less stable isomer to the title compound was observed (as monitored by LC-MS). The solvent was washed with sat. Na_2CO_3 solution, extracted and removed under reduced pressure. The crude was crystallised from acetonitrile to give 1.2 g of the title compound (Yield: 70%).

$C_{19}H_{26}N_4O_2$

Mass (calculated) [342]; (found) [$M+H^+$] =343

LC Rt = 1.54, 100% (10 min method)

^{1}H-NMR (400 MHz, dmso-d_6): 1.34-1.40 (1H, m); 1.52-1.55 (1H, m); 1.62-1.75 (6H, m); 1.94-1.98 (2H, m); 2.37-2.40 (2H, m); 2.81-2.88 (2H, m); 2.97-3.03 (2H, m); 3.39-3.42 (2H, m); 3.77 (3H, s); 6.77 (1H, s); 6.98 (2H, d, *J*= 8.8 Hz); 7.61 (2H, d, *J*= 8.8 Hz); 10.47 (1H, s), 12.66 (1H, s).

Example 17

N-[5-(3-Methoxy-phenyl)-1H-pyrazol-3-yl]-4-morpholin-4-yl-butyramide

a) 3-(3-Methoxy-phenyl)-3-oxo-propionitrile

To a solution of commercially available 3-methoxy-benzoic acid ethyl

ester (3.2 g, 18 mmol) in dry toluene (25 mL), under N_2, NaH (50-60% dispersion in mineral oil, 1.44 g, 36 mmol) was carefully added. The mixture was heated at 90°C and anhydrous CH_3CN was added dropwise (4.45 mL, 85.2 mmol). The reaction was heated for 18 hours and the product precipitated from the reaction mixture as Na salt. The reaction was allowed to cool down to room temperature and the solid formed was filtered and washed with ether, then it was redissolved in water and the solution acidified with 2N HCl solution to pH 3 when precipitation of title compound was observed. Filtration of the solid from the aqueous solution afforded 1.57 g of title product (50% yield).

$C_{10}H_9NO_2$

Mass (calculated) [175]; (found) $[M+H^+]$ =176

LC Rt = 1.69, 94% (5 min method)

b) 5-(3-Methoxy-phenyl)-2H-pyrazol-3-ylamine

To a solution of 3-(3-methoxy-phenyl)-3-oxo-propionitrile (8.96 mmoL) in absolute EtOH (20 mL) hydrazine monohydrate (0.52 mL, 15 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure.

The crude was treated with ether and filtered, to give 1.4 g of title product (83% of yield).

$C_{10}H_{11}N_3O$

Mass (calculated) [189]; (found) $[M+H^+]$ =190

LC Rt = 1.13, 100% (5 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 3.82 (3H, s); 5.93 (1H, s); 6.86-6.88 (1H, m); 7.19-7.31 (3H, m).

c) N-[5-(3-Methoxy-phenyl)-1H-pyrazol-3-yl]-4-morpholin-4-yl-butyramide

A solution of 4-bromobutyryl chloride (0.104 mL, 0.9 mmol) in dry DMA (1 mL) was cooled to -10°C (ice/water bath) under N_2; 5-(3-methoxy-phenyl)-2H-pyrazol-3-ylamine (170 mg, 0.9 mmol) and diisopropylethylamine (0.315 mL, 1.8 mmol) in dry DMA (1 ml) were added. Upon complete conversion to the intermediate 4-Bromo-N-[5-(3-methoxy-phenyl)-1H-pyrazol-3-yl]-butyramide (as monitored by LC-MS), morpholine (0.079 mL, 0.9 mmol) was added and the mixture was heated at 60°C for 16 hours. The residue was dissolved in DCM (2 mL) and washed with sat. Na_2CO_3 solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO_2 column (gradient from Acetonitrile 100% to MeCN/MeOH, NH_3 90/10). The fractions containing the title compound were collected to afford 17 mg (5.5% of yield).

$C_{18}H_{24}N_4O_3$

Mass (calculated) [344]; (found) $[M+H^+]$ =345

LC Rt = 1.36, 95% (10 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.77-1.85 (2H, m); 2.34-2.40 (8H, m); 3.59-3.62 (4H, m); 3.76 (3H, s); 6.79-6.85 (2H, m); 7.15-7.29 (3H, m).

Example 18

4-Azepan-1-yl-N-[5-(3-methoxy-phenyl)-1H-pyrazol-3-yl]-butyramide

A solution of 4-bromobutyryl chloride (0.104 mL, 0.9 mmol) in dry DMA (1 mL) was cooled to -10°C (ice/water bath) under N_2; 5-(3-Methoxy-phenyl)-2H-pyrazol-3-ylamine (170 mg, 0.9 mmol) and diisopropylethylamine (0.315 mL, 1.8 mmol) in dry DMA (1 ml) was added. Upon complete conversion to the ω-bromoamide intermediate (as monitored by LC-MS) 0.101 mL of azepine were added to the solution and the mixture was left stirring at 60°C for 16 hours.

The residue was dissolved in DCM (2 mL) and washed with saturated Na_2CO_3 solution. The organic phase was concentrated under reduced pressure and the crude product was purified by SiO_2 column (gradient from acetonitrile 100% to MeCN/MeOH, NH_3 90/10). The fractions containing the title product were collected and a further purification by preparative HPLC was carried out to afford 20 mg of the title compound as its formate salt (5.5% yield).

$C_{20}H_{28}N_4O_2$

Mass (calculated) [356]; (found) [$M+H^+$] =357

LC Rt=1.71, 99% (10 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.65-1.68 (4H, m); 1.80-1.90 (4H, m); 1.97-2.04 (2H, m); 2.49-2.52 (2H, m); 3.12-3.16 (2H, m); 3.24-3.30 (4H, m, broad); 3.75 (3H, s); 6.76 (1H, s); 6.82-6.85 (1H, m); 6.13-6.15 (2H, m); 6.23-6.27 (1H, m); 8.37 (1H, s, formate)

Example 19

4-Azepan-1-yl-N-[5-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-butyramide

Prepared following the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. Starting from commercially available 5-(4-fluoro-phenyl)-2H-pyrazol-3-ylamine and following the procedure, 25 mg of title compound were recovered as its formate salt after preparative HPLC purification (7% yield).

$C_{20}H_{28}N_4O_2$

Mass (calculated) [344]; (found) [$M+H^+$] =345

LC Rt=1.69, 100% (10 min method).

^{1}H-NMR (400 MHz, MeOH-d_4): 1.66-1.69 (4H, m); 1.80-1.90 (4H, m, broad); 1.97-2.05 (2H, m); 2.52-2.54 (2H, m); 3.12-3.18 (2H, m); 3.25-3.30 (4H, m, broad); 6.67 (1H, s, broad); 7.08-7.12 (2H, m); 7.59-7.63 (2H, m); 8.43 (1H, s, formate).

Example 20

N-[5-(6-Methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

a) 3-(6-Methyl-pyridin-3-yl)-3-oxo-propionitrile

The oxopropionitrile was synthesised following the general method for 3-oxopropionitriles (route A1).

$C_9H_8N_2O$

Mass (calculated) [160]; (found) [$M+H^+$] =161

LC Rt = 0.63, 100% (5 min method)

^{1}H-NMR (400 MHz, dmso-d_6): 2.55 (3H, s); 4.65 (2H, s); 7.43-7.45 (m, 1); 8.13-8.16 (1H, m); 8.94-8.95 (1H, m).

b) 5-(6-Methyl-pyridin-3-yl)-1H-pyrazol-3-ylamine

The aminopyrazole was synthesised following the general method described in route A2.

C_9H10N_4

Mass (calculated) [174]; (found) [$M+H^+$] =175

LC Rt = 0.23, 100% (5 min method)

c) *N-[5-(6-Methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide*

Prepared following the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides to afford 19 mg (6% yield) of title compound as its formate salt after preparative HPLC purification.

$C_{18}H_{25}N_5O$

Mass (calculated) [327]; (found) [$M+H^+$] =328

LC Rt = 0.33, 100% (10 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.40-1.90 (6H, m); 2.30-2.54 (5H, m); 3.05-3.09 (4H, m); 3.20-3.24 (2H, m); 6.72 (1H, s, broad); 7.30 (1H, d J =

8.0 Hz); 7.92-7.94 (1H, m); 8.35 (1H, s, formate); 8.67 (1H, s).

Example 21

N-[5-(5-Methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide

a) 3-(5-Methyl-pyridin-3-yl)-3-oxo-propionitrile

The oxopropionitrile was synthesised following the general method for 3-oxopropionitriles (route A1).

$C_9H_8N_2O$

Mass (calculated) [160]; (found) $[M+H^+]$ =161

LC Rt = 0.63, 100% (5 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 2.55 (3H, s); 4.65 (2H, s); 7.43-7.45 (m, 1); 8.13-8.16 (1H, m); 8.94-8.95 (1H, m).

b) 5-(5-Methyl-pyridin-3-yl)-1H-pyrazol-3-ylamine

The aminopyrazole was synthesised following the general method described in route A2.

C_9H10N_4

Mass (calculated) [174]; (found) $[M+H^+]$ =175

LC Rt = 0.23, 100% (5 min method)

c) *N-[5-(5-Methyl-pyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-yl-butyramide*

Prepared following the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides to afford 25 mg of the title compound as its formate salt (7.4% yield) after preparative HPLC purification.

$C_{18}H_{25}N_5O$

Mass (calculated) [327]; (found) $[M+H^+]$ =328

LC Rt = 0.33, 100% (10 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.52-1.70 (2H, m, broad); 1.72-1.84

(4H, m, broad); 1.98-2.06 (2H, m); 2.45 (3H, s); 2.48-2.54 (2H, m); 3.04-3.10 (4H, m); 3.20-3.24 (2H, m, broad); 6.74 (1H, s, broad); 7.88 (1H, s); 7.28 (1H, s); 8.37 (1H, s, formate); 8.67 (1H, s).

Example 22

4-(4-Acetyl-[1,4]diazepan-1-yl)-N-[5-(6-methoxy-naphthalen-2-yl)-1H-pyrazol-3-yl]-butyramide

a) 6-Methoxy-naphthalene-2-carboxylic acid methyl ester

To a solution of 6-methoxy-naphthalene-2-carboxylic acid (1.01 g, 5 mmol) in methanol (10 mL), a catalytic amount of sulphuric acid was added. The mixture was then heated at 80°C for 8 hours. Upon reaction completion (as monitored by LcMS), the solution was slowly cooled and the precipitation of the product was observed. Filtration of the white solid afforded 1.01 g (94% yield) of title compound.

$C_{13}H_{12}O_3$

Mass (calculated) [216]; (found) $[M+H^+]$ =217

LC Rt = 2.43, 100% (5 min method)

b) 3-(6-Methoxy-naphthalen-2-yl)-3-oxo-propionitrile

To a solution of 6-methoxy-naphthalene-2-carboxylic acid methyl ester (1.0 g, 4.7 mmol) in dry toluene (8 mL), NaH (0.55 mg, 9.4 mmol) were added and the mixture was heated at 90°C. To the hot solution, acetonitrile (1.2 mL) was added dropwise. The reaction was then heated for 18 hours and the product precipitated from the reaction mixture as its sodium salt.

The reaction was allowed to cool down to room temperature and the solid formed was first filtered and washed with ether, then it was dissolved in water and the solution was acidified with HCl 2N to pH 3, upon which precipitation of the title compound was observed. Filtration of the solid from the aqueous solution afforded 1.1 g of title compound (100% of yield).

$C_{13}H_{12}O_3$

Mass (calculated) [225]; (found) [M+H$^+$] =226

LC Rt = 2.13, 90% (5 min method)

c) 5-(6-Methoxy-naphthalen-2-yl)-1H-pyrazol-3-ylamine

To a solution of 3-(6-methoxy-naphthalen-2-yl)-3-oxo-propionitrile (1.1 g, 4.8 mmoL) in absolute EtOH (10 mL) hydrazine monohydrate (0.96 mL, 19.2 mmol) was added and the reaction was heated at reflux for 18 hrs. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude was treated with ether and filtered to afford 0.95 g of title compound (83% of yield).

$C_{14}H_{13}N_3O$

Mass (calculated) [239]; (found) [M+H$^+$] =240

LC Rt = 1.49, 90% (5 min method)

d) 4-(4-Acetyl-[1,4]diazepan-1-yl)-N-[5-(6-methoxy-naphthalen-2-yl)-1H-pyrazol-3-yl]-butyramide

Following the general method for the synthesis of ω-bromo-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides and the general method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides, purification by preparative HPLC afforded 15 mg (3% yield) of title compound as its formate salt.

$C_{25}H_{31}N_5O_3$

Mass (calculated) [449]; (found) [M+H$^+$] =450

LC Rt = 1.91, 100% (10 min method)

^{1}H-NMR (400 MHz, MeOH-d_4): 1.88-2.0 (4H, m); 2.06 (3H, s); 2.48-2.52 (2H, m); 2.94-3.02 (2H, m); 3.08-3.18 (4H, m); 3.52-3.58 (2H, m); 3.64-3.72 (2H, m); 3.82 (3H, s); 6.78-6.82 (1H, m); 7.04-7.10 (1H, m); 7.16-7.18 (1H, m); 7.62-7.78 (3H, m); 7.98-8.02 (1H, m); 8.28 (1H, s, formate).

Example 23

6-(4-Acetyl-[1,4]diazepan-1-yl)-hexanoic acid [5-(4-methoxy-phenyl)-

1H-pyrazol-3-yl]-amide

The product was prepared according to the general synthetic method for the one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides. A solution of 5-bromohexanoyl chloride (0.144 mL, 0.94 mmol) in dry DMA (1 mL) was cooled to -10°C (ice/water bath) under N_2; 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine (178 mg, 0.94 mmol) and diisopropylethylamine (0.324 mL, 1.88 mmol) were added in dry DMA (1 ml).

The reaction was left stirring for 1h at 0°C and then 1-[1,4]diazepan-1-yl-ethanone (0.310 mL, 2.35 mmol,) and NaI (0.94mmol, 1 eq) were added.

The reaction mixture was heated at 60°C until LC-MS analysis showed complete conversion of the bromo-intermediate, at which point the reaction was cooled down and the solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL) and washed with saturated Na_2CO_3 solution.

The organic phase was concentrated under reduced pressure and half of the crude was purified by SiO_2 column (gradient from 100% DCM to DCM-NH3MeOH 2N solution 8:2). The fractions containing the title compound were collected (35 mg).

$C_{23}H_{33}N_5O_3$

Mass (calculated) [427]; (found) [$M+H^+$] =428

LC Rt = 1.61, 96% (10 min method)

^{1}H-NMR (400 MHz, dmso-d6): 1.24-1.29 (2H, m); 1.36-1.44 (2H, m); 1.54-1.58 (2H, m); 1.62-1.76 (2H, m); 1. 94-1.96 (3H, m); 2.25-2.28 (2H, m); 2.35-2.41 (2H, m); 2.51-2.54 (2H, m); 2.60-2.62 (1H, m); 3.38-3.44 (5H, m); 3.77 (3H, s); 6.73 (1H, s); 6.98 (2H, d, J=8.8 Hz); 7.61 (2H, d, J=8.8); 10.32 (1H, s).

Example 24

N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-

butyramide

a) Methyl-4-bromo-2-methyl-butyric acid

4-Bromo-2-methyl-butyric acid (2.16 g, 1 eq, prepared according to the procedure described in *J.Am.Chem.Soc.* **1990**, *112*, 2755) was dissolved in MeOH (10 mL) and a few drops of conc. H_2SO_4 were added. The reaction was stirred at reflux for 16 hours. After reaction completion, as monitored by LC-MS, MeOH was removed under reduced pressure, the oily residue was diluted with water, the pH adjusted to 9 with 10% NaOH, and the product was extracted with Et_2O (2 X 20 mL) and dried over Na_2SO_4. The title compound was obtained as a colourless oil (1.29 g, 55% yield) after solvent removal.

NMR (400 MHz, CDCl3); 1.19 (3H, d); 1.94-1.89 (2H, m); 2.29-2.23 (2H, m); 3.43-3.40 (1H, m); 3.69 (3H, s).

b) 2-Methyl-4-piperidin-1-yl-butyric acid. HCl

Methyl-4-bromo-2-methyl-butyric acid (1.29 g, 1 eq) was dissolved in toluene (15 mL) and piperidine (1.07 mL, 3 eq) was added; the reaction was stirred for 3 hours. After reaction completion, as monitored by LC-MS, toluene was removed under reduced pressure and the crude ester was dissolved in 1M NaOH (14 mL, 1.1 eq) and MeOH (2 mL). The reaction was stirred at reflux for 16 hours; after hydrolysis was complete, the reaction was concentrated under reduced pressure and the pH adjusted to 4 with 6N HCl. EtOH was added to help precipitation of NaCl. The organic phase was filtered and EtOH removed under reduced pressure. The resulting oil was treated with 2M HCl in Et_2O to obtain 2-methyl-4-piperidin-1-yl-butyric acid. HCl (0.96 g, 66% yield).

$C_{10}H_{19}NO_2$

Mass (calculated) [185.27]; (found) $[M+H^+]$=186.27

LC Rt=0.23, 95% (5 min method)

c) N-[5-(4-Methoxy-phenyl)-2H-pyrazol-3-yl]-2-methyl-4-piperidin-1-yl-butyramide

2-Methyl-4-piperidin-1-yl-butyric acid. HCl (0.45 g, 1.2 eq) was suspended in 1,2-DCE (15 mL) and triethylamine (0.29 mL, 1.2 eq) was added: 1,1'-carbonyldiimidazole (0.303 g, 1.1 eq) was added in one portion and the reaction was stirred at room temperature for 2 hours. 5-(4-Methoxy-phenyl)-2H-pyrazol-3-ylamine (0.325 g, 1 eq) was then added and the reaction stirred at room temperature for further 16 hours. After reaction completion, as monitored by LC-MS, the solvent was removed under reduced pressure and the crude amide was purified by column chromatography (Flash-SI 10 g; CH_3CN:MeOH 9:1, CH_3CN:2N NH_3 MeOH 9:1) to give the title compound as thick colourless oil (0.120 g, 0.33 mmol).

$C_{20}H_{28}N_4O_2$

Mass (calculated) [356.48]; (found) $[M+H^+]$=357.25

LC Rt=1.67, 97% (10 min method)

NMR (400 MHz, dmso-d6); 1.18 (3H, d); 1.35-1.31 (2H, m); 1.46-1.41 (4H, m); 1.77-1.72 (1H, m); 2.19-2.16 (2H, m); 2.27-2.23 (4H, m); 2.61-2.58 (2H, m); 3.76 (3H, s); 6.76 (1H, s); 6.92 (2H, d); 7.61 (2H, d); 10.33 (1H, s).

Example 25

N-[4-(4-Methoxy-phenyl)-1H-imidazol-2-yl]-4-piperidin-1-yl-butyramide

To a suspension of 4-piperidin-1-yl-butyric acid (200 mg, 1.17 mmol, 1.0 eq) in 1,2-dichloroethane (2 mL), *N,N'*-carbonyldiimidazole (179.9 mg, 1.11 mmol, 0.95 eq) was added and the mixture was stirred at room temperature for 1 hour until complete activation of the aminoacid and dissolution of the suspension. 4-(4-Methoxy-phenyl)-1H-imidazol-2-ylamine (prepared according to the procedure reported in JOC 1994, 59, 24, 7299;

110.5 g, 0.58 mmol, 0.50 eq) was added and the reaction stirred for 1 day at 50°C. The slow conversion was monitored by LC-MS. Another aliquote of activated acid (4-piperidin-1-yl-butyric acid, 200 mg and carbonyldiimidazole, 179.9 mg in 2 mL of 1,2-dichloroethane) were added and the reaction stirred for further two days at 50°C.

The solvent was evaporated under reduced pressure and the crude mixture purified by preparative HPLC to obtain a 9:1 mixture of the product and unreacted 4-(4-methoxy-phenyl)-1H-imidazol-2-ylamine. The crude was purified by treatment with isocyanate resin and SCX column to give 78.0 mg (Yield: 39%) of the title compound as a white solid.

C19H26N4O2 Mass (calculated) [342]; (found) [$M+H^+$] =343

LC Rt = 1.00 (and solvent front), 99% (10 min method)

^{1}H-NMR (400 MHz, DMSO): 1.30-1.36 (2H, m); 1.43-1.49 (4H, m); 1.67-1.75 (2H, m); 2.22-2.34 (8H, m); 3.73 (3H, s, -OCH3); 6.87 (2H, d, J=8.8 Hz); 7.10 (1H, s); 7.60 (2H, d, *J*= 8.8 Hz); 11.26 (1H, s, NHCO), 11.52 (1H, s, NH).

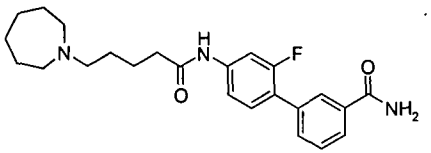
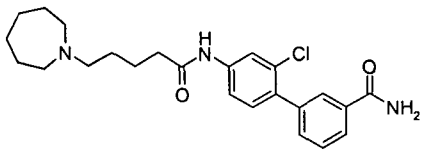
^{13}C-NMR (400 MHz, DMSO): 21.54 (1C); 23.63 (1C); 24.92 (2C); 33.24 (1C); 53.6 (1C, -OCH3); 55.02 (2C); 57.46 (1C); 113.88 (2C); 125.18 (2C), 141.13 (1C); 157.67 (1C); 162.33 (2C); 163.66 (1C); 171.15 (1C, CO).

Table 1- Examples 26-171

Table 1 shows a selection of the compounds synthesised, which were prepared according to the method indicated in the last column of the table and discussed in detail in the Experimental Procedures with the synthesis of *Examples 1-25.*

When the compound is indicated as the HCl salt, the salt was formed by dissolution of the free base in methanol and addition of 1 eq 1M HCl in ether followed by evaporation of the solvents. When the compound is

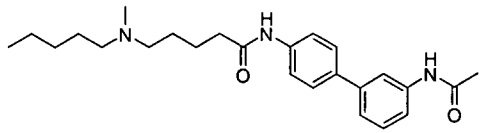
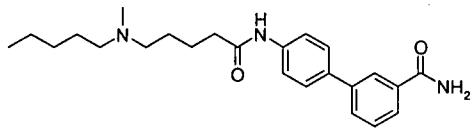
indicated as HCOOH (formic acid) salt, the compound was purified by preparative HPLC.

Example	Structure	Salt	Parent Formula	Parent MW	Mass found	LC purity %	LC Rt	LC method (min)	Synthetic Method
26		HCOOH	C24H30N3O2F	411.51	412.46	100	1.93	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
27			C24H30N3O2Cl	427.97	428.4	97	2.04	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

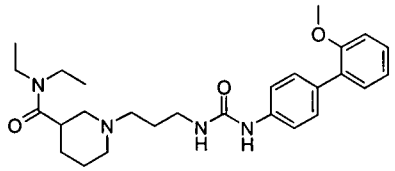
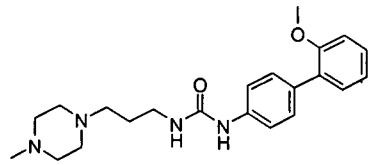
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28		HCOOH	C25H29N3O2	403.52	404.4	95	1.78	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
29			C24H28N4O	388.51	389.41	100	0.32/0.46	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

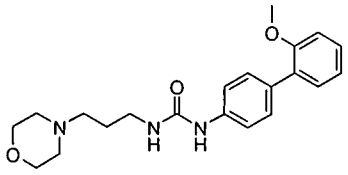
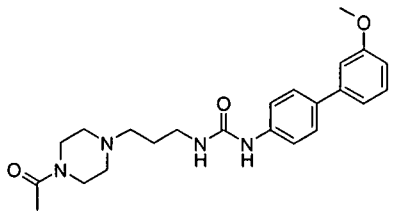
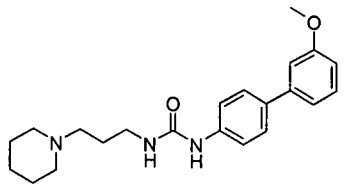
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30			C25H35N3O2	409.56	410.45	100	2.24	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
31		HCOOH	C24H33N3O2	395.54	396.46	100	2.05	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

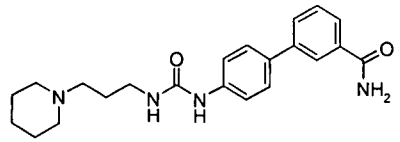
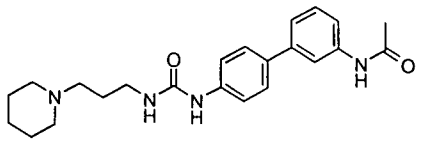
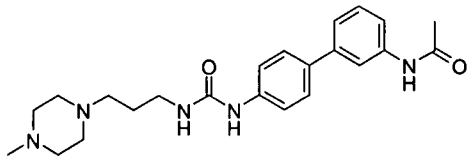
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32			C27H38N4O3	466.62	467	98	3.36	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
33			C22H30N4O2	382.50	383	91	2.49	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

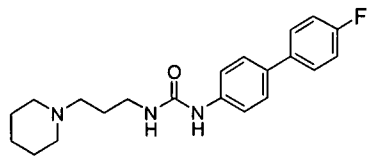
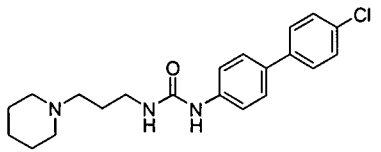
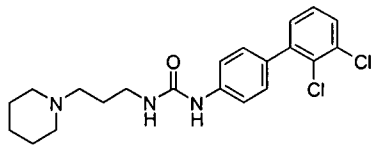
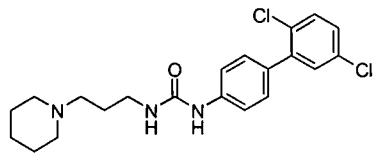
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34			C21H27N3O3	369.46	370	96	2.99	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
35			C23H30N4O3	410.51	411	98	2.96	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
36			C22H29N3O2	367.48	368	96	3.14	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

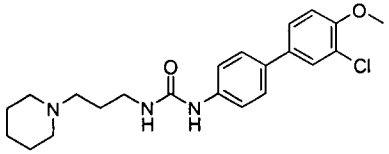
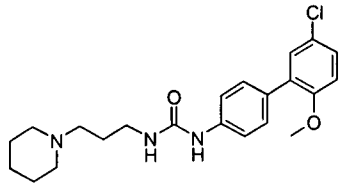
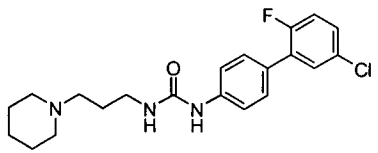
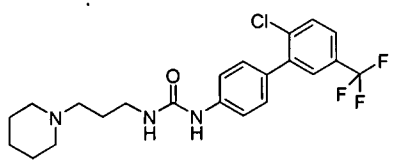
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37			C22H28N4O2	380.48	381	99	2.40	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
38			C23H30N4O2	394.51	395	100	2.64	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
39			C23H31N5O2	409.52	410	100	2.15	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

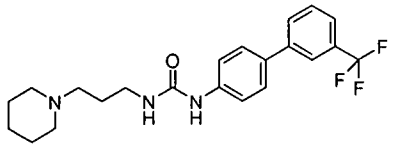
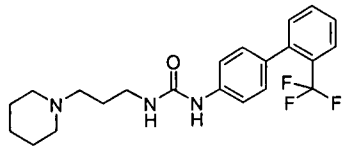
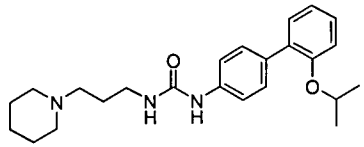
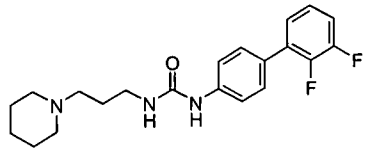
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40			C21H26N3OF	355.45	356	98	2.39	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
41			C21H26N3OCl	371.90	372	97	2.63	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
42			C21H25N3OCl2	406.35	406	96	2.82	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
43			C21H25N3OCl2	406.35	406	96	2.81	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas

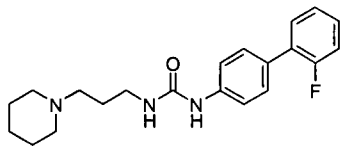
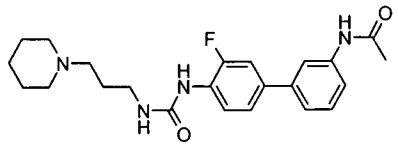
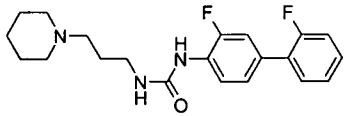
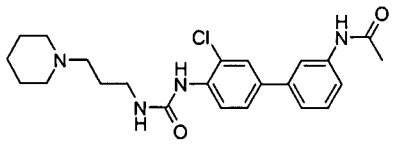
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44			C22H28N3O2Cl	401.93	402	95	2.46	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
45			C22H28N3O2Cl	401.93	402	98	2.60	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
46			C21H25N3OFCl	389.89	390	100	2.69	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
47			C22H25N3OF3Cl	439.90	439	96	2.86	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas

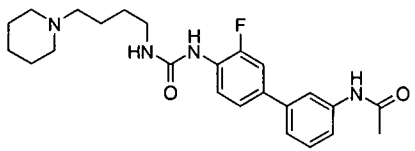
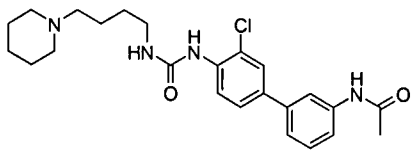
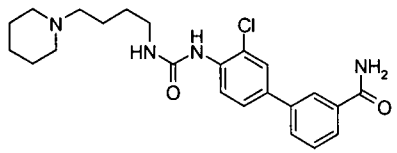
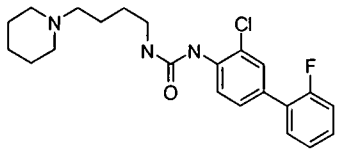
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48			C22H26N3OF3	405.46	406	99	2.73	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
49			C22H26N3OF3	405.46	406	99	2.61	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
50			C24H33N3O2	395.54	396	100	2.61	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
51			C21H25N3OF2	373.44	374.00	98	2.46	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas

(continue)

52			C21H26N3OF	355.45	356	99	2.30	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
53			C23H29FN4O2	412	413	92	2.23	10	General procedure for urea synthesis and Suzuki coupling under thermal conditions for ureas
54			C21H25F2N3O	373	374	99	2.83	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
55			C23H29ClN4O2	428	429	99	2.31	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)

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56			C24H31FN4O2	426	427	95	2.29	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
57			C24H31ClN4O2	442	443	97	2.38	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
58		HCOOH	C23H29ClN4O2	428	429	99	2.34	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
59			C22H27ClFN3O	403	404	96	2.93	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)

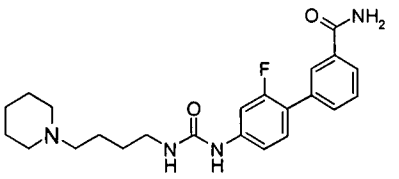
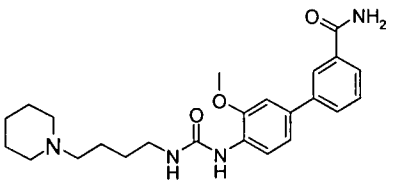
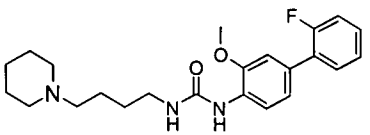
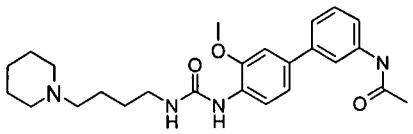
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60		HCOOH	C22H27FN4O2	398	399	98	1.98	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
61		HCOOH	C22H27ClN4O2	414	415	95	2.22	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
62			C24H30F2N4O2	444	445	100	2.23	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas (Tri-o-tolylphosphine)

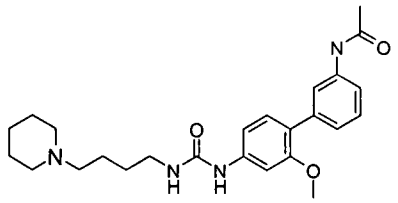
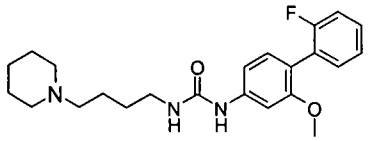
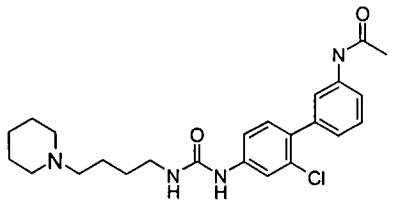
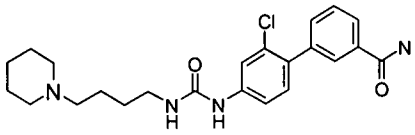
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63		C23H28F2N4O2	430	431	97	2.04	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas (Tri-o-tolylphosphine)
64		C22H26F3N3O HCOOH	405	406	100	2.81	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas (Tri-o-tolylphosphine)
65		C24H31FN4O2	426	427	100	2.38	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas (Tri-o-tolylphosphine)

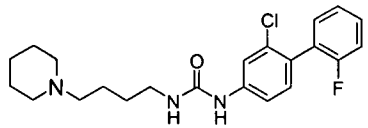
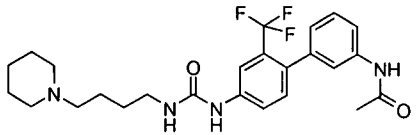
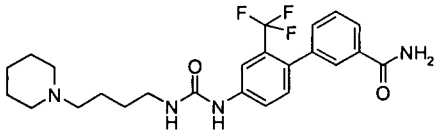
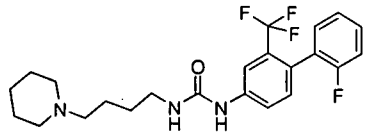
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66			C23H29FN4O2	412	413	99	2.16	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas (Tri-o-tolylphosphine)
67			C24H32N4O3	424	425	95	2.14	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
68			C23H30FN3O2	438	400	100	3.08	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
69		HCOOH	C25H34N4O3	438	439	98	2.43	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)

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70		HCOOH	C25H34N4O3	438	439	95	2.34	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
71		HCOOH	C23H30FN3O2	399	400	100	2.76	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
72		HCOOH	C24H31ClN4O2	442	443	97	2.56	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
73		HCOOH	C23H29ClN4O2	428	429	95	1.81	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)

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74			C22H27ClFN3O	403	404	97	3.13	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
75		HCOOH	C25H31F3N4O2	476	477	100	2.76	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
76		HCOOH	C24H29F3N4O2	462	463	100	2.46	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)
77		HCOOH	C23H27F4N3O	437	438	100	3.19	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas ($Pd(Ph_3)_4$)

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78		HCOOH	C24H33N3O2	395.55	396	100	2.24	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
79			C22H30N4O	366.51	367	95	0.24-0.76	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
80		HCOOH	C23H30FN3O	383.51	384	100	2.24	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)

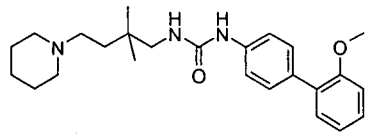
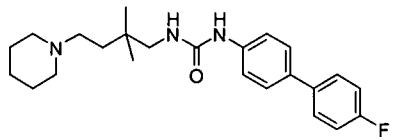
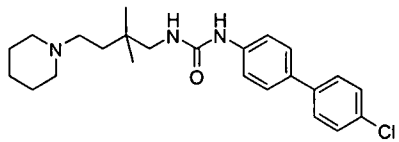
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81			C23H30ClN3O	399.97	400	95	2.59	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
82			C23H32N4O2	396.54	397.35	100	1.91	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
83		HCOOH	C25H34N4O2	422.58	423	100	1.76	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)

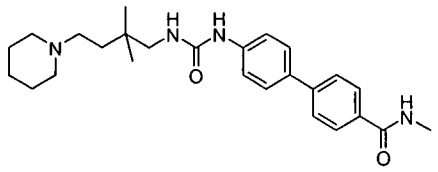
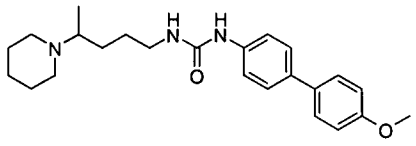
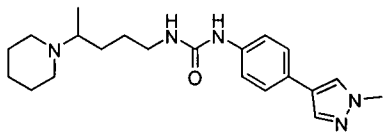
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84		HCOOH	C21H31N5O	369.51	370	100	0.23-1.51	10	Urea formation on 1-methyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
85			C23H32N4O	380.54	381	100	0.24-1.05	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
86			C25H35N3O2	409.58	410	100	2.39	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)

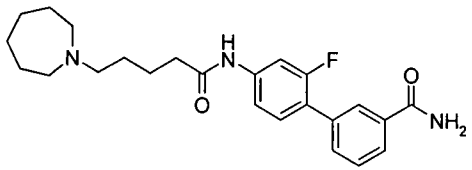
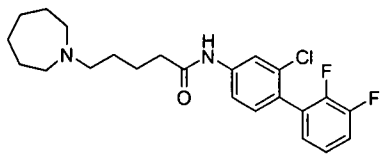
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87		HCOOH	C25H35N3O2	409.58	410	97	2.31	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
88		HCOOH	C24H32FN3O	397.54	398	100	2.39	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
89		HCOOH	C24H32ClN3O	414	414	100	2.66	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)

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90		HCOOH	C26H36N4O2	436.6	437	100	1.94	10	Urea formation on 2,2-dimethyl-4-piperidin-1-yl-butylamine (isocyanate method) and cross-coupling (microwave conditions)
91		HCOOH	C24H33N3O2	395.55	396	100	2.21	10	Urea formation on 4-piperidin-1-yl-pentylamine (isocyanate method) and cross-coupling (microwave conditions)
92		HCOOH	C21H31N5O	369.51	370	100	023-1.47	10	Urea formation on 4-piperidin-1-yl-pentylamine (isocyanate method) and cross-coupling (microwave conditions)

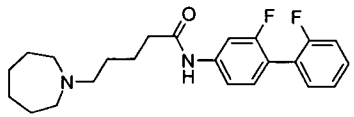
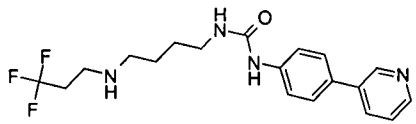
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93		HCOOH	C24H30FN3O2	411.52	412.46	100	1.93	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides
94		HCOOH	C23H27ClF2N2O	420.93	421.41	100	2.85	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides

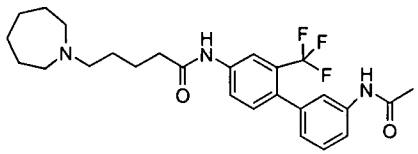
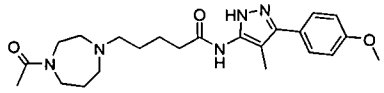
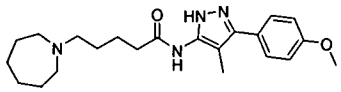
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95			C25H31F3N2O2	448.53	449.16	98	3.26	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides
96		HCOOH	C24H28F4N2O	436.5	437.13	95	3.24	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides

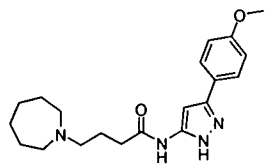
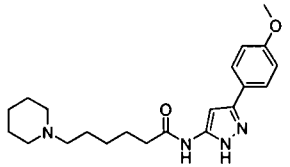
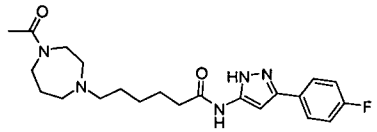
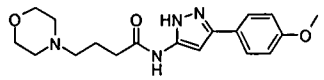
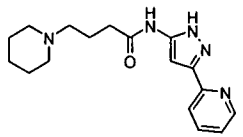
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97		HCOOH	C23H28F2N2O	386.49	387.17	94	3.01	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides
98		HCOOH	C19H23F3N4O	380.42	381.21	95	0.63	10'	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine, followed by Suzuki coupling under microwave conditions for amides

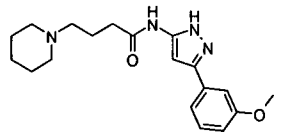
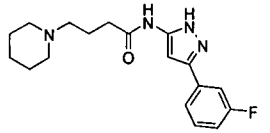
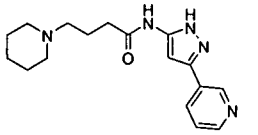
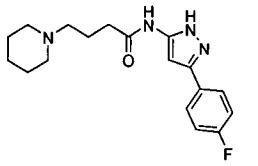
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99			C26H32N3O2F3	475.55	476.46	100	2.39	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
100			C23H33N5O3	427.55	428.31	99	1.48	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides
101			C22H32N4O2	384.53	385.28	99	1.74	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides

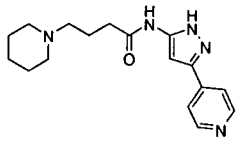
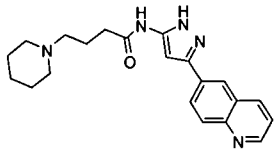
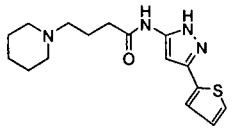
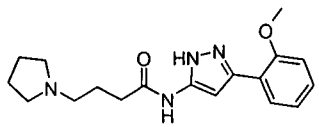
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102		HCOOH	C20H28N4O2	356.46	357	100	1.81	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides
103		HCOOH	C21H30N4O2	370.48	371	99	1.73	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides
104			C22H30N5O2F	415.50	416	100	1.58		one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides
105			C18H24N4O3	344.40	345	97	1.38		one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides
106			C17H23N5O	313	314	100	0.53	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)

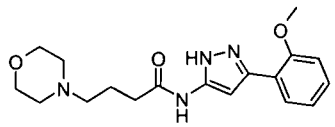
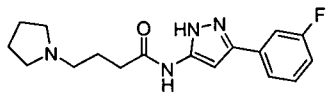
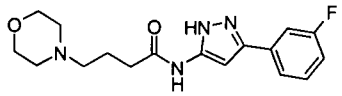
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107			C19H26N4O2	342	343	100	1.59	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
108		HCOOH	C18H23FN4O	330	331	100	1.56	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
109			C17H23N5O	313	314	100	0.22 and 0.32	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
110			C18H23FN4O	330	331	100	1.54	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)

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111			C17H23N5O	313	314	100	0.22	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
112			C21H25N5O	363	364	100	1.33	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
113			C16H22N4OS	318	319	100	1.33	10	one-pot synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides (room temperature)
114		HCOOH	C18H24N4O2	328.4	329	100	1.48	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

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115		HCOOH	C18H24N4O3	344.4	345	99	1.36	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
116		HCOOH	C17H21N4OF	316.4	317	100	1.43	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
117		HCOOH	C17H21N4O2F	332.4	333	100	1.31	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

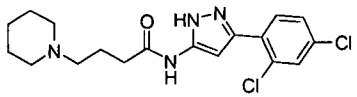
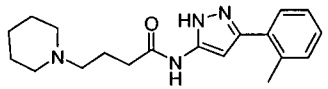
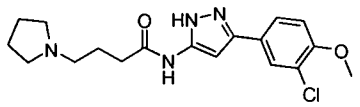
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118		HCOOH	C18H21N4OF3	366.4	367	100	1.89	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
119		HCOOH	C18H21N4O2F3	382.4	383	100	1.81	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
120		HCOOH	C19H25N4O2Cl	376.9	377	100	1.73	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

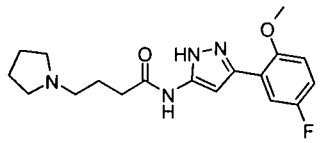
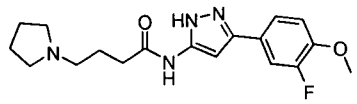
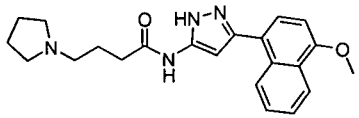
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121		HCOOH	C19H25N4O2F	360.4	361	100	1.66	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
122		HCOOH	C19H25N4O2F	360.4	361	100	1.56	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
123		HCOOH	C23H28N4O2	392.5	393	100	2.06	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

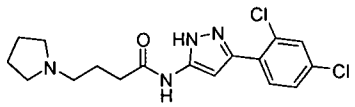
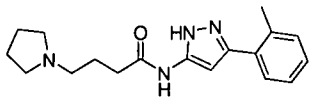
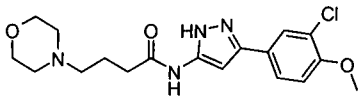
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124		HCOOH	C18H22N4OCl2	381.3	382	100	1.96	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
125		HCOOH	C19H26N4O	326.4	327	100	1.6	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
126		HCOOH	C18H23N4O2Cl	362.9	363	100	1.71	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

127		HCOOH	C18H23N4O2F	346.4	347	100	1.58	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
128		HCOOH	C18H23N4O2F	346.4	347	100	1.49	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
129		HCOOH	C22H26N4O2	378.5	379	100	1.96	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

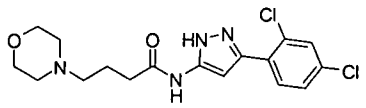
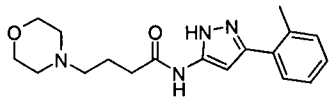
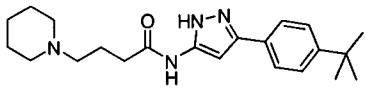
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130		HCOOH	C17H20N4OCl2	367.3	367	100	1.89	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
131		HCOOH	C18H24N4O	312.4	313	100	1.49	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
132		HCOOH	C18H23N4O3Cl	378.9	379	100	1.58	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

133		HCOOH	C18H23N4O3F	362.4	363	100	1.48	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
134			C18H23N4O3F	362.4	363	100	1.39	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
135		HCOOH	C22H26N4O3	394.5	395	100	1.86	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

136		HCOOH	C17H20N4O2Cl2	383.3	383	100	1.78	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
137		HCOOH	C18H24N4O2	328.4	329	99	1.39	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
138		HCOOH		368	369	100	2.33	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

139		HCOOH	376	377	100	1.89	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
140		HCOOH	312	313	95	1.48	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
141		HCOOH	362	363	100	1.83	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

142		HCOOH	298	299		1.34	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
143		HCOOH	C20H27N4O2F	374.45	375.45	99	1.81	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
144		HCOOH	C20H27N4O2F	374.45	375.45	97	1.73	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

145		HCOOH	C24H30N4O2	406.52	407.52	98	2.13	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
146		HCOOH	C19H24N4OCl2	395.33	396.33	99	2.06	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
147		HCOOH	C20H28N4O	340.46	341.46	96	1.73	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

148		N	C21H30N4O2	370.49	371.49	99	2.18	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
149		HCOOH	C18H23N4O3Cl	378.85	379.85	99	1.71	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
150		HCOOH	C17H22N4O2	314.38	315.38	99	Double peak 0.24 1.28	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

151		HCOOH	C23H34N4O	382.54	383.54	99	2.45	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
152		HCOOH	C20H27N4O2Cl	390.91	391.91	99	2.08	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route
153		HCOOH	C19H26N4O	326.44	327.44	99	1.69	10	General method for the synthesis of ω-amino-alkanoic acid (1H-pyrazol-3-yl-5-aryl)-amides via the amino acid route

(continue)

154		HCOOH	C24H30N3O2F	411.51	412.46	100	1.78	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
155		HCOOH	C23H27N2OF3	404.47	405.47	100	2.62	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

(continue)

156		HCOOH	C24H27N2OF5	454.48	455.42	100	2.99	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
157		HCOOH	C23H27N2OF3	404.47	405.47	100	2.74	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

(continue)

158		HCOOH	C23H28N3OF3	419.48	420.46	100	1.78	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
159		HCOOH	C25H32N3O2F	425.54	426.51	100	2.02	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with low molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides

(continue)

160			C23H32N2O2	368.51	369.44	100	2.3	10	General procedure for amide synthesis from ω-haloalkanoyl chlorides, one-pot with high molar excess of amine X, followed by Suzuki coupling under microwave conditions for amides
161			C22H29N3O2	367.48	368	99	3.14	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

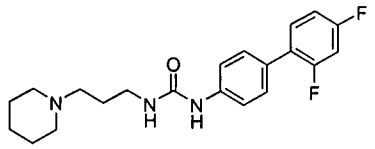
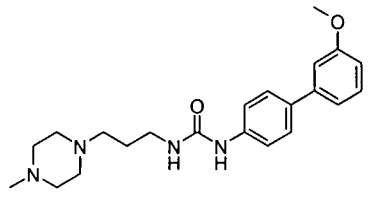
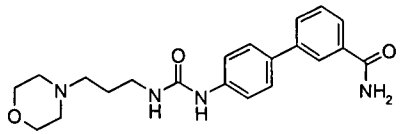
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162			C27H37N5O3	479.61	480	98	2.67	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
163			C26H35N4O2Cl	471.03	471	97	3.55	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

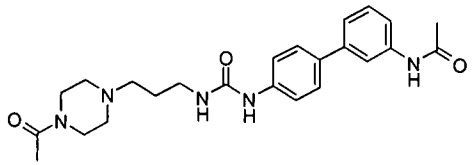
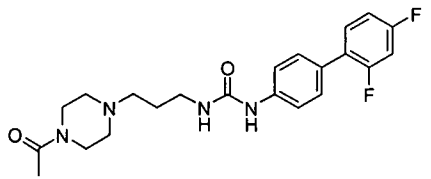
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164			C28H39N5O3	493.64	494	93	2.86	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
165			C26H34N4O2F2	472.57	473	99	2.51	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

(continue)

166			C21H25N3OF2	373.44	374	99	3.08	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
167			C22H30N4O2	382.50	383	100	2.63	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
168			C21H26N4O3	382.46	383	98	2.24	10	General procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

(continue)

169			C24H31N5O3	437.53	438	100	2.44	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas
170			C22H26N4O2F2	416.46	417	98	3.12	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

(continue)

171			C22H29N5O2	395.50	396	90	1.82-1.96 (double peak)	10	General procedure for amine synthesis (phthalimide method) followed by general procedure for urea synthesis and Suzuki coupling under microwave conditions for ureas

Biological activity

Cloning of alpha7 nicotinic acetylcholine receptor and generation of stable recombinant alpha7 nAChR expressing cell lines

Full length cDNAs encoding the alpha7 nicotinic acetylcholine receptor were cloned from a rat brain cDNA library using standard molecular biology techniques. Rat GH4C1 cells were then transfected with the rat receptor, cloned and analyzed for functional alpha7 nicotinic receptor expression employing a FLIPR assay to measure changes in intracellular calcium concentrations. Cell clones showing the highest calcium-mediated fluorescence signals upon agonist (nicotine) application were further subcloned and subsequently stained with Texas red-labelled α-bungarotoxin (BgTX) to analyse the level and homogeneity of alpha7 nicotinic acetylcholine receptor expression using confocal microscopy. Three cell lines were then expanded and one characterised pharmacologically (see *Table 2* below) prior to its subsequent use for compound screening.

Table 2 - Pharmacological characterisation of alpha7 nAChR stably expressed in GH4C1 cells using the functional FLIPR assay

Compound	**EC_{50} [microM]**
Acetylcholine	3.05 ± 0.08 (n=4)
Choline	24.22 ± 8.30 (n=2)
Cytisine	1.21 ± 0.13 (n=5)
DMPP	0.98 ± 0.47 (n=6)
Epibatidine	0.0 12± 0.002 (n=7)
Nicotine	1.03 ± 0.26 (n=22)

Development of a functional FLIPR assay for primary screening and concentration-response analysis

A robust functional FLIPR assay (Z' = 0.68) employing the stable recombinant GH4C1 cell line was developed to screen the alpha7 nicotinic

acetylcholine receptor. The FLIPR system allows the measurements of real time Ca^{2+}-concentration changes in living cells using a Ca^{2+} sensitive fluorescence dye (such as Fluo4). This instrument enables the screening for agonists and antagonists for alpha 7 nAChR channels stably expressed in GH4C1 cells.

Cell culture

GH4C1 cells stably transfected with rat- alpha7-nAChR (see above) were used. These cells are poorly adherent and therefore pretreatment of flasks and plates with poly-D-lysine was carried out. Cells are grown in 150 cm^2 T-flasks, filled with 30ml of medium at 37°C and 5% CO_2.

Data analysis

EC_{50} and IC_{50} values were calculated using the IDBS *XLfit4.1* software package employing a sigmoidal concentration-response (variable slope) equation:

Y= Bottom + ((Top-Bottom)/(1+((EC_{50}/X) ^HillSlope))

Assay validation

The functional FLIPR assay was validated with the alpha7 nAChR agonists nicotine, cytisine, DMPP, epibatidine, choline and acetylcholine. Concentration-response curves were obtained in the concentration range from 0.001 to 30 microM. The resulting EC_{50} values are listed in *Table* 2 and the obtained rank order of agonists is in agreement with published data (Quik et al., 1997)(22).

The assay was further validated with the specific alpha7 nAChR antagonist MLA (methyllycaconitine), which was used in the concentration range between 1 microM to 0.01 nM, together with a competing nicotine concentration of 10 microM. The IC_{50} value was calculated as 1.31±0.43 nM in nine independent experiments.

Development of functional FLIPR assays for selectivity testing

Functional FLIPR assays were developed in order to test the selectivity

of compounds against the alpha1 (muscular) and alpha3 (ganglionic) nACh receptors and the structurally related 5-HT3 receptor. For determination of activity at alpha1 receptors natively expressed in the rhabdomyosarcoma derived TE 671 cell line an assay employing membrane potential sensitive dyes was used, whereas alpha3 selectivity was determined by a calcium-monitoring assays using the native SH-SY5Y cell line. In order to test selectivity against the 5-HT3 receptor, a recombinant cell line was constructed expressing the human 5-HT3A receptor in HEK 293 cells and a calcium-monitoring FLIPR assay employed.

Screening of compounds

The compounds from *Examples 1-171* described showed agonist activity in the functional FLIPR primary screening assay employing the stable recombinant GH4C1 cell line expressing the alpha7 nAChR. The most potent hits identified were validated further by generation of concentration-response curves. The potency of compounds from *Examples 1-153* as measured in the functional FLIPR screening assay was found to range between 10 nM and 30 microM, with the majority showing a potency ranging between 10 nM and 10 microM.

The best exemplified compounds were also demonstrated to be selective against the alpha1 nACh, alpha3 nACh and 5HT3 receptors.

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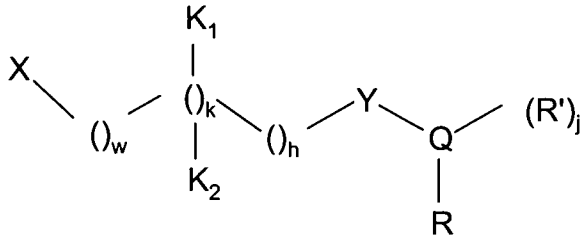
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CLAIMS

1. A compound of formula (I)



(I)

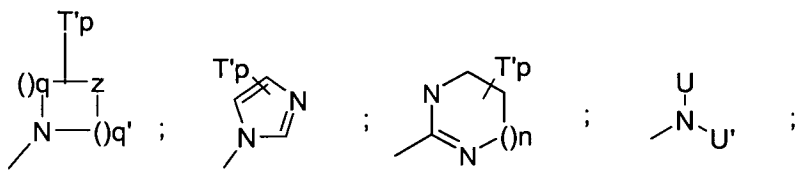
wherein:

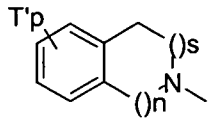
w, h and k are, independently from one another, 0, 1, 2, or 3 with the condition that $3 \leq w + h + k \leq 5$;

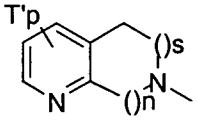
K1 and K2, which are bound to either the same or a different carbon atom where k>1, represent, independently from one another, hydrogen; halogen; (C_1-C_5) alkyl, alkoxy, fluoroalkyl, alkylene, fluoroalkylene; hydroxyalkyl; or K1 and K2 taken together form an alkylidene or a fluoroalkylidene group; or K1 and K2 taken together with the carbon atom to which they are attached form a (C_3-C_6) cycloalkyl group; or when k is ≥ 2, two $()_k$ carbon atoms may form an unsaturated bond; or when w is 1, 2, or 3, and k is 1, K1 and K2 taken together with the carbon atom to which they are attached, may form an oxo group;

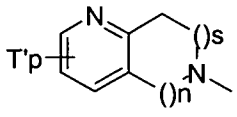
j is 0, 1 or 2;

X is a group of formula

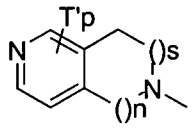


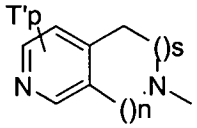


;


;


;



;


;

Z is CH_2, N, O, S, S(=O), or $S(=O)_2$;

p is 0, 1, 2 or 3;

n is 0, 1 or 2;

s is 1 or 2;

q and q' are, independently from one another, integers from 1 to 4;

T' represent, independently from one another, hydroxy; mercapto; amino; cyano; nitro; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; or, when p is 2 or 3, two T' substituents form a 5- to 8-membered ring with spiro or fused junction;

U and U' represent, independently from one another, hydrogen; cyano; hydroxy; amino; a mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino group; a linear or branched (C_1-C_6) alkoxy group; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with hydroxy, mercapto, amino, cyano, nitro, oxo, trihalomethyl, trihalomethoxy, carbamoyl, sulphamoyl, linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl,

alkylcarbonylamino, mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl, mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl, (C_5-C_{10}) aryl- or heteroarylsulphonylamino, (C_1-C_3) alkylsulphonylamino, (C_5-C_{10}) aryl- or heteroarylsulphonyl, (C_1-C_3) alkylsulphonyl, mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl, mono- or di- (C_1-C_3) alkylsulphamoyl, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain bearing a 5- to 10-membered aryl or heteroaryl group optionally substituted with one or more groups independently selected from hydroxy, mercapto, amino, cyano, nitro, trihalomethyl, trihalomethoxy, linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxyxcarbonyl, alkylcarbonylamino, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino, linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl, carbamoyl, (C_5-C_{10}) aryl- or heteroarylsulphonylamino, (C_1-C_3) alkylsulphonylamino, mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl, (C_1-C_3) alkylsulphamoyl, sulphamoyl, mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl, a 5 to 10 membered aromatic or heteroaromatic ring optionally substituted with one or more groups independently selected from hydroxy; halogen; mercapto; amino; cyano; nitro; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_6) alkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl-, alkoxyxcarbonyl, alkylcarbonylamino; mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; carbamoyl; (C_5-C_{10}) aryl- or heteroarylsulphonylamino; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl;

mono- or di- (C_1-C_3) alkylsulphamoyl; sulphamoyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl;

-Y-Q- is –C(=O)NH-Q- or -NH-C(=O)-NH-Q;

Q is a 5 to 10-membered aromatic or heteroaromatic ring;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino, mono- or di- (C_5-C_{10}) aryl- or heteroarylaminocarbonyl; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl; mono- or di- (C_5-C_{10}) aryl- or heteroarylsulphamoyl; mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, (C_1-C_6) alkylthio-(C_1-C_6) alkyl;

R' represent, independently from one another when j = 2, halogen; hydroxy; mercapto; cyano; nitro; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy, hydroxyalkyl, mercaptoalkyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, (C_1-C_6) alkylthio-(C_1-C_6) alkyl;

provided that when k is zero and the sum of w and h is 4, T' is mercapto; amino; trihaloalkyl; hydroxyalkyl; (C_1-C_6) aminoalkyl;

mercaptoalkyl; alkylthio; alkoxycarbonyl; alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; mono- or di- (C_1-C_3) alkylaminosulphonyl, or $j \neq 0$; and that when j=0, and the sum of w, h and k is 4, then K1 and K2 are not both hydrogen;

and with the exclusion of the following compounds:

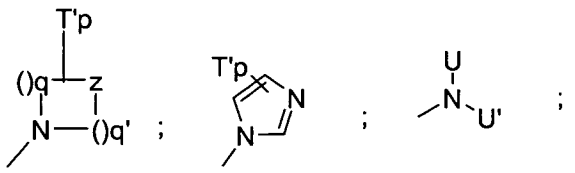
1-[4-(2-Amino-thiazol-5-yl)-phenyl]-3-(3-imidazol-1-yl-propyl)-urea; 1-(Biphenyl-4-yl)-3-(5-(spiro(indane-1,4'-piperidine-10-yl)-pentyl)-urea; 1-(Biphenyl-4-yl)-3-(4-(spiro(indane-1,4'-piperidine-10-yl)-butyl)-urea; 3-{4-[3-(3-Morpholin-4-yl-propyl)-ureido]-phenyl}-1H-indazole-5-carboxylic acid amide;3-{4-[3-(3-Piperidin-1-yl-propyl)-ureido]-phenyl}-1H-indazole-5-carboxylic acid amide;1-[4-(8-Methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-morpholin-4-yl-propyl)-urea;

1-[4-(8-Cyclopropylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-pyrrolidin-1-yl-propyl)-urea;1-(2-Hydroxy-3-morpholin-4-yl-propyl)-3-[4-(8-methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-urea;1-[4-(8-Cyclopropylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-morpholin-4-yl-propyl)-urea;1-[4-(8-Methylamino-imidazo[1,2-a]pyrazin-3-yl)-phenyl]-3-(3-pyrrolidin-1-yl-propyl)-urea; N-Biphenyl-4-yl-4-piperazin-1-yl-butyramide.

2. A compound according to claim 1 wherein:

w, h, k, K1, K2, j, p, q, q' and Y are as described in claim 1

X is



z is selected from CH_2, N, O;

T' represent, independently from one another when p is >1, hydroxy;

amino; cyano; nitro; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, aminoalkyl, mercaptoalkyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; mono- or di-, linear, branched or cyclic (C_1-C_6) alkylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl, or (C_1-C_6) alkylthio-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; or, when p is 2 or 3, two T' substituents form a 5- to 8-membered ring with spiro or fused junction;

U and U' represent, independently from one another, hydrogen; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with hydroxy, oxo, trihalomethyl, trihalomethoxy, carbamoyl, sulphamoyl, pyridyl, linear, branched or cyclic (C_1-C_3) alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino, mono- or di-, linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl, (C_1-C_3) alkylsulphonylamino, (C_1-C_3) alkylsulphonyl, mono- or di- (C_1-C_3) alkylsulphamoyl, mono- or di-, linear, branched, or cyclic (C_1-C_6) alkylamino;

Q is a 6 to 10-membered aromatic or heteroaromatic ring;

R represents a 5 to 10-membered aromatic or heteroaromatic ring optionally substituted with one or more groups independently selected from: halogen; hydroxy; mercapto; cyano; nitro; amino; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_6) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_6) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl; mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl;

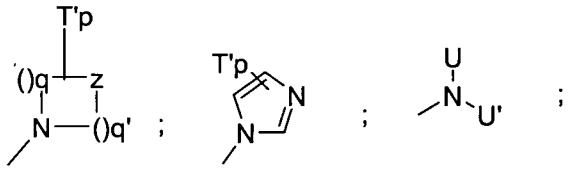
R' represent, independently of one another when j = 2, halogen; hydroxy; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy, hydroxyalkyl, alkoxycarbonyl, alkylcarbonyl, alkylsulphonyl; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl, mono- or di- (C_1-C_3) alkylamino-(C_1-C_3) alkyl, (C_1-C_3) alkylthio-(C_1-C_3) alkyl.

3. A compound according to claim 2, wherein:

K1, K2, j, p, q, q', T', U, U', Q, R, R' and Y are as defined in claim 2

w, h and k are, independently from one another, 0, 1, 2, or 3 with the condition that w + h + k = 4;

X is



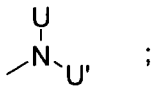
z is selected from CH_2, N, O.

4. The compounds of claim 3 wherein:

h, w, Q, and Y are as defined in claim 3

k is 0

X is a group of formula:



U and U' represent, independently from one another, hydrogen; a linear, branched or cyclic (C_1-C_6) alkyl, azaalkyl, oxaalkyl chain optionally substituted with trihalomethyl, trihalomethoxy, carbamoyl, sulphamoyl, pyridyl;

j is 0, or 1;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

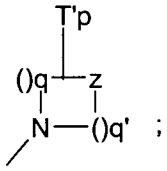
R' represents halogen; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy.

5. A compound according to claim 3 wherein:

j, q, q', Q, and Y are as defined in claim 3;

K1 and K2 represent, independently from one,another hydrogen; halogen; (C_1-C_3) alkyl, alkoxy;

X is a group of formula:



;

z is CH_2, N, O;

p is 0 or 1;

T' represents linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy or alkylcarbonyl; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_6) alkylsulphonyl;

mono- or di- linear, branched, or cyclic (C_1-C_6) alkylsulphamoyl; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl, mono- or di- (C_1-C_6) alkylamino-(C_1-C_6) alkyl;

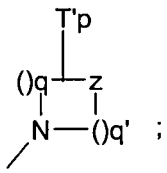
R' represents, independently from one another when j = 2, halogen; hydroxy; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl, mono- or di- (C_1-C_3) alkylamino-(C_1-C_3) alkyl, (C_1-C_3) alkylthio-(C_1-C_3) alkyl.

6. A compound according to claim 5, wherein:

j, Q, and Y are as defined in claim 5;

K1 and K2 represent, independently from one another, hydrogen; halogen; (C_1-C_3) alkyl;

X is a group of formula:



;

z is CH_2, N;

q and q' are, independently from one another, integers from 1 to 3;

T' represents linear, branched or cyclic (C_1-C_3) alkyl, alkylcarbonyl;

R represents a 5 to 10-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

R' represents, independently from one another when j = 2, halogen;

trihalomethyl; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy.

7. A compound according to claim 6 in which

Q, j and R are as defined in claim 6;

Y is –C(=O)NH-.

8. A compound according to claim 7 in which

Q is a phenyl or pyridyl ring;

j is 1 or 2;

R represents a phenyl, pyridyl, pyrazolyl ring, optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

9. A compound according to claim 6 in which

Q and R are as defined in claim 6

Y is –NH-C(=O)-NH-.

10. A compound according to claim 9 in which

Q is a phenyl or pyridyl;

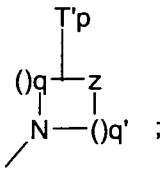
R represents a phenyl, pyridyl or pyrazole ring optionally substituted with one or more groups independently selected from: halogen; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl.

11. A compound according to claim 2 wherein:

j, T', q, q' p, R, R', Q and Y are as defined in claim 2;

w, h and k are, independently from one another, 0,1,2, or 3 with the condition that w+ h+ k= 3

X is



12. A compound according to claim 11 wherein:

w, h, k, j, p and Q are as defined in claim 11

q and q' are, independently from one another, integers from 1 to 3;

T' represent, independently from one another when p >1, hydroxy; cyano; oxo; linear, branched or cyclic (C_1-C_6) alkyl, trihaloalkyl, hydroxyalkyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_6) alkoxy-(C_1-C_6) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylaminosulphonyl; sulphamoyl; linear, branched or cyclic (C_1-C_6) alkylaminocarbonyl; carbamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl; (C_1-C_3) alkylsulphonylamino; mono- or di- (C_1-C_3) alkylsulphamoyl; (C_1-C_3) sulphonyl;

-Y- is -NH-C(=O)-NH-;

R represents a 5 to 6-membered aromatic or heteroaromatic ring, optionally substituted with one or more groups independently selected from: halogen; hydroxy; cyano; linear, branched or cyclic (C_1-C_3) alkyl, trihaloalkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl; linear, branched, or cyclic (C_1-C_3) alkylsulphonylamino; linear, branched, or cyclic (C_1-C_3) alkylsulphonyl; mono- or di- linear, branched, or cyclic (C_1-C_3) alkylsulphamoyl; linear, branched or cyclic (C_1-C_3) alkoxy-(C_1-C_3) alkyl;

R' represents, independently of one another when j = 2, halogen; trihalomethyl; trihalomethoxy; linear, branched or cyclic (C_1-C_3) alkyl, alkoxy;

13. A compound according to claim 12 wherein:

k is 0

p is 0, or 1;

T' represents, independently from one another when p is greater than 1, linear, branched or cyclic (C_1-C_3) alkyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonylamino; linear, branched or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

Q is a phenyl or pyridyl;

j is 0 or 1;

R represents a phenyl or pyridyl ring optionally substituted with one or more groups independently selected from: halogen; hydroxy; linear, branched or cyclic (C_1-C_6) alkyl, alkoxy; linear, branched, or cyclic (C_1-C_3) alkylcarbonylamino; mono- or di, linear, branched, or cyclic (C_1-C_3) alkylaminocarbonyl; carbamoyl;

R' represents halogen.

14. A pharmaceutical composition containing a compound according to claims 1-13 with a pharmaceutically acceptable carrier or excipient.

15. The use of a compound according to claims 1-13 for the preparation of a medicament for the treatment of neurological, psychiatric, cognitive, immunological and inflammatory disorders.

16. The use according to claim 15, for the treatment of a neurodegenerative disease, particularly Alzheimer's disease.

17. A method for the treatment or prevention of diseases, conditions, or dysfunctions involving the alpha 7 nAChR, which comprises administering to a subject in need thereof an effective amount of a compound according to claims 1-13.

18. A method according to claim 17, for the prevention or treatment of a psychiatric or neurodegenerative disease, particularly senile dementia, attention deficit disorders, Alzheimer's disease and schizophrenia.