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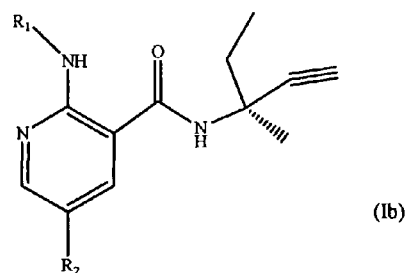
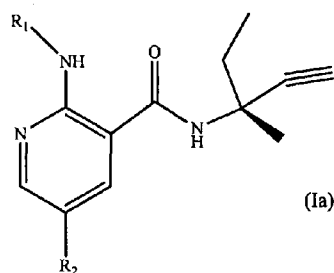
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(54) Title: TRPA1 MODULATORS



(57) Abstract: Compounds of formula Ia or Ib, wherein R₁ and R₂ are as defined in the claims, exhibit TRPA1 activity and are thus useful as TRPA1 modulators.

TRPA1 MODULATORS

TECHNICAL FIELD

The present disclosure relates to pharmacologically active pure enantiomers of certain nicotinamide derivatives, or pharmaceutically acceptable salts thereof, as well as to
5 pharmaceutical compositions comprising them and to their use in the treatment of diseases linked to the activation of the TRPA1 (Transient Receptor Potential subfamily A, member 1) receptors.

BACKGROUND OF THE INVENTION

Human TRPA1 was first cloned from lung fibroblasts. TRPA1 was functionally
10 characterized as a calcium permeable nonselective cation channel that is selectively localized to pain sensing peptidergic unmyelinated sensory neurons, which coexpress TRPV1, substance P and CGRP. TRPA1 exists in both peripheral and central terminals of sensory neurons. Amino acid sequence comparison revealed that TRPA1 is a member of the transient receptor potential ion channel superfamily. A recent study finds a somewhat
15 broader expression of TRPA1 even in myelinated fibers.

Studies in healthy animals suggest that TRPA1 is not activated under physiological conditions. Acute administration of TRPA1 agonists such as mustard oil and cinnamaldehyde to the skin causes acute pain and nocifensive behavior in healthy animals and man. Several pathophysiological conditions such as acute and chronic neuropathic pain,
20 diabetes, cancer, inflammation, asthma, arthritis, migraine, osteoarthritis, sleep deprivation, and bladder dysfunction are known to have increased production of endogenous reactive compounds such as 4-hydroxynonenal, acetaldehyde, hydrogen peroxide, prostaglandin J2, prostaglandin A2, methylglyoxal, which are known to act as TRPA1 agonists. Interestingly, several TRPA1 agonists also can be produced through an oxidative stress-related non-
25 enzymatic route.

TRPA1 is a nonselective cation channel with substantial calcium permeability. TRPA1 is activated through an unusual mechanism in which reactive compounds bind covalently to cysteine and lysine amino acid residues in the N-terminus of the channel protein.

Pathophysiological sustained TRPA1 activation by reactive agonists in sensory neurons may result in axoplasmic calcium dysregulation which causes peripheral axonopathy.

Axonopathy is a common diagnostic finding in chronic pain patients and patients suffering from work-related exposure to neurotoxic compounds. Axonopathy of sensory neurons is often diagnosed in diabetic patients, who suffer from chronic pain, mechanical hypersensitivity, erectile dysfunction, impaired wound healing, numbness, and at later stage, from leg amputations.

Activation of presynaptic TRPA1 facilitates glutamate release from axon terminals of sensory neurons in the spinal cord. Enhanced glutamate release is shown to cause central pain and secondary mechanical hypersensitivity. Spontaneous pain, secondary mechanical hypersensitivity, and mechanical hyperalgesia are common symptoms of neuropathic pain patients. Recently, human TRPA1 gain-of-function mutation carriers were discovered and shown to have enhanced secondary hyperalgesia to peripheral TRPA1 stimulation, which confirms the role of spinal TRPA1 in processing of secondary hyperalgesia. A recent study revealed that spinal TRPA1 plays a key role in neurogenic inflammation reflex, which is evoked by peripheral injury. Neurogenic inflammation is enhanced in several diseases such as fibromyalgia, migraine, complex regional pain syndromes, pain in and around the eye, and urticaria.

TRPA1 activation in the gastrointestinal tract has been shown to release serotonin from enterochromaffin cells. Increased serotonin release induces hypermotility of the gut. Treatment of cancer with reactive compounds increases plasma serotonin level, which is well known to induce nausea and vomiting. TRPA1 activation in airways has been shown to contribute to sensory neuronal hypersensitivity in several airway diseases such as chronic cough, asthma, and chronic obstructive pulmonary disease. TRPA1 activation has been shown to release noradrenaline from superior cervical ganglion sympathetic neurons. Several cardiovascular disorders such as cardiac dysrhythmias and high blood pressure, are well known to be caused by increased plasma noradrenaline level. TRPA1 has been shown to play a critical role in histamine-independent itch transduction. TRPA1 activation has been shown to result in cold hypersensitivity. Cold pain is a common symptom present in several disease conditions such as dental pain, fibromyalgia, complex regional pain syndrome, cancer pain, and neuropathic pain. Selective TRPA1 modulators can be used for treatment of a large number of acute and chronic TRPA1 activation-dependent diseases and symptoms.

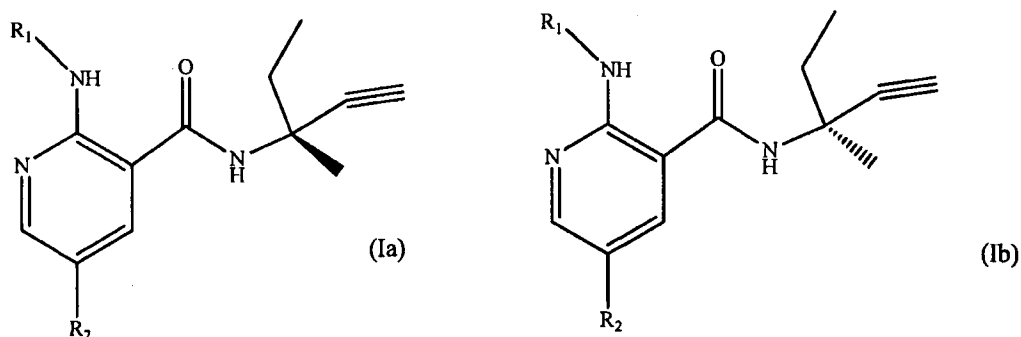
SUMMARY OF THE INVENTION

An object of the present disclosure is to provide novel enantiomers of certain nicotinamide derivatives that can be used for the treatment of disorders, conditions, or diseases mediated by TRPA1 activity. Accordingly, an object of the present disclosure is to provide further
5 enantiomeric compounds to be used as TRPA1 modulators in the treatment of mammals. Furthermore, pharmaceutical compositions comprising the presently disclosed compounds are also provided.

The enantiomers of nicotinamide derivatives of the present disclosure have an enhanced potency and/or improved metabolic stability and/or improved solubility.

10 DETAILED DESCRIPTION OF THE INVENTION

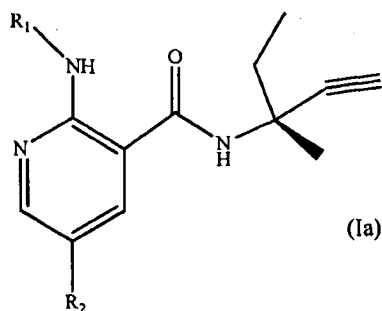
The present disclosure relates to novel compounds having the general formula Ia or formula Ib,



wherein;

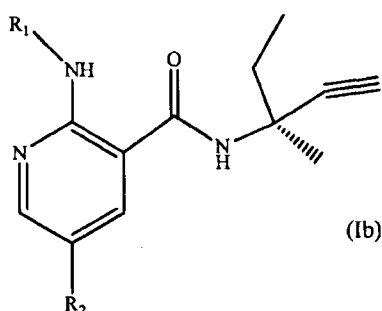
- 15 R_1 is cyclo(C_4 - C_6)alkyl or phenyl, wherein said cyclo(C_4 - C_6)alkyl or phenyl is unsubstituted or substituted with 1 or 2 substituent(s) each independently being halogen, (C_1 - C_2)alkoxy, or CN; and
 R_2 is H or halogen;
or a pharmaceutically acceptable salt thereof.

- 20 In one embodiment the present disclosure relates to compounds of formula Ia,



wherein R_1 and R_2 are as defined above.

In one embodiment the present disclosure relates to compounds of formula Ib,



5 wherein R_1 and R_2 are as defined above.

In one embodiment the present disclosure relates to compounds of formula Ia or Ib, wherein; R_1 is cyclo(C_4 - C_6)alkyl or phenyl, wherein said cyclo(C_4 - C_6)alkyl or phenyl is unsubstituted or substituted with 1 or 2 substituent(s) each independently being fluoro, chloro, methoxy, or CN; and

10 R_2 is H, fluoro or chloro.

In one embodiment the present disclosure relates to compounds of formula Ia or formula Ib, wherein R_1 is C_4 -cycloalkyl substituted with 1 or 2 substituent(s) each independently being halogen; and R_2 is halogen.

In one embodiment the present disclosure relates to compounds of formula Ia or formula Ib,
 15 wherein the compound is (R)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-
 20 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2,4-

difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (S)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (R)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (S)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (R)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, or (S)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to compounds of formula Ia or formula Ib, wherein the compound is enantiomer 1 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, enantiomer 2 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, enantiomer 1 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(3-

chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of
2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of
2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of
2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(2-
5 fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of 2-(4-fluoro-
3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2 of 2-(4-
fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 1 of
2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, enantiomer 2
of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide,
10 enantiomer 1 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide,
enantiomer 2 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide,
enantiomer 1 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide,
enantiomer 2 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide,
enantiomer 1 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-
15 yl)nicotinamide, enantiomer 2 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-
yn-3-yl)nicotinamide, enantiomer 1 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-
methylpent-1-yn-3-yl)nicotinamide, or enantiomer 2 of 2-(2-fluoro-3-
methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-5-chloro-2-(3,3-
20 difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated
from (S)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-
yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-5-chloro-2-(3,3-
difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated
25 from (R)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-
yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(3,3-difluorocyclobutylamino)-5-
fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(3,3-
difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide.

30 In one embodiment the present disclosure relates to (S)-2-(3,3-difluorocyclobutylamino)-5-
fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(3,3-

difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

- 5 In one embodiment the present disclosure relates to (S)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

- In one embodiment the present disclosure relates to (R)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(2,4-
10 difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

- In one embodiment the present disclosure relates to (R)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, substantially separated from (S)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide.
15

In one embodiment the present disclosure relates to (S)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, substantially separated from (R)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide.

- 20 In one embodiment the present disclosure relates to (R)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

- In one embodiment the present disclosure relates to (S)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated
25 from (R)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

5 In one embodiment the present disclosure relates to (R)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

10 In one embodiment the present disclosure relates to (R)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated
15 from (R)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated
20 from (R)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, substantially separated from (S)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide.

25 In one embodiment the present disclosure relates to (S)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, substantially separated from (R)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(4,4-difluorocyclohexylamino)-N-

(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (R)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (S)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to (S)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, substantially separated from (R)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-

yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

- 5 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

- In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as
10 active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

- In one embodiment the present disclosure relates to pharmaceutical composition consisting
15 essentially of (R)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide as active ingredient.

- 20 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

- In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.
25

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

5 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

10 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.
15

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.
20

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide as active ingredient.

25 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting

essentially of (R)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide
5 as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting
10 essentially of (S)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (R)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

15 In one embodiment the present disclosure relates to pharmaceutical composition consisting essentially of (S)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide as active ingredient.

In one embodiment the present disclosure relates to compounds of formula Ia or formula Ib, wherein the compound is not (R)-5-fluoro-2-(3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-5-fluoro-2-(3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-chloro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2-chloro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, 2-(3,3-difluorocyclopentylamino)-5-fluoro-N-((R)-3-methylpent-1-yn-3-yl)nicotinamide, 2-(3,3-difluorocyclopentylamino)-5-fluoro-N-((S)-3-methylpent-1-yn-3-yl)nicotinamide, 2-(3,3-difluorocyclopentylamino)-N-((R)-3-methylpent-1-yn-3-yl)nicotinamide, 2-(3,3-difluorocyclopentylamino)-N-((S)-3-methylpent-1-yn-3-yl)nicotinamide, 5-fluoro-2-(3-fluorocyclobutylamino)-N-((R)-3-methylpent-1-yn-3-yl)nicotinamide, 5-fluoro-2-(3-fluorocyclobutylamino)-N-((S)-3-methylpent-1-yn-3-yl)nicotinamide, 5-chloro-2-(3-fluorocyclobutylamino)-N-((R)-3-methylpent-1-yn-3-yl)nicotinamide, 5-chloro-2-(3-fluorocyclobutylamino)-N-((S)-3-methylpent-1-yn-3-yl)nicotinamide,
20
25
30

yl)nicotinamide, (R)-2-(4,4-difluorocyclohexylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, or (S)-2-(4,4-difluorocyclohexylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide.

The terms employed herein have the meanings indicated below.

- 5 The term “halogen”, as employed herein as such or as part of another group, refers to fluorine, chlorine, bromine, or iodine.

The term “cyclo(C₄-C₆)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having cyclic moiety, containing 4, 5, or 6 carbon atoms.

- 10 Representative examples of cyclo(C₄-C₆)alkyl include, but are not limited to, cyclobutyl, cyclopentyl and cyclohexyl.

The term “(C₁-C₂)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight moiety, containing 1 or 2 carbon atom(s). Representative examples of (C₁-C₂)alkyl include methyl and ethyl.

- 15 The term “(C₁-C₂)alkoxy”, as employed herein as such or as part of another group, refers to an (C₁-C₂)alkyl group, as defined herein, bonded to an oxygen atom. Representative examples of (C₁-C₂)alkoxy include methoxy and ethoxy.

The expression “compounds of the present disclosure” as employed herein refers to the compounds of formula Ia or Ib.

- 20 The term “substantially separated” as employed herein, means that a separated compound of the present disclosure contains greater than 90% by weight of one of the two enantiomers of the compound and less than 10% by weight of the other enantiomer of the compound, preferably greater than 95% by weight of one of the two enantiomers of the compound and less than 5% by weight of the other enantiomer of the compound, even more preferably greater than 97% by weight of one of the two enantiomers of the compound and less than
25 3% by weight of the other enantiomer of the compound.

The term “pharmaceutical composition consisting essentially of” when used in connection with one enantiomer, means that a pharmaceutical composition contains greater than 90% by weight of one of the two enantiomers of the compound and less than 10% by weight of the other enantiomer of the compound, preferably greater than 95% by weight of one of the two

enantiomers of the compound and less than 5% by weight of the other enantiomer of the compound, even more preferably greater than 97% by weight of one of the two enantiomers of the compound and less than 3% by weight of the other enantiomer of the compound.

The term “active ingredient”, as employed herein refers to a compound of formula Ia or Ib
5 that is pharmacologically active and can be used in manufacturing a drug product.

The “pharmaceutically acceptable salts” according to the present disclosure include therapeutically active, non-toxic, base and acid salt forms, which the compounds of formula Ia or Ib are able to form with both organic and inorganic bases and acids. Representative examples of pharmaceutically acceptable base addition salt forms, for example, metal or
10 amine salts, include, but are not limited to, ammonium salts, lithium, sodium, potassium, calcium, magnesium, aluminum and zinc salts, salts with organic bases, such as N-methyl-D-glucamine, hydrabamine salts and salts with amino acids, such as arginine, lysine, and the like. Representative examples of pharmaceutically acceptable acid addition salts include, but are not limited to, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane
15 sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates, acetates and oxalates, fumarates, and succinates.

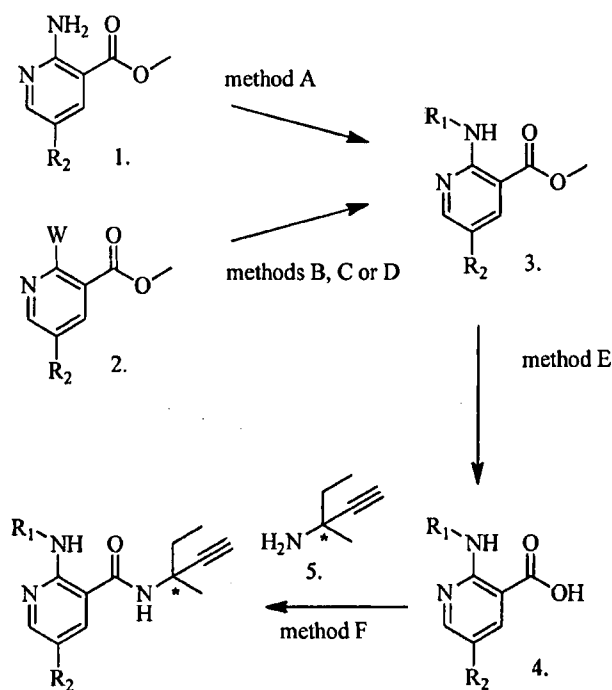
The present disclosure includes all the possible geometric isomers, for example *cis* and *trans* isomers, of the compounds of formula Ia or Ib, as well as all the possible diastereomers of the compound of formula Ia or Ib. Furthermore, the present disclosure includes both the
20 individual isomers and any mixtures thereof.

The compounds of formula Ia or Ib can be prepared by a variety of synthetic routes analogously to, or according to methods known in the literature using suitable starting materials.

Referring to Scheme 1, the compounds of formula Ia or Ib can be prepared from suitably
25 substituted aromatic 1-amino-2-carboxylic esters (1) or aromatic 1-halo-2-carboxylic esters (2). Referring to Scheme 2, the same compounds can be prepared from the corresponding carboxylic acids. The substituent of the amine, R₁, can be attached to the aromatic core, for example, using some of the methods A-D.

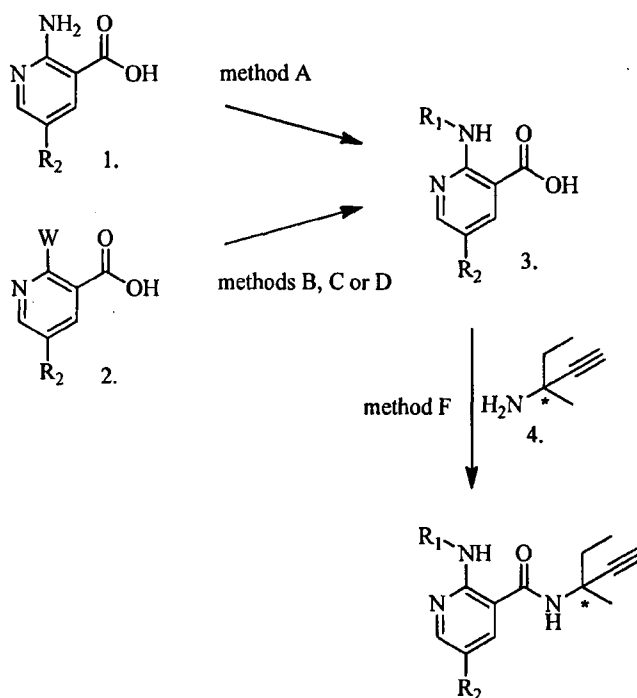
A. Reductive amination, using a suitable aldehyde and a reducing agent, such as sodium
30 tris(acetoxo)borohydride or sodium cyanoborohydride.

- B. The conditions of the Buchwald-Hartwig reaction, using a suitable amine and a suitable Pd-catalyst system.
- C. Aromatic substitution, using a suitable amine, especially when W is F or Cl.
- D. The conditions of the copper mediated Ullman reaction, using a suitable amine and a source of Cu(I), when W is Cl, Br, I or other suitable leaving group.
- 5 E. In those cases where an ester is used, the ester is hydrolysed to give the corresponding acid.
- F. The carboxylic acid can be converted to an amide using a suitable amine and some of the known amide coupling methods, or by converting the carboxylic acid to the corresponding acyl chloride, to form the amides of formula Ia or Ib.
- 10



Scheme 1.

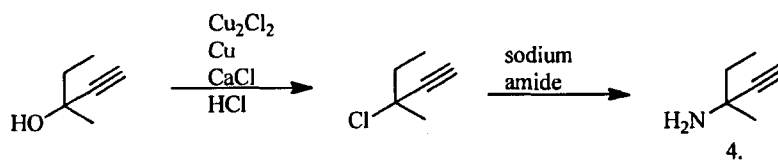
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Scheme 2.

Alternatively, the amide coupling reaction can be performed prior to the construction of the aromatic ring substitution pattern and the attachment of the suitable amine substituent.

- 5 The starting materials depicted above, of formulae 1 and 2, are commercially available or can be prepared *via* synthetic routes known in the literature. The required racemic amines of formula 4, branched at the α -position, are commercially available or can be prepared using the method illustrated in Scheme 3 (Kopka et al, *Journal of Organic Chemistry*, 1980, vol. 45, 4616 – 4622).



10

Scheme 3.

Optically pure amines of formula 4 can be prepared, for example, by chiral SFC chromatography, optical resolution *via* diastereomeric salt formation or by asymmetric synthesis (Patterson et al, *Journal of Organic Chemistry*, 2006, vol. 71, 7110 – 7112).

Alternatively, the enantiomers of compound of formula Ia or Ib may be obtained from the racemic mixtures by using appropriate separation methods for enantiomers. Such methods include, for example, conventional chiral resolution methods such as fractional crystallization or preparative chiral chromatography.

- 5 A person skilled in the art realizes that any starting material or intermediate in the reactions described above can be protected, if necessary, in a manner known in the art. Any protected functionality can subsequently be deprotected in a manner known in the art.

The synthetic routes described above are meant to illustrate the preparation of the compounds of formula Ia or Ib and the preparation is by no means limited thereto, that is,
10 there are also other possible synthetic methods which are within the general knowledge of a person skilled in the art.

The compounds of formula Ia or Ib may be converted, if desired, into their pharmaceutically acceptable salt forms using methods known in the art.

- The present disclosure will be explained in more detail by the following examples. The
15 examples are meant for illustrating purposes only and do not limit the scope of the invention defined in the claims.

Normal phase and reverse phase flash chromatography was performed using CombiFlash instruments together with disposable Redisep columns (Teledyne ISCO). Preparative HPLC purifications were performed with a Waters preparative HPLC/MS autopurification system
20 equipped with an XBridge Prep C18 (5 μ m, 30 x 150 mm) column. Typically, a gradient of water/acetonitrile with 0.1% formic acid was used as eluent. Microwave heating was performed using microwave reactors from Biotage. The structures of the products were confirmed by ¹H NMR. The spectra were measured with a Bruker Avance 400 instrument. LC-MS analyses were performed using a Waters Acquity UPLC/MS/MS with an TQ
25 detector or an Agilent 1290 LC/MS instrument, equipped with Agilent 6150 mass detector. For the chiral HPLC analysis, Agilent 1100-series HPLC instrument equipped with diode array detector was used.

The following general abbreviations are used: Fmoc-Cl = 9-fluorenylmethyl chloroformate, EtOAc = ethyl acetate, SFC = supercritical fluid chromatography, TFA = trifluoroacetic
30 acid, ACN = acetonitrile, DEA = diethylamine, EtOH = ethanol, IPA = isopropyl alcohol,

DMSO-*d*₆ = deuterated dimethyl sulfoxide, CDCl₃ = deuterated chloroform, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DIPEA = N,N-disopropylethylamine, HOBt = 1-hydroxybenzotriazole, DCM = dichloromethane, DMF = N,N-dimethylformamide, MeOD-*d*₄ = deuterated methanol, THF = tetrahydrofuran, TBAF = tetrabutylammonium fluoride, HCl = hydrochloric acid, TMS = trimethylsilyl, HATU = (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)

Preparation of the compounds of the present disclosure

INTERMEDIATE 1: Enantiomers 1 and 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate

Na₂CO₃ (163.9 g, 1546.3 mmol) was added to a stirred solution of 3-methylpent-1-yn-3-amine (50 g, 515.46 mmol) in 1,4-dioxane (500 ml) at 0 °C. Fmoc-Cl (173.7 g, 515.46 mmol) was then added at the same temperature and the mixture was stirred for 16 h at rt. Solvents were evaporated and water (250 ml) was added. Aqueous layer was extracted twice with 200 ml EtOAc. Combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by flash chromatography to give 40 g of the racemic (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate. Enantiomers were further separated with chiral SFC (Chiralcel OZ-H (250x30 mm), CO₂: 0.5 % TFA in ACN (82:12)) to give 13.2 g of Enantiomer 1 and 13.3 g of Enantiomer 2. Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5µm, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.89 (t, 3 H) 1.41 (s, 3 H) 1.58 - 1.96 (m, 2 H) 3.10 (s, 1 H) 4.07 - 4.42 (m, 3 H) 7.30 - 7.36 (m, 2 H) 7.37 - 7.53 (m, 3 H) 7.73 (d, 2 H) 7.89 (d, 2 H).

EXAMPLE 1: Enantiomer 1 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(3,3-difluorocyclobutylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.3 g, 1.934 mmol), 3,3-difluorocyclobutanamine hydrochloride (0.278 g, 1.934 mmol), triethylamine (0.539 ml, 3.87 mmol) and DMF (3 ml) were heated by microwave irradiation at 140 °C for 2 h. Some EtOAc was added and the

organic phase was washed 3 times with H₂O, dried over Na₂SO₄, filtered and evaporated. Crude product was purified by flash chromatography. 0.166 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.42 - 2.66 (m, 2 H) 2.98 - 3.22 (m, 2 H) 3.89 (s, 3 H)
5 4.34 - 4.61 (m, 1 H) 6.60 (dd, 1 H) 8.07 - 8.19 (m, 2 H) 8.29 (dd, 1 H).

Step 2: Methyl 5-chloro-2-(3,3-difluorocyclobutylamino)nicotinate

Methyl 2-(3,3-difluorocyclobutylamino)nicotinate (0.166 g, 0.685 mmol), N-chlorosuccinimide (0.092 g, 0.685 mmol) and DMF (5 ml) were stirred at 65 °C for 7 h. 0.025 g (0.187 mmol) N-chlorosuccinimide was added and the reaction mixture was stirred
10 an additional 1 h at 65 °C. Some water was added and the mixture was acidified with 1M HCl and extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.185 g of the title compound was obtained.

¹H NMR (400 MHz, MeOD-*d*₄) δ ppm 2.45 - 2.64 (m, 2 H) 2.94 - 3.11 (m, 2 H) 3.90 (s, 3 H) 4.32 - 4.42 (m, 1 H) 8.13 (d, 1 H) 8.23 (d, 1 H).

Step 3: 5-Chloro-2-(3,3-difluorocyclobutylamino)nicotinic acid

Lithium hydroxide (0.032 g, 1.337 mmol) was added to a solution of methyl 5-chloro-2-(3,3-difluorocyclobutylamino)nicotinate (0.185 g, 0.669 mmol) in THF (4 ml) and H₂O (2 ml) at 0 °C. The mixture was stirred at rt for 3.5 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4
20 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.159 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.55 - 2.73 (m, 2 H) 2.88 - 3.12 (m, 2 H) 4.26 - 4.42 (m, 1 H) 8.06 (d, 1 H) 8.28 (d, 1 H) 8.32 (d, 1 H).

Step 4: Enantiomer 1 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.136 ml, 0.136 mmol) were stirred in DMF (0.5 ml) at rt for 30 minutes. 5-Chloro-2-(3,3-difluorocyclobutylamino)nicotinic acid (0.049 g, 0.188 mmol), EDCI (0.075g, 0.391 mmol), HOBt (0.011 g, 0.078 mmol) and DIPEA (0.082
30 ml, 0.470 mmol) in DCM (1 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The solvents were evaporated. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 22 mg of the

title compound. Enantiomer 1 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

- 5 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.72 (s, 3 H) 1.84 - 1.97 (m, 1 H) 2.09 - 2.21 (m, 1 H) 2.43 - 2.61 (m, 3 H) 2.96 - 3.11 (m, 2 H) 4.27 - 4.39 (m, 1 H) 5.99 (br. s., 1 H) 7.50 (d, 1 H) 8.15 (d, 1 H) 8.23 (d, 1 H).

EXAMPLE 2: Enantiomer 2 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 10 Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.272 ml, 0.272 mmol) were stirred in DMF (1.0 ml) at rt for 30 minutes. 5-Chloro-2-(3,3-difluorocyclobutylamino)nicotinic acid (0.099 g, 0.376 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.021 g, 0.157 mmol) and DIPEA (0.164 ml, 0.939 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was
- 15 stirred at rt overnight. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 42 mg of the title compound. Enantiomer 2 of 5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.
- 20 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.72 (s, 3 H) 1.83 - 1.98 (m, 1 H) 2.09 - 2.22 (m, 1 H) 2.43 - 2.60 (m, 3 H) 2.96 - 3.11 (m, 2 H) 4.26 - 4.40 (m, 1 H) 6.01 (br. s., 1 H) 7.50 (d, 1 H) 8.15 (d, 1 H) 8.23 (d, 1 H).

EXAMPLE 3: Enantiomer 1 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 25 **Step 1: 2-(3,3-Difluorocyclobutylamino)-5-fluoronicotinic acid**
Methyl 2,5-difluoronicotinate (0.15 g, 0.866 mmol), 3,3-difluorocyclobutanamine hydrochloride (0.124 g, 0.866 mmol) and triethylamine (0.242 ml, 1.733 mmol) in dry ACN (3 ml) were heated in a microwave reactor at 125 °C for 1 hour. The mixture was concentrated to dryness and diluted with THF (6 ml) and water (3 ml). Lithium hydroxide
- 30 (0.062 g, 2.60 mmol) was added at 0 °C and the reaction mixture was stirred at rt for 2 hours. It was concentrated, diluted with water and washed with DCM. pH of the water phase

was then adjusted to 1 by addition of 2 M HCl. The title compound precipitated and was filtered off, washed with water and dried in a vacuum oven. 47 mg of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.54 - 2.65 (m, 2 H) 2.93 - 3.07 (m, 2 H) 4.31 (br. s., 1 H) 7.94 (dd, 1 H) 8.17 (br. s., 1 H) 8.33 (d, 1 H).

Step 2: Enantiomer 1 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-Fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and piperidine (0.037 ml, 0.376 mmol) in DMF (2 ml) were stirred at rt for 75 min. 2-(3,3-Difluorocyclobutylamino)-5-fluoronicotinic acid (0.231 g, 0.939 mmol), EDCI (0.180 g, 0.939 mmol), HOBt (0.042 g, 0.313 mmol) and DIPEA (0.164 ml, 0.939 mmol) in DCM (2 ml) were added to earlier solution and the mixture was stirred at rt for 1 h. Some DCM was added and organic phase was washed twice with water and once with 1 M NaOH. Organic phase was evaporated to dryness and the crude product was purified by preparative HPLC. 0.049 g of the title compound was obtained. Enantiomer 1 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5μm, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.72 (s, 3 H) 1.84 - 1.99 (m, 1 H) 2.07 - 2.23 (m, 1 H) 2.40 - 2.60 (m, 3 H) 2.96 - 3.12 (m, 2 H) 4.24 - 4.40 (m, 1 H) 5.95 (br. s., 1 H) 7.32 (dd, 1 H) 8.04 (d, 1 H) 8.12 (d, 1 H).

EXAMPLE 4: Enantiomer 2 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-Fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and piperidine (0.062 ml, 0.626 mmol) in DMF (2 ml) were stirred at rt for 10 min. 2-(3,3-Difluorocyclobutylamino)-5-fluoronicotinic acid (0.231 g, 0.939 mmol), EDCI (0.180 g, 0.939 mmol), HOBt (0.042 g, 0.313 mmol) and DIPEA (0.164 ml, 0.939 mmol) in DCM (2 ml) were added to earlier solution and the mixture was stirred at rt for 2 days. Some DCM was added and organic phase was washed twice with water and once with 1 M NaOH. Organic phase was evaporated to dryness and the crude product was purified by preparative HPLC. 0.052 g of the title compound was obtained. Enantiomer 2 of 2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of

the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.72 (s, 3 H) 1.84 - 1.98 (m, 1 H) 2.09 - 2.23 (m, 1 H) 2.41 - 2.62 (m, 3 H) 2.94 - 3.13 (m, 2 H) 4.20 - 4.42 (m, 1 H) 5.94 (br. s., 1 H)
5 7.32 (dd, 1 H) 8.04 (d, 1 H) 8.12 (d, 1 H).

EXAMPLE 5: Enantiomer 1 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(4-fluorophenylamino)nicotinate

A mixture of 2-fluoronicotinic acid methyl ester (0.5 g, 3.22 mmol) and 4-fluoroaniline
10 (0.62 ml, 6.45 mmol) was mixed and heated in a microwave reactor at 120 °C for 20 min. The crude product was dissolved in DCM, washed with water, dried and evaporated to dryness. 0.554 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.93 (s, 3 H) 6.71 (dd, 1 H) 6.95 - 7.12 (m, 2 H) 7.55 - 7.70 (m, 2 H) 8.22 (dd, 1 H) 8.34 (dd, 1 H) 10.07 (br. s., 1 H).

15 **Step 2: 2-(4-Fluorophenylamino)nicotinic acid**

To a solution of methyl 2-(4-fluorophenylamino)nicotinate (0.554 g, 2.250 mmol) in methanol/water 4:1 (10 ml) was added potassium hydroxide (0.379 g, 6.75 mmol). The mixture was stirred first at rt for 2 h and then refluxed for 1.5 h. Methanol was evaporated and the remaining aqueous solution was acidified and extracted three times with EtOAc.
20 The organic layers were pooled, dried and evaporated to dryness. 0.47 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.86 (dd, 1 H) 7.12 - 7.21 (m, 2 H) 7.63 - 7.82 (m, 2 H) 8.24 (dd, 1 H) 8.36 (dd, 1 H) 10.38 (s, 1 H) 13.58 (br. s., 1 H).

25 **Step 3: Enantiomer 1 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide**

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.272 ml, 0.272 mmol) were stirred in DMF (1.0 ml) at rt for 60 minutes. 2-(4-Fluorophenylamino)nicotinic acid (0.218 g, 0.939 mmol), EDCI (0.180 g, 0.939 mmol), HOBt (0.042 g, 0.313 mmol) and DIPEA (0.164 ml, 0.939
30 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. Some DCM was added and organic phase was washed twice with water and once

with 1 M NaOH. Organic phase was evaporated to dryness and the crude product was purified by preparative HPLC. 47 mg of the title compound was obtained. Enantiomer 1 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane :

5 EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.74 (s, 3 H) 1.88 - 2.00 (m, 1 H) 2.11 - 2.27 (m, 1 H) 2.45 (s, 1 H) 6.12 (br. s., 1 H) 6.67 (dd, 1 H) 7.00 (t, 2 H) 7.52 - 7.69 (m, 3 H) 8.27 (dd, 1 H) 10.23 (br. s, 1 H).

EXAMPLE 6: Enantiomer 2 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.151 g, 0.474 mmol) and TBAF (1.0 M solution in THF, 0.150 ml, 0.150 mmol) in dry THF (0.5 ml) were stirred at rt for 2 h. 0.07 ml (0.07 mmol) of TBAF solution was added and the mixture was stirred for additional 2h at rt. 2-(4-Fluorophenylamino)nicotinic acid (0.1 g, 0.431 mmol),
15 EDCI (0.206 g, 1.077 mmol), HOBt (0.035 g, 0.258 mmol) and DIPEA (0.375 ml, 2.153 mmol) in dry DCM (5 ml) were added to earlier solution and the mixture was stirred at rt over weekend. Some DCM was added and organic phase was washed once with 1 M NaOH and once with 1 M HCl. Organic phase was evaporated to dryness and the crude product was purified with flash chromatography. 0.049 g of the title compound was obtained.

20 Enantiomer 2 of 2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.75 (s, 3 H) 1.86 - 2.00 (m, 1 H) 2.11 - 2.29 (m, 1 H) 2.45 (s, 1 H) 6.11 (br. s., 1 H) 6.67 (dd, 1 H) 6.96 - 7.06 (m, 2 H) 7.53 - 7.62
25 (m, 2 H) 7.64 (dd, 1 H) 8.28 (dd, 1 H) 10.24 (s, 1 H).

EXAMPLE 7: Enantiomer 1 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(2,4-difluorophenylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.4 g, 2.58 mmol) and 2,4-difluoroaniline (0.310 ml, 3.09 mmol) were heated by microwave irradiation at 130 °C for 20 min. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was dried over Na₂SO₄,

filtered and evaporated. 0.554 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.95 (s, 3 H) 6.76 (dd, 1 H) 6.84 - 6.95 (m, 2 H) 8.26 (dd, 1 H) 8.34 - 8.46 (m, 2 H) 10.19 (br. s., 1 H).

Step 2: 2-(2,4-Difluorophenylamino)nicotinic acid

- 5 Lithium hydroxide (0.100 g, 4.19 mmol) was slowly added to a solution of methyl 2-(2,4-difluorophenylamino)nicotinate (0.554 g, 2.097 mmol) in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was stirred at rt overnight. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over
- 10 Na₂SO₄, filtered and evaporated. 0.455 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.92 (dd, 1 H) 7.04 - 7.14 (m, 1 H) 7.34 (ddd, 1 H) 8.27 (dd, 1 H) 8.39 (dd, 1 H) 8.46 (td, 1 H) 10.47 (s, 1 H) 13.69 (br. s., 1 H).

Step 3: Enantiomer 1 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 15 Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 2-(2,4-Difluorophenylamino)nicotinic acid (0.078 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight.
- 20 The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 39 mg of the title compound. Enantiomer 1 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5μm, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.
- 25 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.77 (s, 3 H) 1.89 - 1.98 (m, 1 H) 2.19 - 2.28 (m, 1 H) 2.44 (s, 1 H) 6.11 (br. s., 1 H) 6.72 (dd, 1 H) 6.81 - 6.92 (m, 2 H) 7.67 (dd, 1 H) 8.20 (td, 1 H) 8.29 (dd, 1 H) 10.20 (br. s., 1 H).

EXAMPLE 8: Enantiomer 2 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 30 Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5

ml) at rt overnight. 2-(2,4-Difluorophenylamino)nicotinic acid (0.078 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 49 mg of the title compound. Enantiomer 2 of 2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (99:1), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.77 (s, 3 H) 1.88 - 2.00 (m, 1 H) 2.17 - 2.31 (m, 1 H) 2.44 (s, 1 H) 6.12 (br. s., 1 H) 6.72 (dd, 1 H) 6.80 - 6.95 (m, 2 H) 7.67 (dd, 1 H) 8.20 (td, 1 H) 8.29 (dd, 1 H) 10.20 (br. s., 1 H).

EXAMPLE 9: Enantiomer 1 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)-nicotinamide

Step 1: 2-(Phenylamino)nicotinic acid

2-Fluoronicotinic acid methyl ester (0.50 g, 3.22 mmol) and aniline (0.587 ml, 6.45 mmol) were heated in a microwave reactor at 120 °C for 20 minutes. The reaction mixture was dissolved in DCM (30 ml) and washed twice with water. The organic phase was dried with Na₂SO₄ and concentrated. The crude product (0.716 g) was redissolved in methanol (5 ml) and water (2 ml), potassium hydroxide (0.528 g, 9.41 mmol) was added and the mixture was stirred at rt for 3 hours. Methanol was evaporated and the reaction mixture was diluted with water. pH was adjusted to 2 by addition of 1 M HCl and the mixture was extracted twice with EtOAc, dried with Na₂SO₄ and concentrated to dryness. 0.653 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.87 (dd, 1 H) 7.02 (tt, 1 H) 7.26 - 7.39 (m, 2 H) 7.69 - 7.77 (m, 2 H) 8.26 (dd, 1 H) 8.40 (dd, 1 H) 10.44 (s, 1 H) 13.58 (br. s., 1 H).

Step 2: Enantiomer 1 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 2-(Phenylamino)nicotinic acid (0.067 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as

eluent to give 35 mg of the title compound. Enantiomer 1 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.75 (s, 3 H) 1.88 - 1.98 (m, 1 H) 2.14 - 2.25 (m, 1 H) 2.44 (s, 1 H) 6.09 (br. s., 1 H) 6.68 (dd, 1 H) 6.98 - 7.05 (m, 1 H) 7.31 (dd, 2 H) 7.61 - 7.70 (m, 3 H) 8.31 (dd, 1 H) 10.26 (br. s. 1 H).

EXAMPLE 10: Enantiomer 2 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)-nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(Phenylamino)nicotinic acid (0.067 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 43 mg of the title compound. Enantiomer 2 of N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.86 - 1.98 (m, 1 H) 2.14 - 2.28 (m, 1 H) 2.44 (s, 1 H) 6.09 (br. s., 1 H) 6.68 (dd, 1 H) 6.97 - 7.06 (m, 1 H) 7.31 (dd, 2 H) 7.62 - 7.70 (m, 3 H) 8.31 (dd, 1 H) 10.25 (br. s, 1 H).

EXAMPLE 11: Enantiomer 1 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(3-chloro-4-methoxyphenylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.3 g, 1.934 mmol) and 3-chloro-p-anisidine (0.494 ml, 3.87 mmol) were heated by microwave irradiation at 120 °C for 20 min. Some DCM was added and the mixture was washed twice with H₂O and twice with 2 M HCl. Organic phase was dried over Na₂SO₄, filtered and evaporated. 0.150 g of the title compound was obtained. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.89 (s, 3 H) 3.93 (s, 3 H) 6.71 (dd, 1 H) 6.91 (d, 1 H) 7.45 (dd, 1 H) 7.81 (d, 1 H) 8.22 (dd, 1 H) 8.35 (dd, 1 H) 10.00 (s, 1 H).

Step 2: 2-(3-Chloro-4-methoxyphenylamino)nicotinic acid

Lithium hydroxide (0.025 g, 1.025 mmol) was added to a solution of methyl 2-(3-chloro-4-

methoxyphenylamino)nicotinate (0.150 g, 0.512 mmol) in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was stirred at rt for 2.5 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.092 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.83 (s, 3 H) 6.85 (dd, 1 H) 7.11 (d, 1 H) 7.46 (dd, 1 H) 7.98 (d, 1 H) 8.23 (dd, 1 H) 8.38 (dd, 1 H) 10.31 (s, 1 H) 13.61 (br. s., 1 H).

Step 3: Enantiomer 1 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(3-Chloro-4-methoxyphenylamino)nicotinic acid (0.044 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBt (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 32 mg of the title compound. Enantiomer 1 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5µm, hexane : EtOH (+ 0.1 % DEA) (95:5), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.87 - 2.00 (m, 1 H) 2.12 - 2.26 (m, 1 H) 2.45 (s, 1 H) 3.88 (s, 3 H) 6.10 (br. s., 1 H) 6.67 (dd, 1 H) 6.89 (d, 1 H) 7.43 (dd, 1 H) 7.64 (dd, 1 H) 7.80 (d, 1 H) 8.29 (dd, 1 H) 10.21 (br. s., 1 H).

EXAMPLE 12: Enantiomer 2 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(3-Chloro-4-methoxyphenylamino)nicotinic acid (0.044 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBt (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 28 mg of the title compound. Enantiomer 2 of 2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the

latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (95:5), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.75 (s, 3 H) 1.87 - 1.98 (m, 1 H) 2.11 - 2.27 (m, 1 H) 2.45 (s, 1 H) 3.88 (s, 3 H) 6.11 (br. s, 1 H) 6.67 (dd, 1 H) 6.89 (d, 1 H) 7.42 (dd, 1 H) 7.64 (dd, 1 H) 7.80 (d, 1 H) 8.29 (dd, 1 H) 10.21 (br. s, 1 H).

EXAMPLE 13: Enantiomer 1 of 2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(3-cyano-4-fluorophenylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.3 g, 1.934 mmol) and 3-cyano-4-fluoroaniline (0.253 ml, 2.321 mmol) were heated by microwave irradiation at 120 °C for 80 min. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was dried over Na₂SO₄, filtered and evaporated. 0.461 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.96 (s, 3 H) 6.84 (dd, 1 H) 7.12 - 7.20 (m, 1 H) 7.73 (ddd, 1 H) 8.28 (dd, 1 H) 8.33 (dd, 1 H) 8.41 (dd, 1 H) 10.34 (s, 1 H).

Step 2: 2-(3-Cyano-4-fluorophenylamino)nicotinic acid

Lithium hydroxide (0.081 g, 3.40 mmol) was slowly added to a solution of methyl 2-(3-cyano-4-fluorophenylamino)nicotinate (0.461 g, 1.700 mmol) in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was stirred at rt for 3.5 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl. Formed precipitate was filtrated, washed with small amount of H₂O and dried in the vacuum oven at 40 °C. 0.365 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.96 (dd, 1 H) 7.48 (t, 1 H) 7.99 (ddd, 1 H) 8.28 (dd, 1 H) 8.38 (dd, 1 H) 8.43 (dd, 1 H) 10.52 (s, 1 H) 13.80 (br. s, 1 H).

Step 3: Enantiomer 1 of 2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 2-(3-Cyano-4-fluorophenylamino)nicotinic acid (0.081 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The following morning, EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188

mmol) and DIPEA (0.273 ml, 1.565 mmol) were added to the reaction mixture and it was stirred at rt for 2.5 hours. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 45 mg of the title compound. Enantiomer 1 of 2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first
5 of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (80:20), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.88 - 1.99 (m, 1 H) 2.13 - 2.26 (m, 1 H) 2.46 (s, 1 H) 6.16 (br. s, 1 H) 6.79 (dd, 1 H) 7.09 - 7.16 (m, 1 H) 7.64 - 7.73 (m, 2 H) 8.27 - 8.36 (m, 2 H) 10.63 (br. s, 1 H).

10 **EXAMPLE 14: Enantiomer 2 of 2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide**

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(3-Cyano-4-fluorophenylamino)nicotinic acid (0.081 g, 0.313 mmol),
15 EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent. Combined fractions were evaporated and diluted with DCM. Water was added and pH of the aqueous phase was adjusted to 4. After stirring for a while,
20 the phases were separated and organic phase was washed once with water, dried and evaporated to dryness to give 34 mg of the title compound. Enantiomer 2 of 2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (80:20), 1 ml/min.

25 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.88 - 1.99 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.46 (s, 1 H) 6.15 (br. s, 1 H) 6.79 (dd, 1 H) 7.09 - 7.15 (m, 1 H) 7.64 - 7.73 (m, 2 H) 8.27 - 8.37 (m, 2 H) 10.63 (br. s, 1 H).

EXAMPLE 15: Enantiomer 1 of 2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

30 **Step 1: Methyl 2-(2-fluorophenylamino)nicotinate**

A mixture of 2-fluoronicotinic acid methyl ester (0.5 g, 3.22 mmol) and 2-fluoroaniline

(0.622 ml, 6.45 mmol) was heated in a microwave oven at 120 °C for 30 minutes. The reaction mixture was then dissolved in DCM and washed twice with water. The organic phase was dried and concentrated. The crude product was purified by trituration with diethyl ether. 0.502 g of the title compound was obtained.

5 ¹H NMR (400 MHz, CDCl₃) δ ppm 3.95 (s, 3 H) 6.77 (dd, 1 H) 6.95 - 7.02 (m, 1 H) 7.10 - 7.17 (m, 2 H) 8.26 (dd, 1 H) 8.40 (dd, 1 H) 8.55 (td, 1 H) 10.37 (br. s., 1 H).

Step 2: 2-(2-Fluorophenylamino)nicotinic acid

A mixture of methyl 2-(2-fluorophenylamino)nicotinate (0.502 g, 2.039 mmol) and potassium hydroxide (0.343 g, 6.12 mmol) in methanol (8 ml) and water (2 ml) was refluxed
10 for 1 h. Methanol was evaporated, the mixture was diluted with water and pH was adjusted to 2 by addition of 2 M HCl. The solution was then extracted three times with EtOAc. The combined organic phases were dried and concentrated. 0.419 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.94 (dd, 1 H) 7.00 - 7.07 (m, 1 H) 7.19 (t, 1 H) 7.27
15 (ddd, 1 H) 8.29 (dd, 1 H) 8.43 (dd, 1 H) 8.58 (td, 1 H) 10.65 (d, 1 H) 13.70 (br. s., 1 H).

Step 3: Enantiomer 1 of 2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)-nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0
20 ml) at rt overnight. 2-(2-Fluorophenylamino)nicotinic acid (0.073 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 39 mg of the title compound. Enantiomer 1 of 2-(2-
25 fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5µm, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.77 (s, 3 H) 1.89 - 1.98 (m, 1 H) 2.20 - 2.29 (m, 1 H) 2.44 (s, 1 H) 6.12 (br. s., 1 H) 6.73 (dd, 1 H) 6.91 - 7.02 (m, 1 H) 7.05 - 7.15
30 (m, 2 H) 7.68 (dd, 1 H) 8.28 - 8.39 (m, 2 H) 10.30 (br. s., 1 H).

EXAMPLE 16: Enantiomer 2 of 2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)-nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(2-Fluorophenylamino)nicotinic acid (0.073 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 41 mg of the title compound. Enantiomer 2 of 2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.77 (s, 3 H) 1.87 - 2.00 (m, 1 H) 2.18 - 2.32 (m, 1 H) 2.44 (s, 1 H) 6.12 (br. s., 1 H) 6.73 (dd, 1 H) 6.92 - 7.02 (m, 1 H) 7.05 - 7.16 (m, 2 H) 7.68 (dd, 1 H) 8.29 - 8.39 (m, 2 H) 10.30 (br. s., 1 H).

EXAMPLE 17: Enantiomer 1 of 2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide**Step 1: Methyl 2-(4-fluoro-3-methoxyphenylamino)nicotinate**

2-Fluoronicotinic acid methyl ester (0.3 g, 1.934 mmol) and 4-fluoro-3-methoxyaniline (0.273 g, 1.934 mmol) were heated by microwave irradiation at 120 °C for 30 min. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was dried over Na₂SO₄, filtered and evaporated. 0.442 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.91 (s, 3 H) 3.94 (s, 3 H) 6.72 (dd, 1 H) 7.03 (dd, 1 H) 7.14 (ddd, 1 H) 7.46 (dd, 1 H) 8.24 (dd, 1 H) 8.36 (dd, 1 H) 10.10 (br. s., 1 H).

Step 2: 2-(4-Fluoro-3-methoxyphenylamino)nicotinic acid

Lithium hydroxide (0.073 g, 3.06 mmol) was slowly added to a solution of methyl 2-(4-fluoro-3-methoxyphenylamino)nicotinate (0.422 g, 1.528 mmol) in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was stirred at rt for 4 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.312 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.85 (s, 3 H) 6.86 (dd, 1 H) 7.13 (dd, 1 H) 7.27 (ddd, 1 H) 7.54 (dd, 1 H) 8.24 (dd, 1 H) 8.37 (dd, 1 H) 10.52 (br. s., 1 H).

Step 3: Enantiomer 1 of 2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 5 Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(4-Fluoro-3-methoxyphenylamino)nicotinic acid (0.041 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBt (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred
- 10 at rt overnight. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 31 mg of the title compound. Enantiomer 1 of 2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5μm, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.
- 15 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.88 - 2.00 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.45 (s, 1 H) 3.90 (s, 3 H) 6.11 (br. s., 1 H) 6.69 (dd, 1 H) 7.01 (dd, 1 H) 7.15 - 7.21 (m, 1 H) 7.36 (dd, 1 H) 7.65 (dd, 1 H) 8.30 (dd, 1 H) 10.28 (br. s., 1 H).

EXAMPLE 18: Enantiomer 2 of 2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 20 Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(4-Fluoro-3-methoxyphenylamino)nicotinic acid (0.041 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBt (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred
- 25 at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent. Combined fractions were evaporated and diluted with DCM. Water was added and pH of the aqueous phase was adjusted to 4. After stirring for a while, the phases were separated and organic phase was washed twice with water and one with brine, dried and evaporated to dryness to give 24 mg of the title compound.
- 30 Enantiomer 2 of 2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5μm, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.87 - 2.00 (m, 1 H) 2.12 - 2.25 (m, 1 H) 2.45 (s, 1 H) 3.90 (s, 3 H) 6.11 (br. s., 1 H) 6.69 (dd, 1 H) 7.01 (dd, 1 H) 7.15 - 7.21 (m, 1 H) 7.36 (dd, 1 H) 7.65 (dd, 1 H) 8.30 (dd, 1 H) 10.28 (br. s., 1 H).

EXAMPLE 19: Enantiomer 1 of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(2-fluoro-5-methoxyphenylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.3 g, 1.934 mmol) and 2-fluoro-5-methoxyaniline (0.278 ml, 2.321 mmol) were heated by microwave irradiation at 130 °C for 20 min. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was dried over Na₂SO₄, filtered and evaporated. Crude product was purified by trituration with diethyl ether. 0.324 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.82 (s, 3 H) 3.95 (s, 3 H) 6.49 (dt, 1 H) 6.78 (dd, 1 H) 7.03 (dd, 1 H) 8.27 (dd, 1 H) 8.33 (dd, 1 H) 8.42 (dd, 1 H) 10.42 (br. s., 1 H).

Step 2: 2-(2-Fluoro-5-methoxyphenylamino)nicotinic acid

Lithium hydroxide (0.056 g, 2.346 mmol) was slowly added to a solution of methyl 2-(2-fluoro-5-methoxyphenylamino)nicotinate (0.324 g, 1.173 mmol) in THF (4 ml) and H₂O (2 ml) at 0 °C. The mixture was first stirred at rt for 2 h and then at 40 °C for 1.5 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc.

Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.290 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.75 (s, 3 H) 6.56 (dt, 1 H) 6.95 (dd, 1 H) 7.18 (dd, 1 H) 8.25 - 8.35 (m, 2 H) 8.46 (dd, 1 H) 10.76 (br. s., 1 H).

Step 3: Enantiomer 1 of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(2-Fluoro-5-methoxyphenylamino)nicotinic acid (0.041 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBt (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The crude product was purified with flash chromatography using gradient of

heptane and EtOAc as eluent to give 40 mg of the title compound. Enantiomer 1 of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.

- 5 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.77 (s, 3 H) 1.86 - 2.01 (m, 1 H) 2.18 - 2.33 (m, 1 H) 2.43 (s, 1 H) 3.80 (s, 3 H) 6.11 (br. s., 1 H) 6.47 (dt, 1 H) 6.74 (dd, 1 H) 7.00 (dd, 1 H) 7.68 (dd, 1 H) 8.13 (dd, 1 H) 8.34 (dd, 1 H) 10.36 (br. s., 1 H).

EXAMPLE 20: Enantiomer 2 of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

- 10 Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.05 g, 0.157 mmol) and TBAF (1.0 M solution in THF, 0.054 ml, 0.054 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(2-Fluoro-5-methoxyphenylamino)nicotinic acid (0.041 g, 0.157 mmol), EDCI (0.075 g, 0.391 mmol), HOBT (0.013 g, 0.094 mmol) and DIPEA (0.136 ml, 0.783 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred
- 15 at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 24 mg of the title compound. Enantiomer 2 of 2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.
- 20 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.77 (s, 3 H) 1.85 - 2.02 (m, 1 H) 2.18 - 2.32 (m, 1 H) 2.43 (s, 1 H) 3.80 (s, 3 H) 6.13 (br. s., 1 H) 6.47 (dt, 1 H) 6.74 (dd, 1 H) 7.00 (dd, 1 H) 7.68 (dd, 1 H) 8.13 (dd, 1 H) 8.34 (dd, 1 H) 10.36 (br. s., 1 H).

EXAMPLE 21: Enantiomer 1 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide

- 25 **Step 1: Methyl 5-fluoro-2-(phenylamino)nicotinate**
Methyl 2,5-difluoronicotinate (1.0 g, 5.78 mmol) and aniline (0.526 ml, 5.78 mmol) were heated by microwave irradiation at 150 °C for 1 h. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was concentrated to dryness and purified by flash chromatography. 0.446 g of the title compound was obtained.
- 30 ¹H NMR (400 MHz, CDCl₃) δ ppm 3.95 (s, 3 H) 7.06 (tt, 1 H) 7.29 - 7.38 (m, 2 H) 7.62 - 7.68 (m, 2 H) 7.98 (dd, 1 H) 8.28 (d, 1 H) 10.01 (br. s., 1 H).

Step 2: 5-fluoro-2-(phenylamino)nicotinic acid

Lithium hydroxide (0.087 g, 3.62 mmol) was slowly added to a solution of methyl 5-fluoro-2-(phenylamino)nicotinate (0.446 g, 1.811 mmol in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was stirred at rt for 2 h. THF was evaporated, some water was added and the

5 mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.392 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) 7.01 (tt, 1 H) 7.25 - 7.39 (m, 2 H) 7.61 - 7.72 (m, 2 H) 8.09 (dd, 1 H) 8.43 (d, 1 H) 10.36 (br. s., 1 H).

10 **Step 3: Enantiomer 1 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)-nicotinamide**

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 5-Fluoro-2-(phenylamino)nicotinic acid (0.073 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in

15 DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The following morning, EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) were added and the mixture was stirred for 2.5 hours. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 43 mg of the title compound. Enantiomer 1 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μm, hexane : IPA (98:2), 1 ml/min.

20 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.74 (s, 3 H) 1.88 - 1.97 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.45 (s, 1 H) 6.04 (br. s., 1 H) 7.02 (tt, 1 H) 7.31 (dd, 2 H) 7.42 (dd, 1 H) 7.57 - 7.63 (m, 2 H) 8.21 (d, 1 H) 9.99 (br. s., 1 H).

25 **EXAMPLE 22: Enantiomer 2 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)-nicotinamide**

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 5-Fluoro-2-(phenylamino)nicotinic acid (0.073 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in

DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven

days. The crude product was purified by preparative HPLC. 19 mg of the title compound was obtained. Enantiomer 2 of 5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

- 5 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.08 (t, 3 H) 1.74 (s, 3 H) 1.88 - 1.97 (m, 1 H) 2.12 - 2.25 (m, 1 H) 2.45 (s, 1 H) 6.05 (br. s., 1 H) 7.01 (tt, 1 H) 7.31 (dd, 2 H) 7.42 (dd, 1 H) 7.57 - 7.63 (m, 2 H) 8.20 (d, 1 H) 9.99 (br. s, 1 H).

EXAMPLE 23: Enantiomer 1 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

10 **Step 1: 2-(4,4-Difluorocyclohexylamino)nicotinic acid**

- 2-Fluoronicotinic acid methyl ester (0.30 g, 1.934 mmol), 4,4-difluorocyclohexylamine hydrochloride (0.332 g, 1.934 mmol) and triethylamine (0.539 ml, 3.87 mmol) in ACN (3 ml) were heated in a microwave oven at 125 °C for 3 h. The formed precipitate was filtered off and rinsed with ACN. The filtrate was concentrated, some diethyl ether was added, and
15 the precipitate was filtered off. The filtrate was concentrated to dryness (0.404 g) and redissolved in methanol (8 ml) and water (2 ml), potassium hydroxide (0.252 g, 4.48 mmol) was added and the mixture was stirred at rt overnight. Methanol was evaporated, the mixture was diluted with water and pH was adjusted to 2 by addition of 2 M HCl. The solution was extracted 3 times with EtOAc. The combined organic phases were dried and concentrated.
20 0.328 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.42 - 1.67 (m, 2 H) 1.89 - 2.13 (m, 6 H) 4.15 (m, 1 H) 6.63 (dd, 1 H) 8.10 (dd, 1 H) 8.14 (m, 1 H) 8.27 (dd, 1 H) 13.48 (br. s., 1 H).

Step 2: Enantiomer 1 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)-nicotinamide

- 25 Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.272 ml, 0.272 mmol) were stirred in DMF (1.0 ml) at rt for 1 hour. 2-(4,4-Difluorocyclohexylamino)nicotinic acid (0.096 g, 0.376 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.021 g, 0.157 mmol) and DIPEA (0.164 ml, 0.939 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt
30 overnight. Some DCM was added and organic phase was washed twice with water and once with 1 M NaOH. Organic phase was evaporated to dryness and the crude product was purified by preparative HPLC. 40 mg of the title compound was obtained. Enantiomer 1 of

2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Lux 3 μ Amylose-2 (4.6x250mm), 3 μ m, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.06 (t, 3 H) 1.59 - 1.77 (m, 5 H) 1.80 - 2.01 (m, 3 H)
5 2.03 - 2.22 (m, 5 H) 2.42 (s, 1 H) 4.06 - 4.22 (m, 1 H) 5.99 (br. s., 1 H) 6.48 (dd, 1 H) 7.52 (dd, 1 H) 8.06 (d, 1 H) 8.19 (dd, 1 H).

EXAMPLE 24: Enantiomer 2 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313
10 mmol) and TBAF (1.0 M solution in THF, 0.272 ml, 0.272 mmol) were stirred in DMF (1.0 ml) at rt overnight. 2-(4,4-Difluorocyclohexylamino)nicotinic acid (0.096 g, 0.376 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.021 g, 0.157 mmol) and DIPEA (0.164 ml, 0.939 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. Some DCM was added and organic phase was washed twice with water and once
15 with 1 M NaOH. Organic phase was evaporated to dryness and the crude product was purified by preparative HPLC. 35 mg of the title compound was obtained. Enantiomer 2 of 2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Lux 3 μ Amylose-2 (4.6x250mm), 3 μ m, hexane : EtOH (+ 0.1 % DEA) (90:10), 1 ml/min.
20 ¹H NMR (400 MHz, CDCl₃) δ ppm 1.06 (t, 3 H) 1.64 - 1.75 (m, 5 H) 1.81 - 2.01 (m, 3 H) 2.02 - 2.23 (m, 5 H) 2.42 (s, 1 H) 4.07 - 4.22 (m, 1 H) 5.98 (br. s., 1 H) 6.49 (dd, 1 H) 7.52 (dd, 1 H) 8.00 - 8.11 (m, 1 H) 8.20 (dd, 1 H).

EXAMPLE 25: Enantiomer 1 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

25 **Step 1: Methyl 2-(3-fluoro-5-methoxyphenylamino)nicotinate**

2-Fluoronicotinic acid methyl ester (0.4 g, 2.58 mmol) and 3-fluoro-5-methoxyaniline (0.354 ml, 3.09 mmol) were heated by microwave irradiation at 120 °C for 50 min. 0.1 ml (0.873 mmol) of 3-fluoro-5-methoxyaniline was added and the mixture was irradiated for 30 min at 120 °C. Some DCM was added and the mixture was washed twice with H₂O. Organic
30 phase was dried over Na₂SO₄, filtered and evaporated. Crude product was purified by trituration with diethyl ether. 0.293 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.78 (s, 3 H) 3.91 (s, 3 H) 6.48 (dt, 1 H) 6.96 (dd, 1 H) 7.03 - 7.11 (m, 1 H) 7.42 (dt, 1 H) 8.29 (dd, 1 H) 8.48 (dd, 1 H) 10.20 (s, 1 H).

Step 2: 2-(3-Fluoro-5-methoxyphenylamino)nicotinic acid

Lithium hydroxide (0.051 g, 2.121 mmol) was slowly added to a solution of methyl 2-(3-fluoro-5-methoxyphenylamino)nicotinate (0.293 g, 1.061 mmol) in THF (4 ml) and H₂O (2 ml) at 0 °C. The mixture was stirred at rt for 2 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc. Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.273 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.77 (s, 3 H) 6.46 (dt, 1 H) 6.93 (dd, 1 H) 7.04 - 7.12 (m, 1 H) 7.41 (dt, 1 H) 8.27 (dd, 1 H) 8.44 (dd, 1 H) 10.59 (br. s., 1 H) 13.66 (s, 1 H).

Step 3: Enantiomer 1 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (1.0 ml) at rt overnight. 2-(3-Fluoro-5-methoxyphenylamino)nicotinic acid (0.082 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBT (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The crude product was purified by preparative HPLC. 22 mg of the title compound was obtained. Enantiomer 1 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μm, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.86 - 1.99 (m, 1 H) 2.13 - 2.25 (m, 1 H) 2.45 (s, 1 H) 3.80 (s, 3 H) 6.11 (br. s., 1 H) 6.29 (dt, 1 H) 6.73 (dd, 1 H) 6.95 - 7.00 (m, 1 H) 7.30 (dt, 1 H) 7.66 (dd, 1 H) 8.35 (dd, 1 H) 10.44 (br. s., 1 H).

EXAMPLE 26: Enantiomer 2 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(3-Fluoro-5-methoxyphenylamino)nicotinic acid (0.082 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBT (0.025 g, 0.188 mmol) and DIPEA (0.273 ml,

1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 36 mg of the title compound. Enantiomer 2 of 2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.09 (t, 3 H) 1.75 (s, 3 H) 1.85 - 1.99 (m, 1 H) 2.12 - 2.26 (m, 1 H) 2.45 (s, 1 H) 3.80 (s, 3 H) 6.11 (br. s, 1 H) 6.29 (dt, 1 H) 6.73 (dd, 1 H) 6.95 - 7.00 (m, 1 H) 7.30 (dt, 1 H) 7.66 (dd, 1 H) 8.34 (dd, 1 H) 10.44 (br. s, 1 H).

EXAMPLE 27: Enantiomer 1 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Step 1: Methyl 2-(2-fluoro-3-methoxyphenylamino)nicotinate

2-Fluoronicotinic acid methyl ester (0.4 g, 2.58 mmol) and 2-fluoro-3-methoxyaniline (0.340 ml, 2.84 mmol) were heated by microwave irradiation at 120 °C for 45 min. Some DCM was added and the mixture was washed twice with H₂O. Organic phase was dried over Na₂SO₄, filtered and evaporated. 0.633 g of the title compound was obtained.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.91 (s, 3 H) 3.95 (s, 3 H) 6.68 (td, 1 H) 6.76 (dd, 1 H) 7.05 (td, 1 H) 8.08 (ddd, 1 H) 8.26 (dd, 1 H) 8.39 (dd, 1 H) 10.30 (br. s., 1 H).

Step 2: 2-(2-Fluoro-3-methoxyphenylamino)nicotinic acid

Lithium hydroxide (0.110 g, 4.58 mmol) was slowly added to a solution of methyl 2-(2-fluoro-3-methoxyphenylamino)nicotinate (0.633 g, 2.291 mmol) in THF (6 ml) and H₂O (3 ml) at 0 °C. The mixture was first stirred at rt for 2 h and then at 40 °C for 2 h. THF was evaporated, some water was added and the mixture was washed once with DCM. pH of the water phase was adjusted to 4 with 2 M HCl and it was extracted 3 times with EtOAc.

Combined organic phases were dried over Na₂SO₄, filtered and evaporated. 0.495 g of the title compound was obtained.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.85 (s, 3 H) 6.84 (td, 1 H) 6.93 (dd, 1 H) 7.09 (td, 1 H) 8.13 (ddd, 1 H) 8.28 (dd, 1 H) 8.42 (dd, 1 H) 10.62 (br. s., 1 H) 12.48 - 15.12 (m, 1 H).

Step 3: Enantiomer 1 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 1 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313

mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(2-Fluoro-3-methoxyphenylamino)nicotinic acid (0.082 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt overnight. The following morning, EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) were added and the mixture was stirred for 2.5 hours. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 41 mg of the title compound. Enantiomer 1 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the first of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.77 (s, 3 H) 1.86 - 2.00 (m, 1 H) 2.16 - 2.32 (m, 1 H) 2.43 (s, 1 H) 3.89 (s, 3 H) 6.10 (br. s., 1 H) 6.62 - 6.76 (m, 2 H) 7.02 (td, 1 H) 7.67 (dd, 1 H) 7.88 (ddd, 1 H) 8.31 (dd, 1 H) 10.21 (br. s., 1 H).

EXAMPLE 28: Enantiomer 2 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide

Enantiomer 2 of (9H-fluoren-9-yl)methyl 3-methylpent-1-yn-3-ylcarbamate (0.1 g, 0.313 mmol) and TBAF (1.0 M solution in THF, 0.109 ml, 0.109 mmol) were stirred in THF (0.5 ml) at rt overnight. 2-(2-Fluoro-3-methoxyphenylamino)nicotinic acid (0.082 g, 0.313 mmol), EDCI (0.150 g, 0.783 mmol), HOBt (0.025 g, 0.188 mmol) and DIPEA (0.273 ml, 1.565 mmol) in DCM (2 ml) were added to the earlier solution and the mixture was stirred at rt for seven days. The crude product was purified with flash chromatography using gradient of heptane and EtOAc as eluent to give 54 mg of the title compound. Enantiomer 2 of 2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide was the latter of the two enantiomers to be eluted when using column Chiralpak AS-H (4.6x250 mm), 5 μ m, hexane : IPA (98:2), 1 ml/min.

¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (t, 3 H) 1.77 (s, 3 H) 1.86 - 2.00 (m, 1 H) 2.16 - 2.32 (m, 1 H) 2.43 (s, 1 H) 3.89 (s, 3 H) 6.10 (br. s., 1 H) 6.62 - 6.76 (m, 2 H) 7.02 (td, 1 H) 7.67 (dd, 1 H) 7.88 (ddd, 1 H) 8.31 (dd, 1 H) 10.21 (br. s., 1 H).

As already mentioned hereinbefore, the compounds of formula Ia or Ib show interesting pharmacological properties, namely they exhibit TRPA1 activity. The said activity is demonstrated with the pharmacological test presented below.

EXPERIMENT 1: Determination of TRPA1 activity *in vitro*

The illustrative examples of the present disclosure were screened for TRPA1 activity according to a procedure described in Wei et al., *Anesthesiology* **111** (2009) 147-154. The results are shown in Table 1.

Compound of example	IC50 (μM)	Compound of example	IC50 (μM)	Compound of example	IC50 (μM)	Compound of example	IC50 (μM)
1	0.01	8	0.51	15	0.29	22	0.29
2	0.09	9	0.17	16	0.65	23	0.14
3	0.10	10	0.44	17	0.72	24	0.43
4	0.37	11	0.45	18	1.40	25	0.42
5	0.24	12	0.53	19	1.16	26	0.49
6	0.23	13	0.45	20	2.62	27	2.49
7	0.15	14	0.50	21	0.14	28	5.57

Table 1. TRPA1 antagonism *in vitro*.

In vivo effects of the compounds of formula Ia or Ib can be demonstrated with the measurement of Complete Freund's adjuvant (CFA) -induced mechanical allodynia in rats using von Frey hair test.

- Complete Freund's adjuvant (CFA) -induced mechanical hypersensitivity in rats (da Costa et al., *Pain*, 2010, vol.148, 431-437; Petrus et al., *Molecular Pain*, 2007, vol.3, 40) is measured using von Frey hairs from 0.07 g to 26 g. A 50% response threshold (g) to light tactile stimuli is quantified by using the up-and-down paradigm (Dixon, *Ann Rev Pharmacol Toxicol*, 1980, vol.20, 441-462; Chaplan et al., *Journal of Neuroscience Methods*, 1994, vol.53, 55-63). Mechanical nociceptive threshold is determined before substance administrations (basal level threshold, day 0), 2 days after CFA (25 μg, i.pl.) injection and subsequently following experimental compound administration on day 2. Testing is performed during the light portion of the circadian cycle (between 06:00–18:00 h). Rats are placed in the observation chamber with a wire mesh bottom which allows full access to the paws. Habituation is allowed until chamber exploration and major grooming activities are ceased i.e. ca. 10 to 15 min. The area tested is the mid-plantar right hind paw. Testing is initiated with the 4 g von Frey hair presented perpendicular to the plantar surface with sufficient force to cause slight buckling against the paw, and held for approximately 8 s. A positive response is noted if the paw is sharply withdrawn and/or flinched immediately upon

removal of the hair. Tactile stimuli are applied in a consecutive fashion, whether ascending or descending. In the absence of a paw withdrawal response (negative response) to the initially selected hair, a stronger stimulus is presented; in the event of paw withdrawal, the next weaker stimulus is chosen. The 50% threshold is determined by counting of the critical
 5 6 data points according to Dixon (1980); all responses are noted and counting of these critical data points starts once the response threshold is first crossed. The resulting pattern of responses is tabulated as follows X = positive response, 0 = negative response, and the 50% response threshold is interpolated using the formula

$$50\% \text{ g threshold} = (10^{[X_f + k\delta]}) / 10,000$$

10 X_f = value (log) of the final von Frey hair used, k = tabular value (Dixon 1980, Chaplan et al. 1994) for the pattern of positive/ negative responses, δ = mean difference (log) between stimuli. Based on the threshold values following parameter is calculated

$$\% \text{ Reversal} = (\text{Threshold post compound} - \text{Threshold post CFA}) / (\text{Basal level threshold} - \text{Threshold post CFA}) * 100\%$$

15 In the repeated dosing set-up, tactile allodynia testing is initiated from 1 day after CFA up to 3 days after CFA. Thus, day 1 representing the acute effect of the experimental compound, and days 2 and 3 indicating the effect of repeated dosing of the experimental compound.

The compounds of formula Ia or Ib exhibit TRPA1 antagonism. The present disclosure thus provides compounds for use as a medicament. Compounds for use in the treatment of
 20 disorder, condition or disease mediated by TRPA1 receptor activity are also provided. Furthermore, a method for the treatment of disorder, condition, or disease mediated by TRPA1 receptor activity is provided. In said method an effective amount of at least one compound of formula Ia or Ib is administered to a mammal, such as human, in need of such treatment. The use of the compounds of formula Ia or Ib for the manufacture of a
 25 medicament for the treatment of disorder, condition, or disease mediated by TRPA1 receptor activity is also provided.

In one embodiment of the invention the aforementioned disorder, condition, or disease mediated by TRPA1 receptor activity is asthma, cough, allodynia, chronic obstructive pulmonary disease (COPD), tear gas irritation, pain in diabetic polyneuropathy, sleep
 30 deprivation-induced pain, sleep deprivation-induced allodynia, neurogenic inflammation,

fibromyalgia, pruritus in diabetes, drug-induced pruritus, insect bite-induced pruritus, itch, neurogenic itch, neuropathic itch, psychogenic itch, mechanical hypersensitivity, migraine, neuropathic pain, nerve injury-induced neuropathic pain, postherpetic neuralgia, low back pain, parkinson pain, postherpetic pain, trigeminal neuralgia, neuropathy in diabetes, 5 environmental chemical-induced neuropathy, neuropathy in parkinson disease, alcohol-induced neuropathy, cancer drug-induced neuropathy and pain, cancer drug-induced cold hypersensitivity, diabetic autonomic neuropathy, cardiovascular autonomic neuropathy, gastrointestinal autonomic neuropathy, polydipsia, psychogenic polydipsia, nocturia, overactive urinary bladder, erectile dysfunction, sudomotor dysfunction, primary headache, 10 dental pain, dental cold hypersensitivity, ear pain, eye pain, spinal cord injury-induced pain, poststroke pain, pancreatitis pain, inflammatory pain, visceral pain, gastric pain, abdominal pain, burn injury-induced pain and allodynia, central pain, coeliac pain, cold pain, cold hypersensitivity, frostbite-induced pain, labor pain, musculoskeletal pain, nausea, vomiting, drug-induced nausea and vomiting, radiation-induced pain and allodynia, opioid-resistant 15 postoperative pain, acute pain, insect bite-induced pain, urticaria, hangover headache, neurocardiogenic syncope, diabetes, severe sepsis, septic shock, sepsis-induced cognitive dysfunction tai cognitive dysfunction following severe sepsis, stroke-induced cognitive dysfunction, cognitive dysfunction, epilepsy, multiple sclerosis, neurodegenerative diseases, delirium, spinal cord injury, gout pain, astrogliosis, acidosis-induced pain, metabolic 20 acidosis-induced pain, acidosis-induced neuropathy, metabolic acidosis-induced neuropathy, allergic contact dermatitis, or diabetic retinopathy; for example neuropathic pain, pain in diabetic polyneuropathy, postoperative pain, cancer pain, migraine, asthma, cough, pain in osteoarthritis, pain in rheumatoid arthritis, inflammatory bowel disease, or diabetes.

The compounds of the present disclosure can be administered, for example, enterally, 25 topically or parenterally by means of any pharmaceutical formulation useful for said administration and comprising at least one active compound of formula Ia or Ib in pharmaceutically acceptable and effective amounts together with pharmaceutically acceptable diluents, carriers, and/or excipients known in the art. The manufacture of such pharmaceutical formulations is known in the art.

30 The therapeutic dose to be given to a subject in need of the treatment will vary depending on the compound being administered, the species, the age and the sex of the subject being treated, the particular condition being treated, as well as the route and method of

administration, and is easily determined by a person skilled in the art. Accordingly, the typical dosage for oral administration is from 10 ng/kg to 100 mg/kg per day and for parenteral administration from 1 ng/kg to 10 mg/kg for an adult mammal.

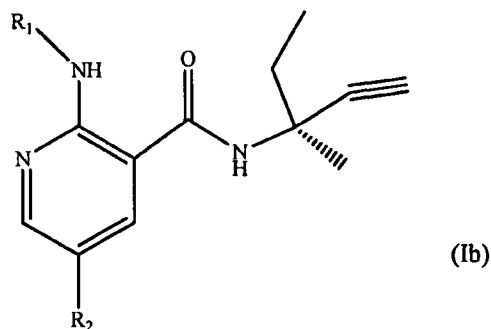
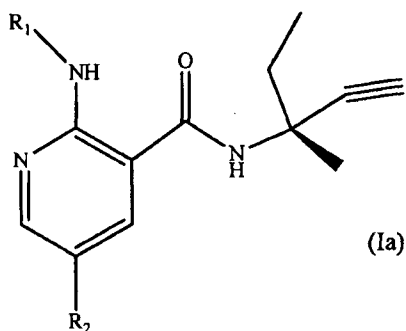
The compounds of the present disclosure are given to the subject as such or in combination with one or more other active ingredients, each in its own composition or some or all of the active ingredients combined in a single composition, and/or suitable pharmaceutical excipients. Suitable pharmaceutical excipients include conventionally used excipients and formulation aids, such as fillers, binders, disintegrating agents, lubricants, solvents, gel forming agents, emulsifiers, stabilizers, colorants, and/or preservatives.

The compounds of the present disclosure are formulated into dosage forms using commonly known pharmaceutical manufacturing methods. The dosage forms can be, for example, tablets, capsules, granules, suppositories, emulsions, suspensions or solutions. Depending on the route of administration and the galenic form, the amount of the active ingredient in a formulation can typically vary between 0.01 % and 100 % by weight.

A person skilled in the art will appreciate that the embodiments described herein can be modified without departing from the inventive concept. A person skilled in the art also understands that the present disclosure is not limited to the particular embodiments disclosed but is intended to also cover modifications of the embodiments that are within the scope of the present disclosure.

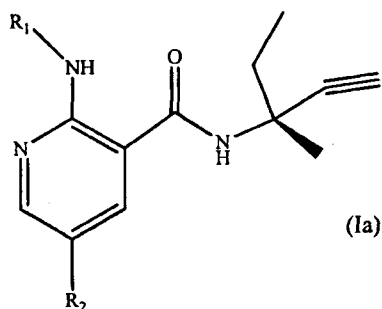
CLAIMS

1. A compound of formula Ia or Ib



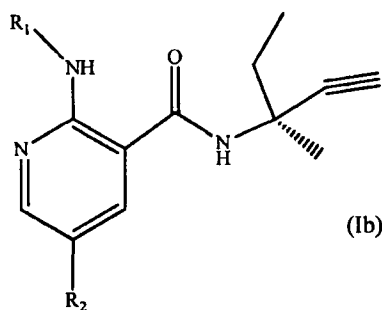
wherein;

- 5 R_1 is cyclo(C₄-C₆)alkyl or phenyl, wherein said cyclo(C₄-C₆)alkyl or phenyl is unsubstituted or substituted with 1 or 2 substituent(s) each independently being halogen, (C₁-C₂)alkoxy, or CN; and
- R_2 is H or halogen;
or a pharmaceutically acceptable salt thereof.
- 10 2. A compound according to claim 1, wherein the compound is a compound of formula Ia,



wherein R_1 and R_2 are as defined in claim 1.

3. A compound according to claim 1, wherein the compound is a compound of formula Ib,



- 15 wherein R_1 and R_2 are as defined in claim 1.

4. The compound according to any one of claims 1 to 3, wherein R₁ is C₄-cycloalkyl substituted with 1 or 2 substituent(s) each independently being halogen; and R₂ is halogen.
5. The compound according to claim 1, wherein the compound is (R)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-5-chloro-2-(3,3-difluorocyclobutylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3,3-difluorocyclobutylamino)-5-fluoro-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2,4-difluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (S)-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (R)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-chloro-4-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-cyano-4-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2-fluorophenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(4-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(2-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (S)-5-fluoro-N-(3-methylpent-1-yn-3-yl)-2-(phenylamino)nicotinamide, (R)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(4,4-difluorocyclohexylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (S)-2-(3-fluoro-5-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, (R)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide, or (S)-2-(2-fluoro-3-methoxyphenylamino)-N-(3-methylpent-1-yn-3-yl)nicotinamide.
6. The compound according to any one of claims 1 to 5 for use as a medicament.

7. The compound according to any one of claims 1 to 5 for use in the treatment of a disorder, condition or disease mediated by TRPA1 receptor activity.
8. The compound according to claim 7, wherein the disorder, condition or disease is neuropathic pain, pain in diabetic polyneuropathy, postoperative pain, cancer pain,
5 migraine, asthma, COPD, cough, pain in osteoarthritis, pain in rheumatoid arthritis, inflammatory bowel disease, or diabetes.
9. A method for the treatment of a disorder, condition, or disease mediated by TRPA1 receptor activity, which method comprises administering to a mammal in need of such treatment an effective amount of at least one compound according to claim 1.
- 10 10. The method according to claim 9, wherein the disorder, condition or disease is neuropathic pain, pain in diabetic polyneuropathy, postoperative pain, cancer pain, migraine, asthma, COPD, cough, pain in osteoarthritis, pain in rheumatoid arthritis, inflammatory bowel disease, or diabetes.
- 11 11. A pharmaceutical composition comprising at least one compound according to any one
15 of claims 1 to 5 and a pharmaceutically acceptable carrier, diluents, and/or excipient.
12. The pharmaceutical composition according to claim 11, wherein the composition further comprises at least one other active ingredient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/FI2015/000012

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/82 A61K31/421
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/053694 A1 (ORION CORP [FI]) 10 April 2014 (2014-04-10) page 1 - page 3; claims; examples -----	1-12
A	VALLIN K S ET AL: "N-1-Alkyl-2-oxo-2-aryl amides as novel antagonists of the TRPA1 receptor", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 22, no. 17, 1 September 2012 (2012-09-01), pages 5485-5492, XP002716178, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2012.07.032 [retrieved on 2012-07-14] figures; tables ----- -/--	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

3 June 2015

Date of mailing of the international search report

12/06/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/FI2015/000012

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GARCIA-ANOVEROS J ET AL: "TRPA1", HANDBOOK OF EXPERIMENTAL PHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 179, 1 January 2007 (2007-01-01), pages 347-362, XP008091335, ISSN: 0171-2004, DOI: 10.1007/978-3-540-34891-7_21 table 2	1-12
A	----- WO 2009/137340 A1 (ALLERGAN INC [US]; TAKEUCHI JANET A [US]; CHOW KEN [US]; LI LING [US];) 12 November 2009 (2009-11-12) page 7, column 0006 - page 8; claims 1,5 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/FI2015/000012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2884922 A1	10-04-2014
		PH 12015500716 A1	18-05-2015
		TW 201427931 A	16-07-2014
		WO 2014053694 A1	10-04-2014

WO 2009137340 A1	12-11-2009	AU 2009244536 A1	12-11-2009
		CA 2723751 A1	12-11-2009
		EP 2280707 A1	09-02-2011
		US 2009275627 A1	05-11-2009
		WO 2009137340 A1	12-11-2009
