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(54) Title: 5,6-DISUBSTITUTED ALKYL 1H AND 2H-INDAZOLES AS DUAL BUTYRYLCHOLINESTERASE AND p38α MITOGEN-ACTIVATED PROTEIN KINASE INHIBITORS FOR USE IN THE TREATMENT OF NEURODEGENERATIVE AND INFLAMMATORY DISEASES

(57) Abstract: The present invention relates to the field of medicinal chemistry and more specifically to 5,6- disubstituted 1H- and 2H- indazoles as pharmaceutically active compounds. The compounds of the present invention are dual inhibitors of butyrylcholinesterase and p38α mitogen-activated protein kinase, and thus are particularly useful for the treatment of various diseases which may be therapeutically modified by altering the activity of butyrylcholinesterase (BChE) and/or p38α MAP kinase such as dementias including Alzheimer's disease (AD) and other conditions involving chronic inflammation.



5,6-DISUBSTITUTED ALKYL 1*H* AND 2*H*-INDAZOLES AS DUAL
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INHIBITORS FOR USE IN THE TREATMENT OF NEURODEGENERATIVE AND
INFLAMMATORY DISEASES

Technical Field

The present invention relates to the field of medicinal chemistry and more specifically to 5,6-disubstituted 1*H*- and 2*H*- indazoles as pharmaceutically active compounds. The compounds of the present invention are dual inhibitors of butyrylcholinesterase and p38 α mitogen-activated protein kinase, and thus are particularly useful for the treatment of various diseases which may be therapeutically modified by altering the activity of butyrylcholinesterase (BChE) and/or p38 α MAP kinase such as dementias including Alzheimer's disease (AD) and other conditions involving chronic inflammation.

Background Art

AD, the most common form of dementia, is an incurable progressive age-related neurodegenerative disorder clinically manifested in four stages. First, a mild memory loss appears, which is followed by the patient becoming disoriented in space and time, losing concentration and feeling depressed. As the disease progresses, difficulties in reading, writing, speaking and recognising people arise. In the final stage the patient is bedridden and completely dependent on custodial care. Impaired hygiene, and difficulties in sitting up, swallowing and urinating lead to complications such as bedsores, skin infections, blood clots, aspiration pneumonia and sepsis which are the major causes of death in AD. For an individual aged 70, together with 10 years of the preclinical stage, 4 years of prodromal stage and approximately 6 years in dementia stage the disease can last up to 20 years¹.

Contemporary evidence presents AD as a complex polygenic disease with its leading cause lying in aberrant interactions among several molecular pathways. This was confirmed by *in vivo* amyloid beta (A β) and protein tau PET scans which revealed A β plaques and neurofibrillary tangles composed of hyperphosphorylated protein tau in the posterior cingulate region of the brain as well as MRI images showing cortical atrophy. Additionally, concentrational changes of certain metal ions in the cerebrospinal fluid (CSF) were shown to correlate with clinical AD progression². Apart from metal ions many neuroinflammatory biomarkers can also be detected in CSF of AD patients. All these findings accumulated in several hypotheses elucidating the disease's pathophysiology.

Among the hypotheses most extensively studied, cholinergic hypothesis is the only one to unambiguously point at its possible pharmacological targets. Acetylcholine (ACh) is a neurotransmitter and neuromodulator of the peripheral nervous system (PNS) and central nervous system (CNS). It is found in the brain stem, basal forebrain, striatum and medial habenular nucleus. Projections from the brain stem reach out to thalamus, basal ganglia, tectum and basal forebrain³. Studies have shown that: i) ACh modulation in healthy subjects affects memory processes in hippocampus-dependent learning⁴, ii) cholinergic receptor activation is crucial in episodic and spatial memory⁵ and iii) depletion of cholinergic neurons in medial septum impairs spatial memory⁶. On the other hand, studies on AD patients show: i) depletion of presynaptic cholinergic markers [ACh and choline acetyltransferase (ChAT)] in cerebral cortex⁷, ii) severe and preferential neurodegeneration of the source of cortical cholinergic innervation – nucleus basalis of Meynert (NBM)⁸, iii) improvement of the disease condition after applying cholinergic agonists and cholinesterase (ChE) inhibitors⁹, iv) decrease in number of postsynaptic nicotinic receptors on cortical neurons¹⁰ and v) upregulation of cortical ChAT expression in the prodromal phase of AD¹⁶. Considering the findings of these studies, cholinergic hypothesis was formed stating that progressive loss of cholinergic innervation presents the key neurochemical event in AD pathophysiology with subsequent cholinergic deafferentation of the cerebral cortex, hippocampus and amygdala resulting in memory and learning deficits. Studies also implied the use of either cholinergic agonists or cholinesterase inhibitors (ChEIs) as therapeutics to improve this condition.

In the normal human brain after ACh interacts with cholinergic receptors on the postsynaptic neuron, acetylcholinesterase (AChE) terminates its effect by hydrolysing it. This way it helps to maintain pulsatile cholinergic stimulation. BChE is another enzyme that catalyses the hydrolysis of ACh. Experiments on ACh-knockout mice showed that they survived to adulthood having intact cholinergic pathways, however very sensitive to a specific butyryl inhibitor¹² implying a compensatory role of BChE when there is lack of, or saturation of AChE. In the hippocampus and neocortex AChE is mostly located in axons and pyramidal neurons while BChE colocalizes in hippocampal neurons but otherwise lies predominantly in glial cells. In brains of healthy subjects AChE comprises approximately 90% of total ChE activity and BChE only 10%, however during AD progression AChE activity can drop between 35% and 45% whereas BChE activity rises between 40% and 90%, mostly in hippocampus and temporal cortex – the brain areas most affected by AD¹³. In affected cortical regions the ratio BChE/AChE changes from 0.5 to as much as 11 which makes BChE the main ACh hydrolysing enzyme in the brains of AD patients. Evidence to support this claim arises from different

studies: i) individuals with a specific mutation in BChE gene producing a subfunctional BChE-K variant are reportedly more susceptible to certain forms of AD, ii) selective inhibition of BChE improved learning in elderly rats, reduced intra- and extracellular amyloid precursor protein (APP) levels in neuroblastoma cell culture¹⁴ and elevated ACh levels by fivefold in AChE-knockout mice¹⁵, iii) treatment with a dual cholinesterase inhibitor rivastigmine showed stronger correlation between cognitive improvement and BChE inhibition than AChE inhibition, iv) while AChE inhibition alone causes parasympathetic side effects such as nausea and vomiting, selective BChE inhibitors showed no such adverse effects¹⁶. All these findings point out cholinesterases (ChEs) as a valid pharmacological target to alleviate AD symptoms with selective inhibition of BChE being an even better approach than dual inhibition. Studies show 70–72% sequence similarity between the two targets, however, 14 aromatic amino acids in the AChE active site gorge are replaced with aliphatic ones in BChE active site, which is especially important in the acyl-binding pocket, where BChE can accommodate larger ligands than AChE. This presents the basis for designing selective BChE inhibitors.

Currently, three ChE inhibitors (ChEIs) represent the standard of care for AD. The first generation of ChEIs was introduced in the mid-1980s with physostigmine. Ten years later a second generation with more suitable compounds launched the first AChE inhibitor in AD treatment - tacrine (discontinued in 2013). The third generation of ChEIs represents clinically more efficacious drugs with metrifonate and the three currently available compounds on the market – AChE inhibitors galantamine and donepezil and a dual AChE/BChE inhibitor rivastigmine. Apart from these traditional ChEIs, selective BChE inhibitors were developed: i) compounds with carbamate structure such as phenserine analogues, dehydroevodiamine derivatives and indoline analogues, ii) tacrine-based inhibitors and iii) BChE inhibitors with miscellaneous scaffolds such as: phenothiazines, azepino[4,3-b]indole derivatives, 8-hydroxyquinolines, derivatives of curcumin and resveratrol, aminothiazolines, naphthamides and tetrahydroquinolin-5(1*H*)-ones.

Despite being generally considered as a short-term intervention to improve AD symptoms, recent discoveries have shown that ChEIs to some extent also exert disease-modifying potential¹⁷. In the aim to elucidate the etiology of AD and finally launch a disease-modifying drug on the market researchers broadened their focus from affected neurons to astrocytes, microglia, cytokines and chemokines. Microglia presents the main immunocompetent cells in the brain. When brain homeostasis is compromised, microglia changes its phenotype to so-called M2 microglia to defend nerve cells. In AD patients, however its pathways and functions are altered leading to the M1 phenotype and subsequent neuroinflammation. Key findings that

support M1 microglia-mediated inflammation as the centre of AD pathogenesis are: i) most of the 25 genetic loci that identify with AD risk code for proteins that are expressed in microglia¹⁸, activated astrocytes and microglia were found in the vicinity of A β deposits and were showing elevated production of proinflammatory cytokines¹⁹, iii) M1 microglial activation of the NLRP3 inflammasome induces cytokine release and neuroinflammation, genetic deletion of NLRP3 in mice, however correlated with improved synaptic functioning and cognitive performances²⁰, iv) A β oligomers increase phagocytic activity of microglia via C3/CR3 complement system activation resulting in synapse elimination which was not observed with CR3-knockout mice, v) downregulation of the P2X7R purinergic receptor decreases pro-inflammatory cytokine release by microglia as well as ameliorates cognitive functions in AD patients²¹, vi) temporary microglial activation serves to eliminate A β , whereas chronic activation amplifies the amyloid cascade – demonstrated with *in vitro* activation of microglia with a lipopolysaccharide, which resulted in inhibition of A β phagocytosis²², vii) intracerebral injection of anti-inflammatory cytokines IL-4 and IL-13 (mimicking M2 microglial response) reduced A β plaque load in APP23 mice with AD and improved cognition²³. All this evidence points out at the pivotal role of pro- and anti-inflammatory cytokine imbalance in AD pathology. Since targeting A β pathway so far yielded only few satisfactory results²⁴, proteins involved in microglia-mediated neuroinflammation are now an emerging hot topic in AD drug development.

To release pro-inflammatory cytokines M1 microglia stimulates cyclooxygenase, Akt/mTOR, NF κ B caspase, NO and p38 MAPK pathways. p38 mitogen-activated protein kinases (p38 MAPKs) are a family of four subfamilies (ERK1/2, ERK5, JNKs and p38s) of protein kinases activated by cells in response to environmental changes like alterations in nutrients, growth factors, elevated levels of cytokines etc. There are four isoforms of the p38 subfamily, namely α , β , γ and δ of which p38 α MAPK is best characterised as it is expressed in most cell types. In the CNS it localises predominantly in hippocampal and cortical neurons²⁵. Global knockout of p38 α is lethal for mice embryo, whereas p38 β -knockout mice are phenotypically normal which impiles unique functions of the α -isoform. In the CNS of healthy individuals, they comprise: i) regulation of neuronal differentiation, migration, cytoskeleton reorganization and synapse formation, ii) involvement in astrocytic activity-dependent glutamate release and consequent responsibility for hippocampal formation of long-term depression (LTD) – a form of synaptic plasticity involved in modulating long-term memory²⁶ and iii) inhibition of long-term-potential (LTP) in the hippocampus²⁷. A plethora of evidence also suggests that p38 α MAPK becomes one of the main enzymes driving the AD neuroinflammatory cascade

activated microglia has triggered as well as an important player in other pathophysiological processes of AD, for example: i) p38 α MAPK is activated in early stages of AD, especially in pyramidal neurons of the hippocampus²⁸, ii) microglia from p38 α -deficient mice showed a diminished cytokine response after intraperitoneal LPS injection, whereas applying a p38 α MAPK inhibitor terminated increased IL-1 β and TNF α production by an LPS-treated microglial BV2 cell line²⁹, iii) selective inhibition of p38 α MAPK annulated A β ₄₀-induced IL-6 overexpression in HMC3 human microglial cells³⁰, iv) compound NJK14047 which selectively binds to the p38 α MAPK ATP-binding site reduced microglia-induced neuroinflammation, A β deposition, neurodegeneration and memory loss in the 5XFAD mouse model of AD³¹, v) p38 α is the most central tau kinase involved in selective hyperphosphorylation of the tau protein at its master sites³² and vi) reduced expression/inhibition of p38 α facilitated lysosomal degradation of beta-secretase 1 (BACE1) which in turn attenuated A β formation in brains of AD mice³³. Results of such extensive studies on p38 MAPK present p38 α inhibitors as a promising target for AD pharmacotherapy. Furthermore, as a consequence of the interplay between p38 MAPK and M1 microglia those inhibitors are also being studied for the treatment of inflammatory diseases³⁴, for example inflammatory dilated cardiomyopathy, chronic airway inflammatory diseases, rheumatoid arthritis, inflammatory bowel disease and depression.

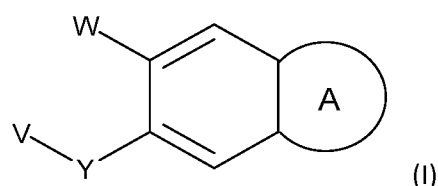
Among the four p38 isoforms α and β share 75% sequence identity, whereas γ and δ are only 62% and 61% identical to α ³⁵. Additionally, the gatekeeper Thr106 that opens up the hydrophobic region I in the p38 α ATP-binding site is substituted by a bulkier Met106 in p38 γ and δ picturing an important site for designing selective inhibitors of the α isoform. To further improve their selectivity for p38 α over p38 β a hydrogen bond donor at the appropriate vicinity to Met109 and Gly110 of the hinge region in the active sites can achieve the so-called »glycine flip« effect. Such an effect is possible in the p38 α and results in a double hydrogen bond between a ligand, Met109 and Gly110, whereas in p38 β only the hydrogen bond with Met109 forms³⁶. Based on these findings and different binding regions in the p38 catalytic site an inhibitor can occupy, four major types of p38 α MAPK inhibitors were developed. Up to the present the most extensively studied were type I inhibitors (TI-Is). They bind to the hinge region of the adenine pocket and hydrophobic regions I and II. Several chemotypes of TI-Is were developed including: pyridinyl and pyrimidinylimidazoles, pyridinylpyridazines, bicyclic 6,6-heterocycles, diphenyl ethers, diaryl ketones, piperazinylaryl ketones, pyrazolopyrimidines and benzylarylethers.

Six medications are approved for the treatment of AD³⁷. Three of them act as ChE inhibitors, one as *N*-methyl-D-aspartate (NMDA) inhibitor and two as monoclonal antibodies against A β ³⁸. The small-molecule drugs cause several adverse effects and have limited effectiveness only in late-stage AD, whereas the recently approved biopharmaceuticals lack convincing evidence of long-term effectiveness and safety. Therefore, there is still a huge demand for the discovery of novel agents for the treatment of AD and other forms of dementia.

Summary of Invention

The invention relates to inhibitors of the enzymes butyrylcholinesterase and p38 α mitogen-activated protein kinase with general formula I. Particularly, this invention relates to the use of the described compounds for the treatment of Alzheimer's disease, other dementias and neurodegenerative conditions as well as inflammatory diseases such as inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis and multiple sclerosis.

In a first aspect, the present invention relates to compounds of formula I and their pharmaceutically acceptable salts, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof,



with V, W, Y and ring A being as defined herein.

In a further aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle.

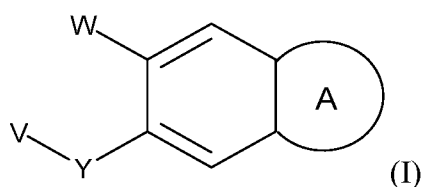
In a further aspect the present invention provides a compound or pharmaceutical composition of the present invention for use in medicine.

In a further aspect the present invention provides a compound or pharmaceutical composition of the present invention for use in the treatment of a neurodegenerative disease, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

In a further aspect the present invention provides a compound or pharmaceutical composition of the present invention for use in the treatment of an inflammatory disease such as inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis and multiple sclerosis.

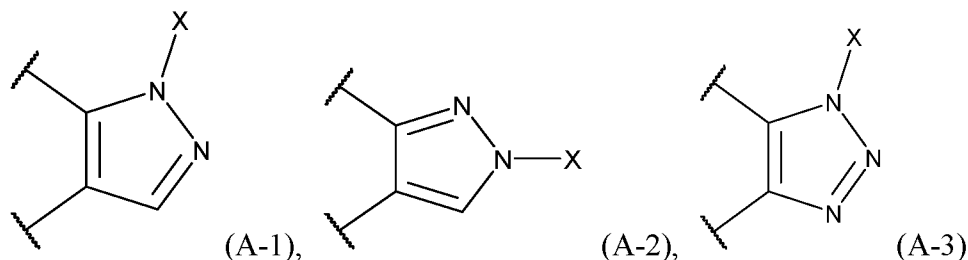
The present invention may be summarized by the following items:

1. A compound of formula (I)

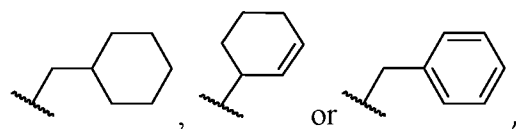
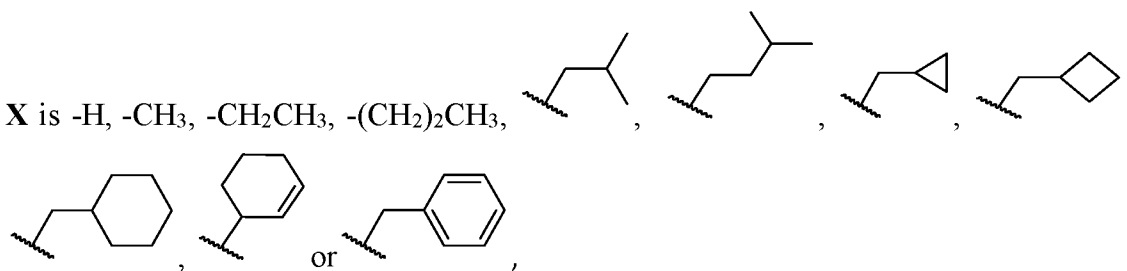


wherein,

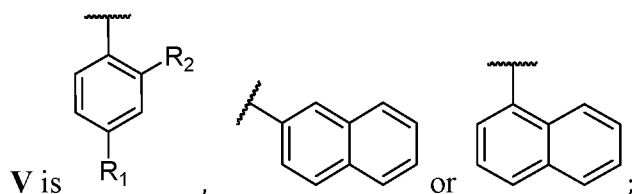
ring **A** is a structure represented by formula (A-1), formula (A-2) or formula (A-3):



X is -H, -CH₃, -CH₂CH₃, -(CH₂)₂CH₃,

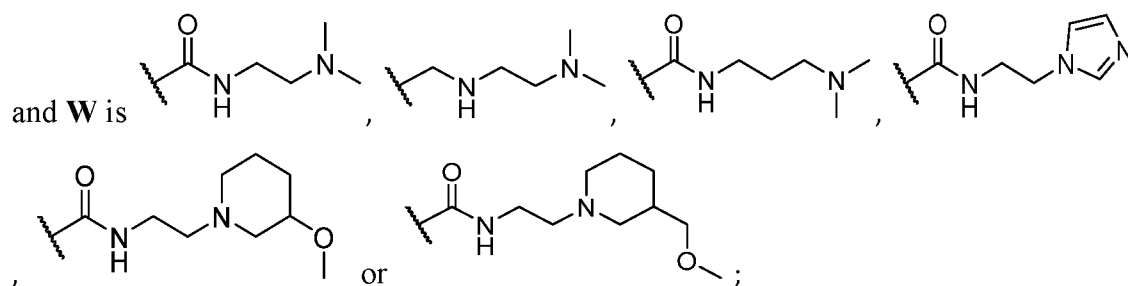


Y is CH₂, O, S or SO₂,



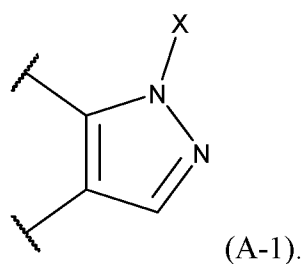
R₁ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;

R₂ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;

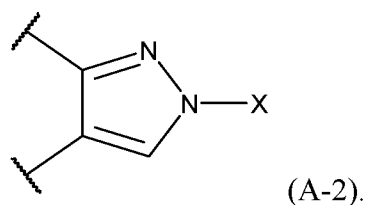


or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof.

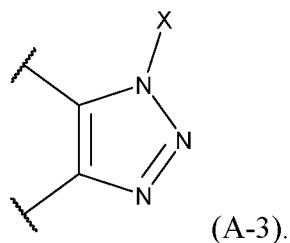
2. Compound according to item 1, wherein **A** is a structure represented by formula (A-1):



3. Compound according to item 1, wherein **A** is a structure represented by formula (A-2):



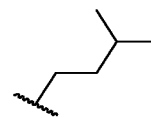
4. Compound according to item 1, wherein **A** is a structure represented by formula (A-3):



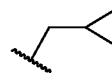
5. Compound according to any one of items 1 to 4, wherein **X** is -H.
6. Compound according to any one of items 1 to 4, wherein **X** is -CH₃.

7. Compound according to any one of items 1 to 4, wherein **X** is
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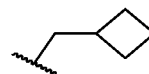
8. Compound according to any one of items 1 to 4, wherein **X** is



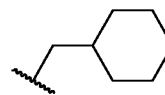
9. Compound according to any one of items 1 to 4, wherein **X** is



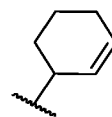
10. Compound according to any one of items 1 to 4, wherein **X** is



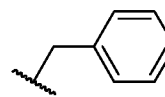
11. Compound according to any one of items 1 to 4, wherein **X** is



12. Compound according to any one of items 1 to 4, wherein **X** is



13. Compound according to any one of items 1 to 4, wherein **X** is



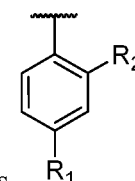
14. Compound according to any one of items 1 to 13, wherein **Y** is CH₂.

15. Compound according to any one of items 1 to 13, wherein **Y** is O.

16. Compound according to any one of items 1 to 13, wherein **Y** is S.

17. Compound according to any one of items 1 to 13, wherein **Y** is SO₂.

18. Compound according to any one of items 1 to 17, wherein **V** is



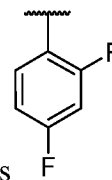
19. Compound according to any one of items 1 to 18, wherein R₁ is -H.

20. Compound according to any one of items 1 to 18, wherein R₁ is halogen.

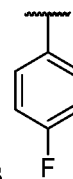
21. Compound according to any one of items 1 to 18, wherein R₁ is C₁₋₄ alkyloxy.

22. Compound according to any one of items 1 to 21, wherein R₂ is halogen

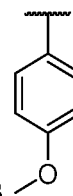
23. Compound according to any one of items 1 to 21, wherein R₂ is -H.



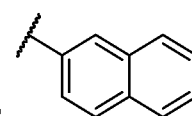
24. Compound according to any one of items 1 to 18, wherein **V** is .



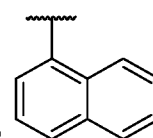
25. Compound according to any one of items 1 to 18, wherein **V** is .



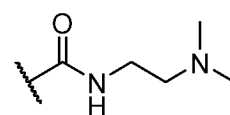
26. Compound according to any one of items 1 to 18, wherein **V** is .



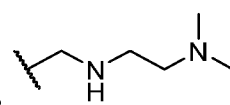
27. Compound according to any one of items 1 to 17, wherein **V** is .



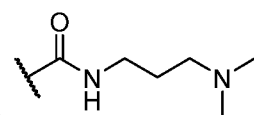
28. Compound according to any one of items 1 to 17, wherein **V** is .



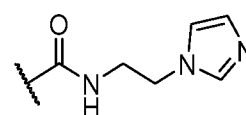
29. Compound according to any one of items 1 to 28, wherein **W** is .



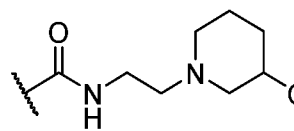
30. Compound according to any one of items 1 to 28, wherein **W** is .



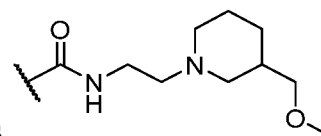
31. Compound according to any one of items 1 to 28, wherein **W** is .



32. Compound according to any one of items 1 to 28, wherein **W** is .



33. Compound according to any one of items 1 to 28, wherein **W** is .



34. Compound according to any one of items 1 to 28, wherein **W** is

.

35. Compound according to item 1, which is selected from the group consisting of:

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isopentyl-1*H*-indazole-6-carboxamide;

1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;

1-(cyclobutylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;

1-benzyl-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-2-yloxy)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-1-yloxy)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(4-methoxyphenoxy)-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)sulfonyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide.

36. Compound according to item 1, which is selected from the group consisting of:

5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(3-(dimethylamino)propyl)-2*H*-indazole-6-carboxamide;

1-benzyl-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide; and

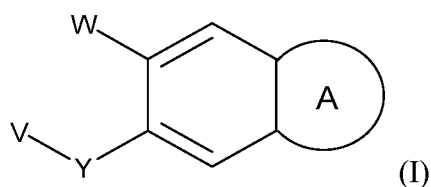
1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide.

37. Compound according to any one of items 1 to 36 for use in medicine.
38. Compound according to any one of items 1 to 36 for use in the treatment of a neurodegenerative disease.
39. Compound for use according to item 38, wherein the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease or amyotrophic lateral sclerosis.
40. Compound according to any one of items 1 to 36 for use in the treatment of an inflammatory disease.
41. Compound for use according to item 40, wherein the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.
42. Pharmaceutical composition comprising a compound according to any one of items 1 to 36, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle.
43. Pharmaceutical composition according to item 42 for use in medicine.
44. Pharmaceutical composition according to item 42 for use in the treatment of a neurodegenerative disease.
45. Pharmaceutical composition for use according to item 44, wherein the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease or amyotrophic lateral sclerosis.

46. Pharmaceutical composition according to item 42 for use in the treatment of an inflammatory disease.
47. Pharmaceutical composition for use according to item 45, wherein the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.

Detailed description of the invention

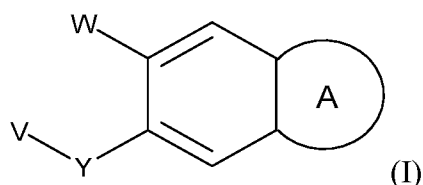
The invention relates to inhibitors of the enzymes butyrylcholinesterase and p38 α mitogen-activated protein kinase with general formula I. Particularly, this invention relates compounds of general formula (I),



or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof, pharmaceutical compositions comprising the same as well as their therapeutic uses, especially in the treatment of a neurodegenerative disease or inflammatory disease.

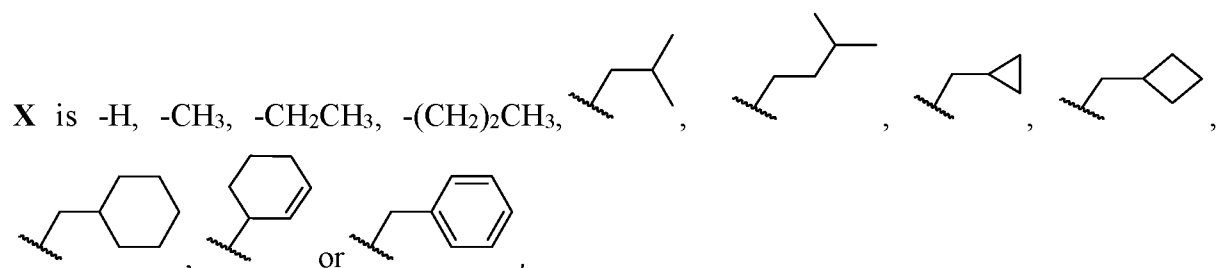
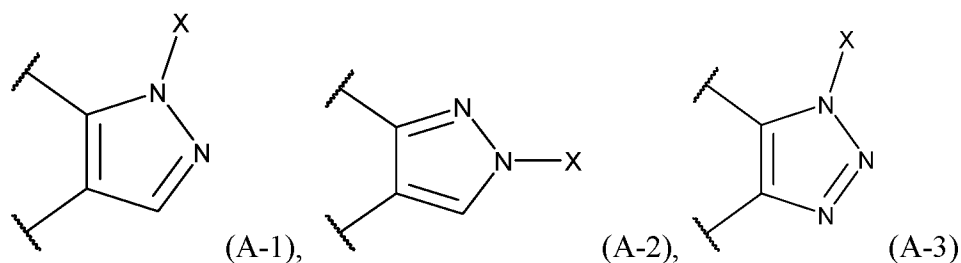
Compounds of the invention

In its broadest aspect the present invention provides a compound of formula I

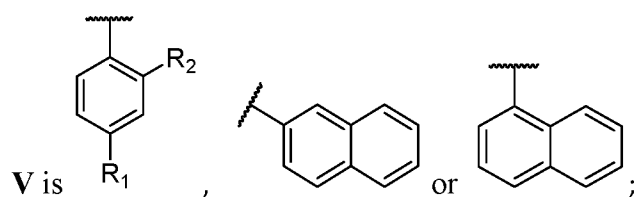


wherein,

ring **A** is a structure represented by formula (A-1), formula (A-2) or formula (A-3):

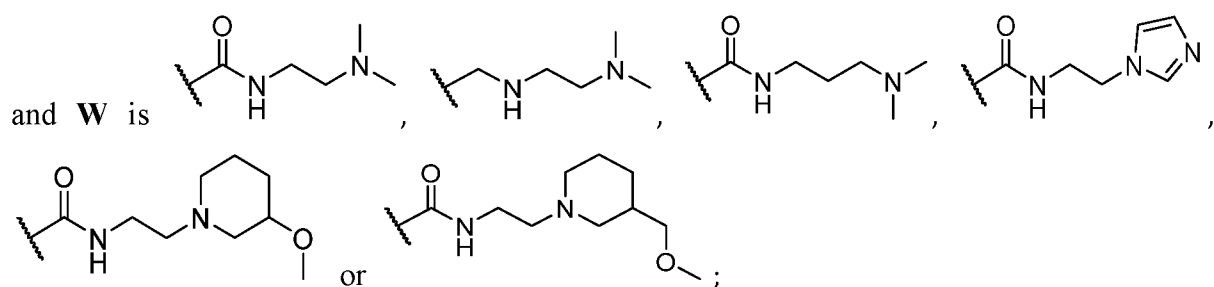


Y is CH₂, O, S or SO₂,



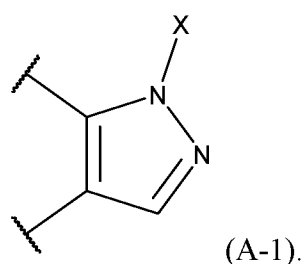
R₁ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;

R₂ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;



or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof.

According to some embodiments, ring **A** is a structure represented by formula (A-1):

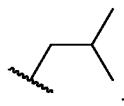


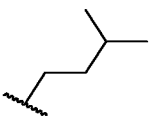
According to some embodiments, **X** in structure A-1 is -H.

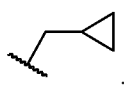
According to some embodiments, **X** in structure A-1 is -CH₃.

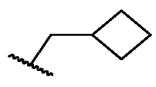
According to some embodiments, **X** in structure A-1 is -CH₂CH₃.

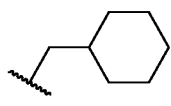
According to some embodiments, **X** in structure A-1 is -(CH₂)₂CH₃.

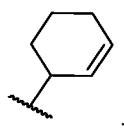
According to some embodiments, **X** in structure A-1 is .

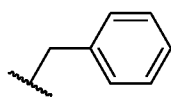
According to some embodiments, **X** in structure A-1 is .

According to some embodiments, **X** in structure A-1 is .

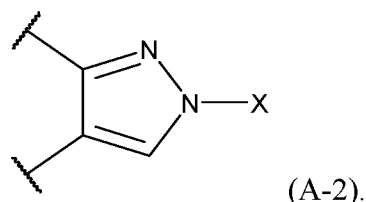
According to some embodiments, **X** in structure A-1 is .

According to some embodiments, **X** in structure A-1 is .

According to some embodiments, **X** in structure A-1 is .

According to some embodiments, **X** in structure A-1 is .

According to some embodiments, ring **A** is a structure represented by formula (A-2):



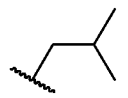
According to some embodiments, **X** in structure A-2 is -H.

According to some embodiments, **X** in structure A-2 is -CH₃.

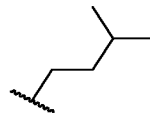
According to some embodiments, **X** in structure A-2 is -CH₂CH₃.

According to some embodiments, **X** in structure A-2 is -(CH₂)₂CH₃.

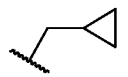
According to some embodiments, **X** in structure A-2 is



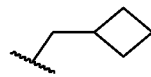
According to some embodiments, **X** in structure A-2 is



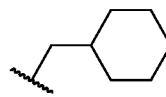
According to some embodiments, **X** in structure A-2 is



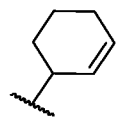
According to some embodiments, **X** in structure A-2 is



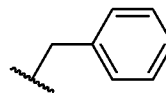
According to some embodiments, **X** in structure A-2 is



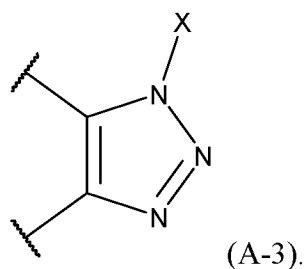
According to some embodiments, **X** in structure A-2 is



According to some embodiments, **X** in structure A-2 is



According to some embodiments, ring **A** is a structure represented by formula (A-3):



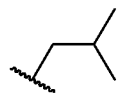
According to some embodiments, **X** in structure A-3 is -H.

According to some embodiments, **X** in structure A-3 is -CH₃.

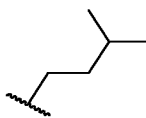
According to some embodiments, **X** in structure A-3 is -CH₂CH₃.

According to some embodiments, **X** in structure A-3 is -(CH₂)₂CH₃.

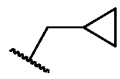
According to some embodiments, **X** in structure A-3 is



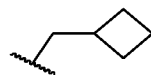
According to some embodiments, **X** in structure A-3 is



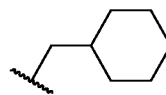
According to some embodiments, **X** in structure A-3 is



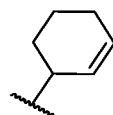
According to some embodiments, **X** in structure A-3 is



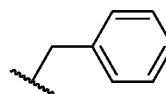
According to some embodiments, **X** in structure A-3 is



According to some embodiments, **X** in structure A-3 is



According to some embodiments, **X** in structure A-3 is

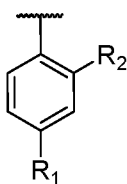


According to some embodiments, **Y** is CH₂.

According to some embodiments, **Y** is O.

According to some embodiments, **Y** is S.

According to some embodiments, **Y** is SO₂.



According to some embodiments, **V** is

According to some embodiments, R₁ is halogen.

According to some embodiments, R₁ is F.

According to some embodiments, R₁ is Br.

According to some embodiments, R₁ is Cl.

According to some embodiments, R₁ is I.

According to some embodiments, R₁ is -H.

According to some embodiments, R₁ is C₁₋₄ alkyl.

According to some embodiments, R₁ is methyl or ethyl.

According to some embodiments, R₁ is C₁₋₄ alkyloxy.

According to some embodiments, R₁ is methoxy or ethoxy.

According to some embodiments, R₂ is halogen.

According to some embodiments, R₂ is F.

According to some embodiments, R₂ is Br.

According to some embodiments, R₂ is Cl.

According to some embodiments, R₂ is I.

According to some embodiments, R₂ is -H.

According to some embodiments, R₁ is halogen or C₁₋₄ alkyloxy, and R₂ is -H.

According to some embodiments, R₁ is halogen, and R₂ is -H.

According to some embodiments, R₁ is C₁₋₄ alkyl, and R₂ is -H.

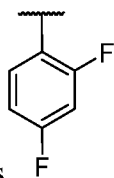
According to some embodiments, R₁ is methyl or ethyl, and R₂ is -H.

According to some embodiments, R₁ is methyl, and R₂ is -H.

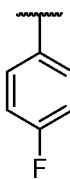
According to some embodiments, R₁ is C₁₋₄ alkyloxy, and R₂ is -H.

According to some embodiments, R₁ is methoxy or ethoxy, and R₂ is -H.

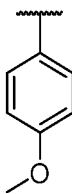
According to some embodiments, R₁ is halogen, and R₂ is halogen.



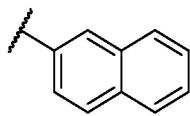
According to some embodiments, V is .



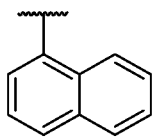
According to some embodiments, V is .



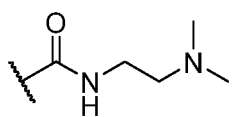
According to some embodiments, **V** is .



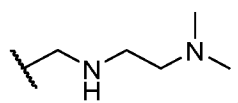
According to some embodiments, **V** is .



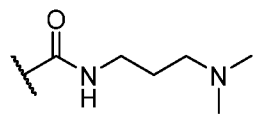
According to some embodiments, **V** is .



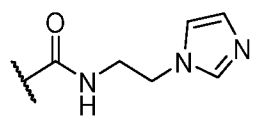
According to some embodiments, **W** is .



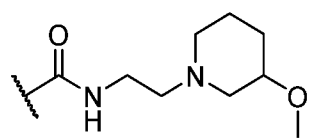
According to some embodiments, **W** is .



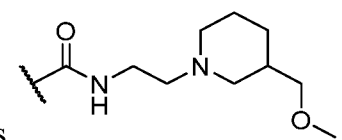
According to some embodiments, **W** is .



According to some embodiments, **W** is .



According to some embodiments, **W** is .



According to some embodiments, **W** is .

According to some embodiments, the compound is selected from the group consisting of:

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1H-indazole-6-carboxamide;

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1H-indazole-6-carboxamide;

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isopentyl-1*H*-indazole-6-carboxamide;

1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;

1-(cyclobutylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;

1-benzyl-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-2-yloxy)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-1-yloxy)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(4-methoxyphenoxy)-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)sulfonyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide.

According to some embodiments, the compound is selected from the group consisting of:

5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(3-(dimethylamino)propyl)-2*H*-indazole-6-carboxamide;

1-benzyl-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide.

According to some embodiments, the present invention provides a compound which is selected from the group consisting of:

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide.

According to some embodiments, the present invention provides a compound which is selected from the group consisting of:

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide.

A compound of the present invention may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described below.

The term "pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcysteine and the like. In addition these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. Particular pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts, methanesulfonic acid salts, and citric acid salts.

Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, *N,N*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, dibenzylamine, morpholine, N-ethylmorpholine, *N*-methylpiperidine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine (i.e., 2-amino-2-hydroxymethylpropane-1,3-diol), tris-(2-hydroxyethyl)amine, and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be

obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent.

Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydroiodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, salicylic, ascorbic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, o-glycerophosphoric, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge, S. M., et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). A preferred pharmaceutically-acceptable salt is the hydrochloride salt.

It will be appreciated by those skilled in the art that the compounds of the present invention can exist as stereoisomers (for example, optical (+ and -), geometrical (cis and trans) and conformational isomers (axial and equatorial). All such stereoisomers are included in the scope of the present invention.

It will be appreciated by those skilled in the art that the compounds of the invention can contain a chiral center. The compounds may thus exist in the form of two different optical isomers (i.e. (+) or (-) enantiomers). All such enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention. The single optical isomer or enantiomer can be obtained by method well known in the art, such as chiral HPLC, enzymatic resolution and chiral auxiliary.

It is also to be understood that compounds of the invention and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms.

The term "solvate" is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent). Especially preferred examples include hydrates and alcoholates, like methanolates or ethanolates.

Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example,

compounds having the present structures except for the replacement of hydrogen by a deuterium or tritium are within the scope of this invention.

Therapeutic uses

The compounds of the present invention have been identified as being dual inhibitors of butyrylcholinesterase and p38 α mitogen-activated protein kinase, and thus are particularly useful for the treatment of various diseases which may be therapeutically modified by altering the activity of butyrylcholinesterase (BChE) and/or p38 α MAP kinase such as dementias including Alzheimer's disease (AD) and other conditions involving chronic inflammation.

Accordingly, another aspect of the invention refers to a compound of the invention for use in medicine.

Another aspect of the invention refers to a compound of the invention for use in the treatment of a neurodegenerative disease. Preferably, the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease, or amyotrophic lateral sclerosis. According to very preferred embodiments, the neurodegenerative disease is Alzheimer's disease.

Another aspect of the invention refers to a compound of the invention for use in the treatment of an inflammatory disease. Preferably, the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.

It is noted that any of the compounds of the present invention can be used separately or in combination, particularly as adjuvant therapy administered simultaneously, alternatively or successively with respect to a first-line therapy suitable for the treatment of a neurodegenerative disease or an inflammatory disease.

Another aspect of the invention provides a pharmaceutical composition which comprises a compound according to the invention as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant or vehicle.

The present invention thus provides pharmaceutical composition comprising a compound of this invention, or a pharmaceutically acceptable salt or stereoisomers thereof together with a

pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle, for administration to a patient, such as a human patient.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) composition. In a preferred embodiment, the pharmaceutical compositions are in oral form, either solid or liquid. Suitable dose forms for oral administration may be tablets, capsules, syrups or solutions and may contain conventional excipients known in the art such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

The solid oral compositions may be prepared by conventional methods of blending, filling, or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may for example be prepared by wet or dry granulation and optionally coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

The pharmaceutical compositions may also be adapted for parenteral administration, such as sterile solutions, suspensions or lyophilized products in the appropriate unit dosage form. Adequate excipients can be used, such as bulking agents, buffering agents or surfactants.

The mentioned formulations will be prepared using standard methods such as those described or referred to in the European and US Pharmacopoeias and similar reference texts.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, and intraperitoneal and intravenous administration. Oral administration is preferred because of the convenience for the patient and the chronic character of the diseases to be treated.

Generally, an effective administered amount of a compound of the Invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 1, 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 1000 mg/kg/day.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition or be provided as a separate composition for administration at the same time or at different time.

Another aspect of the present invention refers to a composition of the invention for use in medicine.

Another aspect of the present invention refers to a composition of the invention for use in the treatment of a neurodegenerative disease. Preferably, the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease, or amyotrophic lateral sclerosis. According to very preferred embodiments, the neurodegenerative disease is Alzheimer's disease.

Another aspect of the present invention refers to a composition of the invention for use in the treatment of an inflammatory disease. Preferably, the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.

Another aspect of the present invention refers to the use of a compound of the invention in the manufacture of a medicament, such as a medicament for the treatment of a neurodegenerative disease or an inflammatory disease. Preferably, the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease, or amyotrophic lateral sclerosis. More preferably, the neurodegenerative disease is Alzheimer's disease. Preferably, the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.

Another aspect of the present invention refers to a method for the treatment of a neurodegenerative disease, said method comprises: administering a therapeutically effective amount of a compound of the invention or of a pharmaceutical composition of the invention to a subject, such as a human, in need thereof. Preferably, the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease, or amyotrophic lateral sclerosis. According to very preferred embodiments, the neurodegenerative disease is Alzheimer's disease.

Another aspect of the present invention refers to a method for the treatment of an inflammatory disease, said method comprises: administering a therapeutically effective amount of a

compound of the invention or of a pharmaceutical composition of the invention to a subject, such as a human, in need thereof. Preferably, the inflammatory disease is inflammatory dilated cardiomyopathy, acute coronary syndrome, atherosclerosis, chronic airway inflammatory diseases, inflammatory bowel disease, depression, diabetic retinopathy, rheumatoid arthritis, atopic dermatitis or multiple sclerosis.

Compounds of the present invention can be prepared using synthetic procedures described in the chapter Synthesis of the compounds with the general formula I.

The invention is clarified, though not limited by the following examples.

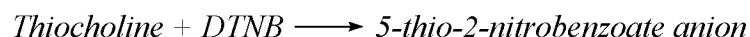
Examples

Biological evaluation

I. Enzyme assay for the determination of BChE inhibitors potency

I. Principle

The inhibitory activities against AChE and BChE were evaluated using Ellman's method³⁹. Employing this method the respective cholinesterase hydrolyses acetylthiocholine(ATCI)/butyrylthiocholine iodide (BTCI) to acetate/butyrate and thiocholine which then reacts with the Ellman's reagent (5,5'-dithiobis(2-nitrobenzoic acid). DTNB) to form a yellow colored product, 5-thio-2-nitrobenzoate anion the concentration of which is monitored as the change in absorbance at 412 nm. Applying a cholinesterase inhibitor prevents ATCI/BTCI hydrolysis and results in lower measured absorbance. The reaction was monitored using a 96-well microtiter plate and a 96-well microplate reader (Synergy™ H4, BioTek Instruments Inc., USA). For the reference sample, 1 % dimethylsulfoxide (DMSO) replaced the inhibitor's solution.



The inhibitor potency is expressed as a residual activity (RA) of the enzyme at the employed inhibitor's concentration, half maximal inhibitory concentration (IC₅₀ value) and as an inhibition constant (K_i).

2. Reagents

Enzymes: The enzyme reactions were carried out using human recombinant acetylcholinesterase (huAChE, 14.3 mg/ml) and butyrylcholinesterase (huBChE, 16.5 mg/ml). From the lyophilised powders of both enzymes, the solutions were obtained by dissolution of the powders in 10mM MES buffer (pH = 6.5) to reach the activity of the enzyme in the assay of approximately 500mAu per minute.

Substrates, ATCI and BTCi: ATCI and BTCi solutions (Sigma Aldrich) were prepared in 100mM phosphate buffer (pH = 8.0) to reach the final concentration in the assay of 500 μ M.

Ellman's reagent, DTNB: DTNB solution was prepared in 100mM phosphate buffer (pH = 8.0) to reach the final concentration in the assay of 333 μ M.

Investigated compounds: Stock solutions of compounds were prepared in DMSO (ACS, Honeywell) in a concentration of 10mM. For the IC₅₀ determination, the stock solutions were further diluted in DMSO to reach the range of inhibition from 5 % to 95 % in the final assay.

3. Procedure

Enzyme solutions were prepared by dilution of the concentrated stocks in the 100 mM phosphate buffer (pH = 8.0). The reactions were then carried out in microtiter plates in a final volume 300 μ L containing phosphate buffer 333 μ M of DTNB, 5×10^{-4} M BTCi/ATCI and 1×10^{-9} M or 5×10^{-11} M of huBChE or huAChE, respectively. Enzyme reaction was started with the addition of the substrate. The DMSO concentration in the test solution was always 1 %. The formation of the yellow colored product of the reaction of DTNB with thiocholines was monitored for 1 minute as a change in absorbance at 412 nm using the microtiter plate reader (Synergy™ H4, BioTek Instruments Inc., USA). For the determination of blank (b) the enzyme solution was replaced by phosphate buffer. The initial velocity of the enzyme reaction (v_0) was determined from the linear curve of the enzyme reaction product formation, where each measurement was performed in triplicate. For the initial screening of inhibition ability, 1 mM concentration of the investigated compounds was used. Compounds were pipetted in the corresponding wells reaching the final concentration of 10 μ m. After the 300s preincubation time of the tested compound in the enzyme solution substrate was added triggering the enzyme reaction. The initial velocity (v_i) in the presence of the inhibitor was further calculated. The inhibition capability was expressed as residual activity ($RA = (v_i - b)/(v_0 - b)$).

For the IC₅₀ value determination, 8 additional different concentrations of the investigated compounds were used, which resulted in the decrease of the enzyme reaction from 5 % to 90

% IC₅₀ values were determined by plotting the RA versus the concentration of the investigated compound. Experimental data were fitted using the following equation (1):

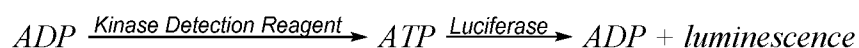
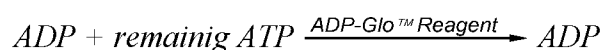
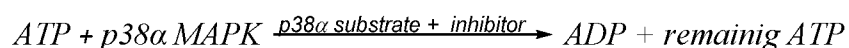
$$Y = \text{Min} + (\text{Max} - \text{Min}) / (1 + 10^{((\text{LogIC}_{50} - X) \times \text{HillSlope}))} \quad (1),$$

Where X is a common logarithm of the concentration of the inhibitor and Y is the residual activity. For solving the equation Gnuplot software and an in-house python script were used. For the determination of the inhibition constant full progress curves of the product formation in the presence and absence of investigated compounds were monitored. The curves were submitted in the ENZO web-application, which allows solving of numerical equations.

II. Enzyme assay for the determination of p38α inhibitors potency

1. Principle

The inhibitory activities against p38α MAPK were evaluated using the commercially available ADP-Glo™ Kinase Assay (Promega, Inc., USA). In this assay the kinase reaction is terminated using the ADP-Glo™ reagent which also depletes the remaining ATP. Addition of the Kinase Detection Reagent converts the ADP from the kinase reaction back to ATP which then reacts in the luciferase reaction. The measured luminescence correlates to p38α inhibitor activity. The reaction was monitored using a 384-well microtiter plate and a 384-well microplate reader (Synergy™ H4, BioTek Instruments Inc., USA). For the reference sample, 1 % DMSO replaced the inhibitor's solution.



The inhibitor potency is expressed as a residual activity (RA) of the enzyme at the employed inhibitor's concentration, half maximal inhibitory concentration (IC₅₀ value) and as an inhibition constant (*K_i*).

2. Reagents

Enzyme: The enzyme reactions were carried out using human recombinant p38α mitogen-activated protein kinase (p38α MAPK, stock: 0.1 μg/μL). The enzyme solution was prepared by diluting the enzyme stock in 1× Kinase Buffer (pH = 7.5).

1× Kinase Buffer: The buffer was prepared from milliQ water and contained 40 mM Tris×HCl, 20 mM MgCl₂, 0.1 % BSA, 5 % DMSO and 50 μM DTT (pH = 7.5).

p38 α substrate/ATP mix: The Substrate/ATP mix was prepared by diluting substrate peptide IPTTPITTTYFFFKKK stock solution ($c_0 = 1$ mg/mL) and ATP stock solution ($c_0 = 1$ mM) in $1\times$ Kinase Buffer to reach the final concentration in the well of $0,2\ \mu\text{g}/\mu\text{L}$ and $100\ \mu\text{M}$ respectively.

Enzyme: The ADP-Glo reaction was carried out using human recombinant p38 α MAPK, expressed in an Sf9 insect cell line (stock: $0,1\ \mu\text{g}/\mu\text{L}$). The stock solution was diluted with $1\times$ Kinase Buffer to reach the final concentration in the well of $1\ \text{ng}/\mu\text{L}$.

Investigated compounds: Stock solutions of compounds were prepared in DMSO (ACS, Honeywell) in a concentration of 10mM. They were then further diluted in $1\times$ Kinase Buffer so that the final % of DMSO in the well did not exceed 1 %. For the IC₅₀ determination, the stock solutions were further diluted in DMSO followed by $1\times$ Kinase Buffer to reach the range of inhibition from 5 % to 95 % in the final assay.

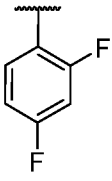
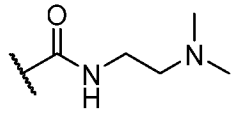
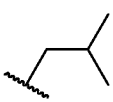
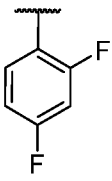
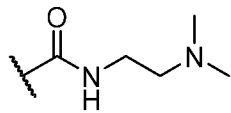
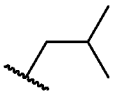
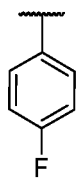
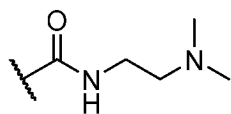
ADP-Glo™ kinase assay: The kinase assay (Promega, Inc., USA) included ADP-Glo™ reagent, Kinase Detection Buffer, Kinase Detection Substrate, Ultra Pure ATP (10 mM) and ADP (10 mM).

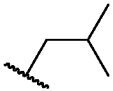
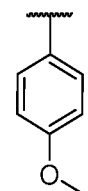
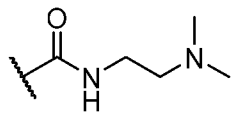
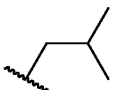
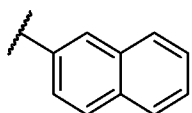
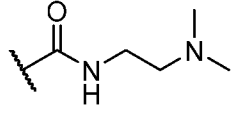
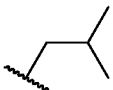
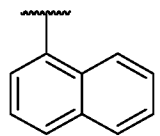
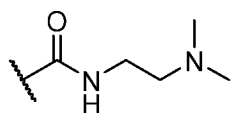
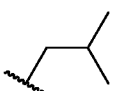
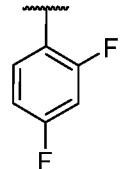
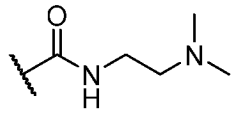
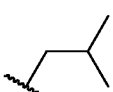
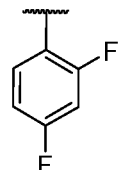
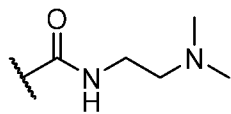
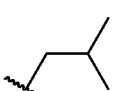
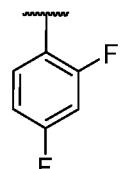
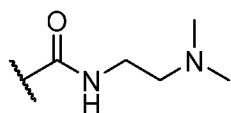
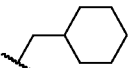
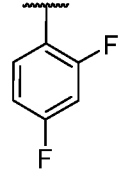
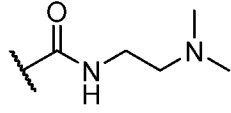
3. Procedure

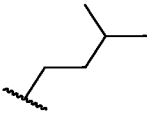
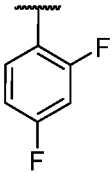
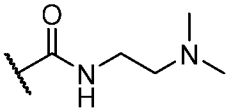
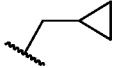
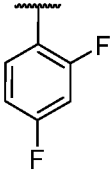
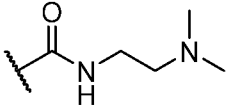
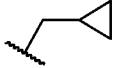
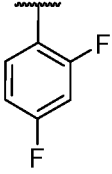
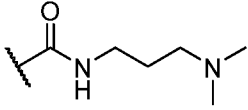
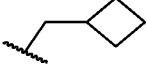
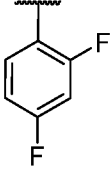
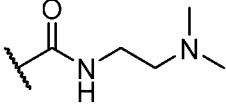
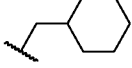
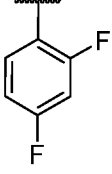
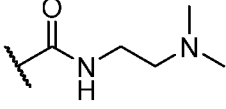
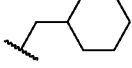
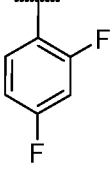
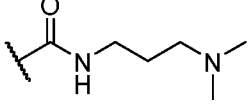
The reactions were carried out in microtiter 384-well plates in a final volume $5\ \mu\text{L}$ containing $1\ \mu\text{L}$ of investigated compounds solution (5 % [v/v] DMSO), $2\ \mu\text{L}$ of p38 α ($2,5\ \text{ng}/\mu\text{L}$ in $1\times$ Kinase Buffer, $2\ \mu\text{L}$ of substrate solution ($0,5\ \mu\text{g}/\mu\text{L}$ in $1\times$ Kinase Buffer) and ATP ($125\ \mu\text{M}$ in $1\times$ Kinase Buffer) Enzyme reaction was started with the addition of the enzyme solution. The DMSO concentration in the test solution was always 1 %. The plate was left to incubate for 60 minutes. Then $5\ \mu\text{L}$ of ADP-Glo reagent was added followed by a 40-minute incubation, addition of $10\ \mu\text{L}$ of Kinase detection substrate, 30-minute incubation and fluorescence measurement at 570 nm using the microtiter plate reader (Synergy™ H4, BioTek Instruments Inc., USA, measurement: top, gain: 150, integration time: 1 s). All incubations were performed at room temperature. The RA and IC₅₀ values were calculated as described in the Procedure section of Enzyme assay for the determination of BChE inhibitors potency.

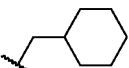
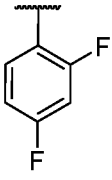
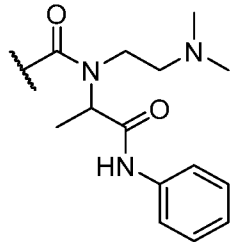
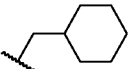
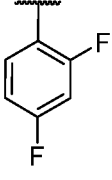
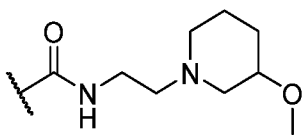
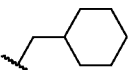
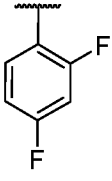
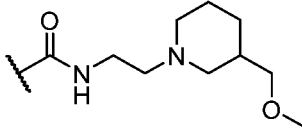
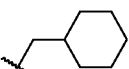
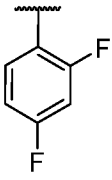
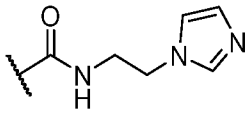
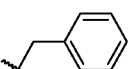
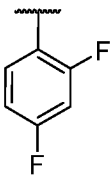
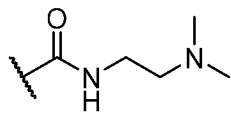
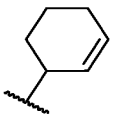
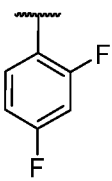
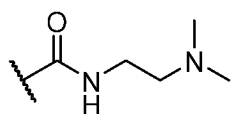
Results of biological evaluation

Table 1: Inhibitory activity of compounds with general formula (I) wherein ring A is the structure represented by formula (A-1):

				$IC_{50} \pm$ STD (μM) or % inhibition $\pm$ STD at 10 μ M inhibitor		
X	Y	V	W			
				huAChE	huBChE	p38 α MAPK
-H	-O-			80.4 $\pm$ 2.9	66.48 $\pm$ 21.75	6.03 $\pm$ 0.92
	-O-			53.8 $\pm$ 2.6	12.01 $\pm$ 1.95	0.132 $\pm$ 0.042
	-O-			71.3 $\pm$ 4.7	6.382 $\pm$ 0.511	0.276 $\pm$ 0.015

	-O-			75.2 ± 3.8	54.1 ± 1.3	TBD
	-O-			116.1 ± 27.8	11.48 ± 2.00	TBD
	-O-			61.28 ± 22.46	10.56 ± 1.06	TBD
	-S-			62.8 ± 3.0	2.253 ± 0.332	0.053 ± 0.017
	-SO ₂ -			98.0 ± 2.7	77.6 ± 3.1	TBD
	-CH ₂ -			69.0 ± 4.0	0.652 ± 0.112	0.377 ± 0.123
	-CH ₂ -			53.4 ± 0.8	0.772 ± 0.057	0.191 ± 0.021

	-O-			51.1 ± 1.4	2.698 ± 0.558	0.189 ± 0.073
	-O-			83.94 ± 28.93	10.46 ± 1.51	0.3621 ± 0.1385
	-O-			109.6 ± 38.4	8.68 ± 1.83	0.0957 ± 0.0114
	-O-			51.9 ± 0.5	6.407 ± 0.565	0.142 ± 0.02
	-O-			64.40 ± 24.49	2.895 ± 0.446	0.142 ± 0.079
	-O-			51.4 ± 1.7	2.622 ± 0.749	0.108 ± 0.007

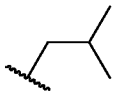
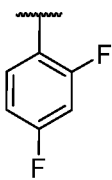
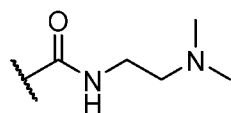
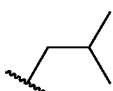
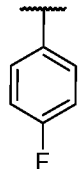
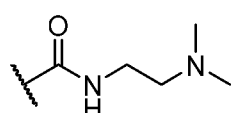
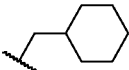
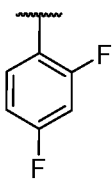
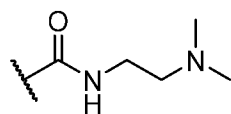
	-O-			50.6 ± 1.7	0.222 ± 0.019	53.9 ± 9.6
	-O-			23.4 ± 1.9	5.219 ± 1.547	0.744 ± 0.191
	-O-			11.6 ± 1.3	3.599 ± 0.825	0.379 ± 0.126
	-O-			65.1 ± 2.5	18.73 ± 6.10	0.218 ± 0.017
	-O-			43.1 ± 1.1	3.947 ± 1.508	0.739 ± 0.400
	-O-			52.9 ± 2.7	8.352 ± 1.671	0.088 ± 0.02

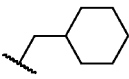
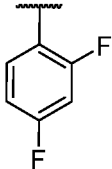
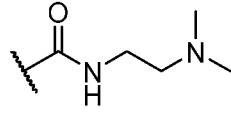
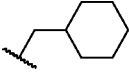
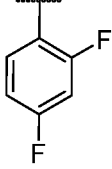
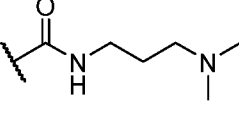
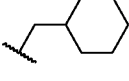
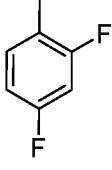
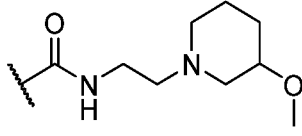
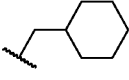
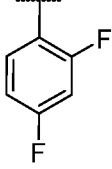
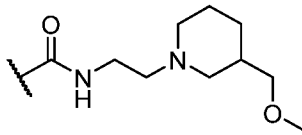
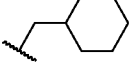
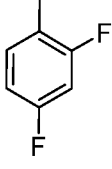
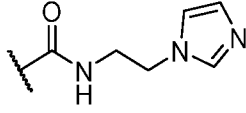
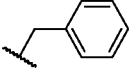
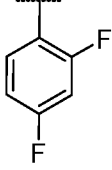
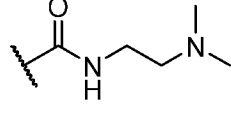
STD = standard deviation

huAChE = human acetylcholinesterase

huBChE = human butyrylcholinesterase

p38 α = p38 α mitogen-activated protein kinase**Table 2:** Inhibitory activity of compounds with general formula (I) wherein ring A is the structure represented by formula (A-2):

				IC ₅₀ ± STD (μM) or % inhibitio n ± STD at 10 μM inhibitor	IC ₅₀ ± STD (μM) or % inhibitio n ± STD at 10 μM inhibitor	IC ₅₀ ± STD (μM) or % inhibitio n ± STD at 10 μM inhibitor
X	Y	V	W	huAChE	huBChE	p38 α MAPK
	-O-			51.8 ± 1.6	16.24 ± 4.87	5.79 ± 0.88
	-O-			57.6 ± 2.2	21.91 ± 5.74	89.3 ± 2.9
	-O-			28.94 ± 8.16	0.167 ± 0.0203	6.776 ± 2.848

	-CH ₂ -			96.49 ± 35.9	0.748 ± 0.0764	91.0 ± 1.7
	-O-			41.93 ± 13.85	0.499 ± 0.045	16.24 ± 2.97
	-O-			51.8 ± 1.6	0.184 ± 0.031	94.3 ± 2.4
	-O-			50.7 ± 3.1	0.0209 ± 0.00188	92.7 ± 25.3
	-O-			55.4 ± 1.3	0.0662 ± 0.00892	19.49 ± 2.87
	-O-			102.6 ± 36.4	1.005 ± 0.133	42.2 ± 29.4

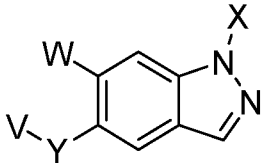
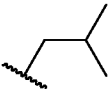
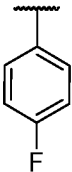
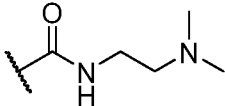
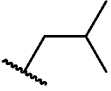
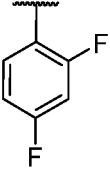
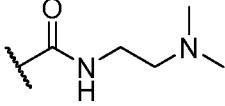
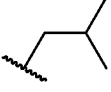
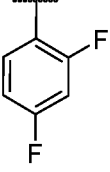
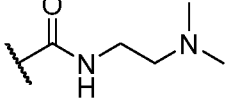
STD = standard deviation

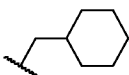
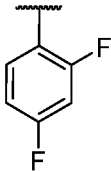
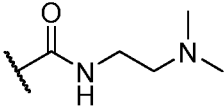
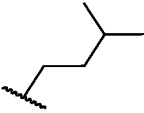
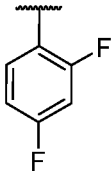
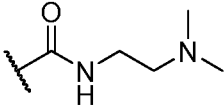
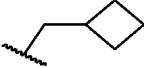
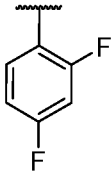
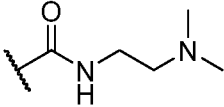
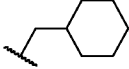
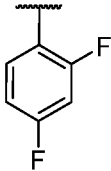
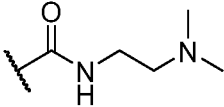
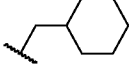
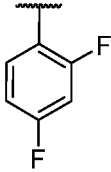
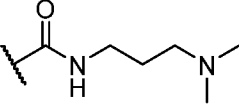
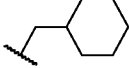
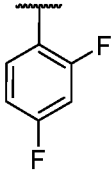
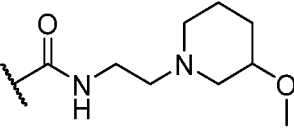
huAChE = human acetylcholinesterase

huBChE = human butyrylcholinesterase

p38α = p38α mitogen-activated protein kinase

Table 3: Inhibitory activity of selected compounds with general formula (I) wherein ring A is the structure represented by formula (A-1):

				$IC_{50} \pm$ STD (μM) or % inhibition $\pm$ STD at 10 μ M inhibitor		
X	Y	V	W			
				huAChE	huBChE	p38 α MAPK
	-O-			71.3 $\pm$ 4.7	6.382 $\pm$ 0.511	0.276 $\pm$ 0.015
	-S-			62.8 $\pm$ 3.0	2.253 $\pm$ 0.332	0.053 $\pm$ 0.017
	-CH ₂ -			69.0 $\pm$ 4.0	0.652 $\pm$ 0.112	0.377 $\pm$ 0.123

	-CH ₂ -			53.4 ± 0.8	0.772 ± 0.057	0.191 ± 0.021
	-O-			51.1 ± 1.4	2.698 ± 0.558	0.189 ± 0.073
	-O-			51.9 ± 0.5	6.407 ± 0.565	0.142 ± 0.02
	-O-			64.40 ± 24.49	2.895 ± 0.446	0.142 ± 0.079
	-O-			51.4 ± 1.7	2.622 ± 0.749	0.108 ± 0.007
	-O-			23.4 ± 1.9	5.219 ± 1.547	0.744 ± 0.191

	-O-			11.6 ± 1.3	3.599 ± 0.825	0.379 ± 0.126
	-O-			43.1 ± 1.1	3.947 ± 1.508	0.739 ± 0.400
	-O-			52.9 ± 2.7	8.352 ± 1.671	0.088 ± 0.02

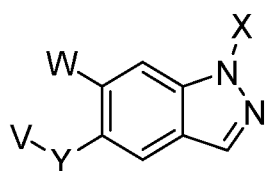
STD = standard deviation

huAChE = human acetylcholinesterase

huBChE = human butyrylcholinesterase

p38α = p38α mitogen-activated protein kinase

Table 4: Inhibitory activity of compounds disclosed in US 2004/176325 A1, WO 2004/078116 A2 and WO 2021/216754.



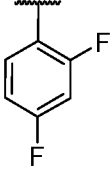
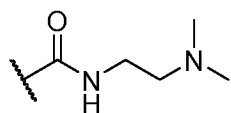
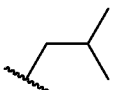
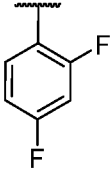
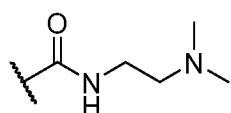
X

Y

V

W

IC ₅₀ ± STD (μM) or % inhibition ± STD at 10 μM inhibitor	IC ₅₀ ± STD (μM) or % inhibition ± STD at 10 μM inhibitor	IC ₅₀ ± STD (μM) or % inhibition ± STD at 10 μM inhibitor
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				huAChE	huBChE	p38 α MAPK
-H	-O-			80.4 $\pm$ 2.9	66.48 $\pm$ 21.75	6.03 $\pm$ 0.92
	-O-			53.8 $\pm$ 2.6	12.01 $\pm$ 1.95	0.132 $\pm$ 0.042

STD = standard deviation

huAChE = human acetylcholinesterase

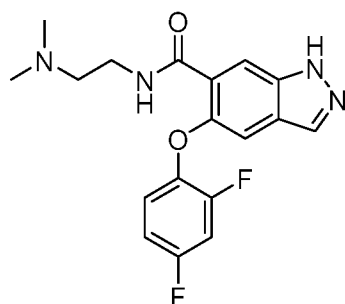
huBChE = human butyrylcholinesterase

p38 α = p38 α mitogen-activated protein kinase

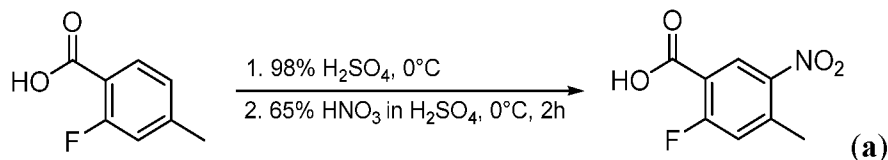
As becomes evident, compounds shown in Table 3 exhibit superior inhibition both with respect to hBChE and p38 α MAPK compared to the prior art compounds shown in Table 4. These superior properties make these compounds attractive therapeutics for the treatment of various diseases which may be therapeutically modified by altering the activity of butyrylcholinesterase (BChE) and/or p38 α MAP kinase such as dementias including Alzheimer's disease (AD) and other conditions involving chronic inflammation.

Synthesis of compounds with general formula (I)

EXAMPLE 1: Synthesis of 5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide



STEP 1: Synthesis of compound **a** – 2-fluoro-4-methyl-5-nitrobenzoic acid:



To a 500-mL round-bottomed flask equipped with a stirring bar, 2-fluoro-4-methylbenzoic acid (10 g, 64.876 mmol, 1.0 equiv) was added and dissolved in 100 mL 96 % H_2SO_4 . The solution was cooled to 0°C and the round-bottomed flask equipped with a dropping funnel through which a mixture of HNO_3 (6.7 mL, 147.802 mmol, 2.3 equiv) in 96 % H_2SO_4 (4.3 mL) was added dropwise over a period of five minutes. The dropping funnel was removed and the reaction mixture was allowed to stir in an ice bath for 2h. After that ice-cold water (250 mL) was gradually added to the mixture resulting in a formation of a precipitate, which was filtered, dissolved in 150 mL of CH_2Cl_2 -MeOH = 3:1, v/v, washed with brine (100 + 50 mL) and dried with Na_2SO_4 . Organic phases were evaporated on rotary evaporator and the solid product was further dried *in vacuo* at room temperature in the presence of NaOH and SICAPENT[®] to constant mass to produce 11.922 g of 2-fluoro-4-methyl-5-nitrobenzoic acid.

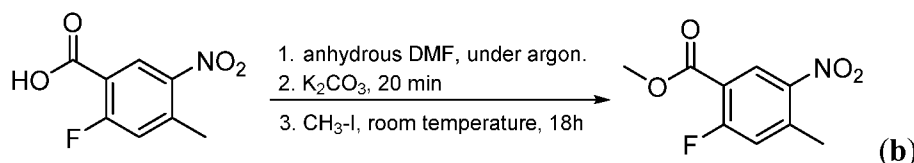
Product appearance: light brown solid

Yield: 92 %

TLC: R_f = 0.22 (CH_2Cl_2 -MeOH = 5:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.77 (s, 1H), 2.67 (s, 3H) ppm Signal for -COOH is not visible.

STEP 2: Synthesis of compound **b** – methyl 2-fluoro-4-methyl-5-nitrobenzoate:



In a 250 mL round-bottom flask equipped with a stirring bar compound **a** (11.918 g, 59.848 mmol, 1.0 equiv) was dissolved in 50 mL anhydrous *N,N*-dimethylformamide under argon atmosphere. K_2CO_3 (19.02 g, 137.578 mmol, 2.3 equiv) was then added in 4 portions. After 20 minutes of stirring at room temperature methyl iodide (11.17 mL, 179.425 mmol, 3.0 equiv) was added dropwise. The reaction mixture was left to stir at room temperature under argon

atmosphere overnight. After 18h water (30 mL) was added and the mixture was transferred to a separatory funnel. The product was extracted with EtOAc (2×50 mL) and the organic phases were then further washed with 50 mL brine, dried with Na_2SO_4 and evaporated under reduced pressure using an oil pump. The product was then purified by recrystallization from the mixture of EtOAc and hexane to obtain 8.46 g of methyl 2-fluoro-4-methyl-5-nitrobenzoate.

Product appearance: dark yellow crystals

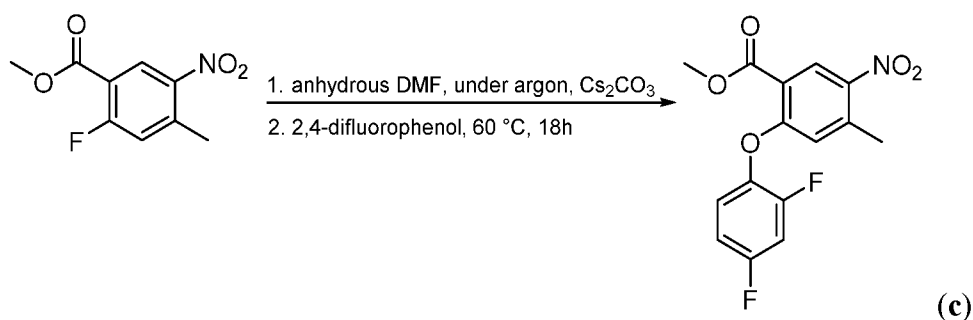
Yield: 66 %

TLC: $R_f = 0.78$ (EtOAc-MeOH = 2:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.67 (d, $J = 6.7$ Hz, 1H), 7.14 (d, $J = 10.6$ Hz, 1H), 3.97 (s, 3H), 2.68 (s, 3H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_9\text{H}_8\text{FNO}_4$: 213.16; found: no ionization.

STEP 3: Synthesis of compound **c** – methyl 2-(2,4-difluorophenoxy)-4-methyl-5-nitrobenzoate:



To a 100 mL round-bottom flask with a stirring bar compound **b** (978 mg, 4.588 mmol, 1.0 equiv) was added and subsequently dissolved in 10 mL of anhydrous DMF under argon atmosphere. Cs_2CO_3 (2.242 g, 6.881 mmol, 1.5 equiv) was added in 2 portions followed by dropwise addition of 2,4-difluorophenol (444 μ , 4.649 mmol, 1.0 equiv). The reaction mixture was then heated to 60 °C and let to stir overnight under argon atmosphere. After 18h the reaction was cooled to room temperature and 30 mL of water were added before transferring the contents of the round-bottom flask to a separatory funnel where the product was extracted with EtOAc (2×30 mL). Combined organic phases were washed with 30 mL 10 % (m/v) citric acid, 30 mL of 1M NaOH solution and 30 mL of brine and dried with Na_2SO_4 . Evaporating the solvent and drying the product on an oil pump gave 1.328 g of methyl 2-(2,4-difluorophenoxy)-4-methyl-5-nitrobenzoate.

Product appearance: light brown solid

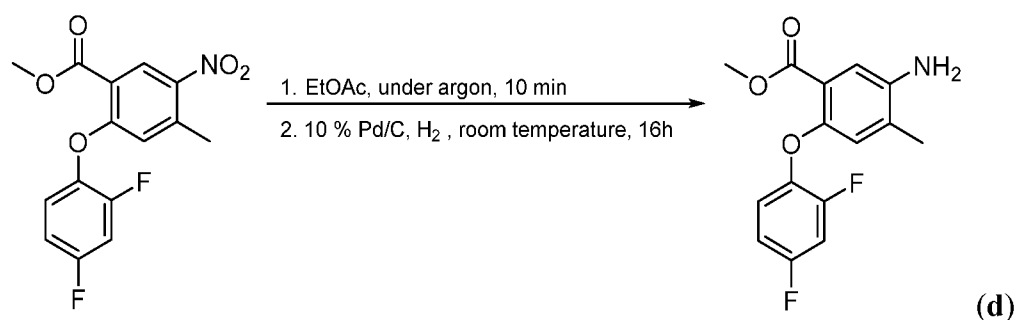
Yield: 90 %

TLC: R_f = 0.26 (EtOAc-hexane = 1:2, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 7.17 (td, J = 8.9, 5.4 Hz, 1H), 7.02 (ddd, J = 10.2, 8.2, 2.9 Hz, 1H), 6.95 (dddd, J = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 6.61 (t, J = 0.9 Hz, 1H), 3.94 (s, 3H), 2.57 (s, 3H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_{15}\text{H}_{11}\text{F}_2\text{NO}_5$: 323.25; found: no ionization.

STEP 4: Synthesis of compound **d** – methyl 5-amino-2-(2,4-difluorophenoxy)-4-methylbenzoate:



Compound **c** (1.325 g, 4.099 mmol, 1.0 equiv) was dissolved in 60 mL EtOAc in a 100 mL round-bottom flask. The contents of the flask were flushed with argon for 10 minutes. After that 10 % Pd/C (130 mg, 1.222 mmol, 0.3 equiv) was added carefully in two portions. The flask was flushed with hydrogen and the reaction mixture was left to stir overnight at room temperature under hydrogen atmosphere. After 16h the flask and its contents were again flushed with argon and left to stir under argon atmosphere for 15 minutes. A pad of Celite[®] 545 was prepared and the reaction mixture was slowly filtered through it. The mother liquor was evaporated under reduced pressure to obtain 1.203 g of methyl 5-amino-2-(2,4-difluorophenoxy)-4-methylbenzoate.

Product appearance: viscous brown oil

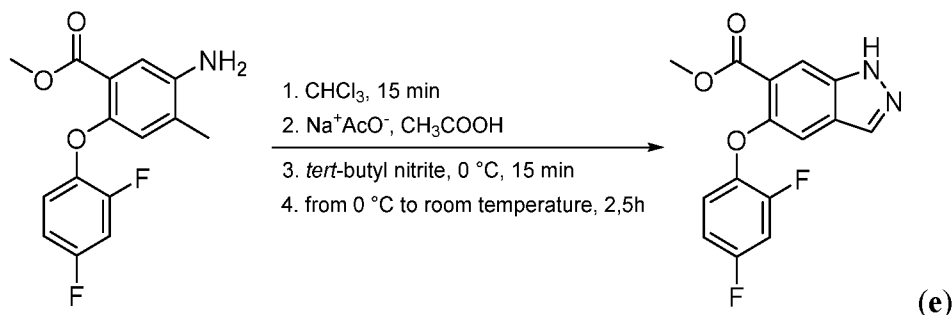
Yield: 100 %

TLC: R_f = 0.26 (EtOAc-hexane = 1:2, v/v)

^1H NMR (400 MHz, CDCl_3) δ 7.26 (s, 1H), 6.92 (dddd, J = 10.9, 8.4, 2.3, 1.1 Hz, 1H), 6.75 (s, 1H), 6.73 – 6.69 (m, 2H), 3.77 (s, 3H), 3.64 (s, 2H), 2.17 (s, 3H) ppm

LC-MS (ESI⁺) (m/z): calculated for C₁₅H₁₃F₂NO₃: 293.3; found: 294.1.

STEP 5: Synthesis of compound **e** – methyl 5-(2,4-difluorophenoxy)-1H-indazole-6-carboxylate:



In a 100 mL round-bottom flask equipped with a stirring bar compound **d** (1.257 g, 4.289 mmol, 1.0 equiv) was dissolved in 60 mL of chloroform. The solution was cooled to 0 ° in an ice bath after which sodium acetate (56 mg, 0.683 mmol, 0.16 equiv) and acetic acid (4 mL, 69.939 mmol, 16.3 equiv) were added to the flask. After 15 minutes of stirring on an ice bath *tert*-butyl nitrite (1.27 mL, 10.678 mmol, 2.5 equiv) was added dropwise. After additional 15 minutes the ice bath was removed and the reaction mixture was left to warm to room temperature. Once all the starting compound was consumed (monitored by TLC) the solvents were evaporated on rotary evaporator and the crude was dissolved in 50 mL of EtOAc which was then carefully washed with a saturated NaHCO₃ solution (2 × 30 mL). The organic phase was dried with Na₂SO₄ and evaporated under reduced pressure. The crude was purified by flash column chromatography using EtOAc-hexane (1:2, v/v) as the eluent to produce 811 mg of methyl 5-(2,4-difluorophenoxy)-1H-indazole-6-carboxylate.

Product appearance: viscous orange oil

Yield: 62 %

TLC: *R_f* = 0.35 (EtOAc-hexane = 1:2, v/v)

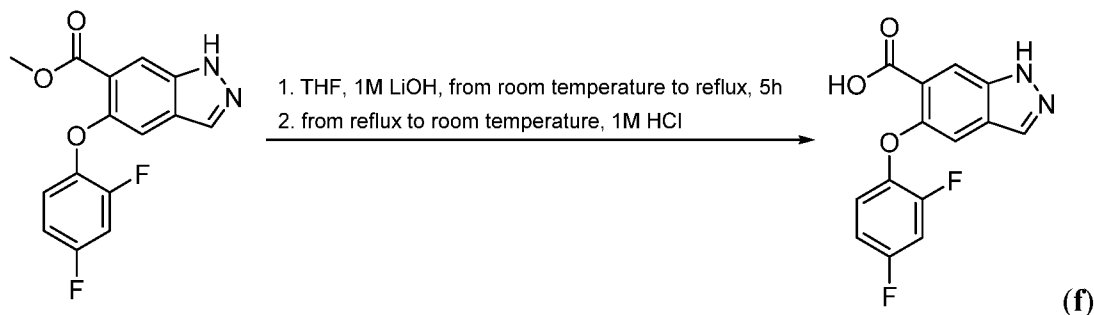
¹H NMR (400 MHz, CDCl₃) δ 11.53 (s, 1H), 8.14 (t, *J* = 0.8 Hz, 1H), 8.05 (d, *J* = 1.1 Hz, 1H), 7.27 (d, *J* = 0.6 Hz, 1H), 6.96 (ddd, *J* = 11.0, 8.4, 2.9 Hz, 1H), 6.87 (td, *J* = 9.0, 5.4 Hz, 1H), 6.78 (dddd, *J* = 9.2, 7.7, 3.0, 1.6 Hz, 1H), 3.88 (s, 3H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 165.05, 160.08 (d, *J* = 10.3 Hz), 157.63 (d, *J* = 10.1 Hz), 155.01 (d, *J* = 12.2 Hz), 152.51 (d, *J* = 12.2 Hz), 149.29, 139.86 (dd, *J* = 11.6, 3.8 Hz), 136.69, 133.96,

124.40, 121.95 (dd, $J = 9.6, 1.9$ Hz), 114.11, 111.53 (dd, $J = 22.9, 3.9$ Hz), 107.25, 105.57 (dd, $J = 26.8, 21.7$ Hz), 57.40, 44.80, 37.58, 29.70 ppm

LC-MS (ESI⁺) (m/z): calculated for C₁₅H₁₀F₂N₂O₃: 304.3; found: 304.9.

STEP 6: Synthesis of compound **f** – 5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylic acid:



To a 25-mL round-bottom flask with a stirring bar was added compound **e** (100 mg, 0.373 mmol, 1.0 equiv) and dissolved in 6 mL of THF. 1M aqueous LiOH (2 mL, 2.0 mmol, 3.0 equiv) was added dropwise during vigorous stirring of the solution at room temperature. The reaction mixture was then left to stir under reflux and monitored by TLC. After 5h the mixture was left to cool and THF was evaporated. The remaining aqueous phase was acidified by dropwise addition of 1M HCl to pH = 0. The precipitate that formed was filtered under suction and dried on rotary evaporator to yield 81 mg of 5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylic acid.

Product appearance: light brown solid

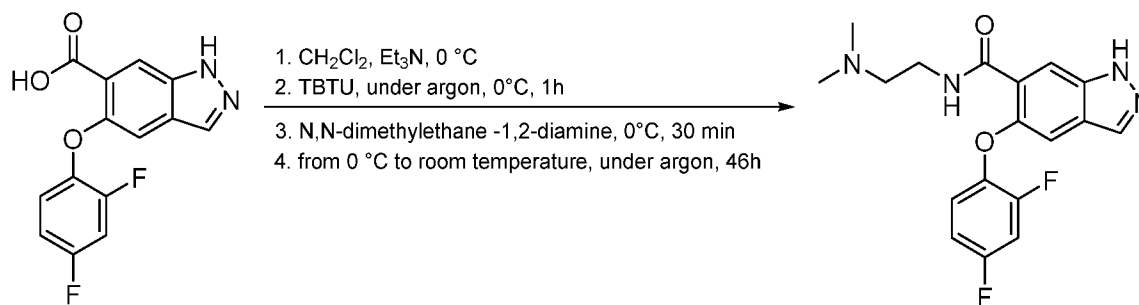
Yield: 84 %

TLC: $R_f = 0.08$ (CH₂Cl₂-MeOH = 10:1, v/v)

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.42 (s, 1H), 8.10 (s, 1H), 8.05 (s, 1H), 7.47 – 7.40 (m, 2H), 6.99 (tdd, $J = 8.1, 3.0, 1.5$ Hz, 1H), 6.88 (td, $J = 9.3, 5.5$ Hz, 1H) ppm Signal for 1*H* of indazole is not visible.

LC-MS (ESI⁺) (m/z): calculated for C₁₄H₈F₂N₂O₃: 290.2; found: 288.8.

STEP 7: Synthesis of 5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



To a 25-mL round-bottom flask equipped with a stirring bar was added compound **f** (74 mg, 0.255 mmol, 1.0 equiv). 15 mL of CH_2Cl_2 was added under argon and a suspension was formed which was cooled to $0\text{ }^\circ\text{C}$ on an ice bath. Subsequently, Et_3N (71 μL , 0.510 mmol, 2.0 equiv) was added dropwise resulting in dissolution of compound **f**. After 10 minutes TBTU (82 mg, 0.255 mmol, 1.0 equiv) was added in two portions and the reaction mixture was left to stir on an ice bath under argon for 1h before *N,N*-dimethylethane-1,2-diamine (56 μL , 0.510 mmol, 2.0 equiv) was added. Finally, the reaction mixture was left to warm to room temperature and stir for two days. After 46h the reaction mixture was washed with saturated NaHCO_3 solution ($2 \times 10\text{ mL}$) and brine ($2 \times 10\text{ mL}$), dried with Na_2SO_4 and CH_2Cl_2 evaporated under reduced pressure. The crude obtained was then purified by flash column chromatography using CH_2Cl_2 -MeOH (1:1, v/v) and reverse-phase preparative chromatography (Biotage® Sfär, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase to obtain 40 mg of 5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide.

Product appearance: white solid

Yield: 43 %

TLC: $R_f = 0.29$ (CH_2Cl_2 -MeOH = 1:1, v/v)

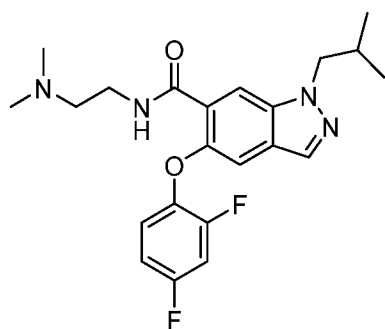
^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 0.9\text{ Hz}$, 1H), 8.19 (s, 1H), 7.95 (d, $J = 1.1\text{ Hz}$, 1H), 7.06 (s, 1H), 7.05 – 6.96 (m, 2H), 6.87 (dddd, $J = 9.2, 7.7, 3.0, 1.7\text{ Hz}$, 1H), 3.60 (q, $J = 5.7\text{ Hz}$, 2H), 2.56 (t, $J = 6.1\text{ Hz}$, 2H), 2.23 (s, 6H) ppm Signal for 1*H*-indzole is not visible.

^{13}C NMR (101 MHz, CDCl_3) δ 165.05, 160.08 (d, $J = 10.3\text{ Hz}$), 157.63 (d, $J = 10.1\text{ Hz}$), 155.01 (d, $J = 12.2\text{ Hz}$), 152.51 (d, $J = 12.2\text{ Hz}$), 149.29, 139.86 (dd, $J = 11.6, 3.8\text{ Hz}$), 136.69, 133.96, 124.40, 121.95 (dd, $J = 9.6, 1.9\text{ Hz}$), 114.11, 111.53 (dd, $J = 22.9, 3.9\text{ Hz}$), 107.25, 105.57 (dd, $J = 26.8, 21.7\text{ Hz}$), 57.40, 44.80, 37.58 ppm

HRMS (ESI⁺) (m/z): calculated for $\text{C}_{18}\text{H}_{18}\text{F}_2\text{N}_4\text{O}_2$: 360.1398; found: 361.1460

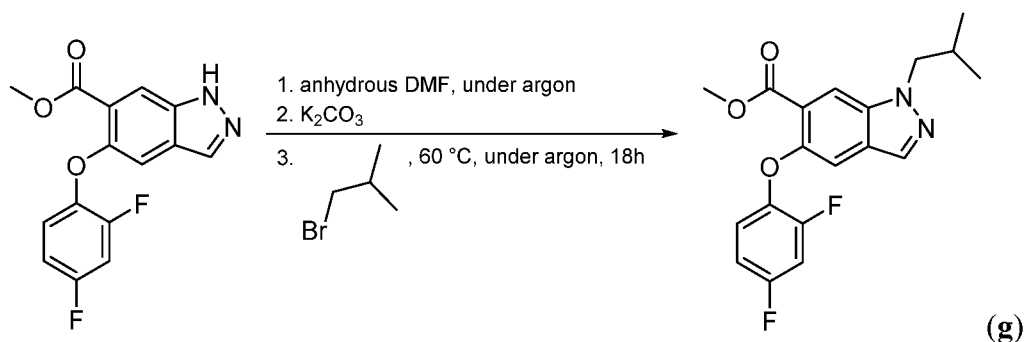
UPLC purity: 95 %

EXAMPLE 2: Synthesis of 5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide



STEPS 1-5 are identical to those described in **EXAMPLE 1**.

STEP 6: Synthesis of compound **g** – methyl 5-(2,4-difluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxylate:



To a 25-mL round-bottom flask with a stirring bar was added compound **e** (200 mg, 0.657 mmol, 1.0 equiv). Anhydrous DMF (20 mL) was added under argon and the contents stirred until compound **g** was completely dissolved. K_2CO_3 (376 mg, 2,720 mmol, 4.14 equiv) was added in two portions followed by 5-minute stirring at room temperature and dropwise addition of 1-bromo-2-methylpropane (98 μ L, 0.907 mmol, 1.38 equiv). The reaction mixture was heated to 60 °C and left to stir overnight. After 18h 10 mL of H_2O were added, the contents of the flask transferred to a separatory funnel and extracted with EtOAc (3 $\times$ 20 mL). Combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash column chromatography using EtOAc-hexane (1:2, v/v) to obtain 109 mg of methyl 5-(2,4-difluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxylate.

Product appearance: white viscous oil

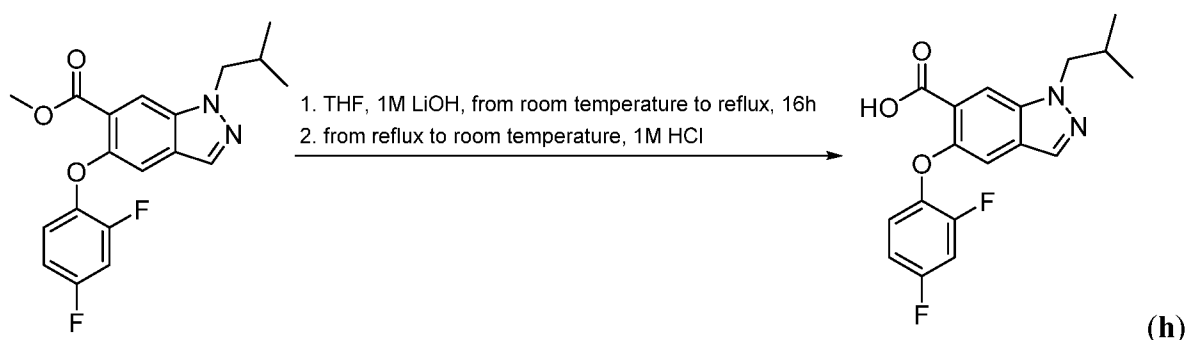
Yield: 53 %

TLC: R_f = 0.58 (EtOAc-hexane = 1:2, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.94 (d, J = 1.0 Hz, 1H), 7.27 (s, 1H), 6.97 (ddd, J = 10.9, 8.3, 2.9 Hz, 1H), 6.85 (td, J = 9.0, 5.5 Hz, 1H), 6.77 (dddd, J = 9.1, 7.8, 2.9, 1.5 Hz, 1H), 4.22 (d, J = 7.4 Hz, 2H), 3.88 (s, 3H), 2.37 (hept, J = 6.9 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H) ppm

LC-MS (ESI^+) (m/z): calculated for $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3$: 360.4; found: 361.9.

STEP 7: Synthesis of compound **h** – 5-(2,4-difluorophenoxy)-1-isobutyl-1H-indazole-6-carboxylic acid:



In a 50-mL round-bottom flask equipped with a stirring bar compound **g** (107 mg, 297 μmol , 1.0 equiv) was dissolved in 12 mL of THF. 1M aqueous LiOH (890 μL , 890 μmol , 3.0 equiv) was added dropwise during vigorous stirring of the solution at room temperature. The reaction mixture was then heated, left to stir under a reflux condenser and monitored by TLC. After 16h the mixture was left to cool and THF was evaporated. The remaining aqueous phase was acidified by dropwise addition of 1M HCl to pH = 0, transferred to a separatory funnel and the product extracted with EtOAc (3×20 mL). Combined organic phases were washed with 10 mL of brine, dried with Na_2SO_4 and evaporated on rotary evaporator to yield 86 mg of 5-(2,4-difluorophenoxy)-1-isobutyl-1H-indazole-6-carboxylic acid.

Product appearance: white viscous oil

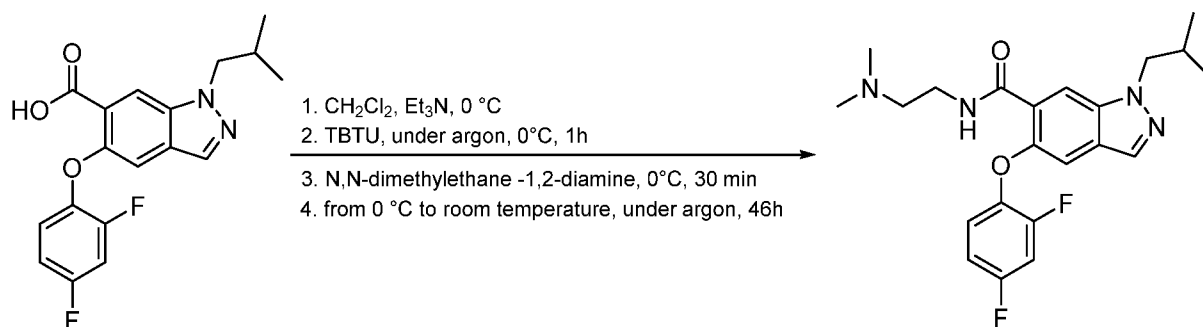
Yield: 82 %

TLC: R_f = 0.43 (CH_2Cl_2 -MeOH = 10:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 7.92 (d, J = 1.0 Hz, 1H), 7.18 (td, J = 8.9, 5.3 Hz, 1H), 7.08 (d, J = 0.8 Hz, 1H), 7.04 (ddd, J = 10.3, 8.2, 2.9 Hz, 1H), 6.95 (dddd, J = 9.2, 7.6, 3.0, 1.7 Hz, 1H), 4.24 (d, J = 7.4 Hz, 2H), 2.36 (hept, J = 6.9 Hz, 1H), 0.94 (d, J = 6.7 Hz, 6H) ppm
Signal for -COOH is not visible.

LC-MS (ESI⁺) (m/z): calculated for C₁₈H₁₆F₂N₂O₃: 346.3; found: 347.9.

STEP 8: Synthesis of 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1H-indazole-6-carboxamide:



The synthetic procedure is identical to STEP 7 of **Example 1**.

Product appearance: white solid

Yield: 50 %

TLC: R_f = 0.39 (CH₂Cl₂-MeOH = 3:1, v/v)

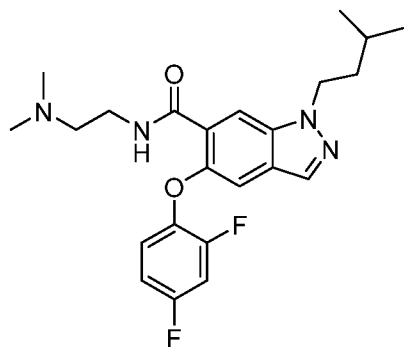
¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 8.20 (s, 1H), 7.88 (d, J = 1.1 Hz, 1H), 7.09 (s, 1H), 7.06 – 6.95 (m, 2H), 6.86 (dddd, J = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 4.23 (d, J = 7.4 Hz, 2H), 3.56 (td, J = 6.1, 4.8 Hz, 2H), 2.50 (t, J = 6.1 Hz, 2H), 2.37 (hept, J = 6.9 Hz, 1H), 2.18 (s, 6H), 0.93 (d, J = 6.7 Hz, 6H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 164.79, 160.02 (d, J = 10.3 Hz), 157.58 (d, J = 10.1 Hz), 155.00 (d, J = 12.0 Hz), 152.49 (d, J = 12.1 Hz), 149.21, 140.05 (d, J = 7.9 Hz), 136.54, 131.96, 125.05, 124.19, 121.74 (d, J = 8.9 Hz), 113.48, 111.50 (dd, J = 22.9, 3.9 Hz), 107.78, 105.56 (dd, J = 26.9, 21.8 Hz), 57.32, 56.69, 44.88, 37.65, 29.57, 20.14 ppm

HRMS (ESI⁺): m/z calculated for C₂₂H₂₆F₂N₄O₂: 417.2097; found: 417.2090.

UPLC purity: 100 %

Synthesis of 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isopentyl-1H-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with 1-bromo-3-methylbutane replacing 1-bromo-2-methylpropane.

Product appearance: white solid

TLC: $R_f = 0.35$ (CH_2Cl_2 -MeOH = 15:1, v/v)

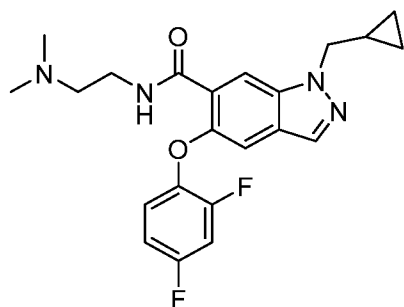
^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1H), 8.20 (s, 1H), 7.87 (d, $J = 1.0$ Hz, 1H), 7.10 (s, 1H), 7.05 – 6.94 (m, 2H), 6.86 (dddd, $J = 9.2, 7.7, 2.9, 1.7$ Hz, 1H), 4.45 (t, $J = 7.4$ Hz, 2H), 3.55 (td, $J = 6.1, 4.8$ Hz, 2H), 2.47 (t, $J = 6.1$ Hz, 2H), 2.16 (s, 6H), 1.83 (dt, $J = 8.9, 7.0$ Hz, 2H), 1.70 – 1.55 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.76, 159.98 (d, $J = 10.3$ Hz), 157.53 (d, $J = 10.2$ Hz), 154.96 (d, $J = 12.2$ Hz), 152.45 (d, $J = 12.2$ Hz), 149.17, 140.15 (dd, $J = 11.6, 3.9$ Hz), 136.04, 131.94, 125.17, 124.24, 121.62 (dd, $J = 9.7, 1.9$ Hz), 113.27, 111.48 (dd, $J = 22.9, 3.9$ Hz), 107.97, 105.55 (dd, $J = 26.8, 21.8$ Hz), 57.32, 47.78, 44.90, 38.59, 37.70, 25.81, 22.39 ppm

HRMS (ESI⁺): m/z calculated for $\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_4\text{O}_2$: 431.2253; found: 431.2247.

UPLC purity: 99 %

Synthesis of 1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1H-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclopropane replacing 1-bromo-2-methylpropane.

Product appearance: white solid

TLC: R_f = 0.20 (EtOAc-MeOH = 2:1, v/v)

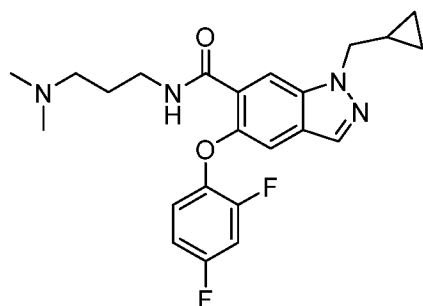
^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 8.22 (s, 1H), 7.89 (d, J = 1.0 Hz, 1H), 7.10 (s, 1H), 7.05 – 6.96 (m, 2H), 6.86 (dddd, J = 9.3, 7.7, 2.9, 1.7 Hz, 1H), 4.31 (d, J = 6.9 Hz, 2H), 3.55 (td, J = 6.1, 4.8 Hz, 2H), 2.48 (t, J = 6.1 Hz, 2H), 2.17 (s, 6H), 1.43 – 1.32 (m, 1H), 0.63 – 0.53 (m, 2H), 0.44 (dt, J = 6.1, 4.8 Hz, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.74, 159.99 (d, J = 10.1 Hz), 157.54 (d, J = 10.1 Hz), 154.96 (d, J = 12.1 Hz), 152.46 (d, J = 12.2 Hz), 149.21, 140.11 (dd, J = 11.5, 3.8 Hz), 136.15, 132.09, 125.26, 124.23, 121.66 (dd, J = 9.6, 2.0 Hz), 113.43, 111.49 (dd, J = 22.9, 3.9 Hz), 107.92, 105.56 (dd, J = 26.9, 21.8 Hz), 57.31, 53.95, 44.88, 37.67, 11.36, 4.01 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{22}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_2$: 415.1867; found: 415.1929

UPLC purity: 99 %

Synthesis of 1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-*N*-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide:



STEPS 1-5 and 7 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclopropane replacing 1-bromo-2-methylpropane. STEP 8 is identical to that of **EXAMPLE 2** with *N,N'*-dimethylpropane-1,3-diamine replacing *N,N'*-dimethylethane-1,2-diamine.

Product appearance: bright yellow solid

TLC: R_f = 0.08 (EtOAc-MeOH = 2:1, v/v)

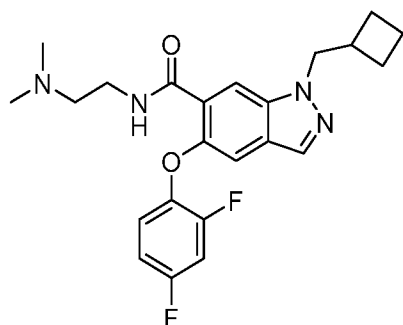
^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.18 (t, $J = 5.6$ Hz, 1H), 7.87 (d, $J = 1.0$ Hz, 1H), 7.09 (td, $J = 9.0, 5.4$ Hz, 1H), 7.03 (s, 1H), 7.03 – 6.99 (m, 1H), 6.91 (dddd, $J = 9.2, 7.7, 2.9, 1.7$ Hz, 1H), 4.31 (d, $J = 6.9$ Hz, 2H), 3.58 (q, $J = 6.7, 5.5$ Hz, 2H), 2.37 (t, $J = 6.8$ Hz, 2H), 2.14 (s, 6H), 1.77 (p, $J = 6.7$ Hz, 2H), 1.42 – 1.31 (m, 1H), 0.64 – 0.54 (m, 2H), 0.44 (dt, $J = 6.1, 4.7$ Hz, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.75, 160.37 (d, $J = 10.3$ Hz), 157.91 (d, $J = 10.2$ Hz), 155.28 (d, $J = 12.3$ Hz), 152.78 (d, $J = 12.2$ Hz), 149.70, 139.59 (dd, $J = 11.7, 4.0$ Hz), 136.03, 132.03, 125.18, 123.89, 122.69 (dd, $J = 9.7, 2.0$ Hz), 113.60, 111.76 (dd, $J = 22.9, 3.9$ Hz), 106.95, 105.77 (dd, $J = 26.9, 21.8$ Hz), 57.99, 53.93, 45.37, 39.24, 26.73, 11.36, 4.01 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{23}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_2$: 429.2024; found: 429.2086.

UPLC purity: 99 %

Synthesis of 1-(cyclobutylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclobutane replacing 1-bromo-2-methylpropane.

Product appearance: white solid

TLC: $R_f = 0.32$ (CH_2Cl_2 -MeOH = 15:1, v/v)

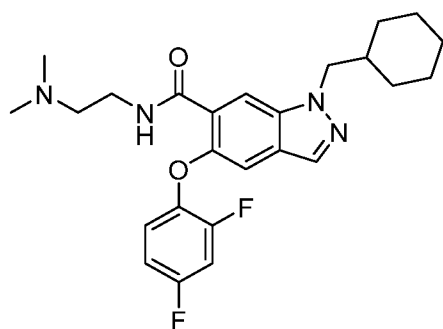
^1H NMR (400 MHz, CDCl_3) δ 8.36 (s, 1H), 8.21 (s, 1H), 7.86 (d, $J = 1.0$ Hz, 1H), 7.09 (s, 1H), 7.04 – 6.96 (m, 2H), 6.86 (dddd, $J = 9.2, 7.7, 2.9, 1.7$ Hz, 1H), 4.44 (d, $J = 7.3$ Hz, 2H), 3.55 (q, $J = 6.1, 4.8$ Hz, 2H), 2.94 (p, $J = 7.6$ Hz, 1H), 2.47 (t, $J = 6.1$ Hz, 2H), 2.16 (s, 6H), 2.08 – 1.99 (m, 2H), 1.94 – 1.80 (m, 4H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.74, 159.98 (d, $J = 10.1$ Hz), 157.54 (d, $J = 10.1$ Hz), 154.97 (d, $J = 12.2$ Hz), 152.46 (d, $J = 12.2$ Hz), 149.17, 140.12 (dd, $J = 11.6, 3.9$ Hz), 136.33, 131.96, 125.06, 124.18, 121.66 (dd, $J = 9.7, 2.0$ Hz), 113.39, 111.48 (dd, $J = 22.9, 3.9$ Hz), 107.86, 105.54 (dd, $J = 26.9, 21.8$ Hz), 57.33, 54.32, 44.90, 37.69, 35.81, 26.11, 18.22 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{23}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_2$: 429.2097; found: 429.2090.

UPLC purity: 98 %

Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclohexane replacing 1-bromo-2-methylpropane.

Product appearance: white solid

TLC: $R_f = 0.39$ (EtOAc-MeOH = 2:1, v/v)

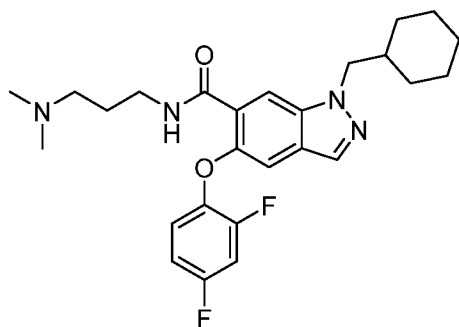
^1H NMR (400 MHz, CDCl_3) δ 8.33 (s, 1H), 8.21 (s, 1H), 7.87 (d, $J = 1.0$ Hz, 1H), 7.09 (s, 1H), 7.05 – 6.97 (m, 2H), 6.86 (dddd, $J = 9.2, 7.7, 3.0, 1.7$ Hz, 1H), 4.25 (d, $J = 7.3$ Hz, 2H), 3.56 (q, $J = 6.2, 4.8$ Hz, 2H), 2.49 (t, $J = 6.1$ Hz, 2H), 2.17 (s, 6H), 2.06 – 1.97 (m, 1H), 1.74 – 1.67 (m, 3H), 1.57 (d, $J = 12.8$ Hz, 2H), 1.23 – 1.14 (m, 3H), 1.10 – 0.98 (m, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.23, 160.44 (d, $J = 10.2$ Hz), 158.00 (d, $J = 10.2$ Hz), 155.43 (d, $J = 12.2$ Hz), 152.92 (d, $J = 12.2$ Hz), 149.62, 140.52 (dd, $J = 11.6, 3.9$ Hz), 137.07, 132.34, 125.42, 124.61, 122.14 (dd, $J = 9.6, 2.0$ Hz), 113.97, 111.94 (dd, $J = 22.8, 4.0$ Hz), 108.23, 106.00 (dd, $J = 26.9, 21.8$ Hz), 57.76, 56.03, 45.33, 39.18, 38.12, 31.28, 26.68, 26.07 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{F}_2\text{N}_4\text{O}_2$: 457.2337; found: 457.2397.

UPLC purity: 100 %

Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide:



STEPS 1-5 and 7 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclohexane replacing 1-bromo-2-methylpropane. STEP 8 is identical to that of **EXAMPLE 2** with *N,N'*-dimethylpropane-1,3-diamine replacing *N,N'*-dimethylethane-1,2-diamine.

Product appearance: white solid

TLC: R_f = 0.28 (CH₂Cl₂-MeOH = 9:1, v/v)

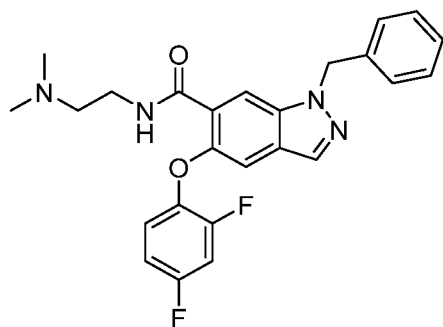
¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 8.16 (s, 1H), 7.85 (d, J = 1.0 Hz, 1H), 7.09 (td, J = 9.0, 5.4 Hz, 1H), 7.05 – 7.02 (m, 1H), 7.01 (s, 1H), 6.90 (dddd, J = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 4.25 (d, J = 7.3 Hz, 2H), 3.58 (q, J = 6.6, 5.6 Hz, 2H), 2.37 (t, J = 6.8 Hz, 2H), 2.14 (s, 6H), 2.06 – 1.96 (m, 1H), 1.78 (p, J = 6.7 Hz, 2H), 1.72 – 1.63 (m, 3H), 1.59 – 1.53 (m, 2H), 1.26 – 1.13 (m, 3H), 1.10 – 0.98 (m, 2H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 164.81, 160.43 (d, J = 11.2 Hz), 157.88 (d, J = 10.0 Hz), 155.25 (d, J = 11.2 Hz), 152.80 (d, J = 12.5 Hz), 149.67, 139.56 (d, J = 11.8 Hz), 136.51, 131.83, 124.91, 123.79, 122.73 (d, J = 9.0 Hz), 113.71, 111.77 (dd, J = 22.9, 4.0 Hz), 106.82, 105.78 (dd, J = 27.0, 21.8 Hz), 57.96, 55.58, 45.36, 39.21, 38.73, 30.84, 26.74, 26.24, 25.63 ppm

HRMS (ESI⁺): m/z calculated for C₂₆H₃₂F₂N₄O₂: 471.2571; found: 471.2560.

UPLC purity: 99 %

Synthesis of 1-benzyl-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with benzyl bromide replacing 1-bromo-2-methylpropane.

Product appearance: bright yellow solid

TLC: R_f = 0.28 (CH_2Cl_2 -MeOH = 10:1, v/v)

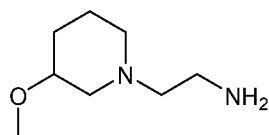
^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 8.17 (s, 1H), 7.93 (d, J = 1.0 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.25 – 7.22 (m, 2H), 7.09 (s, 1H), 7.05 – 6.93 (m, 2H), 6.86 (dddd, J = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 5.63 (s, 2H), 3.53 (td, J = 6.1, 4.8 Hz, 2H), 2.47 (q, J = 6.0 Hz, 2H), 2.16 (s, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 166.81, 164.63, 160.05 (d, J = 10.2 Hz), 157.60 (d, J = 10.2 Hz), 155.00 (d, J = 12.2 Hz), 152.49 (d, J = 12.2 Hz), 149.48, 139.93 (dd, J = 11.6, 3.8 Hz), 136.31 (d, J = 16.0 Hz), 132.69, 128.79, 127.94, 127.34, 125.53, 124.54, 121.82 (dd, J = 9.7, 1.9 Hz), 113.39, 111.52 (dd, J = 22.9, 3.9 Hz), 107.80, 105.56 (dd, J = 26.9, 21.8 Hz), 57.25, 53.22, 44.82, 37.58 ppm

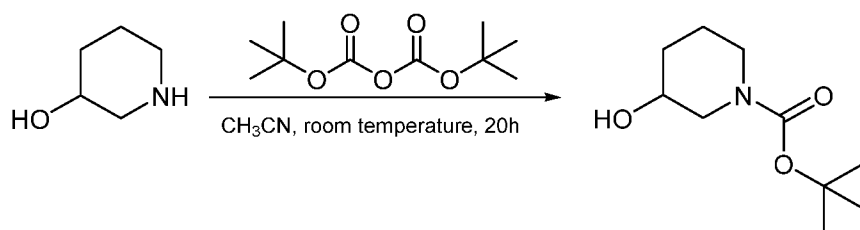
HRMS (ESI⁺): m/z calculated for $\text{C}_{25}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_2$: 451.1867; found: 451.1935.

UPLC purity: 98 %

EXAMPLE 3: Synthesis of 2-(3-methoxypiperidin-1-yl)ethan-1-amine



STEP 1: Synthesis of *tert*-butyl 3-hydroxypiperidine-1-carboxylate:



To a 100 mL round-bottom flask equipped with a stirring bar was added piperidin-3-ol (1 g, 9.886 mmol, 1.0 equiv) and dissolved in 60 mL of CH_3CN . Di-*tert*-butyl dicarbonate (2.156 g, 9.886 mmol, 1.0 equiv) was added in two portions and the reaction mixture was left to stir overnight at room temperature. After 20h CH_3CN was evaporated and the crude filtered through a 30-mL pad of silica using CH_2Cl_2 -MeOH (10:1, v/v) as an eluent which was then evaporated to yield 1262 mg of *tert*-butyl 3-hydroxypiperidine-1-carboxylate.

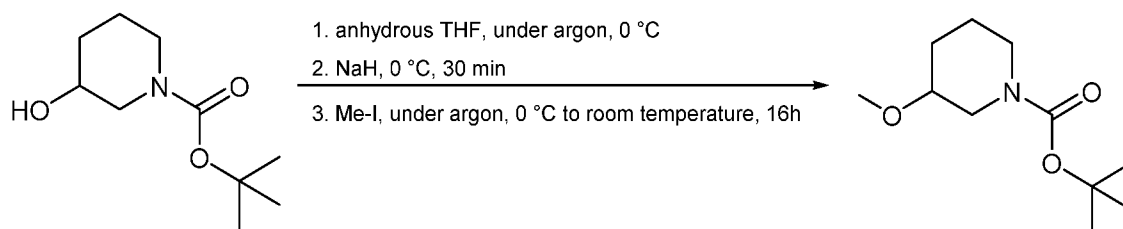
Yield: 63 %

Product appearance: viscous colorless oil

TLC: $R_f = 0.67$ (EtOAc-MeOH = 2:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 3.78 – 3.68 (m, 2H), 3.52 (s, 1H), 3.10 (dd, $J = 17.6, 9.2$ Hz, 2H), 1.93 – 1.83 (m, 1H), 1.81 – 1.70 (m, 1H), 1.62 – 1.61 (m, 1H), 1.57 – 1.48 (m, 2H), 1.46 (s, 9H) ppm

STEP 2: Synthesis of *tert*-butyl 3-methoxypiperidine-1-carboxylate:



To an oven-dried 50-mL round-bottom flask with a stirring bar was added *tert*-butyl 3-hydroxypiperidine-1-carboxylate (1255 mg, 6.240 mmol, 1.0 equiv) dissolved in 30 mL of anhydrous THF under argon and cooled to 0 °C on an ice bath. Subsequently, NaH (60 % dispersion in mineral oil, 90 mg, 6.240 mmol, 1.0 equiv) was added and the reaction mixture left to stir at 0 °C for 30 minutes. After that methyl iodide (457 μL , 7.341 mmol, 1.2 equiv) was added dropwise. The ice bath was removed and the reaction left to stir overnight. After 16h THF was evaporated the crude dissolved in 30 mL of EtOAc, washed with 20 mL of brine,

dried with Na₂SO₄ and the organic phases evaporated to produce 1043 mg of *tert*-butyl 3-methoxypiperidine-1-carboxylate.

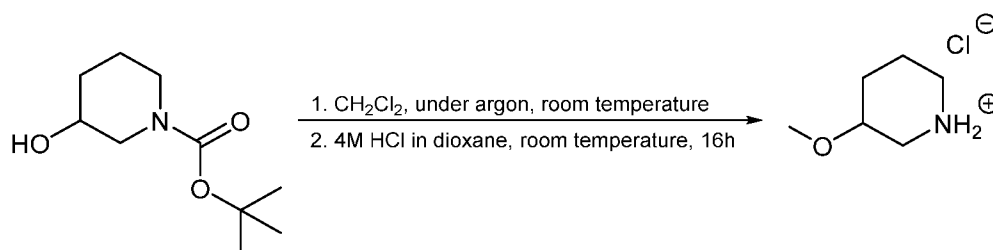
Yield: 78 %

Product appearance: viscous brown oil

TLC: R_f = 0.65 (CH₂Cl₂-MeOH = 30:1, v/v)

¹H NMR (400 MHz, CDCl₃) δ 3.98 – 3.68 (m, 1H), 3.64 – 3.56 (m, 1H), 3.38 (s, 3H), 3.20 (dq, J = 7.7, 3.8 Hz, 1H), 3.14 – 2.98 (m, 2H), 1.98 – 1.88 (m, 1H), 1.79 – 1.70 (m, 1H), 1.46 (s, 9H), 1.44 – 1.37 (m, 2H) ppm

STEP 3: Synthesis of 3-methoxypiperidin-1-ium chloride:



To a 50-mL round-bottom flask with a stirring bar was added *tert*-butyl 3-methoxypiperidine-1-carboxylate (1040 mg, 5.167 mmol, 1.0 equiv) and dissolved in 20 mL of CH₂Cl₂. The flask was flushed with argon and 4M HCl in dioxane (3 mL, 12.918 mmol, 2.5 equiv) was added dropwise. The reaction mixture was left to stir at room temperature overnight. After 16h HCl in dioxane and CH₂Cl₂ were evaporated on a water pump and the crude was further dried on an oli pump for 1h to yield 780 mg of 3-methoxypiperidin-1-ium chloride which was used in the next step without further purification.

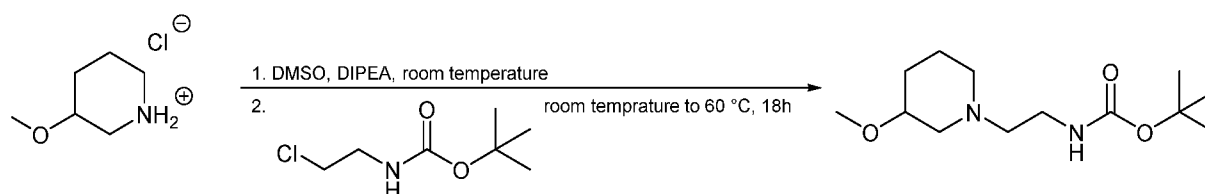
Yield: 100 %

Product appearance: viscous yellow oil

TLC: R_f = 0.18 (CH₂Cl₂-MeOH = 10:1, v/v)

¹H NMR (400 MHz, CDCl₃) δ 9.79 (s, 1H), 9.25 (s, 1H), 3.66 (dq, J = 7.2, 3.6 Hz, 1H), 3.41 (s, 3H), 3.38 – 3.27 (m, 1H), 3.25 – 3.15 (m, 1H), 3.10 – 2.92 (m, 2H), 2.11 – 2.00 (m, 1H), 1.98 – 1.90 (m, 1H), 1.89 – 1.80 (m, 1H), 1.66 (dtd, J = 12.2, 8.0, 3.7 Hz, 1H) ppm

STEP 4: Synthesis of *tert*-butyl (2-(3-methoxypiperidin-1-yl)ethyl)carbamate:



To a 50-mL round-bottom flask equipped with a stirring bar was added 3-methoxypiperidin-1-ium chloride (500 mg, 3.297 mmol, 1.0 equiv) which was dissolved in 12 mL of DMSO. DIPEA (1242 μ L, 7.130 mmol, 2.2 equiv) was added dropwise followed by the addition of *tert*-butyl (2-chloroethyl)carbamate (592 mg, 3.297 mmol, 1.0 equiv) in three portions. The reaction mixture was warmed to 60 °C and left to stir overnight. After 18h DMSO and DIPEA were evaporated on an oil pump and the crude purified by flash column chromatography using CH_2Cl_2 -MeOH (10:1, v/v) as an eluent to produce 223 mg of *tert*-butyl (2-(3-methoxypiperidin-1-yl)ethyl)carbamate.

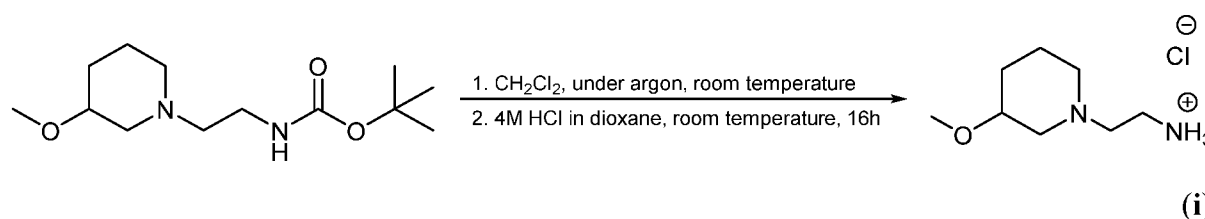
Yield: 26 %

Product appearance: viscous brown oil

TLC: R_f = 0.25 (CH_2Cl_2 -MeOH = 10:1, v/v)

^1H NMR (400 MHz, DMSO) δ 6.62 (t, J = 5.8 Hz, 1H), 3.23 (s, 3H), 3.20 – 3.11 (m, 1H), 3.02 (q, J = 6.6 Hz, 2H), 2.91 (dd, J = 11.0, 3.7 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.35 – 2.27 (m, 2H), 1.94 – 1.84 (m, 2H), 1.79 (t, J = 9.7 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.43 – 1.41 (m, 1H), 1.37 (s, 9H), 1.05 (tdd, J = 12.0, 9.7, 4.2 Hz, 1H) ppm

STEP 5: Synthesis of compound **i** – 2-(3-methoxypiperidin-1-yl)ethan-1-aminium chloride:



The synthetic procedure is identical to that in STEP 4. After evaporation of HCl in dioxane and CH_2Cl_2 the product was dried on an oil pump for 1h and used in **EXAMPLE 4**, STEP 8 without further purification.

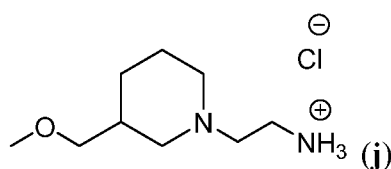
Yield: 92 %

Product appearance: dark brown viscous oil

TLC: $R_f = 0.05$ (CH_2Cl_2 -MeOH = 10:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, $J = 24.3$ Hz, 3H), 4.33 – 4.25 (m, 1H), 3.71 – 3.54 (m, 3H), 3.48 – 3.42 (m, 1H), 3.39 – 3.36 (m, 2H), 3.17 (s, 3H), 3.04 – 2.87 (m, 1H), 2.75 (d, $J = 9.6$ Hz, 1H), 2.10 (d, $J = 12.3$ Hz, 1H), 1.93 – 1.76 (m, 2H), 1.70 – 1.48 (m, 1H) ppm

Synthesis of compound **j** – 2-(3-(methoxymethyl)piperidin-1-yl)ethan-1-aminium chloride:



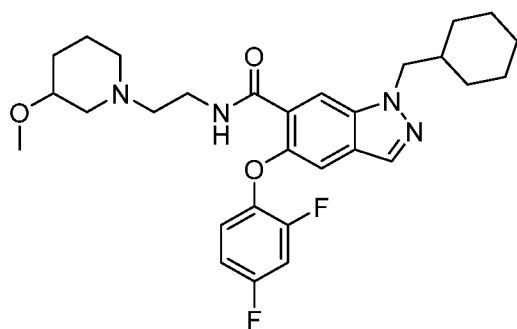
The synthetic procedure is identical to that in **EXAMPLE 3**.

Product appearance: dark brown viscous oil

TLC: $R_f = 0.06$ (CH_2Cl_2 -MeOH = 10:1, v/v)

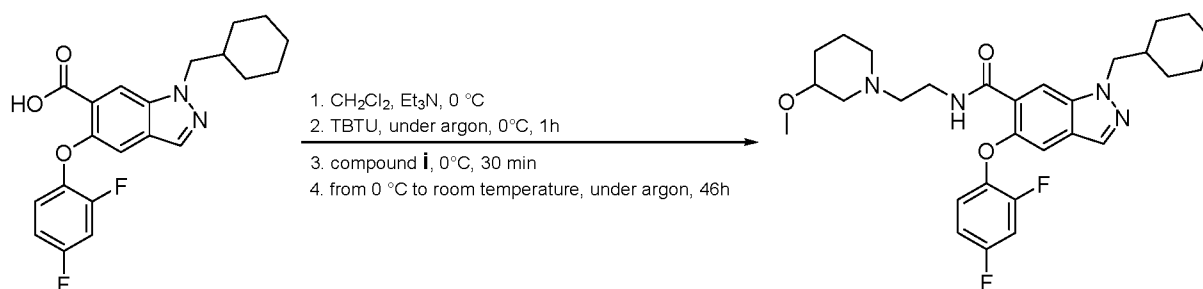
^1H NMR (400 MHz, DMSO) δ 8.38 (s, 3H), 4.33 – 4.25 (m, 1H), 3.58 – 3.39 (m, 5H), 3.33 – 3.30 (m, 3H), 3.17 (s, 3H), 2.90 – 2.82 (m, 1H), 2.75 (q, $J = 11.4$ Hz, 1H), 2.30 – 2.20 (m, 1H), 1.90 – 1.80 (m, 2H), 1.71 (d, $J = 13.4$ Hz, 1H) ppm

EXAMPLE 4: Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide



STEPS 1-5 and 7 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with 2-(3-methoxypiperidin-1-yl)ethan-1-aminium chloride replacing 1-bromo-2-methylpropane.

STEP 8: Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide:



To a 25-mL round-bottom flask equipped with a stirring bar was added compound **f** (100 mg, 0.259 mmol, 1.0 equiv). 15 mL of CH₂Cl₂ was added under argon and a suspension was formed which was cooled to 0 °C on an ice bath. Subsequently, Et₃N (72 µL, 0.517 mmol, 2.0 equiv) was added dropwise resulting in dissolution of compound **f**. After 10 minutes TBTU (83 mg, 0.259 mmol, 1.0 equiv) was added in two portions and the reaction mixture was left to stir on an ice bath under argon for 1h before compound **j** (60 mg, 0.308 mmol, 1.2 equiv) was added. Finally, the reaction mixture was left to warm to room temperature and stir for two days. After 46h the reaction mixture was washed with saturated NaHCO₃ solution (2 × 10 mL) and brine (2 × 10 mL), dried with Na₂SO₄ and CH₂Cl₂ evaporated under reduced pressure. The crude obtained was then purified by reverse-phase preparative chromatography (Biotage® Sfär, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase to obtain 57 mg of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide.

Yield: 42 %

Product appearance: light brown solid

TLC: *R_f* = 0.60 (CH₂Cl₂-MeOH = 10:1, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.38 (s, 1H), 8.32 (s, 1H), 7.85 (d, *J* = 1.1 Hz, 1H), 7.14 (td, *J* = 9.0, 5.4 Hz, 1H), 7.03 (ddd, *J* = 10.3, 8.2, 3.0 Hz, 1H), 6.98 (s, 1H), 6.93 (dddd, *J* = 9.2, 7.7, 3.0, 1.6 Hz, 1H), 4.25 (d, *J* = 7.4 Hz, 2H), 3.62 (p, *J* = 5.5 Hz, 2H), 3.25 (d, *J* = 1.4 Hz, 3H), 2.96 – 2.88 (m, 2H), 2.67 (d, *J* = 11.2 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.06 – 1.95 (m, 3H), 1.93 – 1.82 (m, 2H), 1.73 – 1.54 (m, 6H), 1.27 – 0.98 (m, 6H) ppm

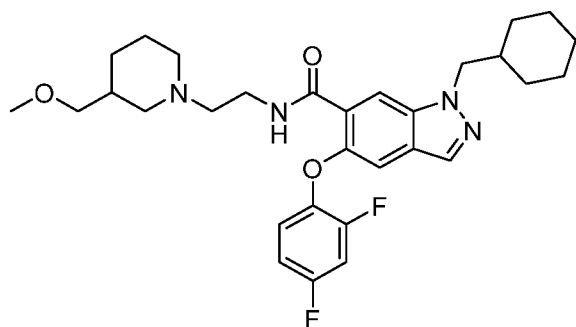
¹³C NMR (101 MHz, CDCl₃) δ 164.61, 160.51 (d, *J* = 10.0 Hz), 158.05 (d, *J* = 10.2 Hz), 155.53 (d, *J* = 12.1 Hz), 153.02 (d, *J* = 12.2 Hz), 150.19, 139.40 (dd, *J* = 11.9, 3.9 Hz), 136.45, 131.80, 124.93, 123.52 – 123.09 (m), 113.71, 111.82 (dd, *J* = 22.9, 3.9 Hz), 106.37, 105.76 (dd, *J* =

26.8, 21.7 Hz), 76.21, 57.69, 56.35, 55.96, 55.58, 53.08, 38.75, 37.02, 30.83, 29.96, 26.23, 25.62, 23.15 ppm

HRMS (ESI⁺): m/z calculated for C₂₉H₃₆F₂N₄O₃: 527.2755; found: 527.2816.

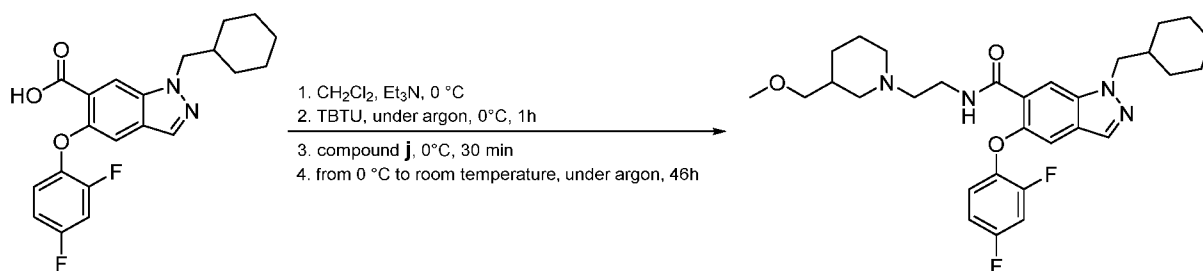
UPLC purity: 99 %

EXAMPLE 5: Synthesis of (±)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide



STEPS 1-7 are identical to those described in **EXAMPLE 3**.

STEP 8: Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide:



To a 25-mL round-bottom flask equipped with a stirring bar was added compound **f** (100 mg, 0.259 mmol, 1.0 equiv). 15 mL of CH₂Cl₂ was added under argon and a suspension was formed which was cooled to 0 °C on an ice bath. Subsequently, Et₃N (72 μL, 0.517 mmol, 2.0 equiv) was added dropwise resulting in dissolution of compound **f**. After 10 minutes TBTU (83 mg, 0.259 mmol, 1.0 equiv) was added in two portions and the reaction mixture was left to stir on an ice bath under argon for 1h before compound **k** (89 mg, 0.426 mmol, 1.6 equiv) was added. Finally, the reaction mixture was left to warm to room temperature and stir for two days. After 46h the reaction mixture was washed with saturated NaHCO₃ solution (2 × 10 mL) and brine

(2 × 10 mL), dried with Na₂SO₄ and CH₂Cl₂ evaporated under reduced pressure. The crude obtained was then purified by reverse-phase preparative chromatography (Biotage® Sfär, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase to obtain 41 mg of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide.

Yield: 29 %

Product appearance: viscous orange oil

TLC: *R_f* = 0.56 (CH₂Cl₂-MeOH = 10:1, v/v)

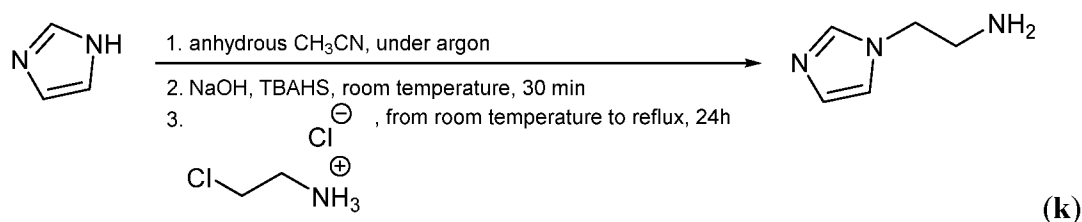
¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 8.31 (t, *J* = 4.7 Hz, 1H), 7.82 (d, *J* = 1.0 Hz, 1H), 7.11 (td, *J* = 9.0, 5.4 Hz, 1H), 7.00 (dt, *J* = 8.4, 2.9, 2.6 Hz, 1H), 6.97 (s, 1H), 6.89 (dddd, *J* = 9.1, 7.6, 3.0, 1.7 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 2H), 3.58 (dt, *J* = 7.4, 5.7 Hz, 2H), 3.24 (s, 3H), 3.11 (qd, *J* = 9.4, 6.2 Hz, 2H), 2.83 (d, *J* = 10.0 Hz, 1H), 2.73 (d, *J* = 11.1 Hz, 1H), 2.50 (t, *J* = 6.0 Hz, 2H), 2.03 – 1.95 (m, 1H), 1.89 (td, *J* = 11.3, 2.6 Hz, 1H), 1.75 – 1.61 (m, 4H), 1.53 (dd, *J* = 14.8, 10.8 Hz, 2H), 1.24 – 1.12 (m, 6H), 1.07 – 0.97 (m, 2H), 0.92 – 0.81 (m, 2H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 162.71, 158.59 (d, *J* = 10.2 Hz), 156.13 (d, *J* = 10.2 Hz), 153.63 (d, *J* = 12.3 Hz), 151.12 (d, *J* = 12.3 Hz), 148.30, 137.52 (dd, *J* = 11.8, 3.9 Hz), 134.54, 129.90, 123.02, 121.67, 121.32 (dd, *J* = 9.7, 1.9 Hz), 111.73, 109.83 (dd, *J* = 22.9, 3.9 Hz), 104.50, 103.84 (dd, *J* = 26.8, 21.7 Hz), 74.24, 56.86, 55.24, 54.87, 53.66, 52.14, 36.85, 35.12, 34.56, 28.93, 25.55, 24.34, 23.73, 22.89 ppm

HRMS (ESI⁺): *m/z* calculated for C₃₀H₃₈F₂N₄O₃: 541.2912; found: 541.2971.

UPLC purity: 98 %

EXAMPLE 6: Synthesis of compound **k** – 2-(1*H*-imidazol-1-yl)ethan-1-amine



Imidazole (1 g, 14.689 mmol, 1.0 equiv) was added to an oven-dried 100-mL round-bottom flask with a stirring bar and dissolved in 30 mL of anhydrous CH₃CN. NaOH (2.9 g, 72.5

mmol, 5 equiv was added in three portions followed by TBAHS (250 mg, 0.736 mmol, 0.05 equiv). The reaction mixture was left to stir at room temperature for 30 minutes before the addition of 2-chloroethylammonium chloride (2044 mg, 17.622 mmol, 1.2 equiv). The flask was equipped with a water condenser and heated to reflux overnight. After 24h CH₃CN was evaporated and the crude material purified by flash column chromatography using EtOAc-MeOH (2:1, v/v) as an eluent to produce 995 mg of 2-(1*H*-imidazol-1-yl)ethan-1-amine.

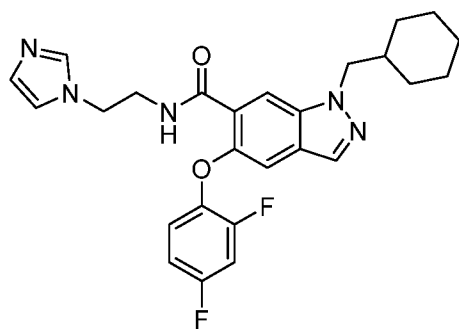
Yield: 61 %

Product appearance: white powder

TLC: R_f = 0.19 (EtOAc-MeOH = 2:1, v/v)

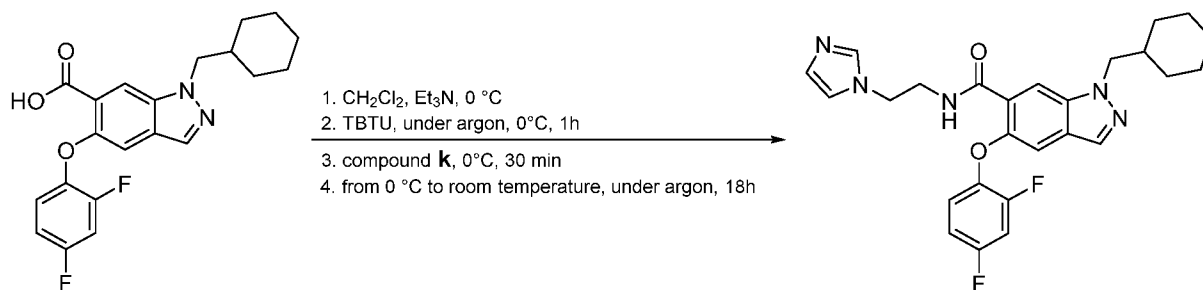
¹H NMR (400 MHz, DMSO) δ 7.59 (s, 1H), 7.15 (t, J = 1.2 Hz, 1H), 6.87 (s, 1H), 3.90 (t, J = 6.3 Hz, 2H), 2.81 (t, J = 6.3 Hz, 2H), 1.65 (s, 2H) ppm

EXAMPLE 7: Synthesis of *N*-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide



STEPS 1-5 and 7 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromomethyl)cyclohexane replacing 1-bromo-2-methylpropane.

STEP 8: Synthesis of *N*-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide:



To a 25-mL round-bottom flask equipped with a stirring bar was added compound **f** (300 mg, 0.777 mmol, 1.0 equiv). 15 mL of CH₂Cl₂ was added under argon and a suspension was formed which was cooled to 0 °C on an ice bath. Subsequently, Et₃N (216 µL, 1.551 mmol, 2.0 equiv) was added dropwise resulting in dissolution of compound **f**. After 10 minutes TBTU (249 mg, 0.777 mmol, 1.0 equiv) was added in two portions and the reaction mixture was left to stir on an ice bath under argon for 1h before compound **I** (172 mg, 1.551 mmol, 2.0 equiv) was added. Finally, the reaction mixture was left to warm to room temperature and stir overnight. After 18 h the reaction mixture was washed with saturated NaHCO₃ solution (2 × 10 mL) and brine (2 × 10 mL), dried with Na₂SO₄ and CH₂Cl₂ evaporated under reduced pressure. The crude obtained was then purified by reverse-phase preparative chromatography (Biotage® Sfär, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase to obtain 130 mg of (±)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide.

Yield: 35 %

Product appearance: viscous brown oil

TLC: *R_f* = 0.21 (CH₂Cl₂-MeOH = 15:1, v/v)

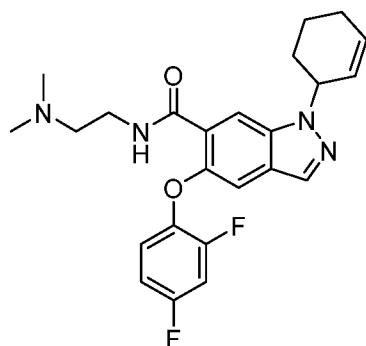
¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 7.90 (t, *J* = 5.9 Hz, 1H), 7.82 (d, *J* = 1.0 Hz, 1H), 7.44 (s, 1H), 7.06 (td, *J* = 9.0, 5.4 Hz, 1H), 6.98 (ddd, *J* = 10.7, 8.2, 2.9 Hz, 1H), 6.93 (s, 1H), 6.94 – 6.88 (m, 3H), 4.22 (d, *J* = 7.2 Hz, 2H), 4.20 (d, *J* = 6.0 Hz, 2H), 3.81 (q, *J* = 5.9 Hz, 2H), 2.00 – 1.93 (m, 1H), 1.71 – 1.59 (m, 3H), 1.54 (d, *J* = 12.6 Hz, 2H), 1.19 – 1.10 (m, 3H), 1.06 – 0.94 (m, 2H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 165.41, 160.75 (d, *J* = 10.2 Hz), 158.29 (d, *J* = 10.3 Hz), 155.40 (d, *J* = 12.3 Hz), 152.90 (d, *J* = 12.3 Hz), 150.00, 138.48 (dd, *J* = 11.8, 4.0 Hz), 137.20, 136.30, 131.91, 129.66, 125.21, 123.38 (dd, *J* = 9.6, 1.8 Hz), 122.14, 118.83, 113.77, 111.99 (dd, *J* = 23.0, 3.9 Hz), 106.18, 105.83 (dd, *J* = 26.8, 21.9 Hz), 55.59, 46.11, 41.27, 38.75, 30.82, 26.21, 25.61 ppm

HRMS (ESI⁺): *m/z* calculated for C₂₆H₂₇F₂N₅O₂: 480.2133; found: 480.2203.

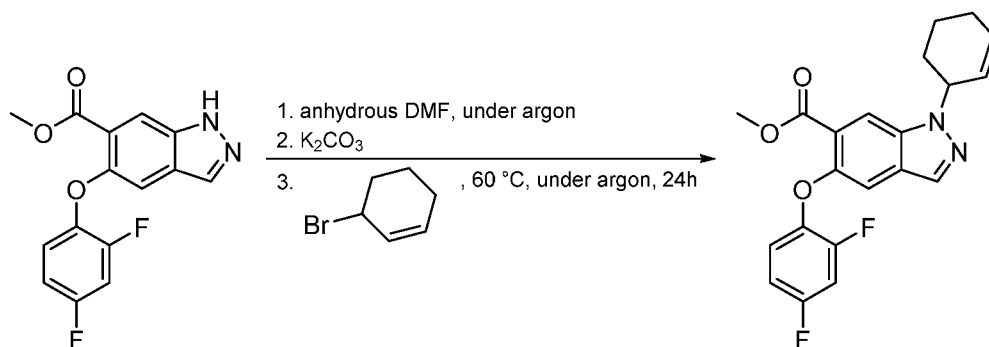
UPLC purity: 99 %

EXAMPLE 8: Synthesis of 1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide



STEPS 1-5 are identical to those described in **EXAMPLE 1**

STEP 6: Synthesis of methyl 1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylate:



To a 50-mL round-bottom flask with a stirring bar was added compound **e** (400 mg, 1.315 mmol, 1.0 equiv). Anhydrous DMF (20 mL) was added under argon and the contents stirred until compound **e** was completely dissolved. K₂CO₃ (364 mg, 2.633 mmol, 2.0 equiv) was added in two portions followed by 5-minute stirring at room temperature and dropwise addition of 3-bromocyclohex-1-ene (209 μ L 1.810 mmol, 1.4 equiv). The reaction mixture was heated to 60 °C, left to stir under a reflux condenser and monitored by TLC. After 24h 15 mL of H₂O were added, the contents of the flask transferred to a separatory funnel and extracted with EtOAc (3 $\times$ 20 mL). Combined organic phases were washed with brine (10 mL), dried with Na₂SO₄ and evaporated under reduced pressure. The crude was purified by flash column chromatography using EtOAc-hexane (1:1, v/v) to obtain 114 mg of 1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylate.

Yield: 23 %

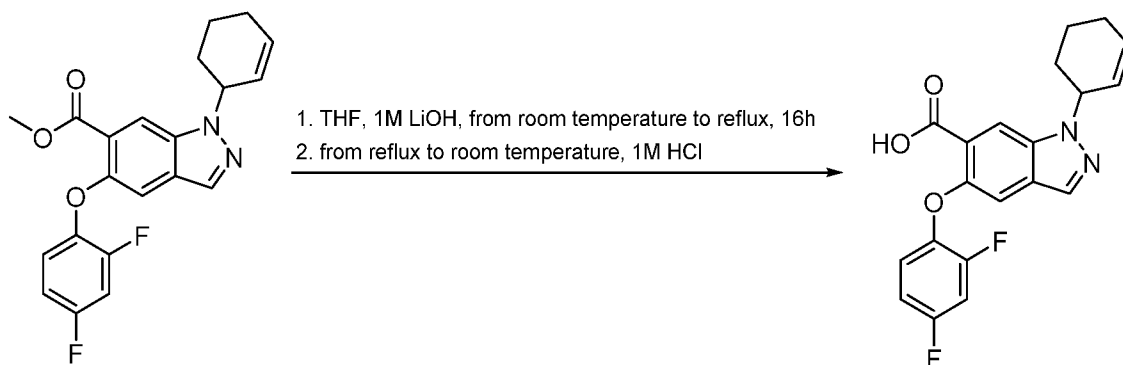
Product appearance: light yellow oil

TLC: R_f = 0.63 (EtOAc-hexane = 1:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.13 (t, J = 0.8 Hz, 1H), 7.95 (d, J = 1.1 Hz, 1H), 7.27 (s, 1H), 6.96 (ddd, J = 10.9, 8.4, 2.9 Hz, 1H), 6.84 (td, J = 9.0, 5.5 Hz, 1H), 6.77 (dddd, J = 9.1, 7.7, 2.9, 1.5 Hz, 1H), 6.15 (dq, J = 9.9, 3.3 Hz, 1H), 5.86 (dd, J = 10.1, 2.4 Hz, 1H), 5.31 (ddt, J = 8.5, 6.1, 2.9 Hz, 1H), 3.87 (s, 3H), 2.30 (dt, J = 17.8, 5.8, 2.8 Hz, 1H), 2.23 – 2.13 (m, 2H), 2.13 – 2.04 (m, 1H), 1.97 (dt, J = 16.1, 6.2 Hz, 1H), 1.80 (ddtt, J = 17.0, 8.8, 5.6, 3.1 Hz, 1H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3$: 385.1; found: 385.8.

STEP 7: Synthesis of 1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylic acid:



The synthetic procedure is identical to STEP 7 of **Example 2**.

Product appearance: light yellow solid

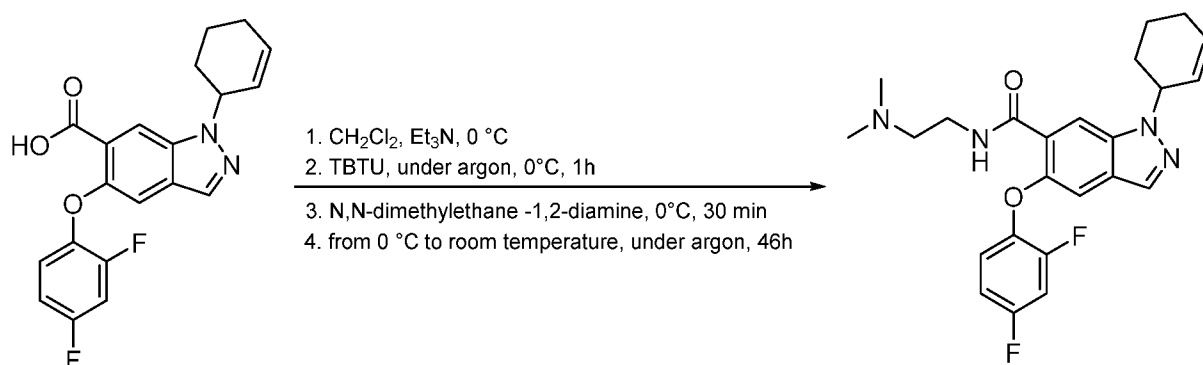
Yield: 65 %

TLC: R_f = 0.36 (CH_2Cl_2 -MeOH = 10:1, v/v)

^1H NMR (400 MHz, DMSO) δ 13.10 (s, 1H), 8.25 (s, 1H), 8.07 (d, J = 0.9 Hz, 1H), 7.45 (ddd, J = 11.4, 8.8, 3.0 Hz, 1H), 7.41 (s, 1H), 6.99 (dddd, J = 9.4, 8.0, 3.0, 1.4 Hz, 1H), 6.91 (td, J = 9.2, 5.5 Hz, 1H), 6.02 (ddd, J = 9.8, 5.0, 2.7 Hz, 1H), 5.76 (dd, J = 10.0, 1.7 Hz, 1H), 5.52 (ddt, J = 8.4, 5.6, 2.7 Hz, 1H), 2.23 – 2.02 (m, 3H), 1.99 – 1.82 (m, 2H), 1.83 – 1.67 (m, 1H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_{20}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_3$: 371.1; found: 371.9.

STEP 8: Synthesis of 1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



The synthetic procedure is identical to STEP 7 of **Example 1**.

Product appearance: light yellow solid

Yield: 70 %

TLC: R_f = 0.30 (EtOAc-MeOH = 2:1, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 8.19 (t, J = 4.8 Hz, 1H), 7.90 (d, J = 1.0 Hz, 1H), 7.11 (s, 1H), 7.04 – 6.95 (m, 2H), 6.86 (dddd, J = 9.2, 7.7, 2.9, 1.7 Hz, 1H), 6.13 (ddt, J = 9.9, 5.0, 2.8 Hz, 1H), 5.85 (dd, J = 10.3, 2.3 Hz, 1H), 5.34 (ddt, J = 8.5, 5.6, 2.8 Hz, 1H), 3.55 (td, J = 6.1, 4.8 Hz, 2H), 2.48 (t, J = 6.1 Hz, 2H), 2.35 – 2.23 (m, 1H), 2.16 (s, 6H), 2.15 – 2.12 (m, 2H), 2.09 – 2.05 (m, 1H), 1.98 – 1.89 (m, 1H), 1.84 – 1.72 (m, 1H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 164.77, 159.96 (d, J = 10.0 Hz), 157.52 (d, J = 10.2 Hz), 154.93 (d, J = 12.2 Hz), 152.43 (d, J = 12.2 Hz), 149.16, 140.17 (dd, J = 11.6, 3.9 Hz), 135.63, 132.04 (d, J = 21.0 Hz), 126.18, 125.51, 124.08, 121.58 (dd, J = 9.6, 2.0 Hz), 113.77, 111.47 (dd, J = 22.9, 3.9 Hz), 108.01, 105.54 (dd, J = 26.9, 21.8 Hz), 57.32, 55.78, 44.90, 37.68, 29.83, 24.62, 20.61 ppm

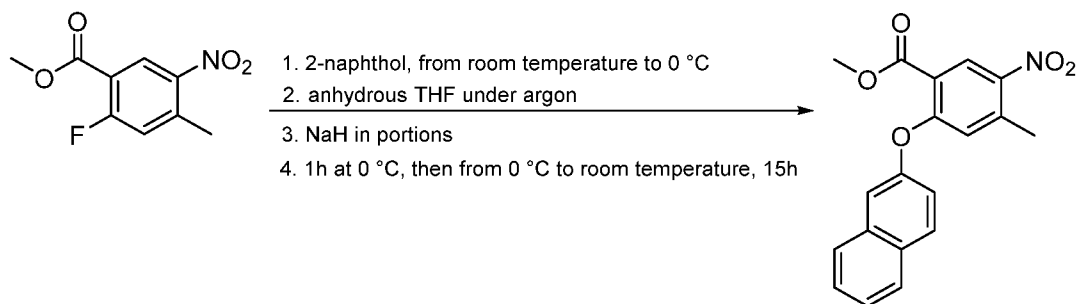
HRMS (ESI⁺): m/z calculated for C₂₄H₂₆F₂N₄O₂: 441.2097; found: 441.2090.

UPLC purity: 100 %

EXAMPLE 9: Synthesis of *N*-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-2-yloxy)-1*H*-indazole-6-carboxamide

STEPS 1-2 are identical to those in **EXAMPLE 1**.

STEP 3: Synthesis of methyl 4-methyl-2-(naphthalen-2-yloxy)-5-nitrobenzoate:



To a 100 mL round-bottom flask with a stirring bar compound **b** (1 g, 4.691 mmol, 1.0 equiv) and 2-naphthol (744 mg, 5.160 mmol, 1.1 equiv) were added and cooled to 0 °C on an ice bath. The flask was flushed with argon for 10 minutes before 30 mL of anhydrous THF were added. When the compounds were completely dissolved, NaH (60% dispersion in mineral oil, 206 mg, 5.160 mmol, 1.1 equiv) was added in portions and the reaction mixture was left to stir at 0 °C for 1h. After that the ice bath was removed and the reaction mixture left to stir overnight under argon atmosphere. After 15h 20 mL of saturated NH₄Cl solution were added dropwise before transferring the contents of the round-bottom flask to a separatory funnel where the product was extracted with EtOAc (3 × 20 mL). Combined organic phases were washed with 30 mL of brine, dried with Na₂SO₄ and evaporated on a rotary evaporator. The crude was purified by recrystallization using EtOAc-*n*-hexane (1:10, v/v) as a solvent system to yield 1080 mg of methyl 4-methyl-2-(naphthalen-2-yloxy)-5-nitrobenzoate.

Product appearance: light brown solid

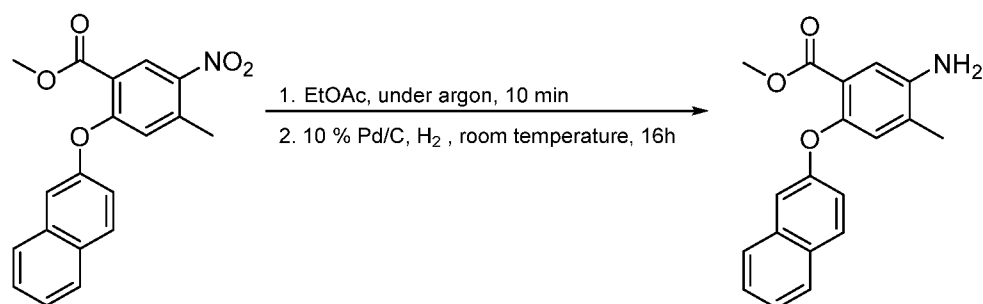
Yield: 69 %

TLC: R_f = 0.77 (EtOAc-hexane = 1:3, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 7.92 (d, J = 8.9 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.80 – 7.73 (m, 1H), 7.55 – 7.47 (m, 2H), 7.44 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.9, 2.4 Hz, 1H), 6.78 (s, 1H), 3.91 (s, 3H), 2.58 – 2.51 (m, 3H) ppm

LC-MS (ESI⁺) (m/z): calculated for C₁₉H₁₅NO₅: 337.1, found: 337.9.

STEP 4: Synthesis of methyl 5-amino-4-methyl-2-(naphthalen-2-yloxy)benzoate:



The synthetic procedure is the same as in **EXAMPLE 1**, STEP 4.

Product appearance: viscous brown oil

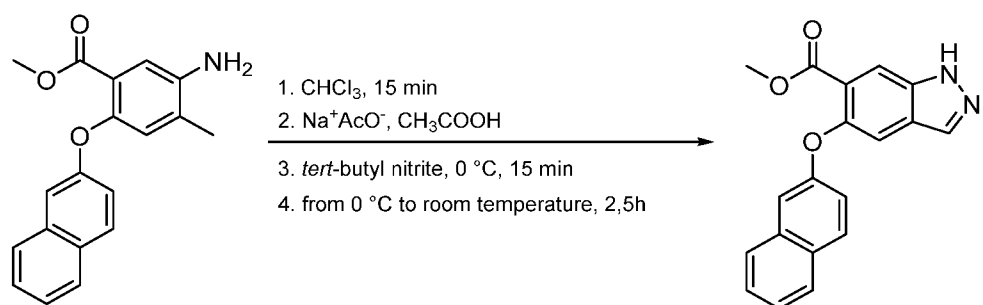
Yield: 99 %

TLC: R_f = 0.37 (EtOAc-hexane = 1:2, v/v)

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.78 (m, 1H), 7.78 – 7.76 (m, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.40 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.31 (s, 1H), 7.26 (dd, J = 8.9, 2.6 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.88 (s, 3H), 3.69 (s, 3H), 2.19 (d, J = 0.7 Hz, 1H) ppm
Signal for -NH₂ is not visible.

LC-MS (ESI⁺) (m/z): calculated for C₁₉H₁₇NO₃: 307.1, found: 308.9.

STEP 5: Synthesis of methyl 5-(naphthalen-2-yloxy)-1H-indazole-6-carboxylate:



The synthetic procedure is the same as in **EXAMPLE 1**, STEP 5.

Product appearance: viscous brown oil

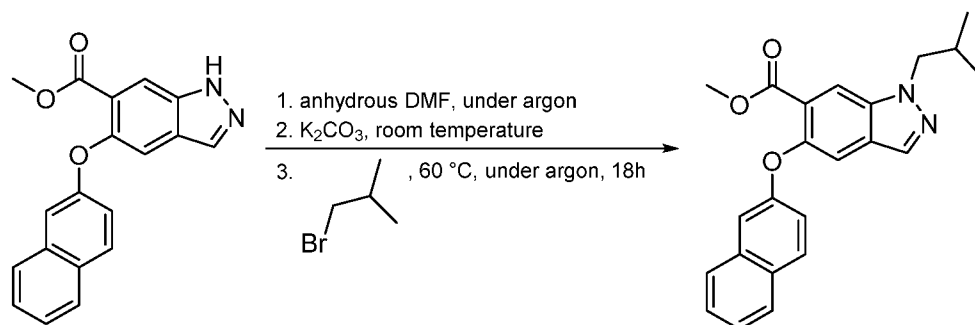
Yield: 50 %

TLC: R_f = 0.37 (EtOAc-hexane = 1:2, v/v)

¹H NMR (400 MHz, CDCl₃) δ 10.53 (s, 1H), 8.19 (s, 1H), 8.08 (d, J = 1.1 Hz, 1H), 7.89 – 7.77 (m, 2H), 7.62 (dd, J = 8.0, 1.4 Hz, 1H), 7.49 (d, J = 0.6 Hz, 1H), 7.39 (dddd, J = 17.4, 8.2, 6.8, 1.4 Hz, 2H), 7.30 (dd, J = 8.9, 2.5 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 3.78 (s, 3H) ppm

LC-MS (ESI⁺) (m/z): calculated for C₁₉H₁₄N₂O₃: 318.10, found: 319.0.

STEP 6: Synthesis of methyl 1-isobutyl-5-(naphthalen-2-yloxy)-1H-indazole-6-carboxylate:



The synthetic procedure is identical to that in **EXAMPLE 2**, STEP 6.

Product appearance: brown viscous oil

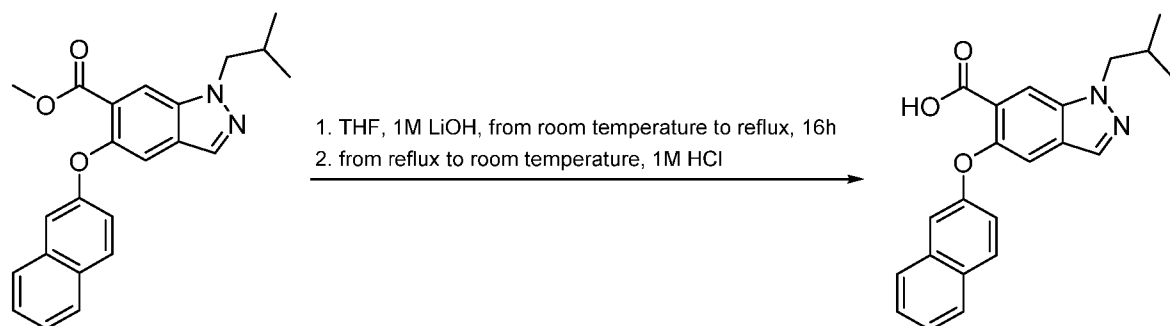
Yield: 22 %

TLC: *R_f* = 0.60 (EtOAc-hexane = 1:2, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.97 (d, *J* = 1.0 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.64 – 7.59 (m, 1H), 7.45 (s, 1H), 7.39 (dddd, *J* = 18.0, 8.2, 6.9, 1.4 Hz, 2H), 7.30 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 4.25 (d, *J* = 7.3 Hz, 2H), 3.78 (s, 3H), 2.40 (hept, *J* = 6.9 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 6H) ppm

LC-MS (ESI⁺) (m/z): calculated for C₂₃H₂₂N₂O₃: 374.16, found: 375.0.

STEP 7: Synthesis of 1-isobutyl-5-(naphthalen-2-yloxy)-1H-indazole-6-carboxylic acid:



The synthetic procedure is identical to that in **EXAMPLE 2**, STEP 7.

Product appearance: yellow viscous oil

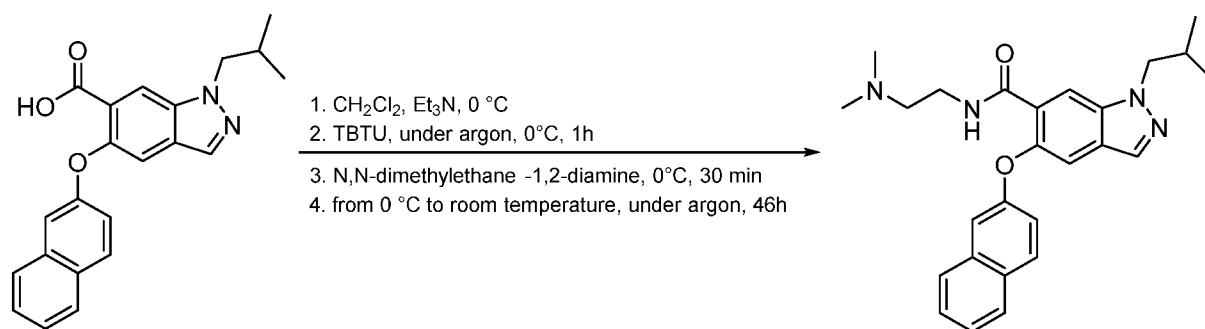
Yield: 98 %

TLC: R_f = 0.76 (CH₂Cl₂-MeOH = 9:1, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.91 – 7.87 (m, 2H), 7.80 – 7.75 (m, 1H), 7.56 – 7.47 (m, 3H), 7.33 (dd, J = 8.9, 2.5 Hz, 1H), 7.21 (s, 1H), 4.26 (d, J = 7.4 Hz, 2H), 2.38 (h, J = 7.0 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H) ppm Signal for -COOH is not visible.

LC-MS (ESI⁺) (m/z): calculated for C₂₂H₂₀N₂O₃: 360.15, found: 361.0.

STEP 8: Synthesis of N-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-2-yloxy)-1H-indazole-6-carboxamide:



The synthetic procedure is identical to that in **EXAMPLE 1**, STEP 7.

Product appearance: brown viscous oil

Yield: 43 %

TLC: R_f = 0.50 (CH₂Cl₂-MeOH = 9:1, v/v)

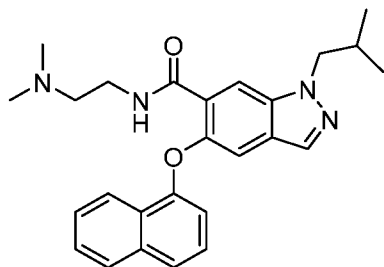
¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.37 (t, J = 5.2 Hz, 1H), 7.90 (d, J = 1.0 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.67 (dd, J = 7.9, 1.5 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.32 (s, 1H), 7.30 (dd, J = 8.9, 2.5 Hz, 1H), 7.24 (d, J = 2.5 Hz, 1H), 4.26 (d, J = 7.4 Hz, 2H), 3.49 (td, J = 6.1, 4.7 Hz, 2H), 2.43 (h, J = 6.9 Hz, 1H), 2.39 (t, J = 6.3 Hz, 2H), 2.11 (s, 6H), 0.96 (d, J = 6.7 Hz, 6H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 164.83, 155.21, 148.40, 136.85, 134.19, 132.08, 130.20, 129.97, 127.72, 127.17, 126.75, 125.38, 125.09, 124.93, 119.09, 113.39, 113.18, 111.13, 57.26, 56.69, 44.95, 37.60, 29.59, 20.18 ppm

HRMS (ESI⁺): m/z calculated for C₂₆H₃₀N₄O₂: 431.2369; found: 431.2437.

UPLC purity: 98 %

Synthesis of *N*-(2-(dimethylamino)ethyl)-1-isobutyl-5-(naphthalen-1-yloxy)-1*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those in **EXAMPLE 9** with 1-naphthol replacing 2-naphthol in STEP 3.

Product appearance: yellow viscous oil

TLC: *R_f* = 0.59 (CH₂Cl₂-MeOH = 9:1, v/v)

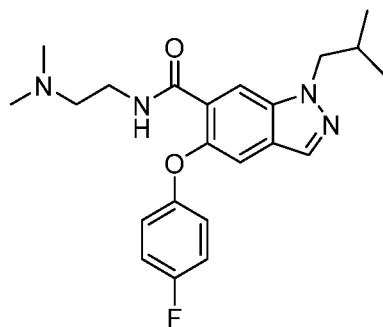
¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.41 (t, *J* = 4.2 Hz, 1H), 8.32 – 8.29 (m, 1H), 7.92 – 7.89 (m, 1H), 7.85 (d, *J* = 1.0 Hz, 1H), 7.64 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.21 (s, 1H), 6.82 (dd, *J* = 7.6, 0.9 Hz, 1H), 4.26 (d, *J* = 7.4 Hz, 2H), 3.46 (td, *J* = 6.2, 4.8 Hz, 2H), 2.39 (h, *J* = 7.2 Hz, 1H), 2.27 (t, *J* = 6.1 Hz, 2H), 1.86 (s, 6H), 0.95 (d, *J* = 6.5 Hz, 6H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 164.96, 153.30, 149.16, 136.74, 134.89, 132.03, 127.83, 126.77, 126.31, 126.15, 125.81, 125.47, 124.90, 123.54, 121.75, 113.32, 112.46, 110.35, 57.12, 56.69, 44.58, 37.57, 29.59, 20.17 ppm

HRMS (ESI⁺): m/z calculated for C₂₆H₃₀N₄O₂: 431.2369; found: 431.2438.

UPLC purity: 99 %

Synthesis of *N*-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those in **EXAMPLE 9** with 4-fluorophenol replacing 2-naphthol in STEP 3.

Product appearance: white solid

TLC: R_f = 0.11 (CH_2Cl_2 -MeOH = 9:1, v/v)

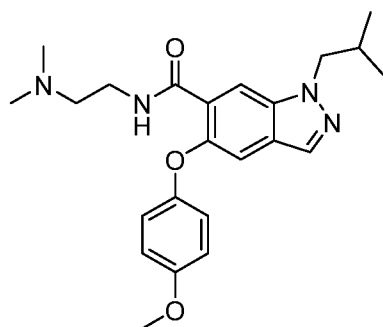
^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 8.31 (t, J = 4.1 Hz, 1H), 7.89 (d, J = 1.0 Hz, 1H), 7.19 (s, 1H), 7.08 – 7.01 (m, 2H), 7.00 – 6.95 (m, 2H), 4.24 (d, J = 7.4 Hz, 2H), 3.51 (td, J = 6.1, 4.7 Hz, 2H), 2.43 (t, J = 6.1 Hz, 2H), 2.36 (h, J = 6.9 Hz, 1H), 2.15 (s, 6H), 0.94 (d, J = 6.7 Hz, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.77, 160.09, 157.68, 153.02 (d, J = 2.5 Hz), 149.03, 136.65, 132.00, 125.29, 124.73, 119.57 (d, J = 8.2 Hz), 116.40 (d, J = 23.4 Hz), 113.39, 110.05, 57.30, 56.67, 44.96, 37.59, 29.58, 20.14 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_2$: 399.2118; found: 399.2186.

UPLC purity: 100 %

Synthesis of *N*-(2-(dimethylamino)ethyl)-1-isobutyl-5-(4-methoxyphenoxy)-1*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those in **EXAMPLE 9** with 4-methoxyphenol replacing 2-naphthol in STEP 3.

Product appearance: yellow viscous oil

TLC: R_f = 0.49 (CH_2Cl_2 -MeOH = 9:1, v/v)

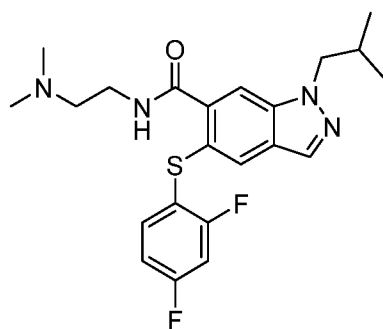
^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 8.31 (t, J = 4.1 Hz, 1H), 7.89 (d, J = 1.0 Hz, 1H), 7.19 (s, 1H), 7.08 – 7.01 (m, 2H), 7.00 – 6.95 (m, 2H), 4.24 (d, J = 7.4 Hz, 2H), 3.51 (td, J = 6.1, 4.7 Hz, 2H), 2.43 (t, J = 6.1 Hz, 2H), 2.36 (h, J = 6.9 Hz, 1H), 2.15 (s, 6H), 0.94 (d, J = 6.7 Hz, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 164.77, 160.09, 157.68, 153.02, 149.03, 136.65, 132.00, 125.29, 124.73, 119.57, 116.52, 116.29, 113.39, 110.05, 57.30, 56.67, 44.96, 37.59, 29.58, 20.14 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_3$: 411.2318; found: 411.2385.

UPLC purity: 98 %

Synthesis of 5-((2,4-difluorophenyl)thio)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those in **EXAMPLE 9** with 2,4-difluorobenzenethiol replacing 2-naphthol in STEP 3.

Product appearance: light brown powder

TLC: R_f = 0.22 (EtOAc-MeOH = 2:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.75 (s, 1H), 7.74 (s, 1H), 7.18 – 7.07 (m, 2H), 6.88 – 6.73 (m, 2H), 4.15 (d, J = 7.3 Hz, 2H), 3.48 (q, J = 5.6 Hz, 2H), 2.47 (t, J = 6.0 Hz, 2H), 2.33 (h, J = 6.8 Hz, 1H), 2.21 (s, 6H), 0.90 (d, J = 6.7 Hz, 6H) ppm

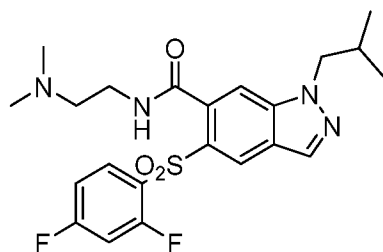
^{13}C NMR (101 MHz, CDCl_3) δ 167.93, 163.66 (d, J = 11.2 Hz), 161.86 (d, J = 12.1 Hz), 161.17 (d, J = 11.3 Hz), 159.39 (d, J = 12.1 Hz), 138.85, 136.74, 133.42 (dd, J = 9.4, 2.8 Hz), 132.51,

127.69, 125.09, 121.43, 119.44 (dd, $J = 17.8, 4.0$ Hz), 112.22 (dd, $J = 21.6, 3.7$ Hz), 110.72, 104.47 (t, $J = 25.9$ Hz), 57.43, 56.61, 45.02, 37.55, 29.48, 20.15 ppm

HRMS (ESI⁺): m/z calculated for C₂₂H₂₆F₂N₄OS: 433.1795; found: 433.1857.

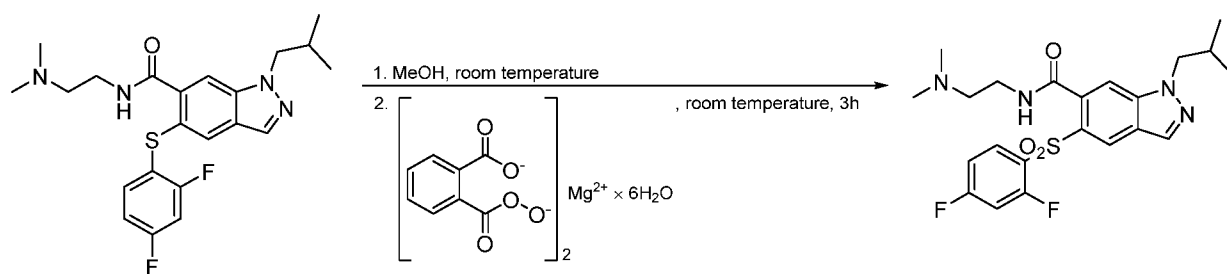
UPLC purity: 96 %

EXAMPLE 10: Synthesis of 5-((2,4-difluorophenyl)sulfonyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide



STEPS 1-8 are identical to those in **EXAMPLE 9** with 2,4-difluorobenzenethiol replacing 2-naphthol in STEP 3.

STEP 9: Synthesis of 5-((2,4-difluorophenyl)sulfonyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide:



To a 25-mL round-bottom flask with a stirring bar was added 5-((2,4-difluorophenyl)thio)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide (59 mg, 0.1364 mmol, 1.0 equiv) and dissolved in 12 mL of methanol. Magnesium monoperoxyphthalate hexahydrate (69 mg, 0.1395 mmol, 1.02 equiv) was added in two portions and the reaction mixture was left to stir at room temperature for 3h. After that MeOH was evaporated, the crude dissolved in 20 mL of EtOAc, washed with 10 mL of saturated NaHCO₃ solution and 10 mL of brine, dried over Na₂SO₄ and EtOAc evaporated under reduced pressure. The product was then purified by reverse-phase preparative chromatography (Biotage® Sfar, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase as an eluent to yield 4 mg of Synthesis of 5-((2,4-

difluorophenyl)sulfonyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide.

Yield: 6 %

Product appearance: brown solid

TLC: R_f = 0.17 (EtOAc-MeOH = 2:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 9.68 (s, 1H), 8.79 (s, 1H), 8.19 (s, 1H), 8.06 (s, 1H), 7.19 (ddd, J = 8.8, 7.7, 6.2 Hz, 1H), 6.89 – 6.76 (m, 2H), 4.26 (d, J = 7.3 Hz, 2H), 3.96 – 3.76 (m, 2H), 3.63 – 3.48 (m, 2H), 3.31 (d, J = 22.0 Hz, 6H), 2.37 (hept, J = 7.0 Hz, 1H), 0.92 (dd, J = 6.6, 1.3 Hz, 6H) ppm

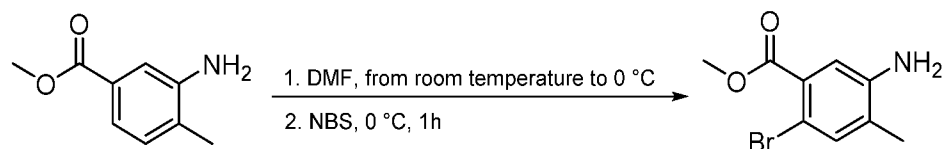
^{13}C NMR (101 MHz, CDCl_3) δ 165.29, 164.50 (d, J = 11.4 Hz), 161.98 (d, J = 11.4 Hz), 160.90 (d, J = 12.6 Hz), 158.36 (d, J = 12.5 Hz), 138.89, 133.96, 132.81, 130.68 (dd, J = 16.3, 4.0 Hz), 128.49, 128.18 (dd, J = 10.3, 3.6 Hz), 123.81, 120.15, 111.22 (dd, J = 21.8, 3.6 Hz), 108.64, 103.45 (t, J = 25.5 Hz), 66.55, 57.93, 55.56, 34.90, 28.68, 19.08 ppm

HRMS (ESI⁺): m/z calculated for $\text{C}_{22}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_3\text{S}$: 464.1694; found: 464.2611

UPLC purity: 95 %

EXAMPLE 11: Synthesis of 5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide

STEP 1: Synthesis of methyl 5-amino-2-bromo-4-methylbenzoate:



To a 50 mL round-bottom flask equipped with a stirring bar was added methyl 3-amino-4-methylbenzoate (10 g, 60.536 mmol, 1.0 equiv) and dissolved in 40 mL of DMF. The solution was cooled to 0 °C on an ice bath and NBS (10.78 g, 60.536 mmol, 1.0 equiv) was added in four portions. The reaction mixture was left to stir at 0 °C whilst monitored by TLC. After 1h DMF was evaporated on an oil pump, the product dissolved in 100 mL of EtOAc, washed with brine (2 × 50 mL), dried over Na_2SO_4 and the solvent evaporated. The crude was then purified

by recrystallization using EtOAc-*n*-hexane (1:10, v/v) as a solvent system to yield 7857 mg of 5-amino-2-bromo-4-methylbenzoate.

Yield: 53 %

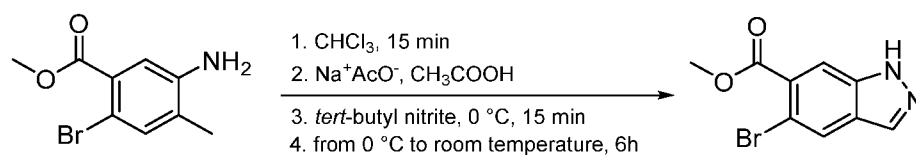
Product appearance: white solid

TLC: R_f = 0.40 (EtOAc-hexane = 1:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 1H), 7.14 (s, 1H), 3.89 (s, 3H), 3.70 (s, 2H), 2.15 (s, 3H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_9\text{H}_{10}\text{BrNO}_2$: 242.9; found: 244.0.

STEP 2: Synthesis of methyl 5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxylate:



The synthetic procedure is identical to that for the synthesis of compound **e**.

Yield: 54 %

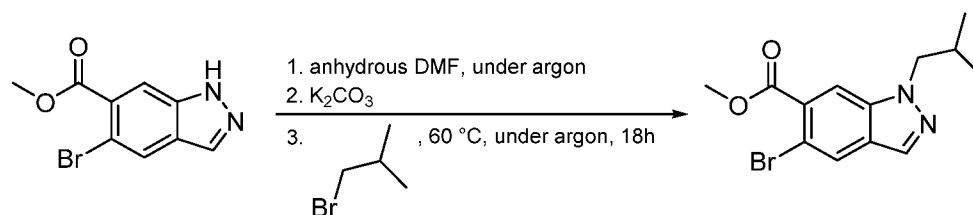
Product appearance: viscous yellow oil

TLC: R_f = 0.32 (EtOAc-hexane = 1:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 11.04 (s, 1H), 8.08 (d, J = 1.1 Hz, 1H), 8.06 (d, J = 0.6 Hz, 1H), 7.97 (t, J = 0.8 Hz, 1H), 3.98 (s, 3H) ppm

LC-MS (ESI^+): m/z calculated for $\text{C}_9\text{H}_7\text{BrN}_2\text{O}_2$: 253.9; found: 255.9.

STEP 3: Synthesis of methyl 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate:



The synthetic procedure is identical to that for the synthesis of compound **g**.

Yield: 55 %

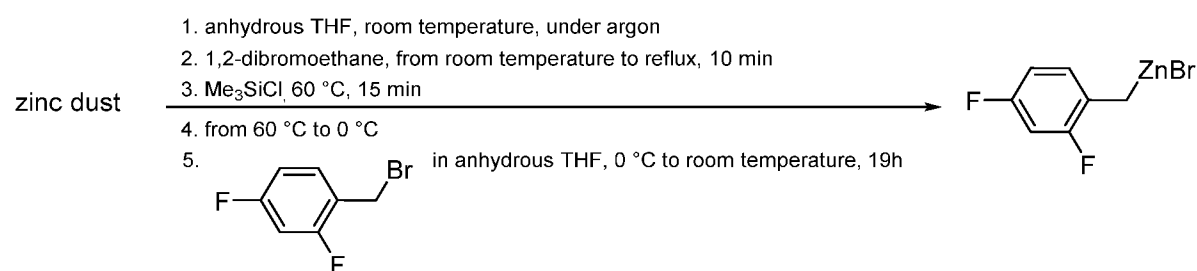
Product appearance: viscous yellow oil

TLC: R_f = 0.63 (EtOAc-hexane = 1:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.98 (d, J = 1.0 Hz, 1H), 7.86 (s, 1H), 4.19 (d, J = 7.4 Hz, 2H), 3.99 (s, 3H), 2.34 (h, J = 6.9 Hz, 1H), 0.92 (d, J = 6.7 Hz, 6H) ppm

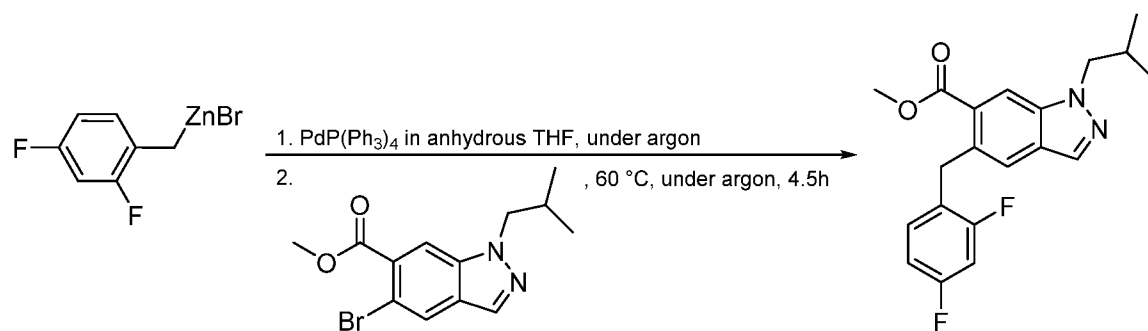
LC-MS (ESI^+): m/z calculated for $\text{C}_{13}\text{H}_{15}\text{BrN}_2\text{O}_2$: 310.0; found: 312.9.

STEP 4: Synthesis of 2,4-difluorobenzylzinc bromide:



Zinc dust (525 mg, 8.034 mmol, 5.0 equiv – relative to 5-bromo-1-isobutyl-1*H*-indazole-6-carboxylate added in the next step) was added to a 50-mL round-bottom flask and suspended in 10 mL of anhydrous THF under argon. 1,2-dibromoethane (17 μL , 0.201 mmol, 5 mol%) was added dropwise and the suspension was heated to reflux for 10 minutes. Chlorotrimethylsilane (10 μL , 0.080 mmol, 2 mol%) was then added dropwise to the hot suspension which was stirred vigorously at 60 °C for additional 15 minutes before it was cooled on an ice bath. 2,4-difluorobenzyl bromide (1031 μL , 1.607 mmol, 5.0 equiv) dissolved in 5 mL of ice-cold anhydrous THF was then added via cannula to the cooled suspension and the reaction mixture left to warm up to room temperature and stir overnight. After 19h the reaction mixture proceeded to the next step without any isolation procedures.

STEP 5: Synthesis of methyl 5-(2,4-difluorobenzyl)-1-isobutyl-1*H*-indazole-6-carboxylate:



To the reaction mixture from STEP 4 was added Tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.203 mmol, 2.5 mol%) dissolved in 10 mL of anhydrous THF. Subsequently, 5-bromo-1-isobutyl-1H-indazole-6-carboxylate (500 mg, 1.607 mmol, 1.0 equiv) was added and the reaction mixture was heated to 60 °C and monitored by LC-MS until all the 5-bromo-1-isobutyl-1H-indazole-6-carboxylate was consumed. After 4.5h the flask was cooled to room temperature and the reaction mixture filtered under suction through a pad of Celite® 545 followed by filtration through a syringe filter (pore size: 0.45 µM, PTFE). THF was evaporated on a rotary evaporator and the crude purified by flash column chromatography using EtOAc-hexane (1:3, v/v) as an eluent. After drying the product on an oil pump for 2h it was purified by reverse-phase preparative chromatography (Biotage® Sfär, C18 D 30 g column) using 0,1% TFA(aq)/MeCN as a mobile phase to yield 120 mg of 5-(2,4-difluorobenzyl)-1-isobutyl-1H-indazole-6-carboxylate.

Yield: 21 %

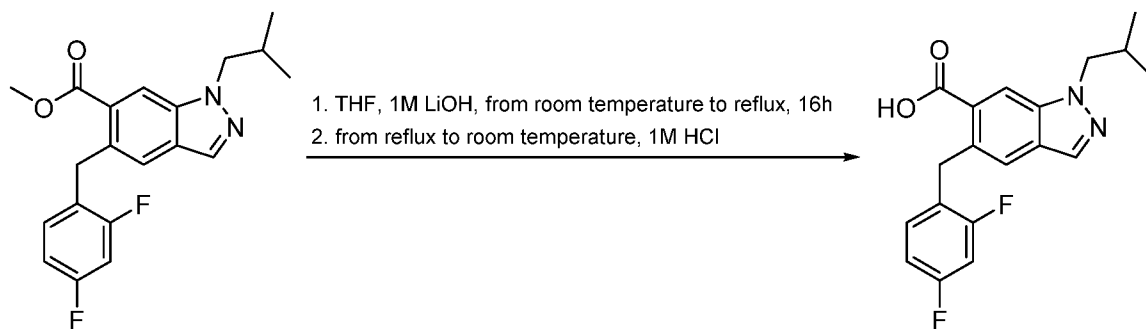
Product appearance: light brown viscous oil

TLC: R_f = 0.60 (EtOAc-hexane = 1:3, v/v)

¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 7.95 (d, J = 1.0 Hz, 1H), 7.49 (s, 1H), 6.94 (td, J = 8.6, 6.5 Hz, 1H), 6.85 – 6.71 (m, 2H), 4.41 (s, 2H), 4.21 (d, J = 7.4 Hz, 2H), 3.87 (s, 3H), 2.36 (hept, J = 6.9 Hz, 1H), 0.94 (d, J = 6.7 Hz, 6H) ppm

LC-MS (ESI⁺): m/z calculated for C₂₀H₂₀F₂N₂O₂: 358.2; found: 359.9.

STEP 6: 5-(2,4-difluorobenzyl)-1-isobutyl-1H-indazole-6-carboxylic acid:



The synthetic procedure is identical to that for the synthesis of compound **f**.

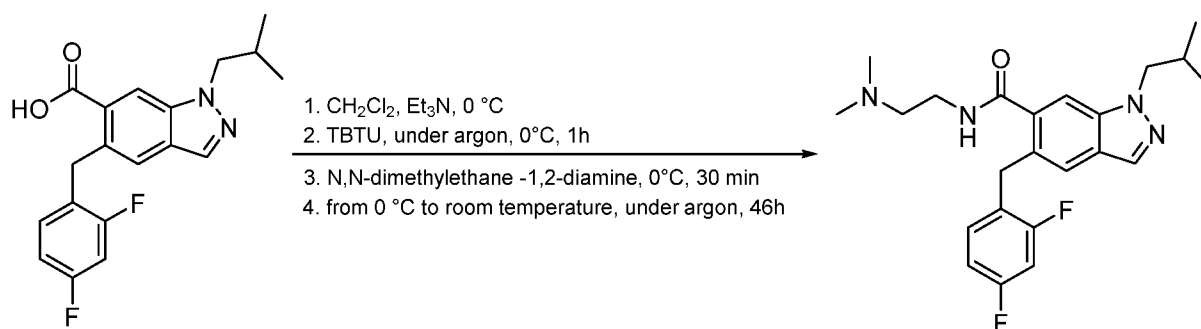
Yield: 78 %

Product appearance: white viscous oil

TLC: R_f = 0.26 (EtOAc-hexane = 1:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 7.98 (d, J = 1.0 Hz, 1H), 7.49 (s, 1H), 6.99 (td, J = 8.6, 6.6 Hz, 1H), 6.86 – 6.73 (m, 2H), 4.49 (s, 2H), 4.24 (d, J = 7.4 Hz, 2H), 2.37 (hept, J = 6.8 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H) ppm Signal for -COOH is not visible.

STEP 7: Synthesis of 5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide:



The synthetic procedure is identical to that in STEP 7 of **EXAMPLE 1**.

Yield: 44 %

Product appearance: light green viscous oil

TLC: R_f = 0.26 (EtOAc-MeOH = 2:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 1.0 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.11 (td, J = 8.8, 6.5 Hz, 1H), 6.81 – 6.68 (m, 2H), 6.40 (s, 1H), 4.24 (s, 2H), 4.15 (d, J = 7.3 Hz, 2H),

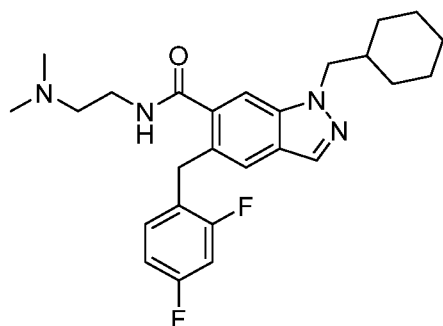
3.46 (q, $J = 5.4$ Hz, 2H), 2.43 (t, $J = 5.9$ Hz, 2H), 2.34 (hept, $J = 6.9$ Hz, 1H), 2.20 (s, 6H), 0.92 (d, $J = 6.7$ Hz, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 170.12, 162.79 (d, $J = 11.4$ Hz), 162.11 (d, $J = 12.1$ Hz), 160.34 (d, $J = 11.4$ Hz), 159.64 (d, $J = 12.1$ Hz), 138.01, 135.55, 132.42, 131.81 (dd, $J = 9.3, 6.2$ Hz), 129.17, 124.49, 123.97 (dd, $J = 15.7, 3.8$ Hz), 122.51 (d, $J = 1.2$ Hz), 110.91 (dd, $J = 20.8, 3.7$ Hz), 108.36, 103.58 (t, $J = 25.6$ Hz), 57.53, 56.46, 44.99, 37.17, 31.43 (d, $J = 2.6$ Hz), 29.49, 20.19 ppm

HRMS (ESI⁺): m/z calculated for $\text{C}_{23}\text{H}_{28}\text{F}_2\text{N}_4\text{O}$: 415.2231; found: 415.2292.

UPLC purity: 98 %

Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide:



The synthetic procedure is identical to that in **EXAMPLE 11**.

Product appearance: light green viscous oil

TLC: $R_f = 0.35$ (CH_2Cl_2 -MeOH = 10:1, v/v)

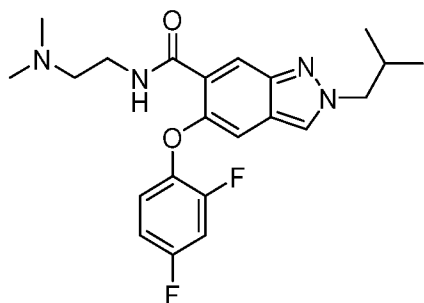
^1H NMR (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.46 (s, 1H), 7.41 (s, 1H), 7.10 (td, $J = 8.8, 6.5$ Hz, 1H), 6.79 – 6.71 (m, 2H), 6.43 (t, $J = 5.0$ Hz, 1H), 4.21 (s, 2H), 4.14 (d, $J = 7.2$ Hz, 2H), 3.42 (q, $J = 5.6$ Hz, 2H), 2.40 (t, $J = 6.0$ Hz, 2H), 2.16 (s, 6H), 1.97 (h, $J = 3.6$ Hz, 1H), 1.70 – 1.60 (m, 3H), 1.57 – 1.51 (m, 2H), 1.20 – 1.09 (m, 3H), 1.03 – 0.92 (m, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 170.13, 162.79 (d, $J = 11.5$ Hz), 162.12 (d, $J = 12.2$ Hz), 160.34 (d, $J = 11.5$ Hz), 159.65 (d, $J = 12.2$ Hz), 138.09, 135.55, 132.37, 131.81 (dd, $J = 9.3, 6.1$ Hz), 129.11, 124.44, 123.97 (dd, $J = 15.7, 3.8$ Hz), 122.66 – 122.37 (m), 110.91 (dd, $J = 20.8, 3.8$ Hz), 108.40, 103.59 (t, $J = 25.6$ Hz), 57.47, 55.38, 45.02, 38.72, 37.20, 31.44 (d, $J = 2.6$ Hz), 30.93, 26.24, 25.64 ppm

HRMS (ESI⁺): m/z calculated for C₂₆H₃₂F₂N₄O: 455.2544; found: 455.2602.

UPLC purity: 100 %

Synthesis of 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-2-isobutyl-2*H*-indazole-6-carboxamide:



The synthetic procedure is identical to that in **EXAMPLE 2** with the isolation steps identical to those for the *N*1-substituted regioisomer.

Product appearance: bright yellow solid

TLC: *R_f* = 0.46 (CH₂Cl₂-MeOH = 9:1, v/v)

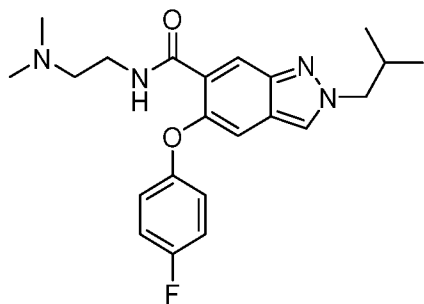
¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.86 (t, *J* = 4.8 Hz, 1H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.07 – 6.98 (m, 2H), 6.96 (s, 1H), 6.85 (dddd, *J* = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 4.20 (d, *J* = 7.3 Hz, 2H), 3.53 (td, *J* = 6.1, 4.8 Hz, 2H), 2.46 (t, *J* = 6.1 Hz, 2H), 2.38 (h, *J* = 6.8 Hz, 1H), 2.16 (s, 6H), 0.94 (d, *J* = 6.8 Hz, 6H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 165.23, 159.89 (d, *J* = 10.2 Hz), 157.44 (d, *J* = 10.2 Hz), 154.97 (d, *J* = 12.3 Hz), 152.47 (d, *J* = 12.2 Hz), 149.70, 145.68, 140.22 (dd, *J* = 11.6, 4.0 Hz), 126.00, 122.74 (d, *J* = 6.4 Hz), 122.15, 121.82 (dd, *J* = 9.6, 2.1 Hz), 111.38 (dd, *J* = 22.8, 3.9 Hz), 105.81, 105.41 (dd, *J* = 26.8, 21.9 Hz), 61.48, 57.43, 44.92, 37.55, 29.95, 19.92 ppm

HRMS (ESI⁺): m/z calculated for C₂₂H₂₆F₂N₄O₂: 417.2097; found: 417.2090.

UPLC purity: 100 %

Synthesis of *N*-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-2-isobutyl-2*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those in **EXAMPLE 9** with 4-fluorophenol replacing 2-naphthol in STEP 3 and with the isolation steps identical to those for the *N*1-substituted regioisomer.

Product appearance: bright yellow solid

TLC: R_f = 0.11 (CH_2Cl_2 -MeOH = 9:1, v/v)

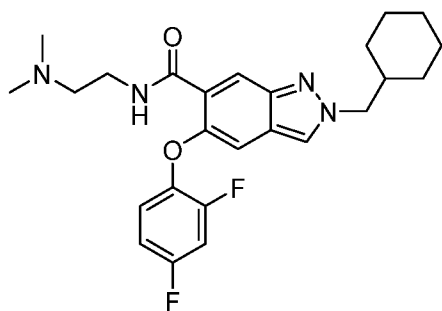
^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 7.97 (s, 1H), 7.77 (d, J = 1.0 Hz, 1H), 7.05 (s, 1H), 7.04 – 6.96 (m, 4H), 4.20 (d, J = 7.4 Hz, 2H), 3.49 (q, J = 6.1 Hz, 2H), 2.42 (t, J = 6.1 Hz, 2H), 2.36 (h, J = 7.0 Hz, 1H), 2.16 (s, 6H), 0.94 (d, J = 6.7 Hz, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.25, 160.02, 157.61, 153.10 (d, J = 2.6 Hz), 149.66, 145.79, 126.32, 122.79 (d, J = 3.7 Hz), 122.42, 119.75 (d, J = 8.3 Hz), 116.42, 116.19, 107.93, 61.51, 57.41, 44.97, 37.43, 29.97, 19.95 ppm

HRMS (ESI⁺): m/z calculated for $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_2$: 399.2118; found: 399.2187 .

UPLC purity: 100 %

Synthesis of 2-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclohexane replacing 1-bromo-2-methylpropane. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: white solid

TLC: R_f = 0.31 (CH_2Cl_2 -MeOH = 9:1, v/v)

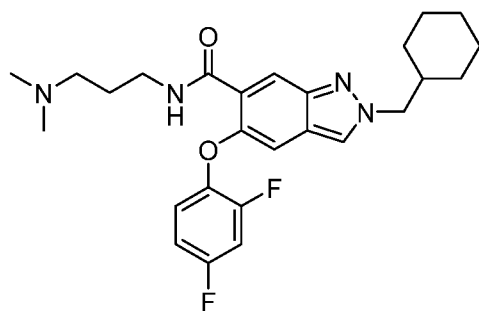
^1H NMR (400 MHz, CDCl_3) δ 8.52 (s, 1H), 7.84 (t, J = 4.9 Hz, 1H), 7.74 (d, J = 0.9 Hz, 1H), 7.02 (dt, J = 9.1, 5.2 Hz, 1H), 6.98 (ddd, J = 5.4, 2.6, 1.4 Hz, 1H), 6.94 (s, 1H), 6.83 (dddd, J = 9.2, 7.8, 3.0, 1.7 Hz, 1H), 4.21 (d, J = 7.2 Hz, 2H), 3.51 (q, J = 6.0 Hz, 2H), 2.45 (t, J = 6.1 Hz, 2H), 2.15 (s, 6H), 2.08 – 1.97 (m, 1H), 1.73 – 1.64 (m, 3H), 1.61 – 1.55 (m, 2H), 1.28 – 1.14 (m, 3H), 0.99 (qd, J = 11.9, 3.4 Hz, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.25, 159.88 (d, J = 10.2 Hz), 157.44 (d, J = 10.2 Hz), 154.96 (d, J = 12.2 Hz), 152.46 (d, J = 12.2 Hz), 149.67, 145.68, 140.25 (dd, J = 11.6, 3.9 Hz), 125.95, 122.92, 122.70, 121.80 (dd, J = 9.6, 2.0 Hz), 111.38 (dd, J = 22.8, 3.9 Hz), 105.83, 105.42 (dd, J = 26.8, 21.9 Hz), 60.43, 57.42, 44.93, 39.01, 37.54, 30.63, 26.17, 25.56 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{F}_2\text{N}_4\text{O}_2$: 457.2415; found: 457.2400.

UPLC purity: 98 %

Synthesis of 2-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(3-(dimethylamino)propyl)-2*H*-indazole-6-carboxamide:



STEPS 1-5 and 7 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with (bromo)methylcyclohexane replacing 1-bromo-2-methylpropane. STEP 8 is identical to that of **EXAMPLE 2** with *N,N'*-dimethylpropane-1,3-diamine replacing *N,N'*-dimethylethane-1,2-diamine. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: bright yellow solid

TLC: R_f = 0.20 (CH_2Cl_2 -MeOH = 9:1, v/v)

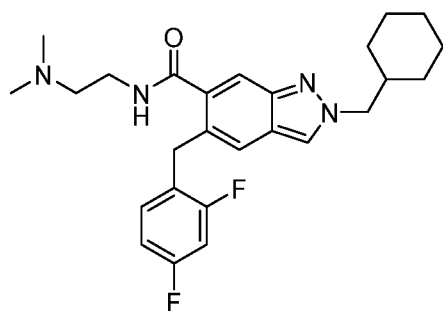
^1H NMR (400 MHz, CDCl_3) δ 8.53 (t, $J = 0.7$ Hz, 1H), 7.87 (d, $J = 5.6$ Hz, 1H), 7.72 (d, $J = 1.0$ Hz, 1H), 7.07 (td, $J = 9.0, 5.4$ Hz, 1H), 6.98 (ddd, $J = 10.4, 8.3, 3.0$ Hz, 1H), 6.87 (d, $J = 0.6$ Hz, 1H), 6.89 – 6.81 (m, 1H), 4.20 (d, $J = 7.3$ Hz, 2H), 3.53 (q, $J = 6.3$ Hz, 2H), 2.32 (t, $J = 6.8$ Hz, 2H), 2.11 (s, 6H), 2.09 – 1.94 (m, 1H), 1.75 (p, $J = 6.6$ Hz, 2H), 1.73 – 1.60 (m, 3H), 1.61 – 1.52 (m, 2H), 1.29 – 1.12 (m, 3H), 1.05 – 0.90 (m, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.20, 160.19 (d, $J = 10.3$ Hz), 157.74 (d, $J = 10.2$ Hz), 155.21 (d, $J = 12.2$ Hz), 152.71 (d, $J = 12.3$ Hz), 150.05, 145.60, 139.78 (dd, $J = 11.7, 3.8$ Hz), 125.71, 122.85 (d, $J = 3.0$ Hz), 122.62 (dd, $J = 9.6, 1.9$ Hz), 122.06, 111.61 (dd, $J = 22.9, 3.9$ Hz), 105.60 (dd, $J = 26.8, 21.8$ Hz), 105.01, 60.41, 58.05, 45.45, 39.08 (d, $J = 14.1$ Hz), 30.62, 26.83, 26.16, 25.55 ppm

HRMS (ESI $^+$): m/z calculated for $\text{C}_{26}\text{H}_{32}\text{F}_2\text{N}_4\text{O}_2$: 471.2571; found: 471.2560.

UPLC purity: 94 %

Synthesis of 2-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide:



The synthetic procedure is identical to that in **EXAMPLE 11**. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: white solid

TLC: $R_f = 0.12$ (CH_2Cl_2 -MeOH = 10:1, v/v)

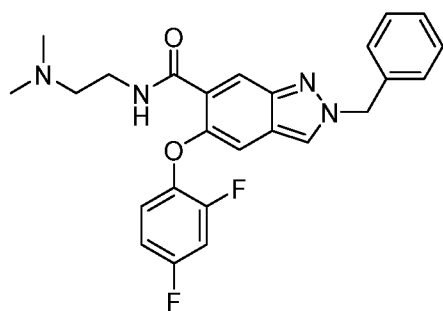
^1H NMR (400 MHz, CDCl_3) δ 7.73 (s, 1H), 7.71 (s, 1H), 7.32 (s, 1H), 7.07 (td, $J = 8.8, 6.5$ Hz, 1H), 6.73 – 6.64 (m, 2H), 6.52 (t, $J = 4.9$ Hz, 1H), 4.18 (s, 2H), 4.12 (d, $J = 7.2$ Hz, 2H), 3.34 (q, $J = 5.6$ Hz, 2H), 2.31 (t, $J = 6.0$ Hz, 2H), 2.10 (s, 6H), 2.01 – 1.91 (m, 1H), 1.67 – 1.56 (m, 3H), 1.54 – 1.46 (m, 2H), 1.21 – 1.04 (m, 3H), 0.92 (qd, $J = 12.0, 3.4$ Hz, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 168.41, 160.91 (d, $J = 11.7$ Hz), 160.44 (d, $J = 11.7$ Hz), 158.47 (d, $J = 11.8$ Hz), 157.97 (d, $J = 11.7$ Hz), 145.19, 133.76, 130.20 (dd, $J = 9.4, 6.2$ Hz), 128.66, 122.32 (dd, $J = 15.6, 3.7$ Hz), 121.47, 120.25, 119.43, 114.96, 108.94 (dd, $J = 20.7, 3.7$ Hz), 101.67 (t, $J = 25.6$ Hz), 58.39, 55.65, 43.18, 37.21, 35.27, 29.93 (d, $J = 2.6$ Hz), 28.82, 24.38, 23.78 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{26}\text{H}_{32}\text{F}_2\text{N}_4\text{O}$: 455.2544; found: 455.2606.

UPLC purity: 98 %

Synthesis of 2-benzyl-5-(2,4-difluorophenoxy)-*N*-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide:



STEPS 1-5, 7 and 8 are identical to those described in **EXAMPLE 1**. STEP 6 is identical to the one described in **EXAMPLE 2** with benzyl bromide replacing 1-bromo-2-methylpropane. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: light yellow solid

TLC: $R_f = 0.20$ (CH_2Cl_2 -MeOH = 10:1, v/v)

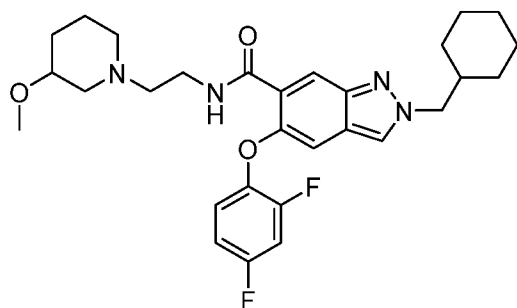
^1H NMR (400 MHz, CDCl_3) δ 8.56 (s, 1H), 7.86 (s, 1H), 7.74 (d, $J = 0.9$ Hz, 1H), 7.38 – 7.32 (m, 3H), 7.29 – 7.27 (m, 2H), 7.02 (dt, $J = 9.2, 5.6$ Hz, 1H), 6.99 – 6.93 (m, 1H), 6.91 (s, 1H), 6.83 (dddd, $J = 9.2, 7.7, 3.0, 1.7$ Hz, 1H), 5.58 (s, 2H), 3.53 (q, $J = 5.8$ Hz, 2H), 2.47 (t, $J = 6.1$ Hz, 2H), 2.17 (s, 6H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.31, 160.09 (d, $J = 10.2$ Hz), 157.64 (d, $J = 10.2$ Hz), 155.12 (d, $J = 12.1$ Hz), 152.62 (d, $J = 12.3$ Hz), 150.06, 145.88, 140.17 (dd, $J = 11.6, 4.0$ Hz), 135.42, 129.13, 128.71, 128.20, 126.32, 123.03, 122.76, 122.63, 122.07 (dd, $J = 9.7, 2.0$ Hz), 111.54 (dd, $J = 22.9, 3.9$ Hz), 105.81, 105.49 (dd, $J = 21.8, 5.0$ Hz), 58.02, 57.52, 45.03, 37.64 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{25}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_2$: 451.1867; found: 451.1934.

UPLC purity: 98 %

Synthesis of 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those described in **EXAMPLE 4**. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: white solid

TLC: R_f = 0.33 (CH_2Cl_2 -MeOH = 10:1, v/v)

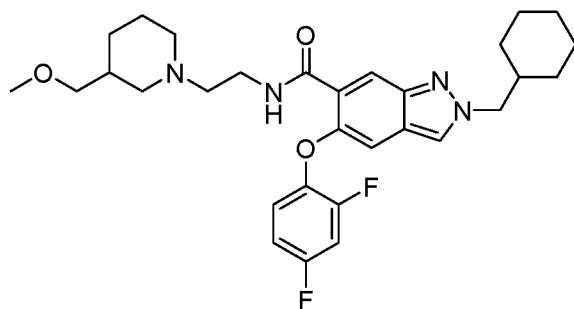
^1H NMR (400 MHz, CDCl_3) δ 8.59 (s, 1H), 7.97 (t, J = 4.9 Hz, 1H), 7.71 (d, J = 1.0 Hz, 1H), 7.13 (td, J = 8.9, 5.4 Hz, 1H), 7.00 (ddd, J = 10.3, 8.2, 3.0 Hz, 1H), 6.90 (dddd, J = 9.2, 7.7, 3.0, 1.7 Hz, 1H), 6.84 (s, 1H), 4.20 (d, J = 7.2 Hz, 2H), 3.63 – 3.51 (m, 2H), 3.24 (s, 3H), 2.98 – 2.88 (m, 2H), 2.70 – 2.61 (m, 1H), 2.55 (td, J = 6.0, 1.4 Hz, 2H), 2.06 – 2.01 (m, 1H), 1.98 – 1.90 (m, 1H), 1.88 – 1.82 (m, 2H), 1.73 – 1.66 (m, 2H), 1.64 – 1.62 (m, 1H), 1.60 – 1.54 (m, 3H), 1.26 – 1.22 (m, 2H), 1.21 – 1.16 (m, 2H), 1.11 (ddd, J = 12.6, 9.5, 3.7 Hz, 1H), 0.98 (qd, J = 12.1, 3.3 Hz, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 163.09, 158.44 (d, J = 10.2 Hz), 155.99 (d, J = 10.1 Hz), 153.55 (d, J = 12.3 Hz), 151.04 (d, J = 12.3 Hz), 148.69, 143.65, 137.64 (dd, J = 11.8, 3.9 Hz), 123.24, 121.29 (dd, J = 9.7, 2.0 Hz), 121.15, 120.90, 120.20, 109.77 (dd, J = 22.9, 3.9 Hz), 103.70 (dd, J = 26.8, 21.7 Hz), 102.51, 58.50, 55.74, 54.55, 54.06, 51.17, 37.10, 34.97, 28.71, 28.10, 24.25, 23.64, 21.24 ppm

HRMS (ESI⁺): m/z calculated for $\text{C}_{29}\text{H}_{36}\text{F}_2\text{N}_4\text{O}_3$: 527.2775; found: 527.2812.

UPLC purity: 99 %

Synthesis of 2-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-*N*-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-2*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those described in **EXAMPLE 4**. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: white solid

TLC: R_f = 0.40 (CH₂Cl₂-MeOH = 10:1, v/v)

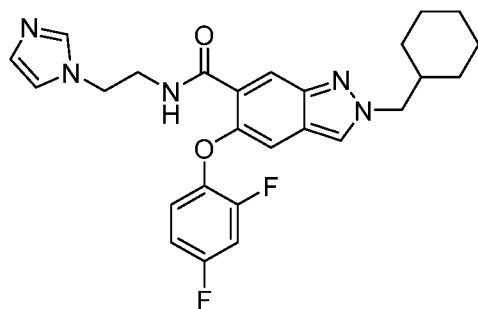
¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H), 7.99 (t, J = 4.8 Hz, 1H), 7.71 (d, J = 1.0 Hz, 1H), 7.12 (td, J = 8.9, 5.4 Hz, 1H), 6.98 (ddd, J = 10.4, 8.3, 3.0 Hz, 1H), 6.88 (dddd, J = 9.2, 7.8, 3.0, 1.7 Hz, 1H), 6.84 (s, 1H), 4.19 (d, J = 7.3 Hz, 2H), 3.57 (q, J = 5.2 Hz, 2H), 3.25 (s, 3H), 3.17 – 3.06 (m, 2H), 2.86 – 2.81 (m, 1H), 2.74 (d, J = 11.0 Hz, 1H), 2.50 (t, J = 6.0 Hz, 2H), 2.08 – 1.97 (m, 1H), 1.90 (td, J = 11.3, 2.7 Hz, 1H), 1.74 – 1.66 (m, 3H), 1.63 (q, J = 4.0, 3.2 Hz, 1H), 1.60 – 1.49 (m, 5H), 1.19 – 1.11 (m, 3H), 0.99 (tt, J = 12.0, 5.9 Hz, 2H), 0.92 – 0.85 (m, 2H) ppm

¹³C NMR (101 MHz, CDCl₃) δ 165.15, 160.44 (d, J = 10.1 Hz), 157.99 (d, J = 10.2 Hz), 155.57 (d, J = 12.4 Hz), 153.06 (d, J = 12.3 Hz), 150.72, 145.67, 139.68 (dd, J = 11.9, 4.0 Hz), 125.43, 123.27 (dd, J = 9.8, 1.9 Hz), 122.98 (d, J = 14.5 Hz), 122.21, 111.71 (dd, J = 22.9, 3.9 Hz), 105.70 (dd, J = 26.8, 21.7 Hz), 104.54, 76.25, 60.51, 58.87, 57.25, 56.99, 54.11, 39.12, 36.99, 36.53, 30.73, 27.58, 26.28, 25.67, 24.87 ppm

HRMS (ESI⁺): m/z calculated for C₃₀H₃₈F₂N₄O₃: 541.2912; found: 541.2972.

UPLC purity: 99 %

Synthesis of *N*-(2-(1*H*-imidazol-1-yl)ethyl)-2-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide:



STEPS 1-8 are identical to those described in **EXAMPLE 7**. The isolation procedures are identical to those for the *N*1-substituted regioisomer.

Product appearance: white solid

TLC: $R_f = 0.11$ (CH_2Cl_2 -MeOH = 15:1, v/v)

^1H NMR (400 MHz, CDCl_3) δ 8.60 (s, 1H), 7.72 (d, $J = 1.0$ Hz, 1H), 7.63 (t, $J = 5.9$ Hz, 1H), 7.46 (s, 1H), 7.08 (td, $J = 9.0, 5.5$ Hz, 1H), 6.99 (ddd, $J = 10.4, 8.2, 2.9$ Hz, 1H), 6.96 – 6.90 (m, 2H), 6.89 (ddd, $J = 9.2, 3.0, 1.6$ Hz, 1H), 6.81 (s, 1H), 4.24 – 4.17 (m, 4H), 3.79 (q, $J = 5.9$ Hz, 2H), 2.10 – 1.95 (m, 1H), 1.73 – 1.63 (m, 3H), 1.59 – 1.53 (m, 2H), 1.21 – 1.11 (m, 3H), 1.04 – 0.92 (m, 2H) ppm

^{13}C NMR (101 MHz, CDCl_3) δ 165.79, 160.75 (d, $J = 10.2$ Hz), 158.29 (d, $J = 10.3$ Hz), 155.50 (d, $J = 12.3$ Hz), 153.00 (d, $J = 12.5$ Hz), 150.49, 145.46, 138.74 (dd, $J = 11.8, 4.0$ Hz), 137.33, 129.71, 123.90, 123.59, 123.64 – 123.34 (m), 123.07, 122.45, 119.00, 111.97 (dd, $J = 22.9, 3.9$ Hz), 105.90 (dd, $J = 26.9, 21.8$ Hz), 104.32, 60.60, 46.27, 41.37, 39.14, 30.72, 26.26, 25.66 ppm

HRMS (ESI^+): m/z calculated for $\text{C}_{26}\text{H}_{27}\text{F}_2\text{N}_5\text{O}_2$: 480.2133; found: 480.2201.

UPLC purity: 98 %

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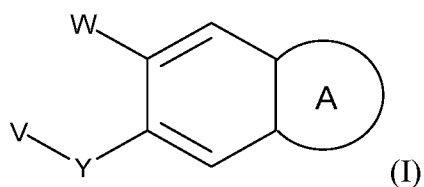
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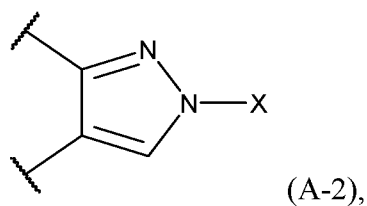
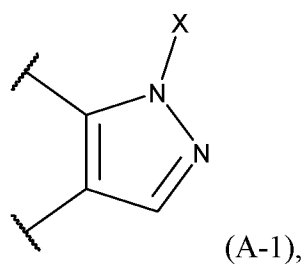
Claims

1. A compound of formula (I)

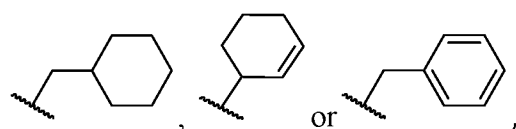
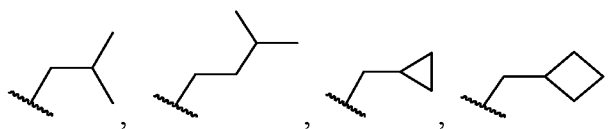


wherein,

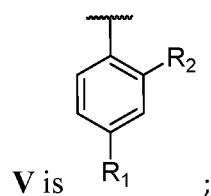
ring A is a structure represented by formula (A-1) or formula (A-2):



X is -H, -CH₃, -CH₂CH₃, -(CH₂)₂CH₃,

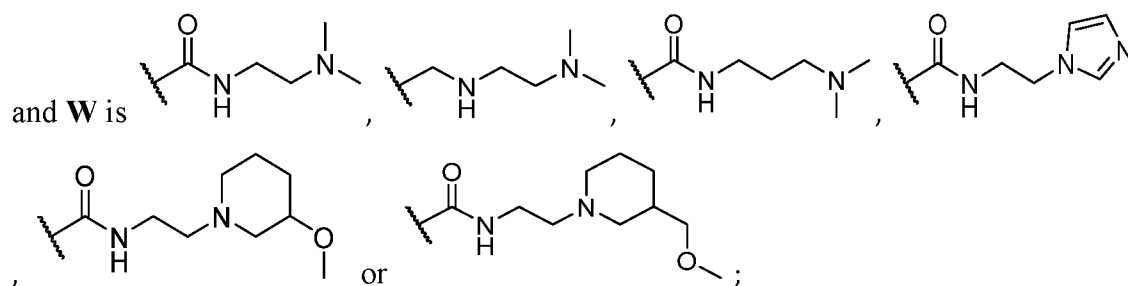


Y is CH₂, O or S,



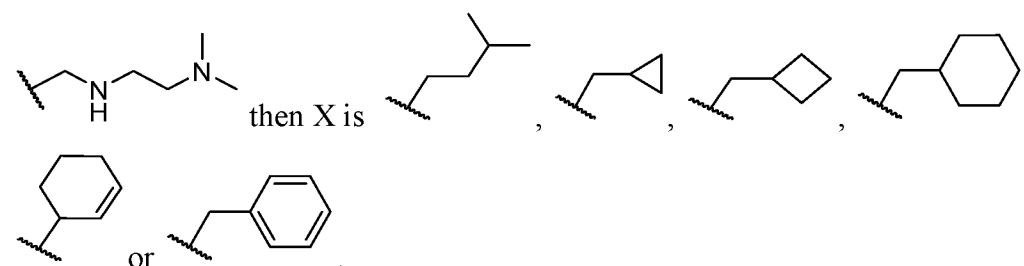
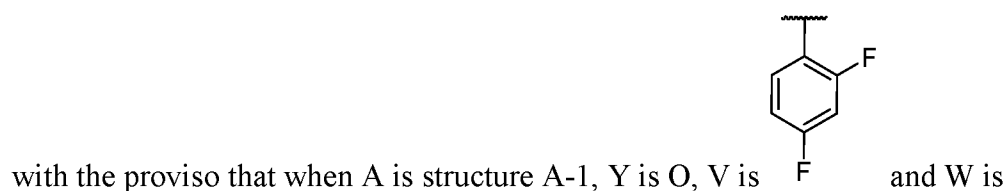
R₁ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;

R₂ is -H, halogen, C₁₋₄ alkyl, C₁₋₄ alkyloxy, -OH, CF₃, -NH₂, -NO₂ or -SO₂;

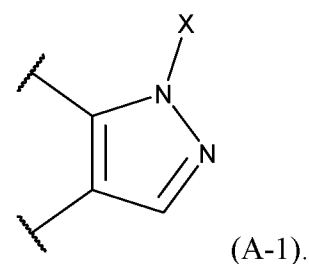


or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof,

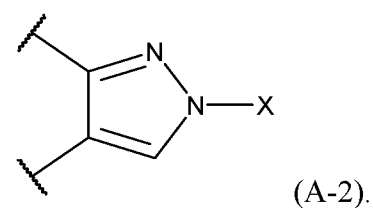
for use in the treatment of a neurodegenerative disease;



- Compound for use according to claim 1, wherein **A** is a structure represented by formula (A-1):

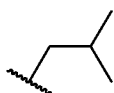


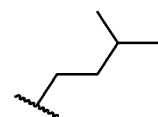
- Compound for use according to claim 1, wherein **A** is a structure represented by formula (A-2):

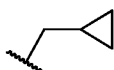


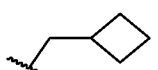
- Compound for use according to any one of claims 1 to 3, wherein **X** is -H.

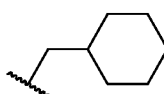
5. Compound for use according to any one of claims 1 to 3, wherein **X** is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$ or $-(\text{CH}_2)_2\text{CH}_3$.

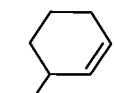
6. Compound for use according to any one of claims 1 to 3, wherein **X** is .

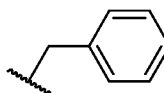
7. Compound for use according to any one of claims 1 to 3, wherein **X** is .

8. Compound for use according to any one of claims 1 to 3, wherein **X** is .

9. Compound for use according to any one of claims 1 to 3, wherein **X** is .

10. Compound for use according to any one of claims 1 to 3, wherein **X** is .

11. Compound for use according to any one of claims 1 to 3, wherein **X** is .

12. Compound for use according to any one of claims 1 to 3, wherein **X** is .

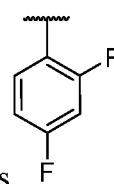
13. Compound for use according to any one of claims 1 to 12, wherein **Y** is CH_2 .

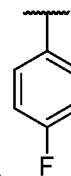
14. Compound for use according to any one of claims 1 to 12, wherein **Y** is O .

15. Compound for use according to any one of claims 1 to 12, wherein **Y** is S .

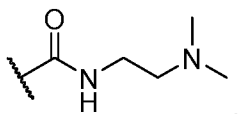
16. Compound for use according to any one of claims 1 to 15, wherein R_1 is halogen, and R_2 is $-\text{H}$ or halogen.

17. Compound for use according to any one of claims 1 to 15, wherein R_1 is methoxy or ethoxy, and R_2 is $-\text{H}$.

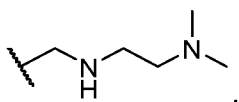
18. Compound for use according to any one of claims 1 to 15, wherein **V** is .



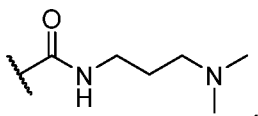
19. Compound for use according to any one of claims 1 to 15, wherein **V** is
20. Compound for use according to any one of claims 1 to 19, wherein **W** is



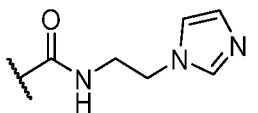
21. Compound for use according to any one of claims 1 to 19, wherein **W** is



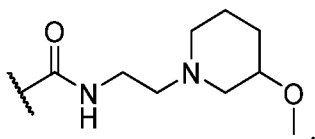
22. Compound for use according to any one of claims 1 to 19, wherein **W** is



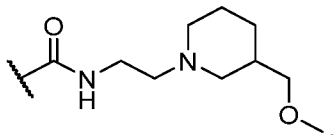
23. Compound for use according to any one of claims 1 to 19, wherein **W** is



24. Compound for use according to any one of claims 1 to 19, wherein **W** is

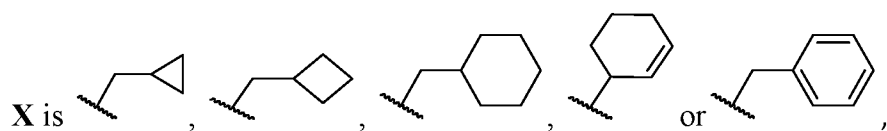
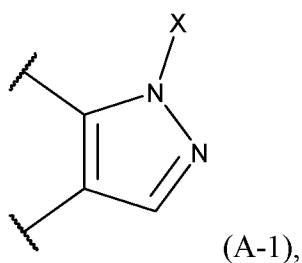


25. Compound for use according to any one of claims 1 to 19, wherein **W** is

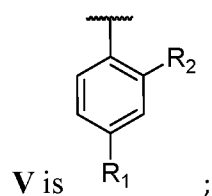


26. Compound for use according to claim 1, wherein

ring **A** is a structure represented by formula (A-1):

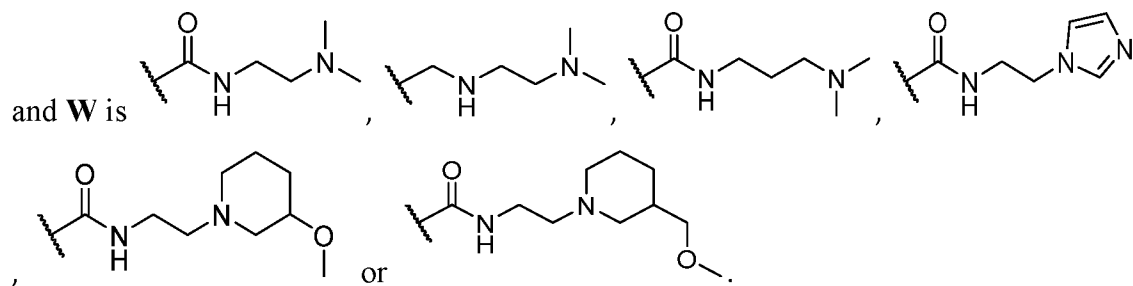


Y is CH₂, O or S,



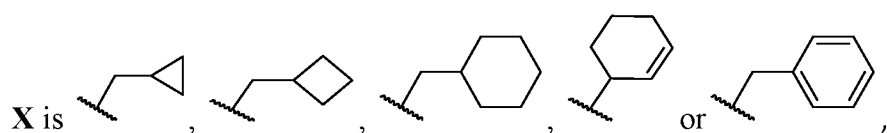
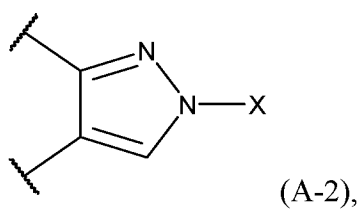
R₁ is halogen;

R₂ is halogen;

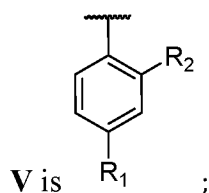


27. Compound for use according to claim 1, wherein

ring **A** is a structure represented by formula (A-2):

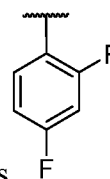
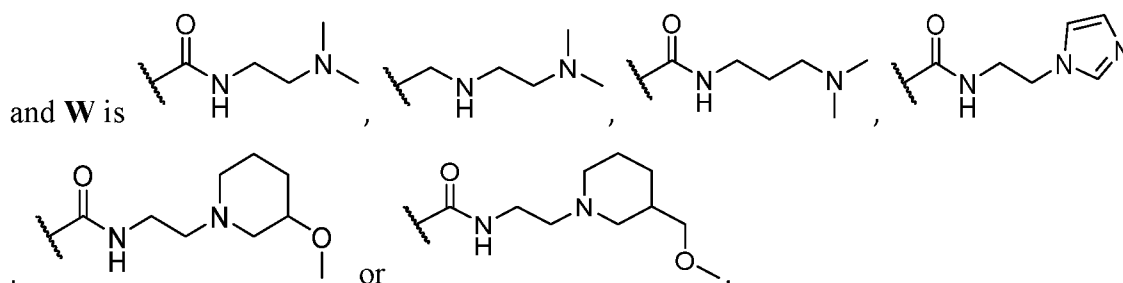


Y is CH₂, O or S,



R₁ is halogen;

R₂ is halogen;



28. Compound for use according to claim 26 or 27, wherein **V** is .
29. Compound for use according to claim 1, which is selected from the group consisting of:
- 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;
 - 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isopentyl-1*H*-indazole-6-carboxamide;
 - 1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclopropylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclobutylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;

1-benzyl-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide.

30. Compound for use according to claim 1, which is selected from the group consisting of:

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isobutyl-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-2*H*-indazole-6-carboxamide; and

N-(2-(1H-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide.

31. Compound for use according to any one of claims 1 to 30, wherein the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease or amyotrophic lateral sclerosis.
32. Compound for use according to any one of claims 1 to 30, wherein the neurodegenerative disease is Alzheimer's disease.
33. Pharmaceutical composition comprising a compound as defined in any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle, for use in the treatment of a neurodegenerative disease.
34. Pharmaceutical composition for use according to claim 33, wherein the neurodegenerative disease is Alzheimer's disease or other form of dementia, Parkinson's disease or amyotrophic lateral sclerosis.
35. Pharmaceutical composition for use according to claim 33, wherein the neurodegenerative disease is Alzheimer's disease.
36. Compound selected from the group consisting of:
 - 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isopentyl-1*H*-indazole-6-carboxamide;
 - 1-(cyclobutylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-1*H*-indazole-6-carboxamide;
 - 1-benzyl-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;
 - 1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxy)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(dimethylamino)ethyl)-5-(4-fluorophenoxy)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-2*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(3-(dimethylamino)propyl)-2*H*-indazole-6-carboxamide; and

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-2*H*-indazole-6-carboxamide

or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof.

37. Compound according to claim 36, which is selected from the group consisting of:

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-methoxypiperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-N-(2-(3-(methoxymethyl)piperidin-1-yl)ethyl)-1*H*-indazole-6-carboxamide;

N-(2-(1*H*-imidazol-1-yl)ethyl)-1-(cyclohexylmethyl)-5-(2,4-difluorophenoxy)-1*H*-indazole-6-carboxamide;

1-(cyclohex-2-en-1-yl)-5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1H-indazole-6-carboxamide;

5-((2,4-difluorophenyl)thio)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1H-indazole-6-carboxamide;

5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1H-indazole-6-carboxamide; and

1-(cyclohexylmethyl)-5-(2,4-difluorobenzyl)-N-(2-(dimethylamino)ethyl)-1H-indazole-6-carboxamide;

or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof.

38. Compound according to claim 36, wherein the compound is:

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1H-indazole-6-carboxamide; or

5-(2,4-difluorophenoxy)-N-(2-(dimethylamino)ethyl)-1-isobutyl-1H-indazole-6-carboxamide

or a pharmaceutically acceptable salt, racemate, diastereomer, enantiomer, regioisomer, hydrate or solvate thereof.

39. Compound according to any one of claims 36 to 38 for use in medicine.

40. Pharmaceutical composition comprising a compound according to any one of claims 36 to 38, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant, or vehicle.

41. Pharmaceutical composition according to claim 40 for use in medicine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/075218

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/416 A61P25/16 A61P25/28 C07D231/56 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) A61K C07D A61P 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.
X	WO 2021/216754 A1 (SPRING DISCOVERY INC [US]) 28 October 2021 (2021-10-28)	1,2,6, 14,16, 18,20, 29-35, 38-41
Y	page 9, lines 12-16; claims 6,7,17,36 -----	1-41
X	WO 2004/078116 A2 (ARRAY BIOPHARMA INC [US]; MUNSON MARK [US] ET AL.) 16 September 2004 (2004-09-16)	1-41
Y	page 52, lines 14-17; claims 20,26;; figure 30c; examples 50-61,83; compounds 11g-5 to 11g-16 -----	1-41
X	US 2004/176325 A1 (MUNSON MARK [US] ET AL) 9 September 2004 (2004-09-09)	1-41
Y	page 15, paragraph 235; claims 20,26; figure 30C; examples 50-61,83; compounds 11g-5 to 11g-16 -----	1-41
☐ Further documents are listed in the continuation of Box C. ☒ 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 13 November 2024		Date of mailing of the international search report 21/11/2024
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 Bareyt, Sébastien

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2024/075218

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2024/075218

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Information on patent family members

International application No

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