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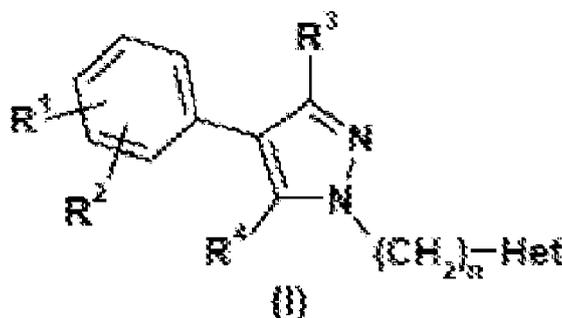
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(54) Title: PYRAZOLES



(57) Abstract: The invention relates to pyrazole derivatives which are NMDA NR2B receptor inhibitors, useful in treating central nervous system diseases.

PYRAZOLES

PRIORITY

[1] This application claims priority to U.S. Provisional Application No. 62/146,629, which was filed on April 13, 2015; and U.S. Provisional Application No. 62/037,815, which was filed on August 15, 2014; the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[2] The invention relates pyrazole derivatives and the use of these compounds for the treatment of various diseases and conditions.

BACKGROUND OF THE INVENTION

[3] Glutamate is one of the major excitatory neurotransmitters that is widely spread in the brain. First indication of its role as an excitatory messenger was in the 1950's when it was observed that intravenous administration of glutamate induces convulsions. However, the detection of the whole glutamatergic neurotransmitter system with its various receptors did not take place before the 1970's and 1980's when numerous antagonists were developed or, as in the case of PCP and ketamine, were identified as antagonists. Finally, in the 1990's molecular biology provided the tools for the classification of the glutamatergic receptors.

[4] Glutamate is a main excitatory neurotransmitter in the mammalian central nervous system and N-methyl-D-aspartate (NMDA) receptors are a subtype of ionotropic glutamate receptors that mediate excitatory synaptic transmission in the brain. NMDA receptors are ubiquitously distributed throughout the brain and play a key role in synaptic plasticity, synaptogenesis, excitotoxicity, memory acquisition and learning. NMDA receptors are distinct from other major subtypes of ionotropic glutamate receptors (AMPA and kainate receptors) in that they are blocked by Mg^{2+} at resting membrane potentials, are highly Ca^{2+} permeable, and require co-activation by two distinct neurotransmitters: glutamate and glycine (or D-serine) (Traynelis SF et al., *Pharmacol Rev.* 2010; 62(3):405-96). The influx of Ca^{2+} through NMDA receptors triggers signaling cascades and regulates gene expression that is critical for different forms of synaptic plasticity including both

long-term potentiation of synapse efficacy (LTP) (Berberich S et al., *Neuropharmacology* 2007; 52(1):77-86) and long-term depression (LTD) (Massey, PV et al., *J Neurosci.* 2004 8;24(36):7821-8).

[5] The vast majority of the mammalian NMDA receptors form a heterotetramer made of two obligatory GluN1 units and two variable GluN2 receptor subunits encoded by the GRIN1 gene and one of four GRIN2 genes, respectively. One or both GluN2 subunits can be potentially replaced by a GluN3A or a GluN3B subunit. The GRIN1 gene product has 8 splice variants while there are 4 different GRIN2 genes (GRIN2A-D) encoding four distinct GluN2 subunits. The glycine binding site is present on the GluN1 subunit and the glutamate binding site is present on the GluN2 subunit.

[6] The GluN2 subunits play a dominant role in determining the functional and pharmacological properties of the NMDA receptor assembly and exhibit distinct distribution in different areas of the brain. For instance, GluN2B subunits are expressed primarily in the forebrain in the adult mammalian brain (Paoletti P et al., *Nat Rev Neurosci.* 2013; 14(6):383-400; Watanabe M et al., *J Comp Neurol.* 1993; 338(3):377-90) and are implicated in learning, memory processing, mood, attention, emotion and pain perception (Cull-Candy S et al., *Curr Opin Neurobiol.* 2001; 11(3):327-35).

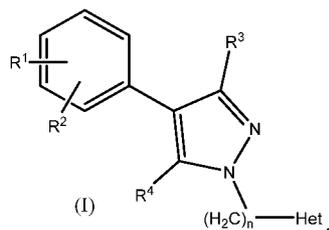
[7] Compounds that modulate GluN2B-containing NMDA receptor function can be useful in treatment of many neurological and psychiatric disorders including but not limited to bipolar disorder, major depressive disorder (Miller OH et al., *eLife.* 2014; 3:e03581; Li N et al., *Biol Psychiatry.* 2011; 69(8):754-61), treatment-resistant depression (Preskorn SH et al. *J Clin Psychopharmacol.* 2008; 28(6):631-7) and other mood disorders (e.g., postpartum depression, seasonal affective disorder and the like), Alzheimer's disease (Hanson JE et al., *Neurobiol Dis.* 2015; 74:254-62; Li S et al., *J Neurosci.* 2011; 31(18):6627-38), Parkinson's disease (Duty S, *CNS Drugs.* 2012;26(12):1017-32; Steece-Collier K et al., *Exp Neurol.* 2000; 163(1):239-43; Leaver KR et al. *Clin Exp Pharmacol Physiol.* 2008; 35(11):1388-94), Huntington's chorea (Tang TS et al., *Proc Natl Acad Sci USA.* 2005; 102(7):2602-7; Li L et al., *J Neurophysiol.* 2004;92(5):2738-46), multiple sclerosis (Grasselli G et al., *Br J Pharmacol.* 2013; 168(2):502-17; Farjam M et al., *Iran J Pharm Res.* 2014; 13(2):695-705), cognitive impairment (Wang D et al. 2014, *Expert Opin Ther Targets Expert Opin Ther Targets.* 2014;18(10):1121-30), head injury (Bullock MR et al., *Ann N Y Acad Sci.* 1999;890:51-8), spinal cord injury, stroke (Yang Y et al., *J Neurosurg.* 2003; 98(2):397-403), epilepsy (Naspolini AP et al., *Epilepsy Res.* 2012 Jun;100(1-2):12-9), movement

disorders (e.g. dyskinesias) (Morissette M et al., *Mov Disord.* 2006;21(1):9-17), various neurodegenerative diseases (e.g. amyotrophic lateral sclerosis (Fuller PI et al., *Neurosci Lett.* 2006; 399(1-2):157-61) or neurodegeneration associated with bacterial or chronic infections), pain (e.g. chronic, cancer, post-operative and neuropathic pain (Wu LJ and Zhuo M, *Neurotherapeutics.* 2009; 6(4):693-702), diabetic neuropathy, migraine (Peeters M et al., *J Pharmacol Exp Ther.* 2007; 321(2):564-72), cerebral ischemia (Yuan H et al., *Neuron.* 2015; 85(6):1305-18), schizophrenia (Grimwood S et al., *Neuroreport.* 1999;10(3):461-5), encephalitis (Dalmau J. et al., *Lancet Neurol.* 2008;7(12):1091-8.), autism and autism spectrum disorders (Won H. et al., *Nature.* 2012; 486(7402):261-5), memory and learning disorders (Tang, Y. P. et al., *Nature.* 1999; 401(6748):63-9), obsessive compulsive disorder (Arnold PD et al., *Psychiatry Res.* 2009;172(2):136-9.), attention deficit hyperactivity disorder (ADHD) (Dorval KM et al., *Genes Brain Behav.* 2007; 6(5):444-52), and addictive illnesses (e.g. alcohol addiction, drug addiction) (Nagy J, 2004, *Curr Drug Targets CNS Neurol Disord.* 2004; 3(3):169-79.; Shen H et al., *Proc Natl Acad Sci USA.* 2011;108(48):19407-12).

SUMMARY OF THE INVENTION

[8] Provided herein are compounds which inhibit the NR2B receptor.

[9] In one aspect, provided herein are compounds, and pharmaceutically acceptable salt, solvate,



polymorph, or N-oxide of Formula (I):

[10] The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof for use in medicine, and optionally a pharmaceutically acceptable carrier. The pharmaceutical composition may be used in human or veterinary medicine.

[11] The present invention further provides a method of treating disorders associated with NMDA hyperactivity, most preferably with NR2B hyperactivity, the method comprising

administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.

[12] The present invention also provides a method of treating a central nervous system disorder in a patient in need thereof comprising, administering to said patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

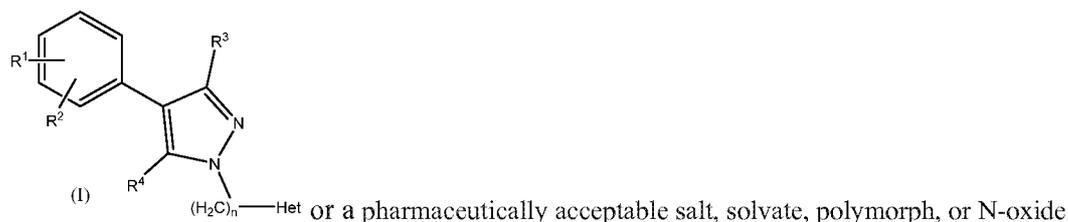
[13] The present invention also provides a compound for use in any of the methods described herein. The present invention further provides use of a compound for the preparation of a medicament for use in any of the methods described herein.

[14] The details of one or more embodiments of the invention are set forth in the accompanying description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

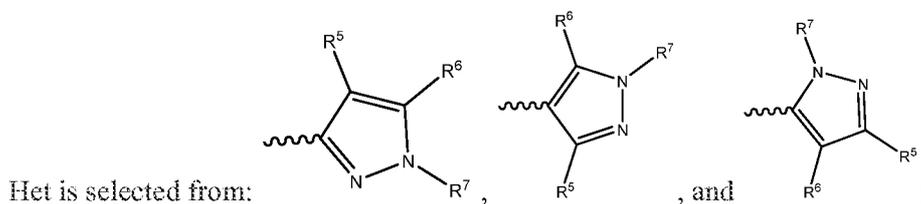
Exemplary Compounds and Compositions

[15] The present invention provides, *inter alia*, a compound of Formula (I):



thereof; wherein:

$n = 1$ or 2 ,



R^1 and R^2 are each independently selected from hydrogen; a halogen selected from F, Cl, Br; C_{1-6} alkyl, straight or branched, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents selected from hydroxy, halogen, C_{1-3} alkoxy optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C_{3-6} cycloalkyl optionally

substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; C₃₋₆ cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; C₁₋₆ alkoxy, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents selected from hydroxy, halogen, C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₃₋₆ cycloalkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; -O-C₃₋₆ cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms and C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; -S-C₁₋₃ alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; and -SO₂-C₁₋₃ alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; and -SF₅; or

R¹ and R² together form a 5 to 7 member carbocycle, optionally substituted with at least one substituent, e.g. 1, 2, 3, 4 or 5 substituents selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms; or a 5 to 7 member heterocycle containing one to three heteroatoms which can be O, S or N, optionally substituted with at least one substituent, e.g. 1, 2, 3, 4 or 5 substituents selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms,

R³ and R⁴ are each independently selected from hydrogen; halogen; and C₁₋₅ alkyl, straight or branched, optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms; provided that at least one of R³ and R⁴ represents hydrogen;

R⁵ and R⁶ are each independently selected from hydrogen; halogen; amino, including C₁₋₆ alkylamino and di(C₁₋₆ alkyl) amino; C₁₋₅ alkyl, straight or branched, optionally substituted with at least one substituent, e.g. with 1, 2 or 3 substituents, selected from halogen, hydroxy, C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen

atoms, and C₃₋₆ cycloalkyl, optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms; C₁₋₅ alkoxy, straight or branched, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₃₋₆ cycloalkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₃₋₆ cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms; and

R⁷ is selected from hydrogen; C₁₋₅ alkyl, straight or branched, optionally substituted with at least one substituent, e.g. with 1, 2 or 3 substituents, selected from halogen, hydroxy, C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, and C₃₋₆ cycloalkyl, optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms; and C₃₋₆ cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms.

[16] In a specific embodiment, n is 1.

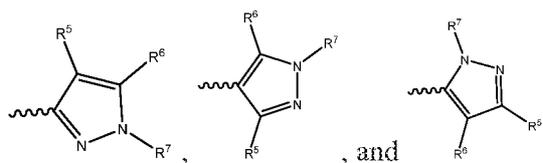
[17] In other embodiments, one of R¹ and R² does not represent hydrogen, or both of R¹ and R² do not represent hydrogen. When different from hydrogen, R¹ and R² are preferably located at a meta-position or para-position of the phenyl ring. For example, the phenyl ring may contain substituents different from hydrogen at position 3, position 4, positions 3 and 4, or positions 3 and 5, and the substituents at all other positions are hydrogen.

[18] In some specific embodiments, R¹ and R² are each independently selected from F, Cl, Br; C₁₋₄ alkyl, straight or branched, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methyl, ethyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl; C₃₋₆ cycloalkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. cyclopropyl; C₁₋₃ alkoxy, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methoxy, difluoromethoxy, trifluoromethoxy; C₁₋₃ alkoxy-C₁₋₃ alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methoxymethyl; C₃₋₆ cycloalkyl-C₁₋₃ alkyl, optionally

substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. cyclopropylmethyl; and C₃₋₆ cycloalkyl-C₁₋₃ alkoxy, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. cyclopropylmethoxy.

[19] In other specific embodiments, R³ and R⁴ are each independently selected from hydrogen; F, Cl, Br; C₁₋₃ alkyl, straight or branched, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methyl; and provided that at least one of R³ and R⁴ is hydrogen.

[20] In some embodiments, R³ and R⁴ are both hydrogen.

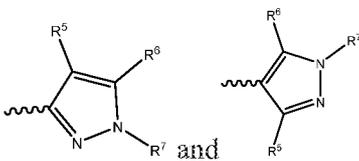


In yet other embodiments, Het is selected from:

wherein R⁵ and R⁶ are each independently selected from hydrogen; F, Cl; amino; C₁₋₃ alkyl, straight or branched, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents selected from halogen atoms, hydroxy, and C₁₋₃ alkoxy, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methyl, ethyl, n-propyl, i-propyl; C₁₋₃ alkoxy, straight or branched, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. methoxy; C₃₋₆ cycloalkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl; and C₃₋₆ cycloalkyl-C₁₋₃ alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, e.g. cyclopropylmethyl; and

R⁷ is hydrogen; C₁₋₃ alkyl, straight or branched, optionally substituted with at least one substituent, e.g. with 1, 2 or 3 substituents, selected from halogen, hydroxy, C₁₋₃ alkoxy optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, and C₃₋₆ cycloalkyl, optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, e.g. methyl, ethyl, n-propyl, i-propyl, cyclopropylmethyl; or C₃₋₆ cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C₁₋₃ alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C₁₋₃ alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl.

[21] In some embodiments, n is 1; R^1 and R^2 are each independently selected from F, Cl; C_{1-2} alkyl, optionally substituted with two to three halogen atoms; C_{1-2} alkoxy, optionally substituted with up to

three halogen atoms and Het is ; wherein

R^3 and R^4 are each independently selected from hydrogen, F, and Cl, provided that at least one of R^3 and R^4 represents hydrogen;

R^5 and R^6 are each independently selected from hydrogen; amino; C_{1-3} alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; C_{3-6} cycloalkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; and C_{3-6} cycloalkyl- C_{1-3} alkyl, optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms; and

R^7 is selected from hydrogen; C_{1-3} alkyl, straight or branched, optionally substituted with at least one substituent, e.g. with 1, 2 or 3 substituents, selected from halogen, hydroxy, C_{1-3} alkoxy optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, and C_{3-6} cycloalkyl, optionally substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, e.g. methyl, ethyl, n-propyl, i-propyl; and C_{3-6} cycloalkyl, optionally substituted with at least one substituent, e.g. 1, 2 or 3 substituents, selected from hydroxy, halogen, C_{1-3} alkyl optionally substituted with at least one halogen atom, e.g. with 1, 2 or 3 halogen atoms, and C_{1-3} alkoxy substituted with at least one halogen atom, e.g. 1, 2 or 3 halogen atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl.

[22] Specific non-limiting compounds of the present invention are:

- 4-[2-[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-methylpyrazole,
- 5-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-4-ylmethyl)pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-ethylpyrazole,

- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[2-(1-ethylpyrazol-4-yl)ethyl]pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-(1-ethylpropyl)-pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-cyclopentyl-pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole,
- 4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
- 4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
- 4-[3-chloro-5-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 1,3-dimethyl-5-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 1-methyl-3-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 3-[[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 4-[4-chloro-3-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 4-[2-[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
- 4-[3-chloro-5-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 5-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole,
- 4-[2-[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole,
- 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1-ethyl-pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole,
- 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole,

- 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole,
- 4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
- 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole,
- 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
- 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
- 4-[3-(difluoromethyl)-5-fluoro-phenyl]-1-[2-(1H-pyrazol-3-ylmethyl)pyrazole,
- 1,3-dimethyl-5-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 1-methyl-3-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 1-methyl-3-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 1,3-dimethyl-5-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
- 5-[[4-(3-fluoro-4-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 5-[[4-(3-fluoro-4-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 4-(4-fluoro-3-methyl-phenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 5-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 3-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 5-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 3-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 4-(3-cyclopropylphenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 4-(3-methylsulfonylphenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
- 1-methyl-4-[[4-(3-methylsulfonylphenyl)pyrazol-1-yl]methyl]-pyrazole,

- pentafluoro-[3-[1-(1H-pyrazol-3-ylmethyl)pyrazol-4-yl]]phenyl]-sulfane,
- 4-[2-[4-(4-chlorophenyl)-pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
- 5-[[4-(4-chlorophenyl)-pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(4-chlorophenyl)-pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 4-(4-chlorophenyl)-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,
- 4-(4-chlorophenyl)-1-(1H-pyrazol-3-ylmethyl)pyrazole,
- 4-(4-chlorophenyl)-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
- 3-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 5-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 5-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
- 3-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
- 1-methyl-3-[(4-phenylpyrazol-1-yl)methyl]pyrazole,
- 1,3-dimethyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole,
- 1-methyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole,
- 4-[[4-(3-difluoromethoxy-4-chloro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,
- 4-[[4-(3-difluoromethyl-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,
- 4-[[4-(3-(1,1-difluoroethyl)-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,
- 3-[[4-[3-(difluoromethoxy)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole,
- 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole,
- 3-[[4-(3-(1,1-difluoroethyl)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole as maleate, and
- 3-[[4-(3-(difluoromethoxy)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole as maleate.

[23] The present invention also provides a pharmaceutical composition a therapeutically effective amount of comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof for use in medicine, and optionally a pharmaceutically acceptable carrier. The pharmaceutical composition may be used in human or veterinary medicine.

Certain Definitions

[24] The term “alkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. In some embodiments, an alkyl group is a C₁-C₆ alkyl group. In some embodiments, an alkyl group is a C₁-C₄ alkyl group. Examples of alkyl groups include methyl (Me) ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isoheptyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples. In some embodiments, alkyl refers to straight or branched chain hydrocarbon groups. Specific examples in these embodiments are methyl, ethyl, propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl and t-butyl), hexyl and the like.

[25] The term “haloalkyl” refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain and having at least one of the hydrogens replaced with a halogen. In some embodiments, a haloalkyl group is a C₁-C₆ haloalkyl group. In some embodiments, a haloalkyl group is a C₁-C₄ haloalkyl group. One exemplary substituent is fluoro. Preferred substituted alkyl groups of the invention include trihalogenated alkyl groups such as trifluoromethyl groups. Haloalkyl includes and is not limited to -CF₃, -CH₂F, -CHF₂, -CH₂Cl, -CH₂-CF₃, and the like. In specific examples, the term (halo)alkyl refers to alkyl substituted by at least one halogen atom. Examples of these embodiments include fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl.

[26] “Cycloalkyl” refers to monocyclic, non-aromatic hydrocarbon groups having from 3 to 7 carbon atoms. Examples of cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[27] The term “cyclic group” includes fully saturated, partially unsaturated and aromatic carbocyclic or heterocyclic rings, including aromatic (“aryl” or “heteroaryl”) or nonaromatic cyclic groups, for example, 5 to 7 membered monocyclic ring systems, which may have at least one heteroatom in at least one carbon atom-containing ring. A heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. In some embodiments, one or more

carbon atoms of the heterocyclic ring are oxidized to form a carbonyl group. The cyclic group may be unsubstituted or carry one or more substituents, e.g. halogen, C₁₋₆ (halo)alkyl, C₁₋₆ (halo)alkoxy, OH, etc.

[28] The term “alkoxy” includes a straight chain or branched alkyl group with a terminal oxygen linking the alkyl group to the rest of the molecule. In some embodiments, an alkoxy group is a C₁-C₆ alkoxy group. In some embodiments, an alkoxy group is a C₁-C₄ alkoxy group. Alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and so on. In specific embodiments, the term alkoxy, employed alone or in combination with other terms, refers to a group of formula -O-alkyl. Example alkoxy groups in these embodiments include methoxy, ethoxy, propoxy (e.g. n-propoxy and isopropoxy), t-butoxy, hexyloxy and the like. The term (halo)alkoxy refers to alkoxy substituted by at least one halogen atom. Examples of (halo)alkoxy groups include fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

[29] The term “heterocycle” represents a mono- or bi-cyclic hydrocarbon ring structure optionally containing heteroatoms selected from O, S, and N. Heterocyclyl rings can have 2 to 10 carbon atoms in the ring.

[30] The term “halogen” represents chlorine, fluorine, bromine, or iodine. The term “halo” or “halogen atom” represents chloro, fluoro, bromo, or iodo. In specific embodiments, halo refers to fluorine, chlorine, bromine and iodine, particularly to fluorine, chlorine and bromine, more particularly to fluorine and chlorine.

[31] “Benzyl” and -CH₂-phenyl are used interchangeably.

[32] “GluN2B receptors” refers to NMDA receptors containing the GluN2B or NR2B subunit.

[33] “Pharmaceutically acceptable” means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans. In specific embodiments, “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[34] The compounds of Formula (I) may form salts which are also within the scope of this invention. Reference to a compound of the Formula (I) herein is understood to include reference

to salts thereof, unless otherwise indicated. In various embodiments, the term “salt(s)”, as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term “salt(s)” as used herein (and may be formed, for example, where the compound comprises an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Salts of the compounds of the Formula (I) may be formed, for example, by reacting the compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilisation.

[35] Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[36] Exemplary basic salts (formed, for example, where the compound comprises an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

[37] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[38] In specific embodiments "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or

acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977).

[39] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered. A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[40] "Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

[41] "Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

[42] In treatment methods according to the invention, a therapeutically effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. A "therapeutically effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the compounds of the present invention may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition,

the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[43] "Compounds of the present invention," "compounds of the invention" and equivalent expressions, are meant to embrace compounds of the Formula (I) as described herein, which expression includes the pharmaceutically acceptable salts, polymorphs, N-oxides, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[44] Furthermore, in the case of the compounds of the invention which contain an asymmetric carbon atom, the invention relates to the D form, the L form and D, L mixtures and also, where more than one asymmetric carbon atom is present, to the diastereomeric forms. Those compounds of the invention which contain asymmetric carbon atoms, and which as a rule accrue as racemates, can be separated into the optically active isomers in a known manner, for example using an optically active acid. However, it is also possible to use an optically active starting substance from the outset, with a corresponding optically active or diastereomeric compound then being obtained as the end product.

[45] Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Exemplary prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[46] Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

[47] Also included are solvates and hydrates of the compounds of Formula (I) and solvates, polymorphs, N-oxides, and hydrates of their pharmaceutically acceptable salts.

[48] The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted, unless otherwise indicated.

[49] As used herein, the term "isotopic variant" refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more non-radioactive or radioactive isotopes, such as for example, deuterium (^2H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be $^2\text{H}/\text{D}$, any carbon may be ^{13}C , or any nitrogen may be ^{15}N , and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. Radiolabeled compounds of the invention can be used in diagnostic methods such as single-photon emission computed tomography (SPECT). The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , and would be useful in positron emission topography (PET) studies for examining substrate receptor occupancy.

[50] All isotopic variants of the compounds of the invention, radioactive or not, are intended to be encompassed within the scope of the invention. In one aspect, provided herein are deuterated or tritiated analogs of compounds of Formula I.

[51] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

[52] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers.” When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R-and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture.”

[53] “Tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

[54] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[55] Compounds of the invention may also exist as “rotamers,” that is, conformational isomers that occur when the rotation leading to different conformations is hindered, resulting in a rotational energy barrier to be overcome to convert from one conformational isomer to another.

[56] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)-or (S)-stereoisomers or as mixtures thereof.

[57] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[58] In some embodiments, the compound can be provided as a prodrug. The term “prodrug”, as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the Formula (I), or a salt and/or solvate thereof.

[59] In some embodiments, the compounds of the invention, and salts thereof, are substantially isolated. By “substantially isolated” is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof

[60] As used herein, the phrase “optionally substituted” means unsubstituted or substituted. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. It is understood that substitution at a given atom is limited by valency.

[61] The compounds according to the invention have been found to have pharmacologically important properties which can be used therapeutically. The compounds of the invention can be used alone, in combination with each other or in combination with other active compounds. Compounds of Formula (I) may be inhibitors of NMDA (N-methyl-D-aspartate)-receptors, more particularly subtype specific inhibitors of NMDA NR2B receptors. It is therefore a part of the subject-matter of this invention that the compounds of the invention and their salts and also pharmaceutical preparations which comprise these compounds or their salts, can be used for treating or preventing disorders associated with, accompanied by and/or covered by NR2B receptor hyperactivity and/or disorders in which inhibiting NR2B receptors is of value.

[62] In various embodiments, the compounds of the invention are inhibitors of the NR2B receptor with IC_{50} values $< 10 \mu M$, preferably $\leq 1 \mu M$ and more preferably $\leq 100 \text{ nM}$.

Exemplary Methods of Treatment

[63] The compounds of the invention including their salts, solvates and hydrates, can be used for the treatment of central nervous system disorders of mammals including a human.

[64] More particularly, the invention relates to the treatment of neurologic and psychiatric disorders including, but not limited to: (1) mood disorders or mood (affective) disorders; (2) neurotic, stress-related and somatoform disorders including anxiety disorders; (3) disorders of psychological development; (4) behavioral syndromes associated with physiological disturbances and physical factors; (5) extrapyramidal and movement disorders; (6) episodic and

paroxysmal disorders, epilepsy; (7) pain; (8) forms of neurodegeneration; (9) cerebrovascular diseases, acute and chronic; and any sequelae of cerebrovascular diseases.

[65] Examples of mood disorders or mood (affective) disorders that can be treated according to the present invention include, but are not limited to, bipolar disorder I, such as depressed, hypomanic, manic and mixed form; bipolar disorder II; depressive disorders, such as single depressive episode or recurrent major depressive disorder, minor depressive disorder, depressive disorder with postpartum onset, depressive disorders with psychotic symptoms; persistent mood disorders, such as cyclothymia, dysthymia, euthymia; and premenstrual dysphoric disorder.

[66] Examples of disorders belonging to the neurotic, stress-related and somatoform disorders that can be treated according to the present invention include, but are not limited to, anxiety disorders, such as general anxiety disorder, panic disorder with or without agoraphobia, specific phobia, social phobia, chronic anxiety disorders; obsessive compulsive disorder; reaction to severe stress and adjustment disorders, such as post-traumatic stress disorder (PTSD); other neurotic disorders such as depersonalisation-derealisation syndrome.

[67] Examples of disorders of psychological development that can be treated according to the present invention include, but are not limited to pervasive developmental disorders, including but not limited to Asperger's syndrome and Rett's syndrome, autistic disorders, childhood autism and overactive disorder associated with mental retardation and stereotyped movements, specific developmental disorder of motor function, specific developmental disorders of scholastic skills.

[68] Examples of behavioral syndromes associated with physiological disturbances and physical factors that can be treated with the present invention include, but are not limited to mental and behavioural disorders associated with the puerperium, including but not limited to postnatal and postpartum depression; eating disorders, including but not limited to anorexia nervosa and bulimia nervosa.

[69] Examples of extrapyramidal and movement disorders that can be treated according to the present invention include, but are not limited to Parkinson's disease; second Parkinsonism, such as postencephalitic Parkinsonism; Parkinsonism comprised in other disorders; Lewis body disease; degenerative diseases of the basal ganglia; other extrapyramidal and movement disorders including but not limited to tremor, essential tremor and drug-induced tremor, myoclonus, chorea and drug-induced chorea, drug-induced tics and tics of organic origin, drug-induced acute dystonia, drug-

induced tardive dyskinesia, L-dopa-induced dyskinesia; neuroleptic-induced movement disorders including but not limited to neuroleptic malignant syndrome (NMS), neuroleptic induced parkinsonism, neuroleptic-induced early onset or acute dyskinesia, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia, neuroleptic-induced tremor; restless leg syndrome, Stiff-man syndrome.

[70] Further examples of movement disorders with malfunction and/or degeneration of basal ganglia that can be treated according to the present invention include, but are not limited to dystonia including but not limited to focal dystonia, multiple-focal or segmental dystonia, torsion dystonia, hemispheric, generalised and tardive dystonia (induced by psychopharmacological drugs). Focal dystonia include cervical dystonia (torticolli), blepharospasm (cramp of the eyelid), appendicular dystonia (cramp in the extremities, like the writer's cramp), oromandibular dystonia and spasmodic dysphonia (cramp of the vocal cord).

[71] Examples for episodic and paroxysmal disorders that can be treated according to the present invention include, but are not limited to epilepsy, including localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, generalized idiopathic epilepsy and epileptic syndromes including but not limited to myoclonic epilepsy in infancy, neonatal convulsions (familial), childhood absence epilepsy (pyknolepsy), epilepsy with grand mal seizures on awakening, absence epilepsy, myoclonic epilepsy (impulsive petit mal) and nonspecific atonic, clonic, myoclonic, tonic, tonic-clonic epileptic seizures.

[72] Further examples of epilepsy that can be treated according to the present invention include, but are not limited to epilepsy with myoclonic absences, myoclonic-astatic seizures, infantile spasms, Lennox-Gastaut syndrome, Salaam attacks, symptomatic early myoclonic encephalopathy, West's syndrome, petit and grand mal seizures; status epilepticus.

[73] Examples of pain include, but are not limited to pain disorders related to psychological factors, such as persistent somatoform disorders; acute, chronic and chronic intractable pain, headache; acute and chronic pain related to physiological processes and physical disorders including but not limited to back pain, tooth pain, abdominal pain, low back pain, pain in joints; acute and chronic pain that is related to diseases of the musculoskeletal system and connective

tissue including, but not limited to rheumatism, myalgia, neuralgia and fibromyalgia; acute and chronic pain that is related to nerve, nerve root and plexus disorders, such as trigeminal pain, postzoster neuralgia, phantom limb syndrome with pain, carpal tunnel syndrome, lesion of sciatic nerve, diabetic mononeuropathy; acute and chronic pain that is related to polyneuropathies and other disorders of the peripheral nervous system, such as hereditary and idiopathic neuropathy, inflammatory polyneuropathy, polyneuropathy induced by drugs, alcohol or toxic agents, polyneuropathy in neoplastic disease, diabetic polyneuropathy.

[74] Examples of diseases that include forms of neurodegeneration include, but are not limited to, acute neurodegeneration, such as intracranial brain injuries, such as stroke, diffuse and local brain injuries, epidural, subdural and subarachnoid haemorrhage, and chronic neurodegeneration, such as Alzheimer's disease, Huntington's disease, and ALS.

[75] Examples of cerebrovascular diseases include, but are not limited to, subarachnoid haemorrhage, intracerebral haemorrhage and other nontraumatic intracranial haemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral and cerebral arteries, not resulting in cerebral infarction, dissection of cerebral arteries, cerebral aneurysm, cerebral atherosclerosis, progressive vascular leukoencephalopathy, hypertensive encephalopathy, nonpyogenic thrombosis of intracranial venous system, cerebral arteritis, cerebral amyloid angiopathy and sequelae of cerebrovascular diseases.

[76] In some embodiments, administration of a compound of the invention, or pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof, is effective in preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Exemplary Pharmaceutical Compositions

[77] The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof for use in medicine, e.g. in human or veterinary medicine. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

[78] An effective dose of the compounds according to the invention, or their salts, solvates or prodrugs thereof is used, in addition to physiologically acceptable carriers, diluents and/or adjuvants for producing a pharmaceutical composition. The dose of the active compounds can vary depending on the route of administration, the age and weight of the patient, the nature and severity of the diseases to be treated, and similar factors. The daily dose can be given as a single dose, which is to be administered once, or be subdivided into two or more daily doses, and is as a rule 0.001-5000 mg. Particular preference is given to administering daily doses of 0.1-3000 mg, e.g. 1-2000 mg.

[79] Suitable administration forms are oral, parenteral, intravenous, transdermal, topical, inhalative, intranasal and sublingual preparations. Particular preference is given to using oral, parenteral, e.g. intravenous or intramuscular, intranasal preparations, e.g. dry powder or sublingual, of the compounds according to the invention. The customary galenic preparation forms, such as tablets, sugar-coated tablets, capsules, dispersible powders, granulates, aqueous solutions, alcohol-containing aqueous solutions, aqueous or oily suspensions, syrups, juices or drops, can be used.

[80] Solid medicinal forms can comprise inert components and carrier substances, such as calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatine, guar gum, magnesium stearate, aluminium stearate, methyl cellulose, talc, highly dispersed silicic acids, silicone oil, higher molecular weight fatty acids, (such as stearic acid), gelatine, agar agar or vegetable or animal fats and oils, or solid high molecular weight polymers (such as polyethylene glycol); preparations which are suitable for oral administration can comprise additional flavourings and/or sweetening agents, if desired.

[81] Liquid medicinal forms can be sterilized and/or, where appropriate, comprise auxiliary substances, such as preservatives, stabilizers, wetting agents, penetrating agents, emulsifiers, spreading agents, solubilizers, salts, sugars or sugar alcohols for regulating the osmotic pressure or for buffering, and/or viscosity regulators.

[82] Examples of such additives are tartrate and citrate buffers, ethanol and sequestering agents (such as ethylenediaminetetraacetic acid and its non-toxic salts). High molecular weight polymers, such as liquid polyethylene oxides, microcrystalline celluloses, carboxymethyl celluloses, polyvinylpyrrolidones, dextrans or gelatine, are suitable for regulating the viscosity. Examples of solid carrier substances are starch, lactose, mannitol, methyl cellulose, talc, highly

dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar agar, calcium phosphate, magnesium stearate, animal and vegetable fats, and solid high molecular weight polymers, such as polyethylene glycol.

[83] Oily suspensions for parenteral or topical applications can be vegetable, synthetic or semisynthetic oils, such as liquid fatty acid esters having in each case from 8 to 22 carbon atoms in the fatty acid chains, for example palmitic acid, lauric acid, tridecanoic acid, margaric acid, stearic acid, arachidic acid, myristic acid, behenic acid, pentadecanoic acid, linoleic acid, elaidic acid, brasidic acid, erucic acid or oleic acid, which are esterified with monohydric to trihydric alcohols having from 1 to 6 carbon atoms, such as methanol, ethanol, propanol, butanol, pentanol or their isomers, glycol or glycerol. Examples of such fatty acid esters are commercially available miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-capric acid, caprylic/capric acid esters of saturated fatty alcohols, polyoxyethylene glycerol trioleates, ethyl oleate, waxy fatty acid esters, such as artificial ducktail gland fat, coconut fatty acid isopropyl ester, oleyl oleate, decyl oleate, ethyl lactate, dibutyl phthalate, diisopropyl adipate, polyol fatty acid esters, *inter alia*. Silicone oils of differing viscosity, or fatty alcohols, such as isotridecyl alcohol, 2-octyl-dodecanol, cetylstearyl alcohol or oleyl alcohol, or fatty acids, such as oleic acid, are also suitable. It is furthermore possible to use vegetable oils, such as castor oil, almond oil, olive oil, sesame oil, cotton seed oil, groundnut oil or soybean oil.

[84] Suitable solvents, gelatinizing agents and solubilizers are water or water-miscible solvents. Examples of suitable substances are alcohols, such as ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethylene glycols, phthalates, adipates, propylene glycol, glycerol, di or tripropylene glycol, waxes, methyl cellosolve, cellosolve, esters, morpholines, dioxane, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran, cyclohexanone, etc.

[85] Cellulose ethers which can dissolve or swell both in water or in organic solvents, such as hydroxypropylmethyl cellulose, methyl cellulose or ethyl cellulose, or soluble starches, can be used as film-forming agents.

[86] Mixtures of gelatinizing agents and film-forming agents are also perfectly possible. In this case, use is made, in particular, of ionic macromolecules such as sodium carboxymethyl cellulose, polyacrylic acid, polymethacrylic acid and their salts, sodium amylopectin semiglycolate, alginic acid or propylene glycol alginate as the sodium salt, gum arabic, xanthan

gum, guar gum or carrageenan. The following can be used as additional formulation aids: glycerol, paraffin of differing viscosity, triethanolamine, collagen, allantoin and novantisolic acid. Use of surfactants, emulsifiers or wetting agents, for example of sodium lauryl sulphate, fatty alcohol ether sulphates, di-Na-N-lauryl- β -iminodipropionate, polyethoxylated castor oil or sorbitan monooleate, sorbitan monostearate, polysorbates (e.g. Tween), cetyl alcohol, lecithin, glycerol monostearate, polyoxyethylene stearate, alkylphenol polyglycol ethers, cetyltrimethylammonium chloride or mono/dialkylpolyglycol ether orthophosphoric acid monoethanolamine salts can also be required for the formulation. Stabilizers, such as montmorillonites or colloidal silicic acids, for stabilizing emulsions or preventing the breakdown of active substances such as antioxidants, for example tocopherols or butylhydroxyanisole, or preservatives, such as phydroxybenzoic acid esters, can likewise be used for preparing the desired formulations.

[87] Preparations for parenteral administration can be present in separate dose unit forms, such as ampoules or vials. Use is preferably made of solutions of the active compound, preferably aqueous solution and, in particular, isotonic solutions and also suspensions. These injection forms can be made available as ready-to-use preparations or only be prepared directly before use, by mixing the active compound, for example the lyophilisate, where appropriate containing other solid carrier substances, with the desired solvent or suspending agent.

[88] Intranasal preparations can be present as aqueous or oily solutions or as aqueous or oily suspensions. They can also be present as lyophilisates which are prepared before use using the suitable solvent or suspending agent.

[89] Inhalable preparations can present as powders, solutions or suspensions. Preferably, inhalable preparations are in the form of powders, e.g. as a mixture of the active ingredient with a suitable formulation aid such as lactose.

[90] The preparations are produced, aliquoted and sealed under the customary antimicrobial and aseptic conditions.

[91] As indicated above, the compounds of the invention may be administered as a combination therapy with further active agents, e.g. therapeutically active compounds useful in the treatment of central nervous system disorders. Exemplary compounds useful in the present invention include, but are not limited to:

- Tricyclic antidepressants, e.g. Imipramine, Desipramine, Clomipramine, Amitriptyline;

- Tetracyclic antidepressants, e.g. Mianserin;
- Serotonin / noradrenaline reuptake inhibitors (SNRI), e.g. Venlafaxine;
- Selective serotonin reuptake inhibitors (SSRI), e.g. Citalopram, Fluoxetine, Paroxetine;
- Selective noradrenaline reuptake inhibitors, e.g. Reboxetine;
- Monoaminoxidase inhibitors, e.g. Tranylcypromine, Moclobemid; and
- other antidepressants, e.g. Oxitriptan, Agomelatine.

[92] For a combination therapy, the active ingredients may be formulated as compositions containing several active ingredients in a single dose form and/or as kits containing individual active ingredients in separate dose forms. The active ingredients used in combination therapy may be co-administered or administered separately.

[93] While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration only, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

EXAMPLES

[94] Chemical names were generated using ChemDraw Ultra 12.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry). A prefix of (R/S*) indicates that the compound(s) is/are single enantiomers; however the stereochemistry shown is arbitrary and the absolute stereochemistry has not been determined.

Abbreviations

[95] Abbreviations and acronyms used herein include the following:

Acronym	Term
ACN	Acetonitrile
aq	Aqueous
Au(III)Cl ₃	Gold(III) chloride
BOP	Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
br.	Broad
Cs ₂ CO ₃	Cesium carbonate

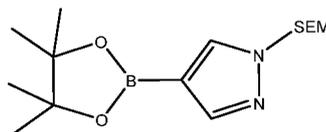
Acronym	Term
CsF	Cesium fluoride
CuI	Copper(I) iodide
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet
ddd	Doublet of doublet of doublets
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
ESI	Electrospray ionization
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
g	Grams
HCl	Hydrogen chloride
H ₂ O	Water
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	High-pressure liquid chromatography
Hz	Hertz
<i>J</i>	Coupling constant
K ₃ PO ₄	Tripotassium phosphate
LiCl	Lithium chloride
LiOH	Lithium hydroxide
M	Molar
m	Multiplet

Acronym	Term
m/z	Mass to charge ratio
MeOH	Methanol
mg	Milligrams
MgSO ₄	Magnesium sulfate
MHz	Mega hertz
min	Minutes
mL	Milliliter
mm	Millimeter
mmol	Millimoles
MS	Mass spectrometry
MsCl	Methanesulfonyl chloride
MTBE	Methyl <i>tert</i> -butyl ether
N	Normal
Na ₂ CO ₃	Sodium carbonate
NaHCO ₃	Sodium bicarbonate
Na ₂ SO ₄	Sodium sulfate
NaH	Sodium hydride
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NFBS	N-fluorobenzenesulfonimide
NH ₃	Ammonia
NMR	Nuclear magnetic resonance
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd(dtbbpf) ₂ Cl ₂	[1,1'-bis(di- <i>tert</i> -butylphosphino)ferrocene]dichloropalladium(II)
Pd(PPh ₃) ₂ Cl ₂	Bis(triphenylphosphine)palladium(II) dichloride
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
PPh ₃	Triphenylphosphine
ppm	Parts per million

Acronym	Term
q	Quadruplet
qt	Quartet of triplets
quint	Quintuplet
Rt	Retention time
rt	Room temperature
s	Singulet
SEMCl	2-(Trimethylsilyl)ethoxymethyl chloride
t	Triplet
T	Temperature
td	Triplet of doublets
TBAF	Tetrabutylammonium fluoride
<i>t</i> BuLi	<i>Tert</i> -butyllithium
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
μ L	Microliter
μ m	Micrometer
x	Times
NT	Not Tested

Chemistry

Synthesis of Intermediate (1): SEM-pyrazolo-4-boronic acid pinacol ester:

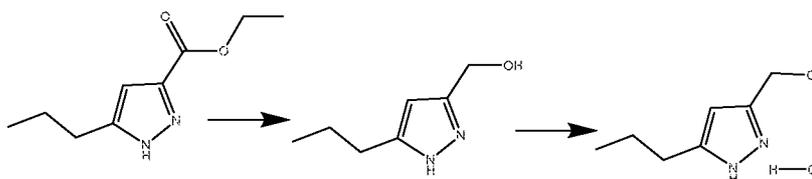


[96] SEM-pyrazolo-4-boronic acid pinacol ester was prepared according the procedure from WO2011/130146, page 84. A solution of pyrazolboronic acid pinacolester (20 g, 103 mmol) in DMF (180 mL) was cooled to 0° C and treated with sodium hydride (60 % dispersion in oil) (6.2 g, 150 mmol) in nitrogen atmosphere.

[97] The reaction mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was then cooled to 0° C and (2-(chloromethoxy)ethyl)trimethylsilane (23.65 mL, 134 mmol) was added. The reaction mixture was stirred at ambient temperature overnight.

[98] The reaction mixture was poured into aqueous saturated ammonium chloride (200 mL) containing ice (approximately 200 mL) and stirred until the ice melted. The cold mixture was extracted with ethyl acetate twice. The combined organic extracts were washed with water, dried over Na₂SO₄, and concentrated under reduced pressure to afford SEM-pyrazolo-4-boronic acid pinacol ester (27.6 g, 86 % yield).

Synthesis of Intermediate (2): 3-(chloromethyl)-5-propyl-1H-pyrazole hydrochloride:



Step 1:

[99] To a suspension of 1.23 g (32 mmol) of LiAlH₄ in THF (100 mL) was added a solution of 5-propyl-1H-pyrazole-3-carboxylic acid ethyl ester (1.82 g, 10 mmol) in THF (50 mL) in small portions at 0°C. After stirring for 1 h at 0°C and 12 h at room temperature, the mixture was hydrolyzed with a water-methanol solution (v/v, 85:15) (100 mL). The metallic hydroxides were filtered off and washed with ethanol.

[100] The organic layer was separated and the aqueous one was extracted with dichloromethane (3 x 100 mL). These extracts were then combined with the above organic layer, dried (Na₂SO₄) and evaporated to dryness. A residual syrup was obtained and purified by flash chromatography on silica gel using toluene-acetone-ethanol (v/v, 1:1:1) as the eluent.

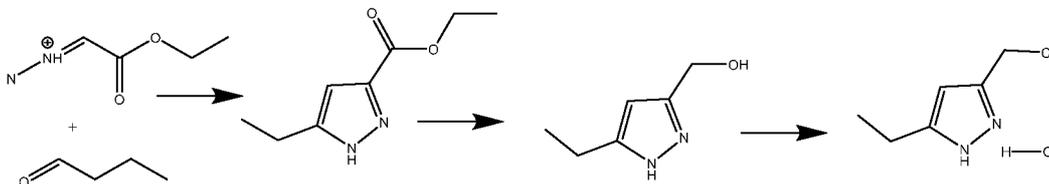
[101] Removal of the solvent from the appropriate fractions gave (5-propyl-1H-pyrazol-3-yl)-methanol. Yield: 840 mg (60%)

Step 2:

[102] To a mixture of (5-propyl-1H-pyrazol-3-yl)-methanol (840 mg, 6 mmol) in dichloromethane (25 mL), neat SOCl₂ (100 mL) was added in portions at 0°C and stirred at room temperature for 12 h. The excess SOCl₂ was removed by distillation under reduced

pressure. The residue was dissolved in ethanol (150 mL) and filtered, and diethylether was added to produce white plates. Yield: 1.11 g (95%) MS (ESI m/z) 159.0 [M+H]⁺

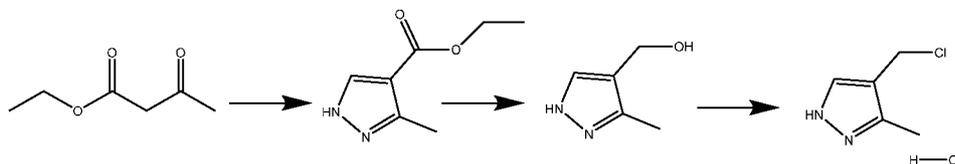
Synthesis of Intermediate (3): 3-(chloromethyl)-5-ethyl-1H-pyrazole hydrochloride:



[103] 5-Ethyl-1H-pyrazole-3-carboxylic acid ethyl ester was obtained by the procedure of L. Wang, Chemistry a European Journal, 2013, vol.19 (23), 7555-7560.

[104] Starting from 5-ethyl-1H-pyrazole-3-carboxylic acid ethyl ester, intermediate (3), i.e. 3-(chloromethyl)-5-ethyl-1H-pyrazole hydrochloride was obtained analogously to the procedure as described for intermediate (2). MS (ESI m/z) 145.6 [M+H]⁺

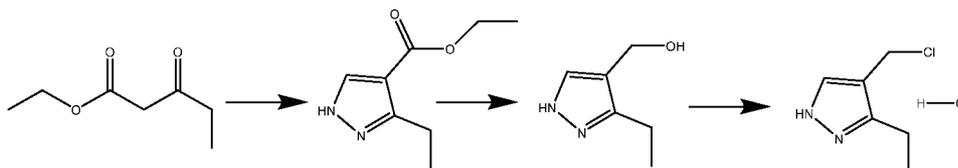
Synthesis of Intermediate (4): 4-(chloromethyl)-3-methyl-1H-pyrazole hydrochloride:



[105] 3-Methyl-1H-pyrazole-4-carboxylic acid ethyl ester was obtained by the procedure of WO2009/137338. N,N-dimethyl-formamide dimethyl acetal and ethyl acetoacetate were refluxed for 1 h followed by stirring with hydrazine hydrate in ethanol at 80°C for 2 h.

[106] Starting from 3-methyl-1H-pyrazole-4-carboxylic acid ethyl ester, intermediate (4), i.e. 4-(chloromethyl)-3-methyl-1H-pyrazole hydrochloride was obtained analogously to the procedure as described for intermediate (2). MS (ESI m/z) 130.5 [M+H]⁺

Synthesis of Intermediate (5): 4-(chloromethyl)-3-ethyl-1H-pyrazole hydrochloride:

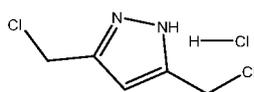


[107] 3-Ethyl-1H-pyrazole-4-carboxylic acid ethyl ester was obtained analogously to the procedure as described for intermediate (4).

[108] N,N-dimethyl-formamide dimethyl acetal and 3-oxo-pentanoic acid ethyl ester were refluxed for 1 h followed by stirring with hydrazine hydrate in ethanol at 80°C for 2 hours.

[109] Starting from 3-ethyl-1H-pyrazole-4-carboxylic acid ethyl ester, intermediate (5), i.e. 4-(chloromethyl)-3-ethyl-1H-pyrazole hydrochloride was obtained analogously to the procedure as described for intermediate (2). MS (ESI m/z) 144.6 [M+H]⁺

Synthesis of Intermediate (6): 3,5-bis(chloromethyl)-1H-pyrazole hydrochloride:



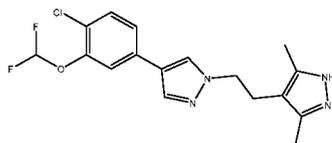
[110] Intermediate (6) was synthesized according to T.G. Schenk et al, Inorg.Chem. 1985, 24, 2334-2337.

[111] Commercially available intermediates useful in the present invention include:

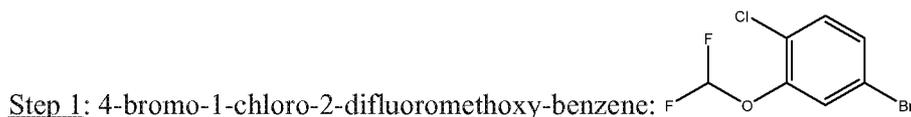
- 5-(chloromethyl)-3-methyl-1H-pyrazole hydrochloride, available from VitasMLab, order ID: BBL019538
- 5-(chloromethyl)-1,3-dimethyl-1H-pyrazole, available from ABCR, order ID: AB 224372
- 3-(chloromethyl)-1-methyl-1H-pyrazole, available from ABCR, order ID: AB 200747
- 4-(chloromethyl)-1-methyl-1H-pyrazole hydrochloride, available from Aldrich, order ID: CBR01696-1G
- 4-(2-chloroethyl)-1H-pyrazole hydrochloride, available from ABCR, order ID: AB 266246
- 3-(chloromethyl)-1-ethyl-1H-pyrazole hydrochloride, available from Fluorochem, order ID: 313369
- 4-(chloroethyl)-3,5-dimethyl-1H-pyrazole, available from ChemDiv, order ID: BB01-4360
- 3-(chloromethyl)-1H-pyrazole hydrochloride, available from ChemDiv, order ID: BB20-2557
- 4-(chloromethyl)-1-ethyl-1H-pyrazole hydrochloride, available from ChemDiv, order ID: BB57-1549

- 5-(chloromethyl)-1-ethyl-1H-pyrazole hydrochloride, available from ChemDiv, order ID: BB57-3435
- 3-(chloromethyl)-1-cyclopentyl-1H-pyrazole, available from Enamine, order ID: EN300-84084
- 3-(chloromethyl)-1-isopropyl-1H-pyrazole, available from Enamine, order ID: EN300-74576
- 3-(chloromethyl)-1-(pentan-3-yl)-1H-pyrazole, available from Enamine, order ID: EN300-84091
- 4-(2-chloroethyl)-1-ethyl-1H-pyrazole, available from Enamine, order ID: BBV-34543900
- 5-(2-chloroethyl)-1-ethyl-1H-pyrazole, available from Enamine, order ID: BBV-38136817
- 4-(2-chloroethyl)-1-methyl-1H-pyrazole, available from Enamine, order ID: BBV-41178358
- 5-(2-chloroethyl)-1-methyl-1H-pyrazole, available from Enamine, order ID: BBV-38136179
- 4-(4-chlorophenyl)-1H-pyrazole, available from Peakdale, UK, order ID: 1002465
- 4-(3,5-difluorophenyl)-1H-pyrazole, available from Peakdale, UK, order ID: 3002914
- 4-(4-bromophenyl)-1H-pyrazole, available from ABCR, order ID: AB 235347
- 4-(3-bromophenyl)-1H-pyrazole, available from ABCR, order ID: AB 233743
- 4-phenyl-1H-pyrazole, available from Enamine, order ID: EN300-07023

Example 1: Succinate salt of 4-[2-[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]ethyl]-



3,5-dimethyl-1H-pyrazole:

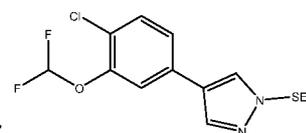


[112] 4-bromo-1-chloro-2-difluoromethoxy-benzene was prepared according to the method described in WO2007/065655, which is incorporated herein by reference in its entirety.

[113] 4-bromo-2-chlorophenol (10.0 g; 48 mmol) was dissolved in DMF (100 mL) and water (15 mL) was added followed by sodium chloro-2,2-difluoro acetate (21.5 g, 150 mmol) and potassium carbonate (13.2 g, 96 mmol).

[114] The mixture was stirred for 15 minutes at room temperature and then heated to 100°C for 2 hours under nitrogen. The mixture was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic phase was separated, dried over sodium sulphate, filtered, and concentrated in vacuum to give a crude product.

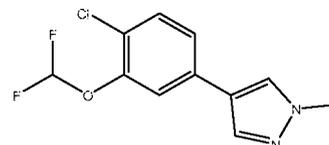
[115] The crude product was purified by silica gel chromatography eluting with 0-80% EtOAc in hexane to give 4-bromo-1-chloro-2-difluoromethoxy-benzene (7.5 g, 61% yield) as colorless oil.



Step 2: 4-(4-chloro-3-difluoromethoxy-phenyl)-1-SEM-1H-pyrazole:

[116] The mixture of 4-bromo-1-chloro-2-difluoromethoxy-benzene (7.5 g, 29 mmol), SEM-pyrazolo-4-boronic acid pinacol ester (17.2 g, 53 mmol), Na₂CO₃ (6.4 g, 60 mmol), toluene (300 mL), ethanol (50 mL) and water (25 mL) was vacuumed and refilled with nitrogen, followed by the addition of Pd(PPh₃)₄ (1.155 g, 1 mmol).

[117] After stirring at 90 °C for 6 hours the mixture was cooled to room temperature and water (200 mL) was added. The organic phase was separated, dried over sodium sulphate, filtered, and concentrated in vacuum to give a crude product. Purification using column chromatography (5-10% methanol in dichloromethane as eluent) and recrystallization from ethanol provided the product. Yield: 6.08 g (56 %).

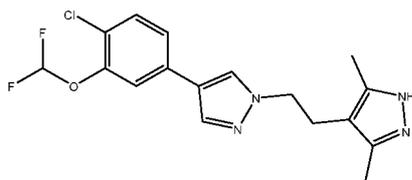


Step 3: 4-(4-chloro-3-difluoromethoxy-phenyl)-1H-pyrazole:

[118] To a solution of 4-(4-chloro-3-difluoromethoxy-phenyl)-1-SEM-1H-pyrazole (5.1 g, 13.6 mmol) in dry dioxane (50 mL) was added hydrogen chloride, 4.0 M solution in dioxane (34 mL, 136 mmol). The reaction mixture was stirred at room temperature for 16 hours, then concentrated in vacuum to give a solid, which was dissolved in EtOAc (200 mL).

[119] An aqueous saturated NaHCO₃ solution was added (200 mL), the layers were separated, and the aqueous phase was extracted 3 times with EtOAc (3 x 100 mL). The combined organic phases were dried over sodium sulphate and concentrated in vacuum to give a solid. This product was then dissolved CH₂Cl₂ and purified by flash column chromatography on silica gel (elution with CH₂Cl₂/MeOH 100/0 to 95/5). The fraction with the product was concentrated to give a white solid. Yield: 2.6 g (78 %). MS (ESI m/z) 245.6 [M+H]⁺

Step 4: 4-{2-[4-(4-Chloro-3-difluoromethoxy-phenyl)-pyrazol-1-yl]-ethyl}-3,5-dimethyl-1H-



pyrazole:

[120] To a solution of 4-(4-chloro-3-difluoromethoxy-phenyl)-1H-pyrazole (123 mg, 0.50 mmol) in dry DMF (4.0 mL) was vacuumed and refilled with nitrogen, followed by addition of sodium hydride, 60% in paraffin oil (22 mg, 0.55 mmol).

[121] The reaction mixture was stirred at room temperature for 20 minutes, then 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole (159 mg, 1.0 mmol) (ChemDiv, BB01-4360) was added. The reaction mixture was stirred at room temperature for 20 hours. The mixture was partitioned between water (50 mL) and ethyl acetate (50 mL).

[122] The organic phase was separated, dried over sodium sulphate, filtered, and concentrated in vacuo to give a crude product. The crude product was purified by silica gel chromatography eluting with 0-100% EtOAc in hexane to give 4-{2-[4-(4-Chloro-3-difluoromethoxy-phenyl)-pyrazol-1-yl]-ethyl}-3,5-dimethyl-1H-pyrazole (123 mg, 67% yield) as colorless resin. MS (ESI m/z) 367.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 1.98 (s, 6H); 2.82 (t, 2H, J=7.35); 4.12 (t, 2H, J=7.35); 7.18 (t, 1H, J=7.34); 7.46 (m, 1H); 7.52 (m, 2H); 7.95 (s, 1H); 8.11 (s, 1H); 11.92 (s, 1H).

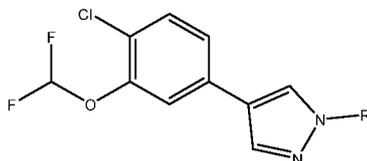
Step 5: Formation of the succinate salt of 4-{2-[4-(4-chloro-3-difluoromethoxy-phenyl)-pyrazol-1-yl]-ethyl}-3,5-dimethyl-1H-pyrazole

[123] To a mixture of 4-{2-[4-(4-chloro-3-difluoromethoxy-phenyl)-pyrazol-1-yl]-ethyl}-3,5-dimethyl-1H-pyrazole (1.00 g, 2.83 mmol) and succinic acid (1.00 g, 2.83 mmol), was added ethanol (30 mL) and the mixture was heated to 78 °C and stirred for 5 minutes until clear solution. The solvent was evaporated and the resulting solid was dried overnight at 50 °C under

reduced pressure, to yield example 1 (1.00 g, 2.83 mmol) as a white solid. Succinate salt ($C_4H_6O_4$) (m.p.: 79-81°C)

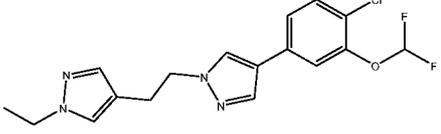
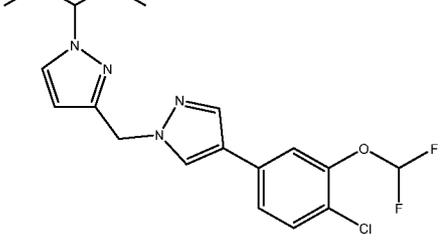
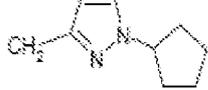
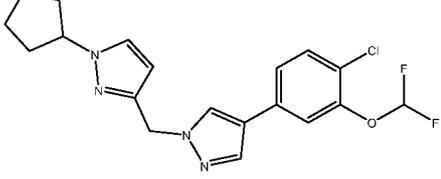
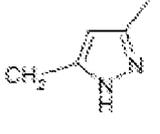
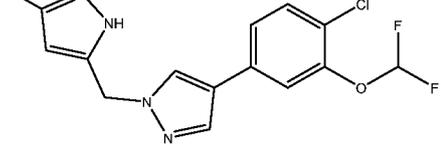
[124] The examples in Table 1 were prepared as described in example 1 replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with the appropriate chloroalkyl-1H-pyrazole derivative.

Table 1: [4-(4-chloro-3-difluoromethoxy-phenyl)-pyrazol-1-yl]- derivatives.



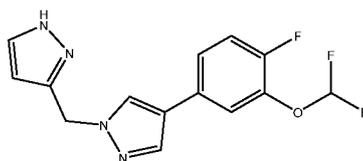
Example	R	Name - Structure	form	MW	m.p. °C
2		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole 	base	339.7	88-91
3		5-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole 	base	353.7	80-84
4		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole 	base	339.7	106-107
5		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole 	base	339.7	63-66

Example	R	Name - Structure	form	MW	m.p. °C
6		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole 	base	325.7	110-114
7		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-4-ylmethyl)pyrazole 	base	325.7	170-173
8		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-ethyl-pyrazole 	base	353.7	65-68
9		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole 	base	339.7	108-111

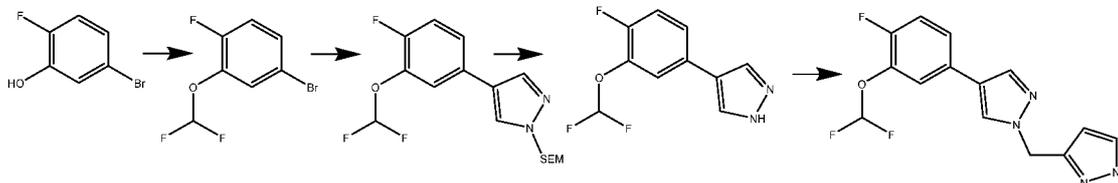
Example	R	Name - Structure	form	MW	m.p. °C
10		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[2-(1-ethylpyrazol-4-yl)ethyl]pyrazole 	suc-cinate	366.7	63-67
11		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-(1-ethylpropyl)pyrazole 	suc-cinate	394.8	resin
12		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-cyclopentyl-pyrazole 	suc-cinate	392.8	resin
13		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole 	base	339.7	107-110

Example	R	Name - Structure	form	MW	m.p. °C
14		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole 	base	353.7	103-104
15		3-[[4-[4-Chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole 	citrate	367.4	resin
16		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole 	base	339.7	134-136
17		4-[4-Chloro-3-(difluoromethoxy)phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole 	citrate	352.4	resin

Example 18: 4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl) pyrazole:

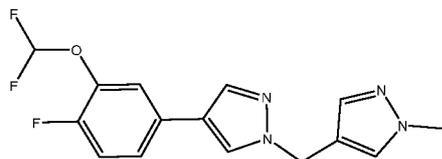


[125] The compound of example 18 was prepared as described in example 1 replacing 5-bromo-2-chloro-phenol with 5-bromo-2-fluoro-phenol and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.



[126] m.p.: 78-81°C; MS (ESI m/z) 309.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 3.31 (s, 2H); 7.14 (t, 1H, J=7.27); 7.44 (m, 1H); 7.57 (m, 2H); 8.26 (s, 2H); 8.14 (dd, 1H, J=8.01); 12.80 (s, 1H).

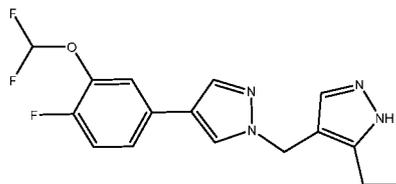
Example 19: 4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]



pyrazole:

[127] The compound of example 19 was prepared as described in example 18 replacing 3-chloromethyl-1H-pyrazole with 4-chloromethyl-1-methyl-1H-pyrazole. m.p.: 105-110°C; MS (ESI m/z) 323.2 [M+H]⁺.

Example 20: 4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-

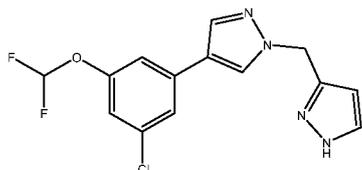


yl)methyl]pyrazole tartrate:

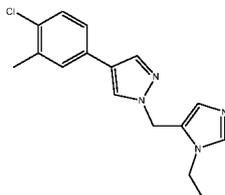
[128] The compound of example 20 was prepared as described in example 18 replacing 3-chloromethyl-1H-pyrazole with 4-chloromethyl-5-ethyl-1H-pyrazole hydrochloride.

m.p.: resin; MS (ESI m/z) 337.3 [M+H]⁺

Example 21: 4-[3-chloro-5-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-yl)methyl pyrazole:

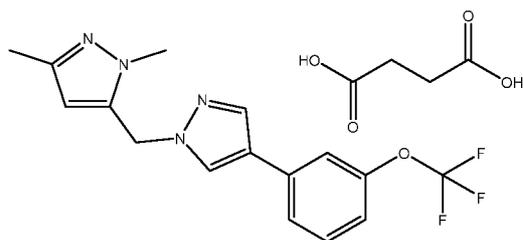


[129] The compound of example 21 was prepared as described in example 1 replacing 5-bromo-2-chloro-phenol with 5-bromo-3-chloro-phenol and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.



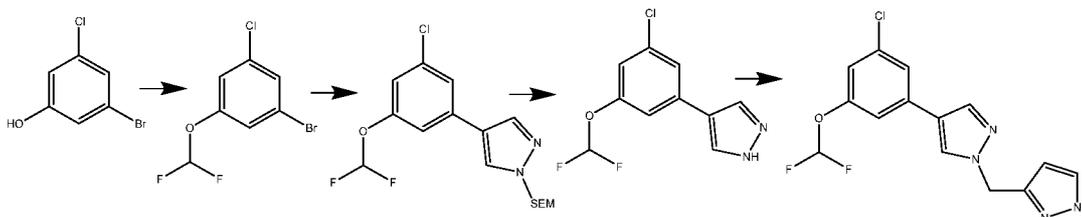
[130] m.p.: 87-90°C; MS (ESI m/z) 325.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 5.31 (s, 2H); 6.22 (s, 1H); 7.34 (t, 1H, J=7.35); 7.49 (m, 1H); 8.02 (s, 1H); 8.36 (s, 1H); 12.81 (s, 1H)

Example 22: 1,3-dimethyl-5-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl] pyrazole



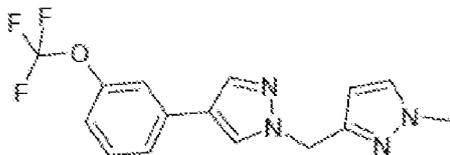
succinate:

[131] The compound of example 22 was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 1-bromo-3-trifluoromethoxy-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.



[132] m.p.: 69-73°C succinate salt, 1:1; MS (ESI m/z) 336.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.51 (s, 3H); 3.31 (s, 3H); 3.75 (s, 2H); 5.40 (s, 1H); 6.01 (s, 1H); 7.18 (d, 1H, J=8.46); 7.49 (dd, 1H, J=8.22); 7.62 (d, 1H, J=8.22); 8.02 (s, 1H); 8.33 (s, 1H).

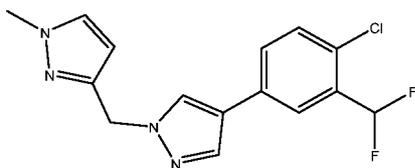
Example 23: 1-Methyl-3-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl]pyrazole



succinate:

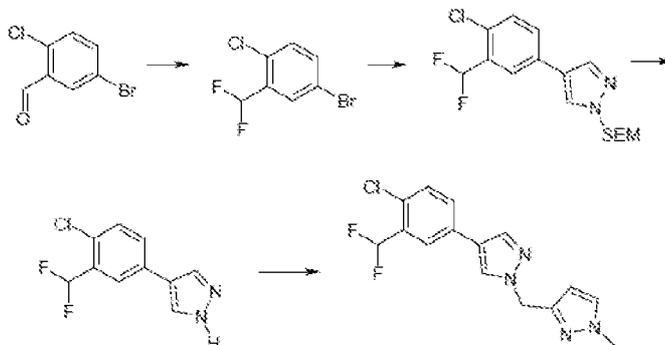
[133] The compound of example 23 was prepared as described in example 22 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole. m.p.: 90-95°C, succinate salt, 1:1; MS (ESI m/z) 323.2 [M+H]⁺

Example 24: 3-[[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-



pyrazole:

[134] The compound of example 24 was prepared according to following reaction scheme:



Step 1: 4-bromo-1-chloro-2-difluoromethyl-benzene

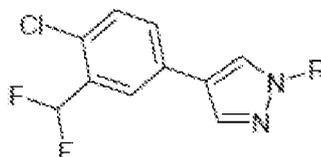
[135] To a solution of 5-bromo-2-chloro-benzaldehyde (4.4 g, 20 mmol) in dichloromethane (DCM) (50 mL) was added DAST (diethylaminosulfur trifluoride) (4.03 g, 25 mmol) and the mixture was stirred at room temperature for 18 hours under nitrogen atmosphere. The reaction mixture was quenched into ice-water and extracted with DCM. The organic layer was dried and concentrated. Yield: 3.1 g (64 %)

[136] The compound of example 24 was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-1-chloro-2-difluoromethyl-benzene and

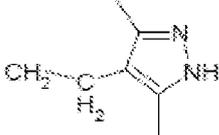
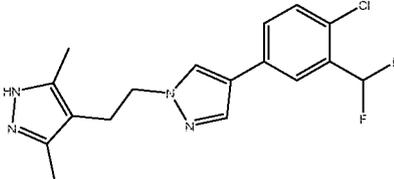
replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole. m.p.: 84-88°C; MS (ESI m/z) 323.7 [M+H]⁺.

[137] The examples in Table 2 were prepared as described in example 24 replacing 3-chloromethyl-1-methyl-1H-pyrazole with the appropriate chloroalkyl-1H-pyrazole derivative.

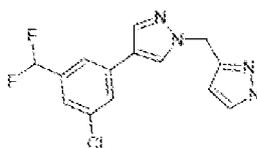
Table 2: [4-(4-chloro-3-difluoromethyl-phenyl)-pyrazol-1-yl]- derivatives



Example	R	Name - Structure	form	MW	m.p. °C
25		5-[[4-[4-Chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethylpyrazole 	base	337.7	85-87
26		4-[4-Chloro-3-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-yl)methylpyrazole 	base	309.7	102-106

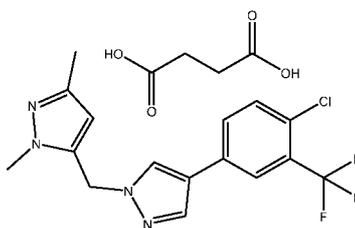
Example	R	Name - Structure	form	MW	m.p. °C
27		4-[2-[4-[4-Chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole 	HCl	351.8	49-53

Example 28: 4-[3-chloro-5-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole:

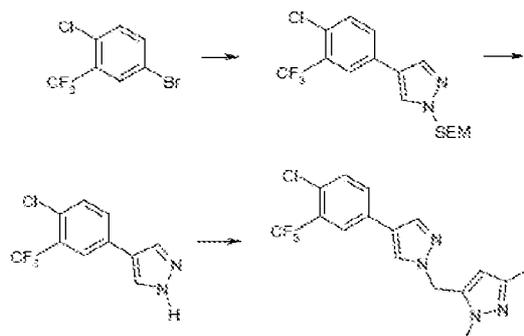


[138] The compound of example 28 was prepared as described in example 24 replacing 5-bromo-2-chloro-benzaldehyde with 5-bromo-3-chloro-benzaldehyde and replacing 3-chloromethyl-1-methyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole. m.p.: 104-105°C; MS (ESI m/z) 309.7 [M+H]⁺

Example 29: 5-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole succinate:

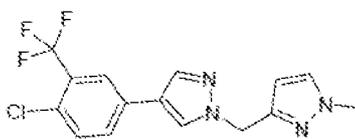


[139] The compound of example 29 was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 5-bromo-2-chloro-1-trifluoromethyl-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.



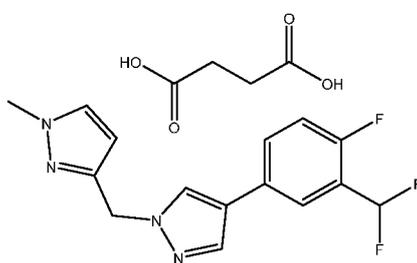
[140] m.p.: 133-136°C succinate salt, 1:1; MS (ESI m/z) 355.7 $[M+H]^+$; 1H NMR (500 MHz, DMSO- d_6) δ 2.51 (s, 3H); 3.32 (s, 3H); 3.76 (s, 2H); 5.41 (s, 1H); 6.10 (s, 1H); 7.69 (d, 1H, $J=8.17$); 7.20 (dd, 1H, $J=8.50$); 8.01 (s, 1H); 8.44 (s, 1H).

Example 30: 3-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole:

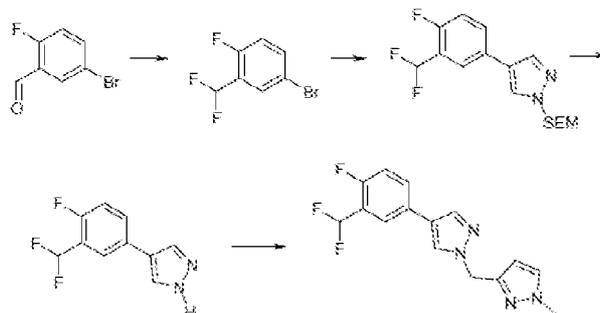


[141] The compound of example 30 was prepared as described in example 29 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole. m.p.: 84-88°C; MS (ESI m/z) 341.7 $[M+H]^+$

Example 31: 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



[142] The compound of example 31 was prepared according to following reaction scheme:



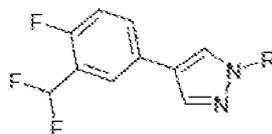
Step 1: 4-Bromo-1-fluoro-2-difluoromethyl-benzene

[143] To a solution of 5-bromo-2-fluoro-benzaldehyde (4.06 g, 20 mmol) in DCM (50 mL) was added DAST (diethylaminosulfur trifluoride) (4.03 g, 25 mmol) and the mixture was stirred at room temperature for 18 hours under nitrogen atmosphere. The reaction mixture was quenched into ice-water and extracted with DCM. The organic layer was dried and concentrated. Yield: 2.74 g (61 %)

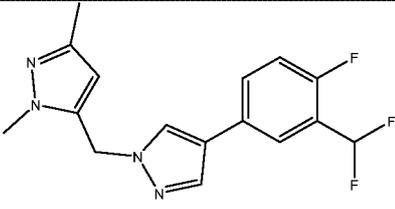
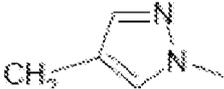
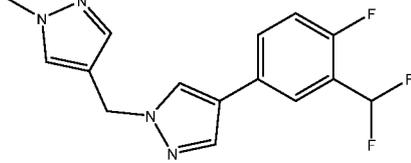
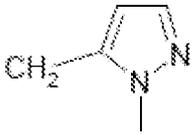
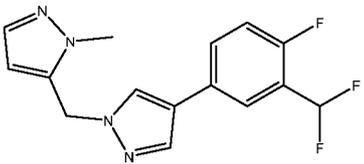
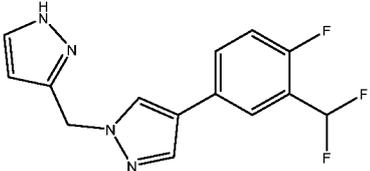
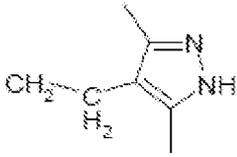
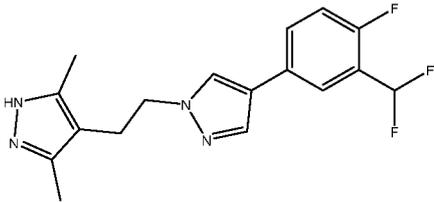
[144] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-1-fluoro-2-difluoromethyl-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole. m.p.: 100-103°C; MS (ESI m/z) 307.2 [M+H]⁺

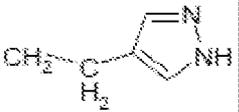
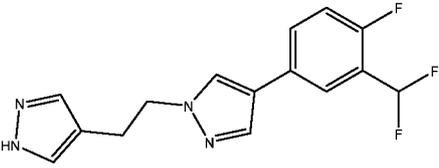
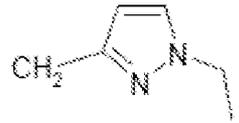
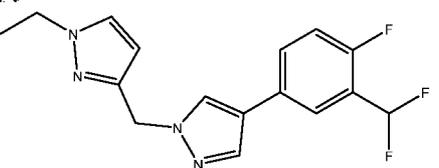
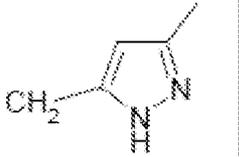
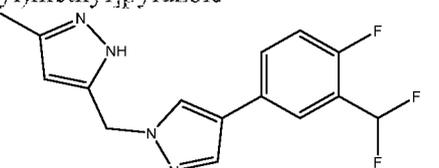
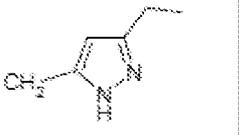
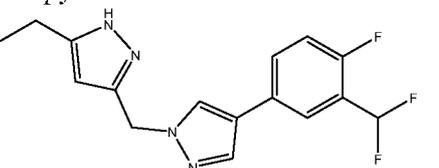
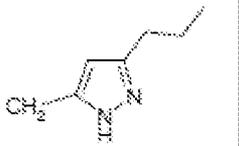
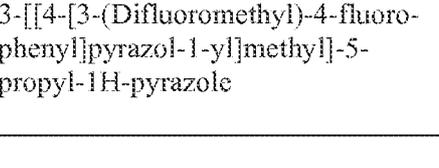
[145] The examples in Table 3 were prepared as described in example 31 replacing 3-chloromethyl-1-methyl-1H-pyrazole with the appropriate chloroalkyl-1H-pyrazole derivative.

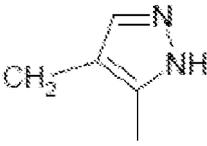
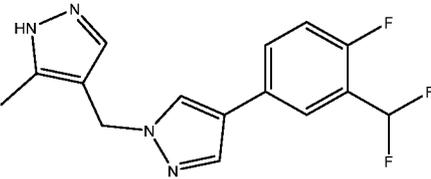
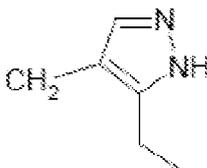
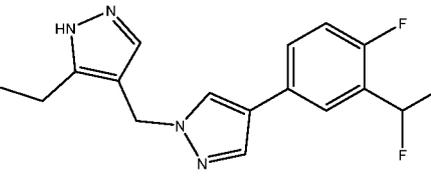
Table 3: [4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]- derivatives



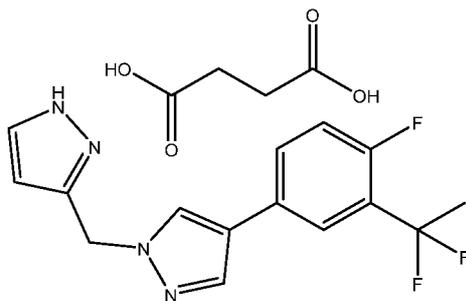
Example	R	Name - Structure	form	MS	m.p. °C
32		5-[[4-[3-(Difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole	base	321.3	44-48

Example	R	Name - Structure	form	MS	m.p. °C
					
33		4-[3-(Difluoromethyl)-4-fluorophenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole 	base	307.2	71-73
34		4-[3-(Difluoromethyl)-4-fluorophenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole 	base	307.2	90-92
35		4-[3-(Difluoromethyl)-4-fluorophenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole 	base	293.2	resin
36		4-[2-[4-[3-(Difluoromethyl)-4-fluorophenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole 	base	335.3	resin

Example	R	Name - Structure	form	MS	m.p. °C
37		4-[3-(Difluoromethyl)-4-fluorophenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole 	suc-cinate	307.2	104-106
38		3-[[4-[3-(Difluoromethyl)-4-fluorophenyl]pyrazol-1-yl]methyl]-1-ethylpyrazole 	suc-cinate	321.3	106-108
39		4-[3-(Difluoromethyl)-4-fluorophenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole 	base	307.2	113-115
40		3-[[4-[3-(Difluoromethyl)-4-fluorophenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole 	citrate	321.0	resin
41		3-[[4-[3-(Difluoromethyl)-4-fluorophenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole 	citrate	335.0	140-142

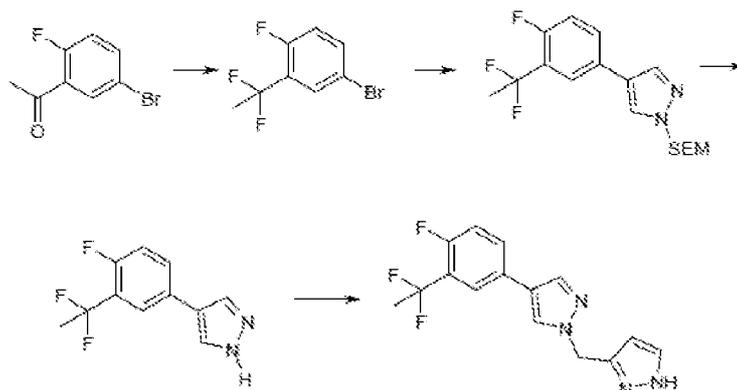
Example	R	Name - Structure	form	MS	m.p. °C
42		4-[3-(Difluoromethyl)-4-fluoro-phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole 	citrate	306.9	resin
43		4-[3-(Difluoromethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole 	L(+)-tartrate	321.3	resin

Example 44: 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole



succinate:

[146] The compound of example 44 was prepared according to following reaction scheme:



Step 1: 4-bromo-2-(1,1-difluoro-ethyl)-1-fluoro-benzene

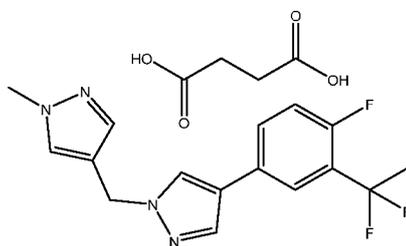
[147] To a solution of 1-(5-bromo-2-fluoro-phenyl)-ethanone (4.34 g, 20 mmol) in DCM (50 mL) was added DAST (diethylaminosulfur trifluoride) (4.03 g, 25 mmol) and the mixture was stirred at room temperature for 18 hours under nitrogen atmosphere.

[148] The reaction mixture was quenched into ice-water and extracted with DCM. The organic layer was dried and concentrated. Yield: 2.78 g (58 %)

[149] The compound was prepared as described in example 1, replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-2-(1,1-difluoro-ethyl)-1-fluoro-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[150] m.p.: 96-98°C, succinate salt; MS (ESI m/z) 307.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.03 (t, 3H, J=19.11); 2.50 (s, 2H); 3.31 (s, 2H); 5.30 (s, 2H); 6.21 (s, 1H); 7.33 (dd, 1H, J=10.01); 7.70 (m, 1H); 8.27 (s, 1H); 8.53 (s, 1H); 12.80 (s, 1H)

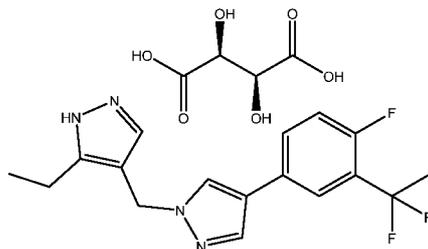
Example 45: 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-



yl)methyl]pyrazole succinate:

[151] The compound of example 45 was prepared as described in example 44 replacing 3-chloromethyl-1H-pyrazole with 4-chloromethyl-1-methyl-1H-pyrazole. m.p.: resin, succinate salt, 1:1; MS (ESI m/z) 321.3 [M+H]⁺

Example 46: 4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-

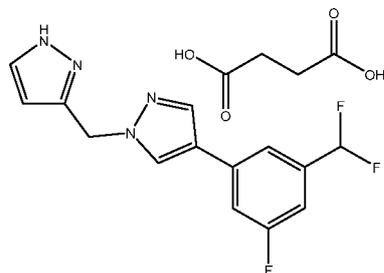


yl)methyl]pyrazole tartrate:

[152] The compound of example 46 was prepared as described in example 44 replacing 3-chloromethyl-1H-pyrazole with 4-chloromethyl-5-ethyl-1H-pyrazole hydrochloride.

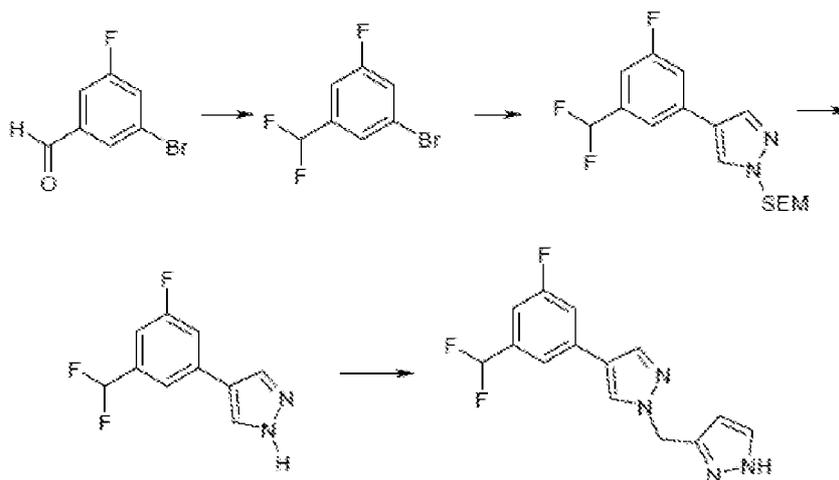
[153] m.p.: resin, L(+)-tartaric salt, 1:1; MS (ESI m/z) 335.3 [M+H]⁺

Example 47: 4-[3-(difluoromethyl)-5-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl) pyrazole



succinate:

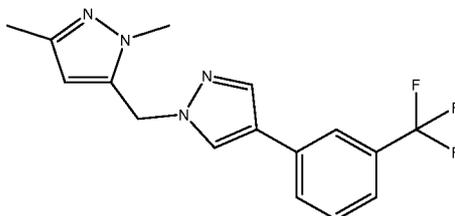
[154] The compound of example 47 was prepared according to following reaction scheme:



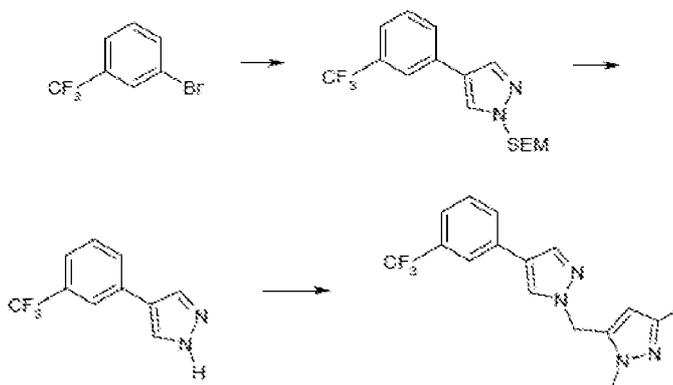
[155] The compound was prepared as described in example 31 replacing 5-bromo-2-fluorobenzaldehyde with 5-bromo-3-fluoro-benzaldehyde and replacing 3-chloromethyl-1-methyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[156] m.p.: 126-128°C, succinate salt; MS (ESI m/z) 293.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.42 (s, 2H); 2.50 (s, 2H); 5.32 (s, 2H); 6.22 (t, 1H, J=1.99); 7.02 (t, 1H, J=55.86); 7.13 (m, 1H, J=8.75); 7.65 (m, 1H); 8.02 (s, 1H); 8.35 (s, 1H); 12.32 (s, 1H)

Example 48: 1,3-dimethyl-5-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole:



[157] The compound of example 48 was prepared according to following reaction scheme:

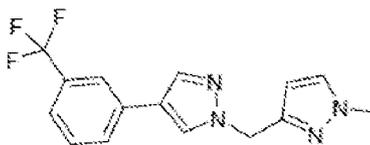


[158] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 1-bromo-3-trifluoromethyl-benzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[159] m.p.: 68-71°C; MS (ESI m/z) 321.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.11 (s, 3H); 3.74 (s, 3H); 5.41 (s, 2H); 6.02 (s, 1H);

7.59 (d, 1H, J=8.27); 7.90 (d, 1H, J=8.27); 8.06 (s, 1H); 8.39 (s, 1H)

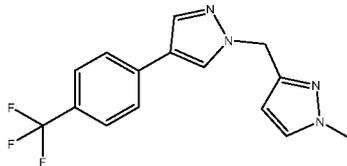
Example 49: 1-methyl-3-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole succinate



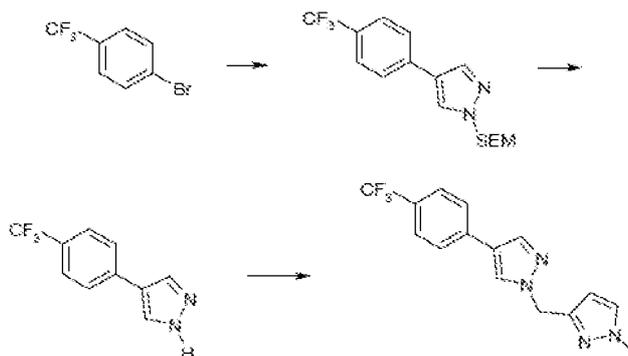
[160] The compound of example 49 was prepared as described in example 48 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[161] m.p.: 90-94°C, succinate salt; MS (ESI m/z) 307.2 [M+H]⁺.

Example 50: 1-methyl-3-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole:



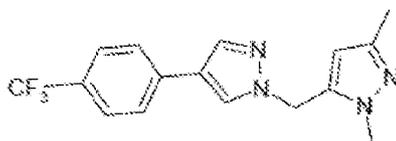
[162] The compound of example 50 was prepared according to following reaction scheme:



[163] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 1-bromo-4-trifluoromethyl-benzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[164] m.p.: 73-77°C; MS (ESI m/z) 307.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 3.32 (s, 3H); 3.81 (s, 2H); 5.27 (s, 1H); 6.18 (s, 1H); 7.63 (m, 1H, J=8.27); 7.67 (d, 1H, J=8.19); 7.79 (d, 1H, 8.19); 7.99 (s, 1H); 8.34 (s, 1H)

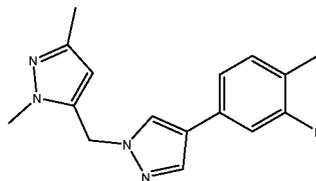
Example 51: 1,3-Dimethyl-5-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-Pyrazole:



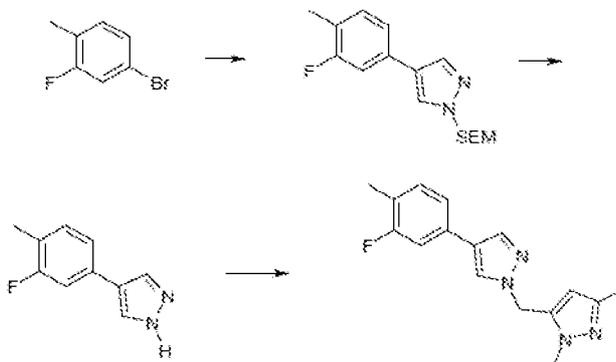
[165] The compound of example 51 was prepared as described in example 50 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[166] m.p.: 110-112°C; MS (ESI m/z) 321.3 [M+H]⁺

Example 52: 5-[[4-(3-fluoro-4-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



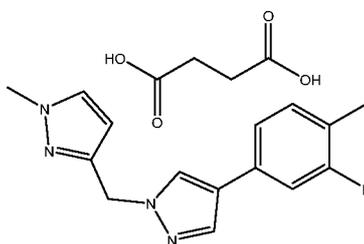
[167] The compound of example 52 was prepared according to following reaction scheme:



[168] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-2-fluoro-1-methylbenzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[169] m.p.: 65-67°C; MS (ESI m/z) 285.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.13 (s, 3H); 3.35 (s, 3H); 3.79 (s, 3H); 5.42 (s, 2H); 6.03 (s, 1H); 7.28 (dd, 1H, J=8.05); 7.34 (dd, 1H, J=7.82); 7.40 (d, 1H, J=11.30); 7.96 (s, 1H); 8.21 (s, 1H)

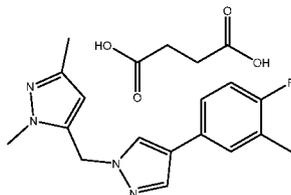
Example 53: 3-[[4-(3-fluoro-4-methylphenyl)pyrazol-1-yl]methyl]-1-methylpyrazole succinate:



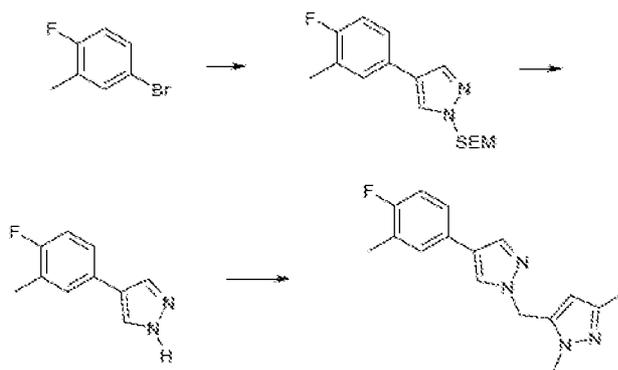
[170] The compound of example 53 was prepared as described in example 52 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[171] m.p.: 83-86°C, succinate salt; MS (ESI m/z) 271.3 [M+H]⁺.

Example 54: 5-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole succinate:



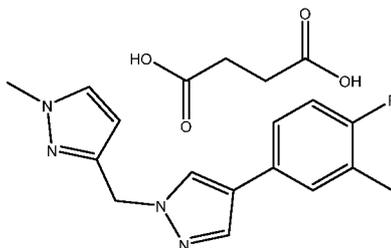
[172] The compound of example 54 was prepared according to following reaction scheme:



[173] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 5-bromo-2-fluoro-1-methyl-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[174] m.p.: 80-82°C, succinate salt. MS (ESI m/z) 285.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.13 (s, 3H); 3.34 (s, 3H); 3.34 (s, 4H), 3.78 (s, 3H); 5.42 (s, 2H); 6.04 (s, 1H); 7.14 (dd, 1H, J=9.24); 7.34 (m, 1H); 7.53 (d, 1H, J=7.84); 7.92 (s, 1H); 8.00 (s, 1H); 8.18 (s, 1H)

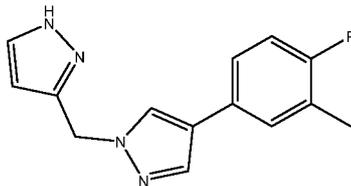
Example 55: 3-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



[175] The compound of example 55 was prepared as described in example 54 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[176] m.p.: resin, succinate salt; MS (ESI m/z) 271.3 [M+H]⁺

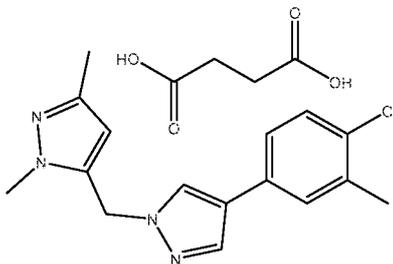
Example 56: 4-(4-fluoro-3-methyl-phenyl)-1-(1H-pyrazol-3-ylmethyl)pyrazole:



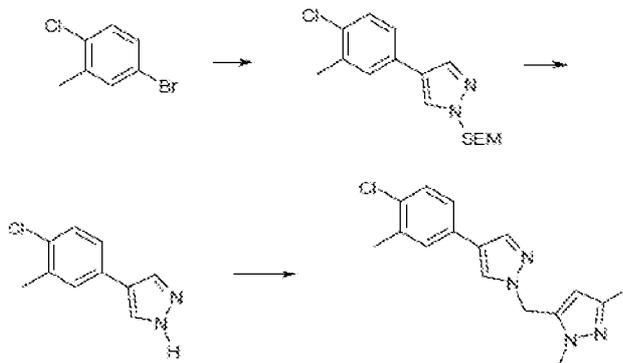
[177] The compound of example 56 was prepared as described in example 54 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[178] m.p.: 135-139°C; MS (ESI m/z) 256.2 [M+H]⁺

Example 57: 5-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole succinate:



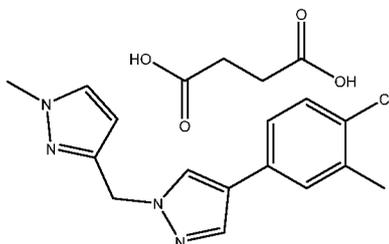
[179] The compound of example 57 was prepared according to following reaction scheme:



[180] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 5-bromo-2-chloro-1-methyl-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[181] m.p.: 70-74°C, succinate salt; MS (ESI m/z) 301.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.10 (s, 3H); 2.89 (s, 3H); 3.30 (d, 4H), 3.75 (s, 3H); 5.39 (s, 2H); 6.01 (s, 1H); 7.38 (d, 1H, J=8.74); 7.41 (d, 1H, J=8.74); 7.59 (s, 1H); 7.92 (s, 1H); 7.96 (s, 1H); 8.21 (s, 1H)

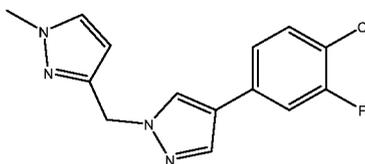
Example 58: 3-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



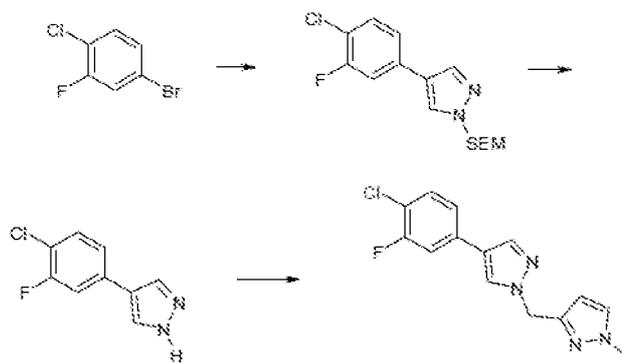
[182] The compound of example 58 was prepared as described in example 57 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[183] m.p.: resin, succinate salt; MS (ESI m/z) 287.7 [M+H]⁺

Example 59: 3-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole:



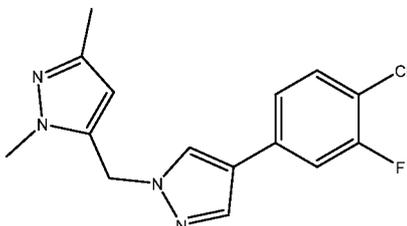
[184] The compound of example 59 was prepared according to following reaction scheme:



[185] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 5-bromo-2-chloro-1-fluoro-benzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.\

[186] m.p.: 62-65°C; MS (ESI m/z) 291.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 3.80 (s, 3H); 5.25 (s, 2H); 6.16 (s, 1H); 7.44 (d, 1H, J=9.17); 7.51 (dd, 1H, J=7.80); 7.63 (m, 1H); 7.68 (d, 1H, J=10.60); 7.95 (s, 1H); 8.28 (s, 1H)

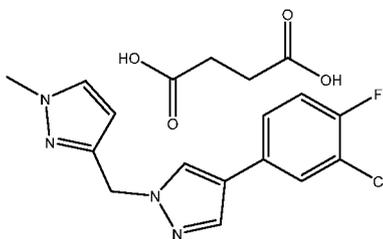
Example 60: 5-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



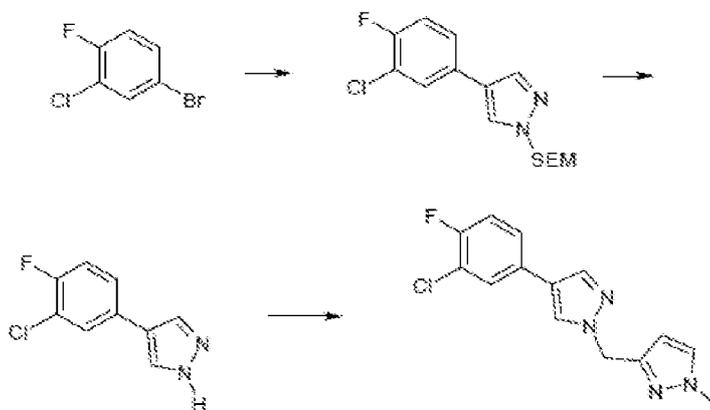
[187] The compound of example 60 was prepared as described in example 59 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[188] m.p.: 90-92°C; MS (ESI m/z) 305.7 [M+H]⁺

Example 61: 3-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



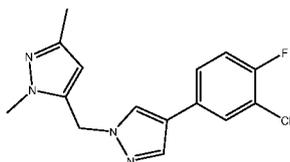
[189] The compound of example 61 was prepared according to following reaction scheme:



[190] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-2-chloro-1-fluoro-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[191] m.p.: 109-112°C, succinate salt, 1:1; MS (ESI m/z) 291.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 3.30 (d, 4H); 3.81 (s, 3H); 5.24 (s, 2H); 6.14 (s, 1H); 7.42 (d, 1H, J=9.12); 7.50 (dd, 1H, J=7.85); 7.61 (m, 1H); 7.66 (d, 1H, J=10.64); 7.94 (s, 1H); 8.27 (s, 1H)

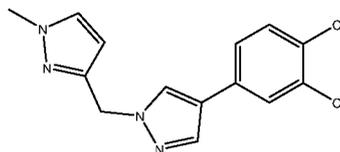
Example 62: 5-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



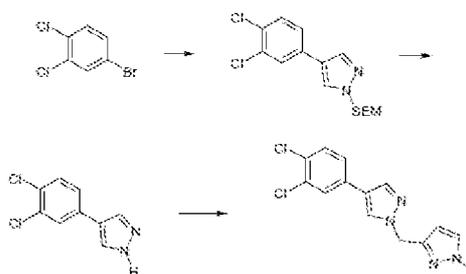
[192] The compound of example 62 was prepared as described in example 62 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[193] m.p.: 56-60°C; MS (ESI m/z) 305.7 [M+H]⁺

Example 63: 3-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole:



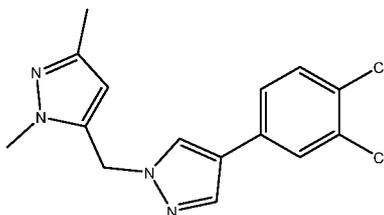
[194] The compound of example 63 was prepared according to following reaction scheme:



[195] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-1,2-dichloro-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[196] m.p.: 106-110°C; MS (ESI m/z) 308.1 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 3.80 (s, 3H); 5.24 (s, 2H); 6.17 (s, 1H); 7.58 (s, 2H); 7.63 (s, 1H); 7.89 (m, 1H); 7.98 (s, 1H); 8.31 (s, 1H)

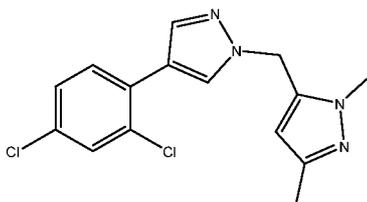
Example 64: 5-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



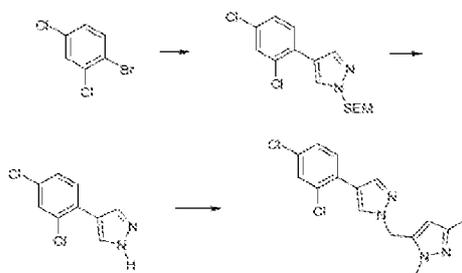
[197] The compound of example 64 was prepared as described in example 64 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[198] m.p.: 56-60°C; MS (ESI m/z) 322.2 [M+H]⁺

Example 65: 5-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



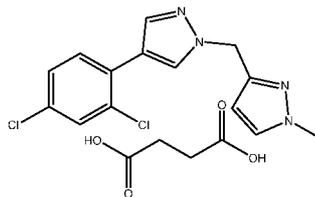
[199] The compound of example 65 was prepared according to following reaction scheme:



[200] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-1,3-dichloro-benzene and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[201] m.p.: 60-64°C; MS (ESI m/z) 322.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.13 (s, 3H); 2.85 (s, 3H); 3.31 (d, 4H), 3.71 (s, 3H); 5.38 (s, 2H); 6.00 (s, 1H); 7.34 (d, 1H, J=8.79); 7.48 (d, 1H, J=8.76); 7.51 (s, 1H); 7.92 (s, 1H); 7.99 (s, 1H); 8.28 (s, 1H)

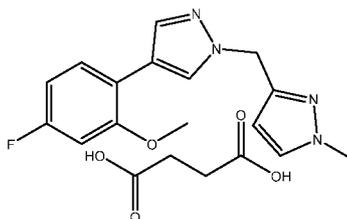
Example 66: 3-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



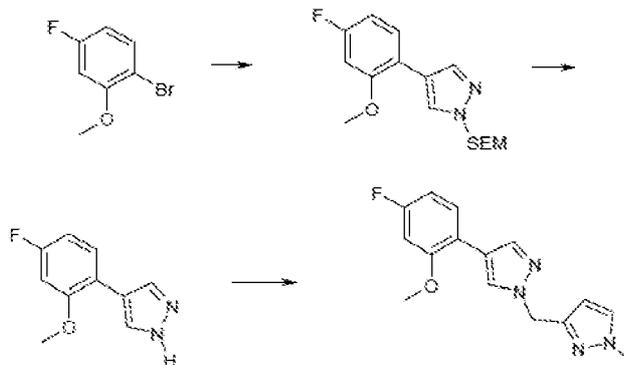
[202] The compound of example 66 was prepared as described in example 65 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[203] m.p.: resin, succinate salt; MS (ESI m/z) 308.1 [M+H]⁺

Example 67: 3-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



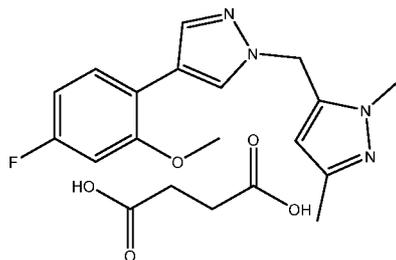
[204] The compound of example 67 was prepared according to following reaction scheme:



[205] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 2-bromo-5-fluoro-1-methoxy-benzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[206] m.p.: 111-114°C, succinate salt, 1:1; MS (ESI m/z) 287.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.25 (s, 3H); 3.35 (s, 3H); 3.87 (d, 4H); 5.29 (s, 2H); 6.17 (s, 1H); 6.81 (dd, 1H, J=8.78); 6.98 (dd, 1H, J=11.09); 7.64 (m, 1H); 7.89 (s, 1H); 8.16 (s, 1H); 12.19 (s, 2H)

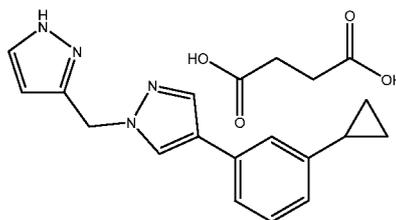
Example 68: 5-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole succinate:



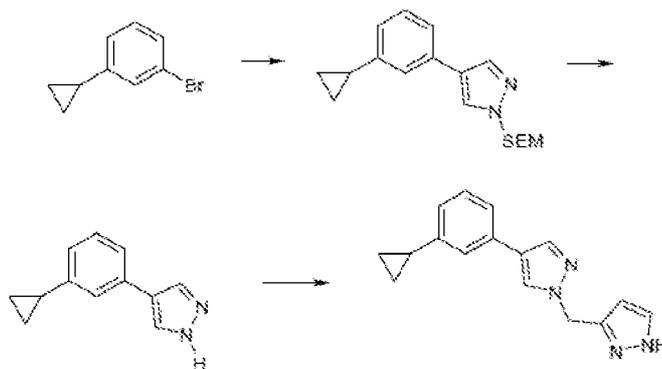
[207] The compound of example 68 was prepared as described in example 67 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[208] m.p.: resin, succinate salt, 1:1; MS (ESI m/z) 301.3 [M+H]⁺

Example 69: 4-(3-cyclopropylphenyl)-1-(1H-pyrazol-3-ylmethyl)pyrazole succinate:



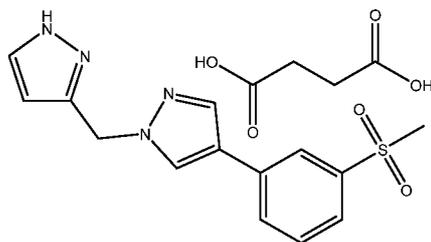
[209] The compound of example 69 was prepared according to following reaction scheme:



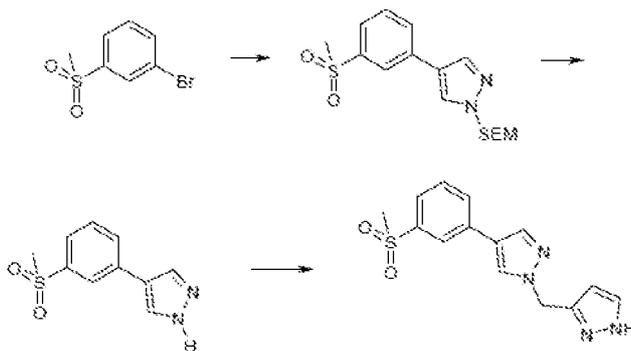
[210] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 3-bromo-1-cyclopropylbenzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[211] m.p.: 122-125°C, succinate salt, 1:1; MS (ESI m/z) 265.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 0.72 (m, 2H); 0.95 (m, 2H); 2.42 (s, 2H); 2.50 (s, 2H); 3.31 (s, 1H); 5.30 (s, 2H); 6.89 (d, 1H, J=2.06); 7.18 (d, 1H, J=7.57); 7.20 (s, 1H); 7.26 (dd, 1H, J=7.50); 7.64 (m, 1H); 7.86 (s, 1H); 8.16 (s, 1H); 12.29 (s, 2H)

Example 70: 4-(3-methylsulfonylphenyl)-1-(1H-pyrazol-3-ylmethyl)pyrazole succinate:



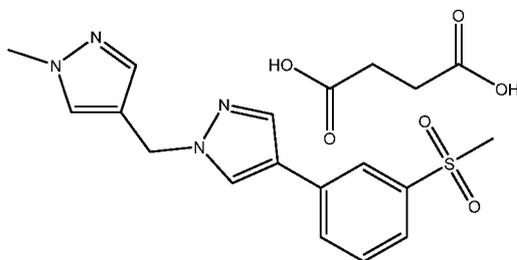
[212] The compound of example 70 was prepared according to following reaction scheme:



[213] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 1-bromo-3-methanesulfonyl-benzene and replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[214] m.p.: 122-125°C, succinate salt, 1:1; MS (ESI m/z) 303.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.30 (s, 3H); 3.05 (s, 2H); 3.10 (s, 2H); 5.13 (s, 2H); 6.02 (s, 1H); 7.41 (m, 1H); 7.52 (d, 1H, J=8.54); 7.71 (d, 1H, J=8.54); 7.82 (m, 1H); 7.89 (s, 1H); 8.17 (s, 1H); 12.55 (s, 1H)

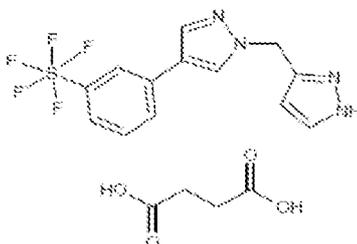
Example 71: 1-methyl-4-[[4-(3-methylsulfonylphenyl)pyrazol-1-yl]methyl]pyrazole succinate:



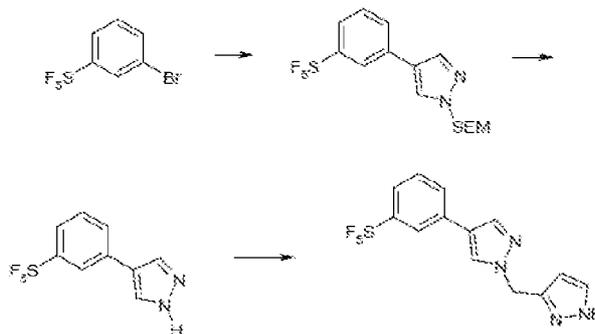
[215] The compound of example 71 was prepared as described in example 70 replacing 3-chloromethyl-1H-pyrazole with 4-chloromethyl-1-methyl-1H-pyrazole.

[216] m.p.: resin, succinate salt, 1:1; MS (ESI m/z) 317.3 [M+H]⁺.

Example 72: 1-((1H-pyrazol-3-yl)methyl)-4-(3-(pentafluoro-16-sulfanyl)phenyl)-1H-pyrazole succinate:



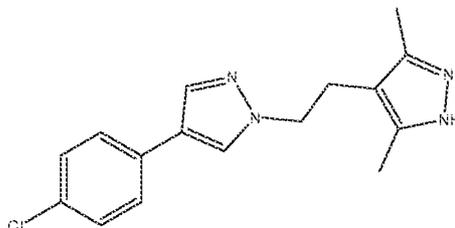
[217] The compound of example 72 was prepared according to following reaction scheme:



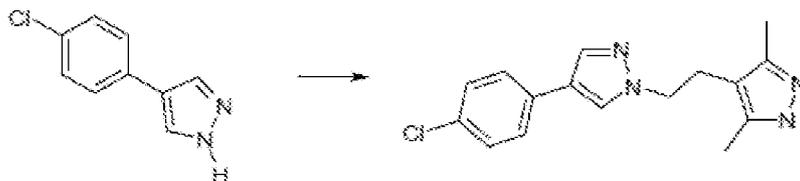
[218] The compound was prepared as described in example 1 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 1-bromo-3-pentafluoro-phenyl-sulfane and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[219] m.p.: 142-145°C, succinate salt, 1:1; MS (ESI m/z) 351.3 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 2.42 (s, 2H); 2.51 (s, 2H); 3.31 (s, 2H); 5.32 (s, 2H); 6.22 (d, 1H, J=2.24); 7.58 (dd, 1H, J=7.75); 7.64 (m, 1H); 7.87 (d, 1H, J=7.75); 8.04 (m, 1H); 8.42 (s, 1H); 12.44 (s, 1H)

Example 73: 4-[2-[4-(4-chlorophenyl)pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole:



[220] The compound of example 73 was prepared according to following reaction scheme:

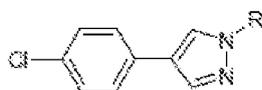


[221] The compound was prepared as described in example 1 replacing 4-(4-chloro-3-difluoromethoxy-phenyl)-1H-pyrazole with 4-(4-chlorophenyl)-1H-pyrazole.

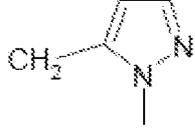
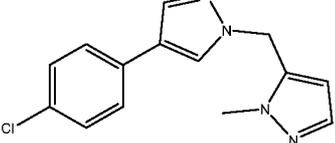
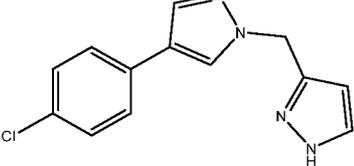
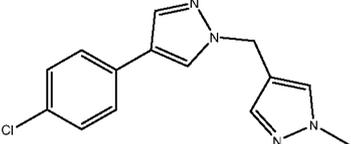
[222] m.p.: 130-134°C; MS (ESI m/z) 301.7 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ 1.94 (s, 3H); 2.50 (s, 3H); 2.80 (t, 2H, J=6.99); 4.12 (t, 2H, J=6.99); 7.39 (d, 2H, J=8.09); 7.55 (d, 2H, J=8.09); 7.90 (s, 1H); 8.01 (s, 1H); 11.91 (s, 1H).

[223] The examples in Table 4 were prepared as described in example 73 replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with the appropriate chloroalkyl-1H-pyrazole derivative.

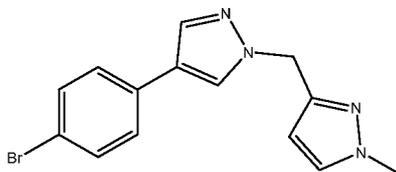
Table 4: 4-[2-[4-(4-chlorophenyl)pyrazol-1-yl] – derivatives



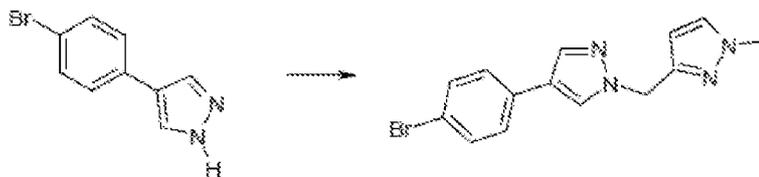
Example	R	Name – Structure	form	MW	m.p. °C
74		5-[[4-(4-Chlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole 	base	287.7	85-89
75		3-[[4-(4-Chlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole 	base	273.7	63-66

Example	R	Name – Structure	form	MW	m.p. °C
76		4-(4-Chlorophenyl)-1-[(2-methylpyrazol-3-yl)methyl]pyrazole 	HCl	273.7	106-110
77		4-(4-Chlorophenyl)-1-(1H-pyrazol-3-ylmethyl) pyrazole 	base	259.7	120-124
78		4-(4-Chlorophenyl)-1-[(1-methylpyrazol-4-yl)methyl]pyrazole 	base	273.7	111-112

Example 79: 3-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole:



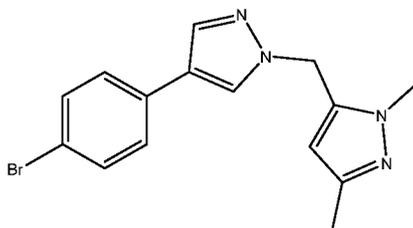
[224] The compound of example 79 was prepared according to following reaction scheme:



[225] The compound was prepared as described in example 1 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 4-(4-bromophenyl)-1H-pyrazole and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1H-pyrazole.

[226] m.p.: 104-106°C; MS (ESI m/z) 318.1 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ

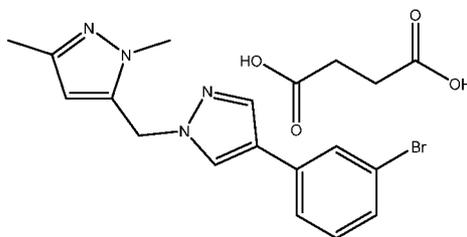
Example 80: 5-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



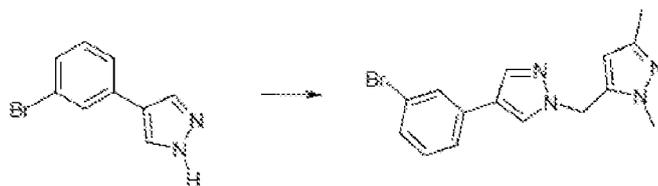
[227] The compound of example 80 was prepared as described in example 79 replacing 3-chloromethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[228] m.p.: 91-96°C; MS (ESI m/z) 332.2 [M+H]⁺

Example 81: 5-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole succinate



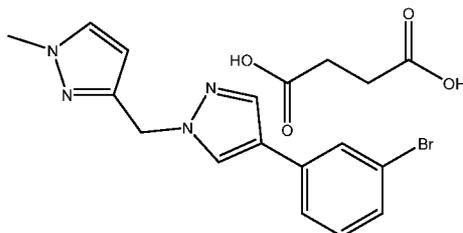
[229] The compound of example 81 was prepared according to following reaction scheme:



[230] The compound was prepared as described in example 1 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 4-(3-bromophenyl)-1H-pyrazole and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[231] m.p.: 97-99°C, succinic salt, 1:1; MS (ESI m/z) 332.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ

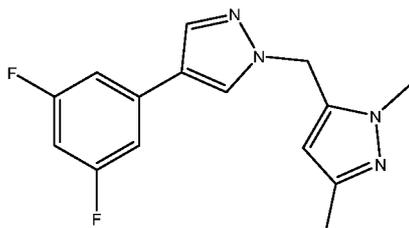
Example 82: 3-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole succinate:



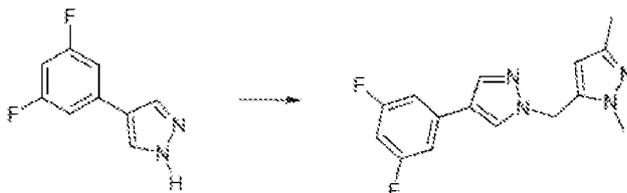
[232] The compound of example 82 was prepared as described in example 81 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[233] m.p.: 116-118°C succinic salt, 1:1; MS (ESI m/z) 318.1 [M+H]⁺

Example 83: 5-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole:



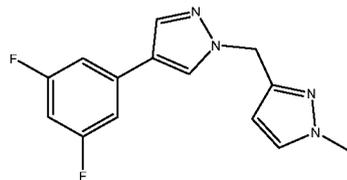
[234] The compound of example 83 was prepared according to following reaction scheme:



[235] The compound was prepared as described in example 1 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 4-(3,5-difluorophenyl)-1H-pyrazole and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-chloromethyl-1,3-dimethyl-1H-pyrazole.

[236] m.p.: 90-93°C; MS (ESI m/z) 289.2 [M+H]⁺; ¹H NMR (500 MHz, DMSO-d₆) δ

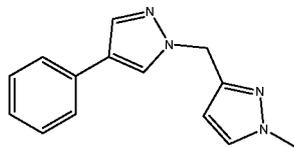
Example 84: 3-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole:



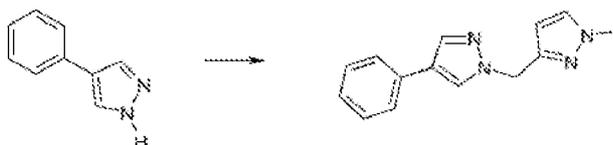
[237] The compound of example 84 was prepared as described in example 83 replacing 5-chloromethyl-1,3-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

[238] m.p.: 96-100°C; MS (ESI m/z) 275.2 [M+H]⁺

Example 85: 1-methyl-3-[(4-phenylpyrazol-1-yl)methyl]pyrazole:



[239] The compound of example 85 was prepared according to following reaction scheme:

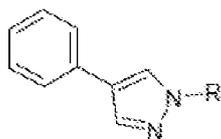


[240] The compound was prepared as described in example 1 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 4-phenyl-1H-pyrazole and replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 3-chloromethyl-1-methyl-1H-pyrazole.

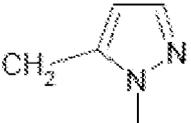
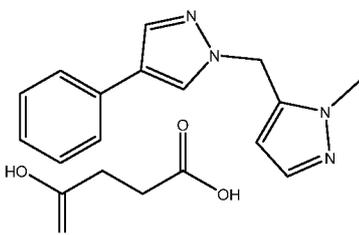
[241] m.p.: 91-95°C; MS (ESI m/z) 239.2 [M+H]⁺

[242] The examples in Table 5 were prepared as described in example 85 replacing 3-chloromethyl-1-methyl-1H-pyrazole with the appropriate chloroalkyl-1H-pyrazole derivative.

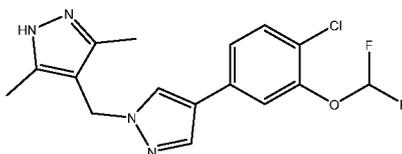
Table 5: 4-phenylpyrazol-1-yl- derivatives



Example	R	Name - Structure	form	MW	m.p. °C
86		1,3-Dimethyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole 	base	253.3	82-84

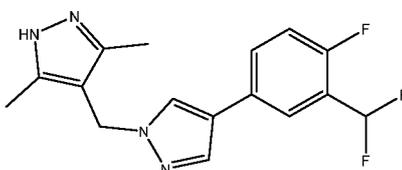
87		<p>1-Methyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole; succinic acid</p> 	succinate	239.2	85-87
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Example 88: 4-[[4-(3-difluoromethoxy-4-chloro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole



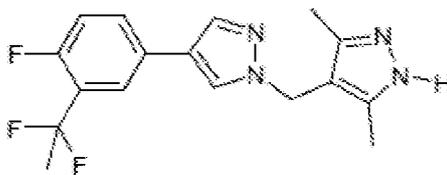
[243] The compound of example 88 was prepared as described in example 1 replacing 4-(2-chloroethyl)-3,5-dimethyl-1H-pyrazole with 4-(2-chloromethyl)-3,5-dimethyl-1H-pyrazole in step 4. MS[M+H]⁺ = 353.8; melting range: 146-148 °C

Example 89: 4-[[4-(3-difluoromethyl-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole:



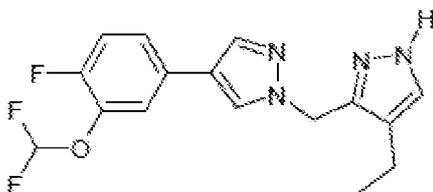
[244] The compound of example 89 was prepared as described in example 31 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 4-(2-chloromethyl)-3,5-dimethyl-1H-pyrazole in step 4. MS[M+H]⁺ = 321.3; melting range: 154-155 °C

Example 90: 4-[[4-(3-(1,1-difluoroethyl)-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole:



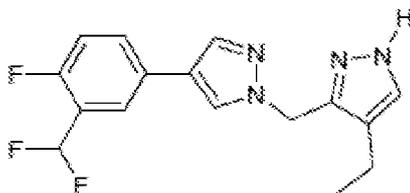
[245] The compound of example 90 was prepared as described in example 45 replacing 4-chloromethyl-1-methyl-1H-pyrazole with 4-(2-chloromethyl)-3,5-dimethyl-1H-pyrazole in step 4. MS[M+H]⁺ = 335.3; melting range: 118-120 °C

Example 91: 3-[[4-[3-(difluoromethoxy)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole succinate:



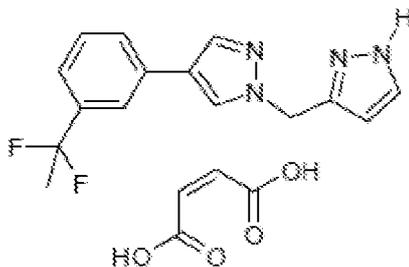
[246] The compound of example 91 was prepared as described in example 20 replacing 4-chloromethyl-5-ethyl-1H-pyrazole with 3-chloromethyl-4-ethyl-1H-pyrazole in step 4. MS[M+H]⁺ = 337.3

Example 92: 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole:



[247] The compound of example 92 was prepared as described in example 31 replacing 3-chloromethyl-1-methyl-1H-pyrazole with 3-chloromethyl-4-ethyl-1H-pyrazole in step 4. MS[M+H]⁺ = 321.3

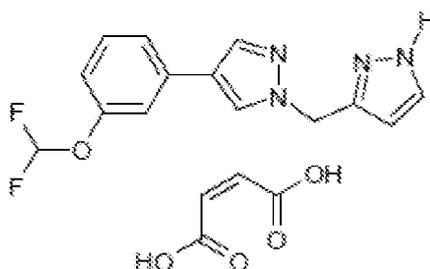
Example 93: 3-[[4-(3-(1,1-difluoroethyl)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole maleate:



[248] The compound of example 93 was prepared as described in example 6 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 3-bromo-1-(1,1-difluoroethyl)-benzene in step 1.

[249] $MS[M+H]^+ = 289.4$

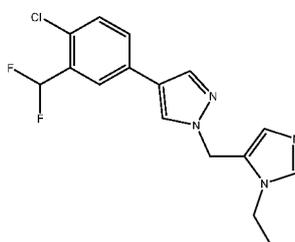
Example 94: 3-[[4-(3-(difluoromethoxy)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole maleate:



[250] The compound of example 94 was prepared as described in example 6 replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 3-bromo-1-difluoromethoxy-benzene in step 1.

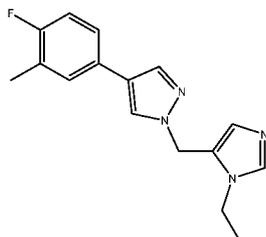
[251] $MS[M+H]^+ = 291.3$

Example 95: 4-(4-chloro-3-(difluoromethyl)phenyl)-1-((1-ethyl-1H-imidazol-5-yl)methyl)-1H-pyrazole:



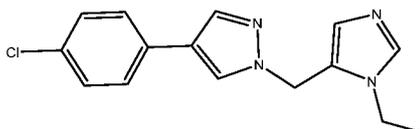
[252] The compound of example 95 was prepared as described in example 24 replacing 5-(chloromethyl)-1-methyl-1H-pyrazole with 5-(chloromethyl)-1-ethyl-1H-imidazole.

Example 96: 4-(4-fluoro-3-methylphenyl)-1-((1-ethyl-1H-imidazol-5-yl)methyl)-1H-pyrazole:



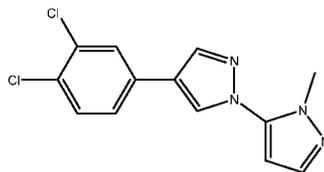
[253] The compound of example 96 was prepared using the methods described herein.

Example 98: 4-(4-chlorophenyl)-1-((1-ethyl-1H-imidazol-5-yl)methyl)-1H-pyrazole:



[254] The compound of example 98 was prepared as described in example 73 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 5-(chloromethyl)-1-ethyl-1H-imidazole.

Example 100: 4-(3,4-dichlorophenyl)-2'-methyl-2'H-1,3'-bipyrazole:

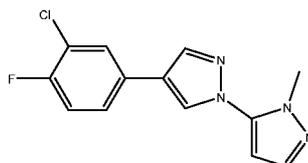


[255] 4-(3,4-dichlorophenyl)-1H-pyrazole was prepared as described in Example 1 Steps 1-3, replacing 4-bromo-1-chloro-2-difluoromethoxy-benzene with 4-bromo-1,2-dichloro-benzene in Step 1.

Step 4: 4-(3,4-dichlorophenyl)-2'-methyl-2'H-1,3'-bipyrazole

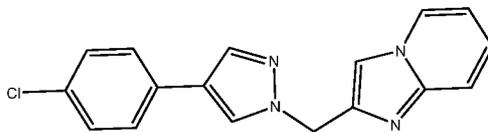
[256] Copper (II) Acetate (110 mg, 0.6 mmol), pyridine (0.08 mL, 1 mmol), 1-methyl-1H-pyrazole-5-boronic acid pinacol ester and 4-(3,4-dichlorophenyl)-1H-pyrazole (383 mg, 1.8 mmol) were combined in DMF and stirred for 20h at 95 degrees C. Extractions were carried out using water and ethyl acetate and the crude product was purified by flash chromatography using DCM/MeOH (95:5).

Example 101: 4-(3-chloro-4-fluorophenyl)-2'-methyl-2'H-1,3'-bipyrazole:



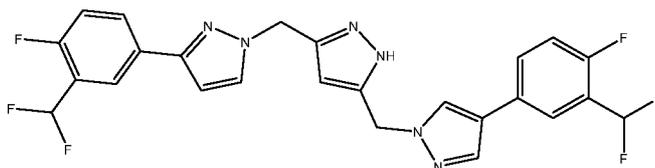
[257] The compound in example 101 was prepared as described for example 100, replacing 4-bromo-1,2-dichloro-benzene with 4-bromo-2-chloro-1-fluorobenzene in Step 1.

Example 102: 2-((4-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine:

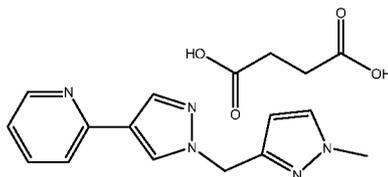


[258] The compound of example 102 was prepared as described in example 73 replacing 4-(2-chloro-ethyl)-3,5-dimethyl-1H-pyrazole with 2-(chloromethyl)imidazo[1,2-a].

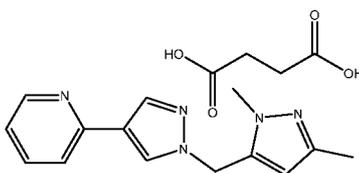
Example 103: 3-(3-(difluoromethyl)-4-fluorophenyl)-1-((5-((4-(3-(difluoromethyl)-4-fluorophenyl)-1H-pyrazol-1-yl)methyl)-1H-pyrazol-3-yl)methyl)-1H-pyrazole:



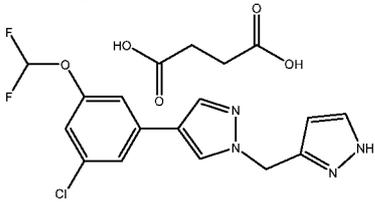
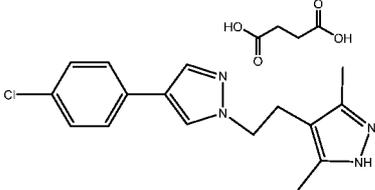
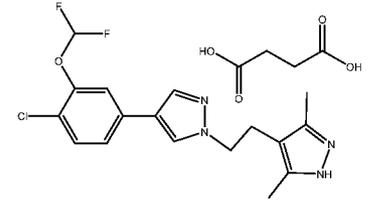
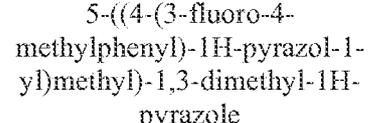
Example 104: 2-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-pyrazol-4-yl)pyridine succinate:

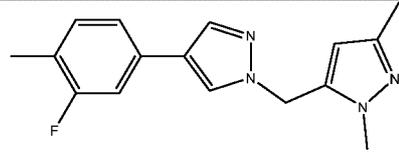
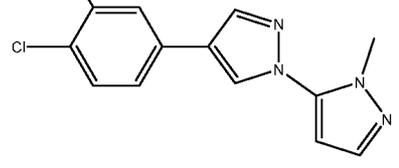
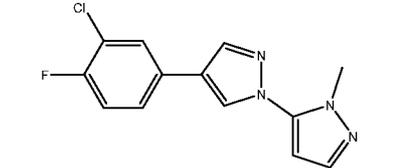


Example 105: 2-(1-((1,3-dimethyl-1H-pyrazol-5-yl)methyl)-1H-pyrazol-4-yl)pyridine succinate:



[259] Examples 106-111 were prepared according to the methods described herein with the appropriate starting materials.

Example	Structure
106	1-((1H-pyrazol-3-yl)methyl)-4-(3-chloro-5-(difluoromethoxy)phenyl)-1H-pyrazole succinate 
107	4-(2-(4-(4-chlorophenyl)-1H-pyrazol-1-yl)ethyl)-3,5-dimethyl-1H-pyrazole succinate 
108	4-(2-(4-(4-chloro-3-(difluoromethoxy)phenyl)-1H-pyrazol-1-yl)ethyl)-3,5-dimethyl-1H-pyrazole succinate 
109	5-((4-(3-fluoro-4-methylphenyl)-1H-pyrazol-1-yl)methyl)-1,3-dimethyl-1H-pyrazole 

Example	Structure
	
110	4-(3,4-dichlorophenyl)-2'-methyl-2'H-1,3'-bipyrazole 
111	4-(3-chloro-4-fluorophenyl)-2'-methyl-2'H-1,3'-bipyrazole 

Biological Assays

Inhibition of Specific Binding to the Rat NR1/NR2B Receptor

[260] Male Wistar rats (180 to 200 g) were killed by suffocation in a CO₂ chamber for two minutes. Whole brains without cerebellum were removed and dissected on ice, placed into closed vials and stored at -70 °C.

[261] Membrane fractions were prepared and tested using standard techniques. At the time of the assay, 1 g of the brains was placed into 25 ml of 50 mM Tris/10 mM EDTA buffer, pH 7.1, (25 vol. per g of original tissue) and homogenized for 30 sec at 20000 rpm with an Ultraturrax T25 (Jahnke & Kunkel, IKA-Labortechnik, Staufen, Germany). The homogenate was centrifuged at 4 °C for 10 min at 48000 g (OPTIMA L-70, Beckman, Palo Alto, CA 94304, USA).

[262] The supernatant was discarded and the pellet was homogenized on ice for 30 sec at 20000 rpm with an Ultraturrax and again centrifuged at 48000 g for 30 minutes at 4°C. The resultant pellet was resuspended in 25 ml of 50 mM Tris/10 mM EDTA buffer, homogenized for 30 sec with an Ultraturrax, aliquoted, frozen at -70°C and stored until use.

[263] After thawing on the day of the assay, a 5 ml membrane aliquot was centrifuged at 48000 g for 30 min at 4°C. The pellet was resuspended in 5 ml of 5 mM Tris/1 mM EDTA buffer, pH 7.4, homogenized for 30 sec at 20000 rpm with an Ultraturrax and centrifuged at 48000 g for 30 min at 4°C. This was repeated twice. The final pellet was homogenized in 5 ml of 5 mM Tris/1 mM EDTA buffer at 4°C with an Ultraturrax and used for the Ifenprodil-binding assay as described in the following.

[264] The incubation mixture of 200 µl contained 5 nmol/l [³H]-Ifenprodil, an optimised amount of membrane preparation, 5 mM Tris/1 mM EDTA (pH 7.4, 100µM R(+)-3-PPP, 1 µM GBR-12909, 1 µM GBR-12935) and test compound in 1% DMSO. Nonspecific binding was estimated in the presence of 10M CP101.606. The samples were incubated for 60 min. at 4°C.

[265] The incubation was terminated by filtration of the membrane preparations using Filtermat B (Pharmacia, Uppsala Sweden) and a Micro Cell Harvester (Skatron, Lier, Norway). The Filtermat B had been presoaked with 1% polyethylene imine and carefully washed with 50 mM Tris/HCl-buffer pH 7.7 after the filtration to separate free and bound radioactivity. The filters were counted in a scintillation counter (Betaplate 1205, Berthold, Wildbad, Germany) in order to determine the specific binding of [³H]-Ifenprodil.

[266] The optimal amount of membrane preparation in the assay was determined and optimized for each membrane preparation separately before the test.

[267] Test compounds were either screened at 6 to 10 increasing concentrations for the determination of IC₅₀ and Ki or at 2 - 4 concentrations for the determination of the percent

inhibition. For pipetting of the incubation mixture the robot Biomek2000 (Fa. Beckman) was used.

[268] For determination of IC₅₀ values the Hill-plot, 2-parameter-model was used. In the NR1/NR2B binding assay a dissociation constant (K_D) of [³H]-Ifenprodil of 9 nM was determined.

NR2B Inhibition, IC₅₀ values

Example	NR2B binding assay		
	IC ₅₀ [nM]	% INH @ 1μM	%INH @ 10 μM
1	65.5	NT	NT
2	78.4	NT	NT
3	146	NT	NT
4	119	NT	NT
5	148	NT	NT
6	5.21	NT	NT
7	8.23	NT	NT
8	281	NT	NT
9	152	NT	NT
10	250	NT	NT
11	NT	2.7	NT
12	280	NT	NT
13	22.1	NT	NT
14	76.2	NT	NT
15	163	NT	NT
16	41.1	NT	NT
17	56.0	NT	NT
18	8.01	NT	NT
19	202	NT	NT
20	22.2	NT	NT
21	1021	NT	NT
22	2760	NT	NT
23	1590	NT	NT
24	410	NT	NT
25	980	NT	NT
26	30.1	NT	NT
27	7170	NT	NT
28	638	NT	NT
29	2540	NT	NT
30	1010	NT	NT
31	264	NT	NT
32	323	NT	NT

Example	NR2B binding assay		
	IC ₅₀ [nM]	% INH @ 1μM	%INH @ 10 μM
33	371	NT	NT
34	866	NT	NT
35	17.6	NT	NT
36	424	NT	NT
37	2060	NT	NT
38	443	NT	NT
39	102	NT	NT
40	47.0	NT	NT
41	114	NT	NT
42	202	NT	NT
43	134	NT	NT
44	17.1	NT	NT
45	261	NT	NT
46	106	NT	NT
47	203	NT	NT
48	1970	NT	NT
49	2250	NT	NT
50	4250	NT	NT
51	9210	NT	NT
52	522	NT	NT
53	3840	NT	NT
55	871	NT	NT
56	78.7	NT	NT
57	967	NT	NT
58	668	NT	NT
59	2190	NT	NT
60	2170	NT	NT
61	1380	NT	NT
62	857	NT	NT
63	612	NT	NT
64	1100	NT	NT
65	3810	NT	NT

Example	NR2B binding assay		
	IC50 [nM]	% INH @ 1µM	%INH @ 10 µM
66	5210	NT	NT
67	NT	15.1	16.0
68	NT	8.7	26.3
69	831	NT	NT
70	2690	NT	NT
71	9330	NT	NT
72	95.1	NT	NT
73	1157	NT	NT
74	6060	NT	NT
75	3040	NT	NT
76	7350	NT	NT
77	1040	NT	NT
78	8280	NT	NT
79	4720	NT	NT
80	6210	NT	NT
81	4630	NT	NT
82	2620	NT	NT
83	6020	NT	NT
84	NT	14.6	45.7

Example	NR2B binding assay		
	IC50 [nM]	% INH @ 1µM	%INH @ 10 µM
85	NT	22.5	25.3
86	NT	3.8	10.9
87	NT	-3.3	28.8
88	152	NT	NT
89	736	NT	NT
90	422	NT	NT
91	43.8	NT	NT
92	71.2	NT	NT
93	25.2	NT	NT
94	279	NT	NT
95	63.5	NT	NT
96	77.8	NT	NT
98	1060	NT	NT
100	3170	NT	NT
101	5600	NT	NT
102	NT	23.3	NT
103	NT	15.5	NT
104	NT	20.9	-0.6
105	NT	-1.3	4.4

HNR2BC: Effects of Test Articles on Cloned Human NR1/NR2B Ion Channels Expressed in Mammalian Cells

[269] The ability of test compounds to act as an antagonist of NR1/NR2B was evaluated with a calcium influx assay (Calcium 5 Assay Kit, Molecular Devices).

[270] For the antagonist assessment, NR1/NR2B was activated with the positive control agonist (Mg²⁺-free HBPS + 100 µM glutamic acid + 100 µM glycine). The effect of each test article to inhibit the signal was examined after agonist stimulation and compared to the positive control antagonist (MK-801). The signal elicited in the presence of the positive agonist (Mg²⁺-free HBPS + 100 µM glutamic acid + 100 µM glycine) was set to 100 (0% inhibition) and the signal from the positive antagonist (Mg²⁺-free HBPS + 100 µM glutamic acid + 100 µM glycine + 100 µM MK-801) was set to 0 (100% inhibition).

Cell Culture:

[271] A HEK cell line, stable transfected with hNR1/NR2B was used. This tetracycline inducible cell line is transfected with GRIN1 (GeneBank accession number NM_007327.2) and

GRIN2B (GeneBank accession number NM_000834.3.). The cells were cultured in cell culture flasks with DMEM/F12 supplemented with 10% FCS, 1%PenStrep and a selection of additional antibiotics.

[272] Forty-Eight (48) hours before the assay the cells were plated into 96-well black well, flat clear bottom microtiter plates at a density of 50000 cells/well. Twenty-Four (24) hours later the receptor expression was induced by the addition of 1µg/ml tetracycline in the presence of 2mM ketamine and 200µM 7-CKA. After 24h of receptor induction the plates were used for the assay.

Assay:

[273] The medium was removed and the cells were loaded with 200µl loading buffer (Molecular Devices) in Mg²⁺-free HBPS containing 100µM 7-CKA at 37°C for one (1) hour.

[274] The test compounds were then solubilized in 100% DMSO and diluted to yield eight (8) different concentrations in 100% DMSO. A 96 well drug plate was prepared by diluting with water and glycine/glutamate to a 5-fold of final test concentration. Fluorescence intensity of the cells in the plate was measured in a FlexStation using an excitation wavelength of 485nm and an emission wavelength of 525nm. Twenty (20) seconds after starting the recordings the compounds together with the agonists glycine (100µM) and glutamate (100µM) were added into the wells and the fluorescence measured for ninety (90) seconds in summary.

[275] The IC₅₀ values provided in the paragraph below were determined using a 3 parameter plot.

Example	IC50 [µM]
2	2.46
4	1.75
6	0.23
7	0.35
14	>10
16	2.15
17	3.7
18	0.37

Example	IC50 [µM]
20	5.97*
26	0.89
31	7.77
35	0.69
39	2.4
40	3.3
41	59.7*
42	2.3

Example	IC50 [µM]
43	2.66
44	0.53
74	51*
75	33.8*
88	>10
91	1.25
92	11.9*

Inhibition of Specific Binding to the hERG - Receptor (HERGBD)

[276] A HEK cell line with stable transfected human ERG receptor was used for the assay. The cells were grown adherently and maintained in DULBECCOS' MEM medium with 10% FBS, 1% non-essential amino acids, 1% Penicillin/Streptomycin and 400µg/ml G418 (Calbiochem).

[277] Cells were split 2 - 3 times weekly between 1:3 and 1:4. For binding assays and membrane preparations the cell culture medium was removed, cells were washed with PBS. Crude membranes for radioligand binding experiments were prepared by scraping the cells off the dishes in ice cold 20mM HEPES/ 0.1mM KCl/ pH 7.2. The cell suspension was homogenized on ice (Ultra turrax, 3 x 20 sec.) and the homogenate was spun for 10 min (1°C, 1000g, OPTIMA, SW28, 2800 U/min). The supernatant was then centrifuged for 40min at 100000g (1°C, OPTIMA, SW28, 23000 U/min). The membrane pellet was re-suspended in 20mM HEPES/ 0.1mM KCl/ pH 7.2, frozen and stored at -80°C.

[278] After thawing on the day of the assay, the membrane suspension was diluted further with 20mM HEPES/ 0.1mM KCl/ pH 7.2.

[279] The incubation mixture of 200µl contained 1.5 nmol/l 3H-Dofetilide, optimized amount of membrane preparation, 20 mM HEPES/ 0.1mM KCl/ (pH 7.2) and inhibitor in 1%DMSO. Nonspecific binding was estimated in the presence of 10 M Dofetilide. The samples were incubated for 90 min. at RT.

[280] Binding was terminated by filtration of the incubated membrane preparations using Filtermat B (Pharmacia, Uppsala Sweden) and a Micro Cell Harvester (Skatron, Lier, Norway). The Filtermat B had been presoaked with 1% polyethylen imine and carefully washed with 0.05 M Tris/HCl-buffer pH=7.7 after the filtration to separate free and bound radioactivity. The filters were counted in a scintillation counter (Betaplate 1205, Berthold, Wildbad, Germany) in order to determine the specific binding of [³H]-Dofetilide.

[281] The optimal amount of membrane preparation in the assay was determined and optimized for each membrane preparation separately in front of using the membranes in compound testing.

[282] Test compounds were either screened at 6 to 10 increasing concentrations for the determination of IC50 and Ki or at 2 - 4 concentrations for the determination of the percent inhibition. For pipetting of the incubation mixture we routinely use the robot Biomek2000 (Fa. Beckman).

[283] The IC₅₀ values in the table below were determined using the Hill-plot, 2-parameter-model.

Example	IC ₅₀ [uM]
1	12.8
2	8.08
3	23.3
4	52.4
5	64.3
6	9.56
7	52.6
8	41
9	21.5
10	18.4
11	12.65
12	8.06
13	37
14	16.1
15	7.93
16	64.7
17	35
18	135
19	>100
20	22.6
21	33.5
22	22.6
23	9.24
24	4.89
25	49.6
26	4.75
27	35.1
28	54.6

Example	IC ₅₀ [uM]
29	17.9
30	3.47
31	19.7
32	38.6
33	>100
34	85.8
35	22.6
36	29.6
37	38.1
38	>100
39	90.2
40	23.3
41	16
42	71.6
43	57.4
44	>100
45	67.8
46	72.9
47	>100
48	37.4
49	19
50	17
51	137
52	>100
54	>100
55	21.1
56	93.8
57	126

Example	IC ₅₀ [uM]
58	12.6
59	7.28
60	31.6
61	24.7
62	41.9
63	10.8
64	14.4
65	40.4
66	8.86
67	63.3
68	93.6
69	>100
70	>100
71	>100
72	44.7
73	98
74	>100
75	131
76	120
77	16.9
78	>100
87	>100
88	43.2
89	88.2
90	84
91	48.9
92	27.4
93	129

Example	IC50 [uM]
94	120
95	6.36
96	7.96

Example	IC50 [uM]
98	3.55
100	60.3
101	118

Example	IC50 [uM]
102	10.24
103	>10
104	>100

RRNR2BB - Inhibition of Specific Binding to the rat NR1/NR2B receptor

[284] Male Wistar rats (180 to 200 g) were killed by suffocation in a CO₂ chamber for two minutes. Whole brains without cerebellum were removed and dissected on ice, placed into closed vials and stored at - 70 °C.

[285] Membrane fractions were prepared and tested using standard techniques. At the time of the assay, 1 g of the brains were placed into 25 ml of 50mM Tris/10mM EDTA buffer, pH=7.1, (25 vol. per g of original tissue) and was homogenized for 30 sec at 20000 U/min with an Ultraturrax T25 (Jahnke & Kunkel, IKA-Labortechnik, Staufen, Germany). The homogenate was centrifuged at 4 °C for 10 min at 48000 g (OPTIMA L-70, Beckman, Palo Alto, CA 94304, USA). The supernatant was discarded and the pellet was homogenized on ice for 30 sec at 20000 U/min with an Ultraturrax and again centrifuged at 48000 g for 30 minutes at 4 °C. The resulted pellet was resuspended in 25 ml of 50mM Tris/10mM EDTA buffer, homogenized for 30 sec with an Ultraturrax, aliquoted, frozen at -70 °C and stored until use

[286] After thawing on the day of the assay, a 5ml membrane aliquote was centrifuged at 48000g for 30 min at 4 °C. The pellet was resuspended in 5 ml of 5mM Tris/1mM EDTA buffer, pH=7.4, homogenized for 30 sec at 20000 U/min with an Ultraturrax and centrifuged at 48000g for 30 min at 4 °C. This step was repeated twice. The final pellet was homogenized in 5 ml of 5mM Tris/1mM EDTA buffer at 4 °C with an Ultraturrax and used for the Ifenprodil-binding assay.

[287] The incubation mixture of 200µl contained 5 nmol/l [³H]-Ifenprodil, optimised amount of membrane preparation, 5mM Tris/1mM EDTA (pH 7.4, 100µM R(+)-3-PPP, 1µM GBR-12909, 1µM GBR-12935) and inhibitor in 1%DMSO. Nonspecific binding was estimated in the presence of 10⁻⁶ M CP101.606. The samples were incubated for 60 min. at 4°C

[288] Binding was terminated by filtration of the incubated membrane preparations using Filtermat B (Pharmacia, Uppsala Sweden) and a Micro Cell Harvester (Skatron, Lier, Norway). The Filtermat B had been presoaked with 1% polyethylen imine and carefully washed with

50mM Tris/HCl-buffer pH=7.7 after the filtration to separate free and bound radioactivity. The filters were counted in a scintillation counter (Betaplate 1205, Berthold, Wildbad, Germany) in order to determine the specific binding of [³H]-Ifenprodil.

[289] The optimal amount of membrane preparation in the assay has been determined and optimised for each membrane preparation separately in front of using the membranes in compound testing.

[290] Test compounds were either screened at 6 to 10 increasing concentrations for the determination of IC₅₀ and K_i or at 2 - 4 concentrations for the determination of the percent inhibition. For pipetting of the incubation mixture the robot Biomek2000 (Fa. Beckman) was used.

[291] The IC₅₀ values in the tables below were determined using the Hill-plot, 2-parameter-model. In the NR1/NR2B binding assay a dissociation constant (K_D) of [³H]-Ifenprodil was determined to be 9 nM. The specific binding in this assay was about 80%.

[292] Reference compounds and their IC₅₀ values tested in the hERG receptor binding assay are provided below.

Example	IC ₅₀ [nM]
1	65.5
2	78.4
3	146
4	119
5	148
6	5.21
7	8.23
8	281
9	152
10	250
11	>1000
12	280
13	22.1
14	76.2

Example	IC ₅₀ [nM]
15	163
16	41.1
17	56
18	8.005
19	202
20	22.2
21	1021
22	2760
23	1590
24	410
25	980
26	30.1
27	7170
28	638

Example	IC ₅₀ [nM]
29	2540
30	1010
31	264
32	323
33	371
34	866
35	17.6
36	424
37	2060
38	443
39	102
40	47
41	114
42	202

Example	IC50 [nM]
43	134
44	17.1
45	261
46	106.2
47	203
48	1970
49	2250
50	4250
51	9210
52	522
53	3840
54	522
55	871
56	78.7
57	967
58	668
59	2190
60	2170
61	1380
62	857
63	612
64	1100
65	3810
66	5210
67	>10000
68	>10000
69	831
70	2690
71	9330
72	95.1

Example	IC50 [nM]
73	1157
74	6060
75	3040
76	7350
77	1040
78	8280
79	4720
81	4630
81	6210
82	2620
83	6020
84	>10000
85	>10000
86	>10000
87	>10000
88	152
89	736
90	422
91	43.8
92	71.2
93	25.2
94	279
95	63.5
96	77.8
97	807
98	1060
99	3150
100	3170
101	5600
102	>1000

Example	IC50 [nM]
103	>1000
104	>10000
105	>10000

Forced Swim Test in Mice

[293] The compounds of the invention show significant antidepressive effects in the forced swim test in mice, an animal model of depression at doses of 100 mg/kg or below.

[294] The method, which detects antidepressant activity, follows that described by Porsolt et al (*Arch. Int. Pharmacodyn.*, 229, 327-336, 1977), which is incorporated by reference herein in its entirety.

[295] Mice forced to swim in a situation from which they cannot escape rapidly become immobile. Antidepressants decrease the duration of immobility.

[296] Male NMRI mice (Janvier, France), weighing 20 – 30 g, were individually placed in a cylinder (height = 24 cm; diameter = 13 cm) containing 10 cm water (22°C) from which they cannot escape.

[297] The mice were placed in the water for 6 minutes and the duration of immobility during the last 4 minutes was measured. The latency to the first bout of immobility was also recorded starting from the beginning of the test. 10 mice were studied per group. The test substance was administered p.o. 30 minutes before the test and compared with vehicle control group. The test was performed blind. The results are shown in the table below.

Example	Minimum effective dose (mg/kg p.o.)
2	30
18	10

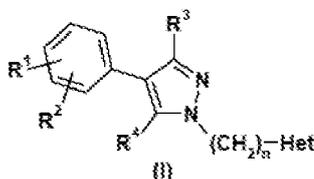
[298] All patents, patent applications, publications and presentations referred to herein are incorporated by reference in their entirety.

[299] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[300] While the foregoing specification teaches the principles of the present invention, and specific embodiments of the invention have been described for the purposes of illustration, and examples have been provided for the purposes of illustration, it will be understood that various modifications may be made without deviating from the spirit and scope of the invention as come within the scope of the

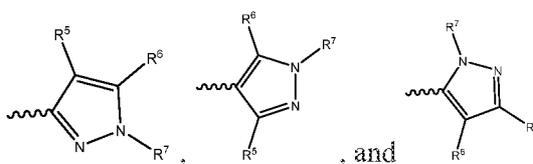
Claims

1. A compound of Formula (I):



or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof; wherein:

n is 1 or 2,



Het is selected from:

R^1 and R^2 are each independently selected from hydrogen; a halogen selected from F, Cl, and Br; C_{1-6} alkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkoxy, and C_{3-6} (halo)cycloalkyl; C_{3-6} cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy; C_{1-6} alkoxy, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkoxy and C_{3-6} (halo)cycloalkyl; $-O-C_{3-6}$ cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy; $-S-C_{1-3}$ alkyl, optionally substituted with at least one halogen atom; $-SO_2-C_{1-3}$ alkyl, optionally substituted with at least one halogen atom; and $-SF_5$; or

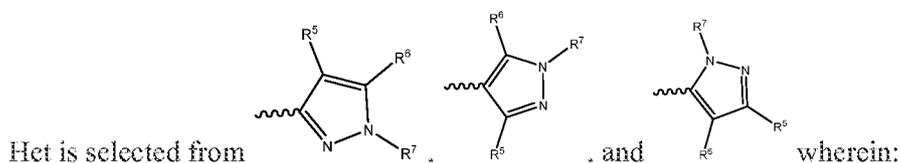
R^1 and R^2 together form a 5 to 7 member carbocycle, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy; and a 5 to 7 member heterocycle containing one to three heteroatoms which can be O, S or N, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy;

R^3 and R^4 are each independently selected from hydrogen; halogen; C_{1-5} (halo)alkyl, optionally substituted with at least one halogen atom, provided that at least one of R^3 and R^4 is hydrogen;

R^5 and R^6 are each independently selected from hydrogen; halogen; amino; C_{1-5} alkyl, optionally substituted with at least one substituent, selected from halogen, hydroxy, C_{1-3} (halo)alkoxy and C_{3-6} (halo)cycloalkyl; C_{1-5} alkoxy, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkoxy, and C_{3-6} (halo)cycloalkyl, and C_{3-6} cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy; and

R^7 is hydrogen; C_{1-5} alkyl, optionally substituted with at least one substituent, selected from halogen, hydroxy, C_{1-3} (halo)alkoxy and C_{3-6} (halo)cycloalkyl; or C_{3-6} cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy.

- The compound of claim 1, wherein n is 1.
- The compound of claim 1, wherein at least one of R^1 and R^2 is not hydrogen.
- The compound of claim 2, wherein at least one of R^1 and R^2 is not hydrogen.
- The compound of claim 1, wherein at least one of R^1 and R^2 is selected from F, Cl, Br, C_{1-4} (halo)alkyl, C_{3-6} (halo)cycloalkyl, C_{1-3} (halo)alkoxy, C_{1-3} (halo)alkoxy- C_{1-3} (halo)alkyl, C_{3-6} (halo)cycloalkyl- C_{1-3} (halo)alkyl, and C_{3-6} (halo)cycloalkyl- C_{1-3} (halo)alkoxy.
- The compound of claim 1, wherein R^3 and R^4 are each independently selected from hydrogen, F, Cl, Br, and C_{1-3} (halo)alkyl, with the proviso that at least one of R^3 and R^4 is hydrogen.
- The compound of Claim 1, wherein:



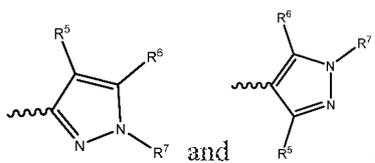
R^5 and R^6 are each independently selected from hydrogen, F, Cl, amino, C_{1-3} alkyl, optionally substituted with at least one substituent selected from halogen, hydroxy, and C_{1-3} (halo)alkoxy, C_{1-3} (halo)alkoxy, C_{3-6} (halo)cycloalkyl, and C_{3-6} (halo)cycloalkyl- C_{1-3} (halo)alkyl; and

R^7 is hydrogen, C_{1-3} alkyl, optionally substituted with at least one substituent, selected from halogen, hydroxy, C_{1-3} (halo)alkoxy and C_{3-6} (halo)cycloalkyl, or C_{3-6} cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy.

8. The compound of claim 1, wherein:

n is 1,

R^1 and R^2 are each independently selected from F, Cl, C_{1-2} (halo)alkyl, and C_{1-2} (halo)alkoxy;



Het is selected from:

R^3 and R^4 are each independently selected from hydrogen, F, and Cl, with the proviso that at least one of R^3 and R^4 is hydrogen;

R^5 and R^6 are each independently selected from hydrogen, C_{1-3} (halo)alkyl, C_{3-6} (halo)cycloalkyl, C_{3-6} (halo)cycloalkyl, and C_{3-6} (halo)cycloalkyl- C_{1-3} (halo)alkyl; and

R^7 is hydrogen, C_{1-3} alkyl, optionally substituted with at least one substituent, selected from halogen, hydroxy, C_{1-3} (halo)alkoxy and C_{3-6} (halo)cycloalkyl, C_{3-5} cycloalkyl, optionally substituted with at least one substituent, selected from hydroxy, halogen, C_{1-3} (halo)alkyl and C_{1-3} (halo)alkoxy.

9. The compound of claim 1 selected from the group consisting:

4-[2-[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,

3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-methylpyrazole,

5-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,

4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,

4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,

4-[4-chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,

4-[4-chloro-3-(difluoromethoxy)phenyl]-1-(1H-pyrazol-4-ylmethyl)pyrazole,

3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-ethylpyrazole,
4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole,
4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[2-(1-ethylpyrazol-4-yl)ethyl]pyrazole,
3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-(1-ethylpropyl)-
pyrazole,
3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-1-cyclopentyl-pyrazole,
4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole,
3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole,
3-[[4-[4-chloro-3-(difluoromethoxy)phenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole,
4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole,
4-[4-chloro-3-(difluoromethoxy)phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
4-[3-(difluoromethoxy)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
4-[3-chloro-5-(difluoromethoxy)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
1,3-dimethyl-5-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl]pyrazole,
1-methyl-3-[[4-[3-(trifluoromethoxy)phenyl]pyrazol-1-yl]methyl]pyrazole,
3-[[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
4-[4-chloro-3-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
4-[2-[4-[4-chloro-3-(difluoromethyl)phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
4-[3-chloro-5-(difluoromethyl)phenyl]-1-(1H-pyrazol-3-ylmethyl)-pyrazole,

5-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-[4-chloro-3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole,
4-[2-[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[2-(1H-pyrazol-4-yl)ethyl]pyrazole,
3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-1-ethyl-pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(3-methyl-1H-pyrazol-5-yl)methyl]pyrazole,
3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-5-ethyl-1H-pyrazole,
3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-5-propyl-1H-pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(5-methyl-1H-pyrazol-4-yl)methyl]pyrazole,
4-[3-(difluoromethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-(1H-pyrazol-3-ylmethyl)pyrazole,
4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
4-[3-(1,1-difluoroethyl)-4-fluoro-phenyl]-1-[(5-ethyl-1H-pyrazol-4-yl)methyl]pyrazole,
4-[3-(difluoromethyl)-5-fluoro-phenyl]-1-[2-(1H-pyrazol-3-ylmethyl)pyrazole,
1,3-dimethyl-5-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
1-methyl-3-[[4-[3-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,

1-methyl-3-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
1,3-dimethyl-5-[[4-[4-(trifluoromethyl)phenyl]pyrazol-1-yl]methyl]pyrazole,
5-[[4-(3-fluoro-4-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
5-[[4-(3-fluoro-4-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-(4-fluoro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
4-(4-fluoro-3-methyl-phenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
5-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-(4-chloro-3-methyl-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
3-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-(4-chloro-3-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-(3-chloro-4-fluoro-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-(3,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
5-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
3-[[4-(2,4-dichlorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
3-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
5-[[4-(4-fluoro-2-methoxy-phenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
4-(3-cyclopropylphenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,
4-(3-methylsulfonylphenyl)-1-(1H-pyrazol-3-ylmethyl)-pyrazole,

1-methyl-4-[[4-(3-methylsulfonylphenyl)pyrazol-1-yl]methyl]-pyrazole,
 pentafluoro-[3-[1-(1H-pyrazol-3-ylmethyl)pyrazol-4-yl]]phenyl]-sulfane,
 4-[2-[4-(4-chlorophenyl)-pyrazol-1-yl]ethyl]-3,5-dimethyl-1H-pyrazole,
 5-[[4-(4-chlorophenyl)-pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
 3-[[4-(4-chlorophenyl)-pyrazol-1-yl]methyl]-1-methyl-pyrazole,
 4-(4-chlorophenyl)-1-[(2-methylpyrazol-3-yl)methyl]pyrazole,
 4-(4-chlorophenyl)-1-(1H-pyrazol-3-ylmethyl)pyrazole,
 4-(4-chlorophenyl)-1-[(1-methylpyrazol-4-yl)methyl]pyrazole,
 3-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
 5-[[4-(4-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
 5-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
 3-[[4-(3-bromophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
 5-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1,3-dimethyl-pyrazole,
 3-[[4-(3,5-difluorophenyl)pyrazol-1-yl]methyl]-1-methyl-pyrazole,
 1-methyl-3-[(4-phenylpyrazol-1-yl)methyl]pyrazole,
 1,3-dimethyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole, and
 1-methyl-5-[(4-phenylpyrazol-1-yl)methyl]pyrazole; and
 pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.

10. The compound of claim 1 selected from the group consisting of:

4-[[4-(3-difluoromethoxy-4-chloro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,
 4-[[4-(3-difluoromethyl-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,

4-[[4-(3-(1,1-difluoroethyl)-4-fluoro-phenyl)pyrazol-1-yl]methyl]-3,5-dimethyl-1H-pyrazole,
 3-[[4-[3-(difluoromethoxy)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole,
 3-[[4-[3-(difluoromethyl)-4-fluoro-phenyl]pyrazol-1-yl]methyl]-4-ethyl-1H-pyrazole,
 3-[[4-(3-(1,1-difluoroethyl)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole as maleate, and
 3-[[4-(3-(difluoromethoxy)-phenyl)pyrazol-1-yl]methyl]-1H-pyrazole as maleate; and
 pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.

11. The compound of claim 1 selected from the group consisting of:

4-(4-chloro-3-(difluoromethyl)phenyl)-1-((1-ethyl-1H-imidazol-5-yl)methyl)-1H-pyrazole,
 4-(4-chlorophenyl)-1-((1-ethyl-1H-imidazol-5-yl)methyl)-1H-pyrazole,
 4-(3,4-dichlorophenyl)-2'-methyl-2'H-1,3'-bipyrazole,
 4-(3-chloro-4-fluorophenyl)-2'-methyl-2'H-1,3'-bipyrazole,
 2-((4-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine,
 3-(3-(difluoromethyl)-4-fluorophenyl)-1-((5-((4-(3-(difluoromethyl)-4-fluorophenyl)-1H-pyrazol-1-yl)methyl)-1H-pyrazol-3-yl)methyl)-1H-pyrazole, and
 2-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-1H-pyrazol-4-yl)pyridine; and
 pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof, and at least one pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim 12, further comprising a second active ingredient.

14. A method of treating a disease, disorder or condition associated with NMDA receptor hyperactivity comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.

15. The method of claim 14, wherein the disorder, disease or condition mediated by GluN2B receptors is selected from the group consisting of: bipolar disorder, major depressive disorder, treatment-resistant depression, postpartum depression, seasonal affective disorder, Alzheimer's disease, Parkinson's disease, Huntington's chorea, multiple sclerosis, cognitive impairment, head injury, spinal cord injury, stroke, epilepsy, dyskinesias, amyotrophic lateral sclerosis, neurodegeneration associated with bacterial or chronic infections, pain, diabetic neuropathy, migraine, cerebral ischemia, schizophrenia, encephalitis, autism and autism spectrum disorders, memory and learning disorders, obsessive compulsive disorder, attention deficit hyperactivity disorder (ADHD) and addictive illnesses
16. A method for treating a disease, disorder or condition mediated by GluN2B receptors comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.
17. The method of claim 16, wherein the disorder, disease or condition mediated by GluN2B receptors is selected from the group consisting of treatment resistant depression and major depressive disorder.
18. A method of treating a disease, disorder or condition in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt, solvate, polymorph, or N-oxide thereof.
19. The method of claim 18, wherein the disease or disorder is a central nervous system disorder.
20. The method of claim 18, wherein the disease or disorder is a neurologic or psychiatric disorder.
21. The method of claim 18, wherein the disease or disorder is (1) a mood disorder; (2) a neurotic, stress-related or somatoform disorder; (3) psychological development; (4) behavioral syndromes associated with physiological disturbances and physical factors (5) an extrapyramidal and movement disorder; (6) an episodic or paroxysmal; (7) pain; (8) forms of neurodegeneration, or (9) a cerebrovascular diseases.

22. The method of claim 21, wherein the neurotic, stress-related or somatoform disorder is an anxiety disorder; the episodic or paroxysmal disorder is epilepsy; and the cerebrovascular disease is an acute cerebrovascular disease or a chronic cerebrovascular disease.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2015/045413

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D231/12 C07D403/06 A61K31/4155 A61P25/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/130855 A1 (TAKEDA PHARMACEUTICAL [JP]; CHERUVALLATH ZACHARIA [US]; ERICKSON PHILI) 6 September 2013 (2013-09-06) claim 1, example 410 -----	1-22
A	EP 2 194 045 A1 (TAKEDA PHARMACEUTICAL [JP]) 9 June 2010 (2010-06-09) claim 1 and examples -----	1-22
A	WO 2008/145616 A1 (ABBOTT GMBH & CO KG [DE]; GENESTE HERVE [DE]; SAUER DARYL [US]; BRAJE) 4 December 2008 (2008-12-04) claim 19: formulae Ia.1 and Ia.2; p. 68-75 -----	1-22
A	WO 2009/118187 A1 (EVOTEC NEUROSCIENCES GMBH [DE]; KEMP JOHN ALAN [CH]; TASKER TIMOTHY [G]) 1 October 2009 (2009-10-01) claim 1 -----	1-22
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search	Date of mailing of the international search report	
16 November 2015	27/11/2015	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sahagún Krause, H	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/045413

Patent document cited in search report	A1	Publication date		Patent family member(s)	Publication date
WO 2013130855	A1	06-09-2013	US	2015005232 A1	01-01-2015
			WO	2013130855 A1	06-09-2013

EP 2194045	A1	09-06-2010	AR	068813 A1	09-12-2009
			AU	2008292429 A1	05-03-2009
			BR	PI0816095 A2	03-03-2015
			CA	2697663 A1	05-03-2009
			CN	101842357 A	22-09-2010
			CO	6190530 A2	19-08-2010
			DO	P2010000068 A	15-03-2010
			EA	201070323 A1	29-10-2010
			EC	SP10010060 A	30-04-2010
			EP	2194045 A1	09-06-2010
			KR	20100046275 A	06-05-2010
			MA	31714 B1	01-09-2010
			PE	06102009 A1	11-06-2009
			TW	200913993 A	01-04-2009
			US	2009270359 A1	29-10-2009
			US	2010227846 A1	09-09-2010
			WO	2009028543 A1	05-03-2009

WO 2008145616	A1	04-12-2008	AU	2008257559 A1	04-12-2008
			BR	PI0812163 A2	16-12-2014
			CA	2686651 A1	04-12-2008
			CN	101687790 A	31-03-2010
			EP	2167464 A1	31-03-2010
			ES	2530431 T3	02-03-2015
			JP	5615700 B2	29-10-2014
			JP	2010527974 A	19-08-2010
			KR	20100017372 A	16-02-2010
			NZ	581127 A	29-06-2012
			RU	2009148336 A	27-06-2011
			TW	200902501 A	16-01-2009
			US	2008300260 A1	04-12-2008
			WO	2008145616 A1	04-12-2008

WO 2009118187	A1	01-10-2009	AU	2009228660 A1	01-10-2009
			CA	2719749 A1	01-10-2009
			CN	101977606 A	16-02-2011
			EP	2254580 A1	01-12-2010
			JP	2011516417 A	26-05-2011
			JP	2014098018 A	29-05-2014
			KR	20100135847 A	27-12-2010
			NZ	588698 A	29-06-2012
			RU	2010143864 A	10-05-2012
			US	2011053951 A1	03-03-2011
			WO	2009118187 A1	01-10-2009
