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(54) Title: ISOINDOLINE DERIVATIVES COMPRISING PHENYL GROUPS AND THEIR USE IN THE TREATMENT OF PAIN DISORDERS

(57) Abstract: Compounds of formula I are claimed, (I) wherein R1 is hydrogen, C1-3alkyl, Ci_3alkoxy, cyano, hydroxy or halo; and wherein said Ci^alkyl is optionally substituted by one or more substituents independently selected from hydroxy, Ci^alkoxy andfluoro; and said Ci^alkoxy is optionally substituted by one or morefluoro; m is 1 or 2; R2 and R3 is each and independently selected from hydrogen, Ci_4haloalkyl, Ci_4haloalkoxy, halo, Ci_4alkoxy, Ci_4alkyl and C3_7cycloalkyloxy; wherein said C3. γcycloalkyloxy is optionally substituted by one or morefluoro; and R2 and R3 may not both be hydrogen; D is C3_7cycloalkyl or C3_7heterocycloalkyl; and wherein said Cs-jcycloalkyl or Cs- γheterocycloalkyl may optionally be substituted by one or more X*; X4 is halo, Ci_3alkyl, Ci_3alkyl0Ci_3alkyl, Ci_3alkoxy, benzyl, Ci_4alkylsulfonyl, oxo, R4O(C=O), R5(C=O), or C5.6 heteroaryl; wherein said Cisalkyl, CisalkylOCisalkyl, Ci^alkoxy and C i^alkylsulfonyl is optionally substituted by one or more fluoro; R4 is Ci_4alkyl, Ci_4alkyl0Ci_4alkyl, C5_6cycloalkyl, or aryl; R5 is Ci_4alkyl, Ci_4fluoroalkyl or Cs_6 heteroaryl; Li is Ci_4alkylene or a bond; L2 is Ci_3alkylene; with the exception of the compound 2-(cyclohexylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-l-carboxamide; as well as a pharmaceutically acceptable salt, or isomer thereof, or a salt of said isomer. The compounds of the invention are useful in therapy such as pain therapy.

Isoindoline derivatives comprising phenyl groups and their use in the treatment of pain disorders

FIELD OF THE INVENTION

The present invention relates to new compounds, to a pharmaceutical composition containing said compounds and to the use of said compounds in therapy. The present invention also relates to processes for the preparation of said compounds.

BACKGROUND

The current treatment regimes for pain conditions utilise compounds which exploit a very limited range of pharmacological mechanisms. One class of compounds, the opioids, stimulates the endogenous endorphine system; an example from this class is morphine. Compounds of the opioid class have several drawbacks that limit their use, e.g. emetic and constipatory effects and negative influence on respiratory capability. The second major class of analgesics, the non-steroidal antiinflammatory analgesics of the COX-1 or COX-2 types, also have liabilities such as insufficient efficacy in severe pain conditions and at long term use the COX-1 inhibitors cause ulcers of the mucosa. Mechanisms of analgesic effects of other currently used medicines are insufficiently characterized and/or have limited therapeutic potential.

Local anesthetics, that are known to block most types of sodium channels in nerves, are useful for relieving pain in small areas of the human body and for blocking nerve conduction from the periphery to the central nervous system. They can also be used in the last-mentioned way to block sensory signalling by instilling solutions of local anesthetics at the spinal cord. Due to their high toxicity, in particular heart toxicity, they can not, however, be used for systemic administration as generally useful analgesics. There remains thus a need for more selective modulators of sodium channels involved in pain signal conduction.

Nine sodium channel subtypes have been cloned and functionally expressed to date. (Wood JN, Baker M.. *Current Opinion in Pharmacology* 2001, 1, 17-21). They are differentially expressed throughout muscle and nerve tissues and show distinct biophysical properties. All voltage-gated sodium channels (NaV:s) are characterized by a high degree of selectivity for sodium over other ions and by their voltage-dependent gating. By application of genetic analysis it has been shown that a mutation in the gene coding for sodium channel NaV1.7, making this protein non-functional, can make a human become almost insensitive to pain (Cox JJ et al. *Nature* 2006, 444, 894-898).

It is well known that the voltage-gated sodium channels in nerves play a critical role in neuropathic pain (Baker MD and Wood JN. *Trends in Pharmacological Sciences* 2001, 22, 27-31). Injuries of the peripheral nervous system often result in neuropathic pain persisting long after the initial injury resolves. Examples of neuropathic pain include, but are not limited to, postherpetic neuralgia, trigemina1 neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias. It has been shown in human patients as well as in animal models of neuropathic pain, that damage to primary afferent sensory neurons can lead to neuroma formation and spontaneous activity, as well as evoked activity in response to normally innocuous stimuli. NaV1.7 is expressed in human neuromas, which are swollen and hypersensitive nerves and nerve endings that are often present in chronic pain states (*Acta Neurochirurgica* 2002, 144, 803-810).

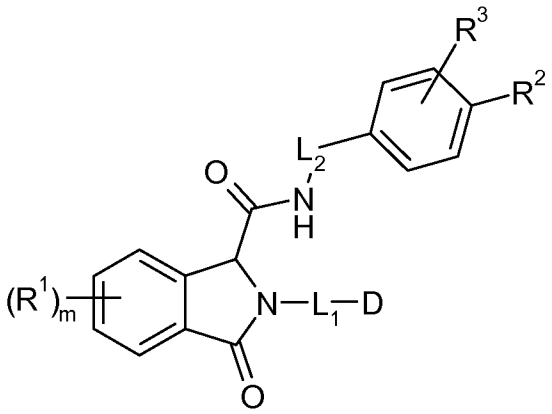
In rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioral signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behavior and motor function (Mao J and Chen LL, *Pain*, 2000, 87, 7-17).

In addition to neuropathic pain, sodium channel blockers have clinical uses in the treatment of epilepsy and cardiac arrhythmias. Recent evidence from animal models suggests that

sodium channel blockers may also be useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and in patients with multiple sclerosis (MS).

DISCLOSURE OF THE INVENTION

According to the invention there is provided a compound of formula I



I

wherein

R^1 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, cyano, hydroxy or halo; *and wherein said C_{1-3}alkyl is optionally substituted by one or more substituents independently selected from hydroxy, C_{1-3}alkoxy and fluoro; and said C_{1-3}alkoxy is optionally substituted by one or more fluoro;*

m is 1 or 2

R^2 and R^3 is each and independently selected from hydrogen, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, halo, C_{1-4}alkoxy, C_{1-4}alkyl and C_{3-7}cycloalkyloxy; *wherein said C_{3-7}cycloalkyloxy is optionally substituted by one or more fluoro;* and R^2 and R^3 may not both be hydrogen;

D is C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl; *and wherein said C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl may optionally be substituted by one or more **X^4***;

X^4 is halo, C_{1-3}alkyl, C_{1-3}alkylOC_{1-3}alkyl, C_{1-3}alkoxy, benzyl, C_{1-4}alkylsulfonyl, oxo, $R^4O(C=O)$, $R^5(C=O)$, or C_{5-6} heteroaryl; *wherein said C_{1-3}alkyl, C_{1-3}alkylOC_{1-3}alkyl, C_{1-3}alkoxy and C_{1-4}alkylsulfonyl is optionally substituted by one or more fluoro;*

R^4 is C_{1-4}alkyl, C_{1-4}alkylOC_{1-4}alkyl, C_{5-6}cycloalkyl, or aryl;
R^5 is C_{1-4}alkyl, C_{1-4}fluoroalkyl or C_{5-6} heteroaryl;

L_1 is C_{1-4}alkylene or a bond;
L_2 is C_{1-3}alkylene

with the exception of the compound
2-(cyclohexylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

as well as a pharmaceutically acceptable salt, or isomer thereof, or a salt of said isomer.

One embodiment of the invention relates to a compound of formula I, wherein
R^1 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, halo, or hydroxy;
m is 1;
R^2 is selected from hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, halo, C_{1-4}alkoxy, and C_{1-4}haloalkoxy;
R^3 is hydrogen, C_{1-4}alkyl, halo, or C_{1-4}haloalkoxy;
and R^2 and R^3 may not both be hydrogen;

D is C_{4-6}cycloalkyl or C_{4-6}heterocycloalkyl;
wherein C_{4-6}cycloalkyl or C_{4-6}heterocycloalkyl is optionally substituted with one or more X^4;
X^4 is halo, oxo, $R^4O(C=O)$, $R^5(C=O)$ or C_{5-6}heteroaryl;
R^4 is C_{1-4}alkyl;
R^5 is C_{5-6} heteroaryl;
L_1 is C_{1-2}alkylene or a bond; and
L_2 is C_{1-2}alkylene.

One embodiment of the invention is related to a compound of formula I, wherein $\mathbf{R^1}$ is hydrogen.

One embodiment of the invention is a compound of formula I, wherein **m** is 1.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{R^1}$ is hydrogen.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^1}$ is methyl.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^1}$ is methoxy.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^1}$ is fluoro.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^1}$ is hydroxy.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is $-O-CF_3$.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is chloro or bromo.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is methoxy.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is CF_3 or $-CH_2-CF_3$.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is methyl.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^2}$ is iso-propyl.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{R^3}$ is hydrogen.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^3}$ is methyl.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^3}$ is chloro.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{R^3}$ is $-OCF_3$.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{L_1}$ is a bond.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{L_1}$ is methylene.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{L_1}$ is ethylene.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{L_2}$ is methylene.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{L_2}$ is $-CH(CH_3)-$.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{L_2}$ is cyclopropylene.

One embodiment of the invention is a compound of formula I, wherein **D** is selected from any one of azetidinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, pyrrolidinyl-2-on, piperidinyl, and morpholinyl.

Yet an embodiment of the invention is a compound of formula I, wherein **D** is cyclobutyl or cyclohexyl.

One embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is fluoro.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is –C(O)-O-$C(CH_3)_3$.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is –C(O)-O-$CH(CH_3)_2$.

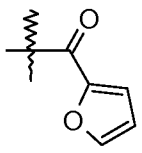
Yet an embodiment of the invention is a compound of formula I,, wherein $\mathbf{X^4}$ is –C(O)-CH_2-CH_3.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is –C(O)-CH_2-CF_3.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is -SO_2-CH_3.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is pyrimidinyl.

Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is



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Yet an embodiment of the invention is a compound of formula I, wherein $\mathbf{X^4}$ is benzyl.

One embodiment of the invention is a compound of formula I, wherein **D** is di-substituted by X^4.

One embodiment of the invention is a compound selected from any one of:

2-(Oxan-4-yl)-3-oxo-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

3-Oxo-2-[[(2S)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

N-[1-(4-Chlorophenyl)ethyl]-3-oxo-2-[[(2S)-oxolan-2-yl]methyl]-1H-isoindole-1-carboxamide;

3-Oxo-2-[[(2R)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

N-[1-(4-chlorophenyl)ethyl]-2-(oxan-4-yl)-3-oxo-1H-isoindole-1-carboxamide;

3-Oxo-2-[2-(2-oxopyrrolidin-1-yl)ethyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

tert-Butyl 3-(1-oxo-3-{[4-(trifluoromethoxy)benzyl]carbamoyl}-1,3-dihydro-2*H*-isoindol-2-yl)azetidine-1-carboxylate;

2-[1-(2-Furoyl)piperidin-4-yl]-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

3-Oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-*N*-(4-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-[1-(3-Chlorophenyl)ethyl]-2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxamide;

N-[1-(3-Chlorophenyl)ethyl]-3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxamide;

2-((3,3-Difluorocyclobutyl)methyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(3,3-Difluorocyclobutyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-7-methoxy-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-7-methyl-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

tert-Butyl 3-(4-methyl-1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;

3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethoxy)phenyl)ethyl)isoindoline-1-carboxamide, ISOMER 4;

tert-Butyl 3-(1-oxo-3-(1-(4-(trifluoromethoxy)phenyl)ethylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate, ISOMER 3&4;

2-(2-Morpholinoethyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

3-Oxo-2-((tetrahydrofuran-3-yl)methyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(1-Benzylpiperidin-4-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

7-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

4-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

3-Oxo-N-(4-(trifluoromethoxy)benzyl)-2-(1-(3,3,3-trifluoropropanoyl)azetidin-3-yl)isoindoline-1-carboxamide;

2-(1-(Methylsulfonyl)azetidin-3-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

Isopropyl 3-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;

tert-Butyl 4-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)piperidine-1-carboxylate;

3-Oxo-2-(1-propionylpiperidin-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

3-Oxo-2-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

tert-Butyl 3-(1-oxo-3-(3-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;

tert-Butyl 3-(1-(2-methyl-4-(trifluoromethoxy)benzylcarbamoyl)-3-oxoisoindolin-2-yl)azetidine-1-carboxylate;
2-(4,4-Difluorocyclohexyl)-3-oxo-N-(4-(2,2,2-trifluoroethyl)benzyl)isoindoline-1-carboxamide;
N-(3,4-Dimethylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide;
3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)isoindoline-1-carboxamide;
4-Hydroxy-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;
4-Hydroxy-N-(4-isopropylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide;
2-(4,4-Difluorocyclohexyl)-4-hydroxy-3-oxo-N-(4-(trifluoromethyl)benzyl)isoindoline-1-carboxamide;
N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide; and
N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide, ISOMER 2.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon containing group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neo-pentyl, n-hexyl or i-hexyl.

The term C_{1-4}alkyl as used herein is defined as a straight, branched or cyclic (cyclic where at least three carbon atoms are present) alkyl chain, having from 1 to 4 carbon atoms and may be but are not limited to methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclobutyl or *tert*-butyl. The term C_{1-3} alkyl as used herein is defined as a straight, branched or cyclic alkyl chain (cyclic when three carbon atoms are present), having from 1 to 3 carbon atoms, namely: methyl, ethyl, n-propyl, iso-propyl, or cyclopropyl.

The term C_{1-4}alkylene as used herein for L_1 may be a straight, branched or cyclic alkylene group, and includes but is not limited to a methylene, ethylene, n-propylene, i-propylene, cyclopropylene, n-butylene, iso-butylene, *tert*-butylene, and cyclobutylene hydrocarbon chain.

The term C_{1-3}alkylene as used herein for L_2 may be a straight, branched or cyclic alkylene group, and includes but is not limited to a methylene, ethylene, n-propylene, i-propylene, and cyclopropylene hydrocarbon chain.

The term "alkoxy", unless stated otherwise, refers to radicals of the general formula –O-R, wherein R is selected from a hydrocarbon radical. The term "C_{1-6}alkoxy" may include, but is not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy,cyclopropylmethoxy, allyloxy or propargyloxy.

The term "C_{1-3} alkoxy" as used herein may include, but is not limited to methoxy, ethoxy, or propoxy. The term "C_{1-4} alkoxy" as used herein may include, but is not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy.
In one embodiment of the invention, "C_{1-3} alkoxy" may be substituted by one or more fluoro atoms whereby one or more hydrogen atoms in the alkoxy group is replaced by one or more fluoro atoms such as -O-CH_2-CF_3; -O-CH_2-CH_2-CF_3; -O-CH-F_2.

The term "C_{1-3}alkyl-O-C_{1-3}alkyl, unless stated otherwise, refers to an ether group with the general formula R-O-R, wherein R is selected from a hydrocarbon radical. The term "C_{1-3}alkylOC_{1-3}alkyl" may include, but is not limited to dimethylether, metylethylether, methylpropylether, diethylether, dipropylether or methylisopropylether.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-4}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl or fluorochloromethyl.

In this specification, unless stated otherwise, the term "haloalkoxy" means an alkoxy group as defined above, which is substituted with halo as defined above.The term "C_{1-4}haloalkoxy" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, partially or completely saturated monocyclic, bicyclic or bridged hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. The term "C_{5-6} cycloalkyl" is defined as cyclopentyl or cyclohexyl.

The term "cycloalkyloxy-" refers to a cycloalkyl group attached to the rest of the molecule *via* the O-atom of the oxy-group. Examples of C_{3-7} cycloalkyloxy as used herein, are without limitation –O-cyclohexyl, -O-cyclopropyl, O-cyclobutyl, and -O-cyclopentyl.

In this specification, unless stated otherwise, the term "heterocycloalkyl" refers to an optionally substituted, partially or completely saturated monocyclic, bicyclic or bridged hydrocarbon ring system and which further comprises one or more heteroatoms selected from O, N or S. The term "C_{3-7} heterocycloalkyl" may be, but is not limited to, tetrahydropyranyl, tetrahydrofuranyl, morpholinyl, pyrrolidinyl, pyrrolidinyl-2-on, azetidinyl, piperidinyl.

The term "aryl" used alone or as suffix or prefix, refers to a hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, wherein the radical is located on a carbon of the aromatic ring. The term "C_{6-10}aryl", may be, but is not limited to phenyl, naphthyl and the like.

Unless otherwise specified, aryl group may be substituted by one or more substituents including -OH, halo, cyano, nitro, C_{1-6}alkyl, C_{1-6}alkoxy or sulfamoyl. When substituted, aryl is preferably substituted by between one and three substitutents.

The term "$R^5(C=O)$", unless stated otherwise, refers to a acyl group with the general formula R-C=O.

The term "$R^4O(C=O)$", unless stated otherwise, refers to an alkoxycarbonyl group with the general formula R-O-(C=O).

The term "heteroaryl" used alone or as suffix or prefix, refers to an aromatic ring in which at least one atom in the ring are elements other than carbon, such as N, S and O. Each heteroaryl may be bonded to the rest of the molecule either *via* a carbon atom of said heteroaryl, or *via* one nitrogen atom of said heteroaryl.

The term "$C_{5\text{-}6}$ heteroaryl" as used herein is an aromatic ring having from 5 to 6 ring atoms and wherein at least one of said 5 to 6 ring atoms is a heteroatom selected from N, S and O. Examples of such "$C_{5\text{-}6}$ heteroaryl" are pyridinyl, thiophenyl, imidazolyl, pyrazolyl.

In this specification, unless stated otherwise, the terms "halo" and "halogen" may be fluorine, iodine, chlorine or bromine.

The term "alkylsulfonyl", unless stated otherwise, refers to radicals of the general formula $-SO_2$-R, wherein R is selected from a hydrocarbon radical. The term "$C_{1\text{-}4}$alkylsulfonyl" may include, but is not limited to methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl, n-butylsulfonyl, iso-butylsulfonyl or *tert*-butylsulfonyl.

It will be appreciated that throughout the specification, the number and nature of substituents on rings in the compounds of the invention will be selected so as to avoid sterically undesirable combinations.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

The present invention relates to compounds of formula I as hereinbefore defined, as well as to pharmaceutically acceptable salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts.

Examples of useful pharmaceutically acceptable salts of a compound of the invention is, for example an acid-addition salt such as a salt formed with an inorganic or organic acid. A further example of useful salts is an alkali metal salt such as an alkaline earth metal salt; or a salt formed with an organic base. Examples of useful salts in accordance with the invention are an acetate, fumarate, maleate, tartrate, citrate, hydrochloride, hydrobromide, sulphate and phosphate salt.

Still other pharmaceutically acceptable salts useful in accordance with the invention and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18^{th} Edition, Mack Publishing Co.).

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention. The wording "tautomerism" refers to a chemical equilibrium between a keto form and an enol form where the enol and keto forms are tautomers of each other.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical isomerism, such as one or more enantiomers and/or diastereoisomers. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

PHARMACEUTICAL COMPOSITIONS

According to one embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The pharmaceutical composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

A suitable daily dose of a compound of the invention in the treatment of a mammal, including man, is approximately from 5 to100 mg/kg bodyweight at peroral administration and from about 0.01 to 250 mg/kg bodyweight at parenteral administration.

The typical daily dose of the active ingredient varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

MEDICAL USE

Compounds according to the present invention are contemplated to be useful in therapy. Compounds of formula I as herein described and claimed, or a pharmaceutically acceptable salt thereof, as well as their corresponding active metabolites, exhibit a high degree of potency at the sodium channel NaV1.7 and also selectivity for this channel compared with other essential sodium channels. Accordingly, compounds of the present invention are expected to be useful in the treatment of conditions associated with upregulation of NaV1.7 and other sodium channels present in C-fibers.

Compounds of the invention may be used to produce an inhibitory effect of sodium channels in mammals, including man.

One embodiment of the invention relates to the use of a compound of formula I as hereinbefore defined, in the manufacture of a medicament for the treatment of NaV1.7 mediated disorders.

Compounds of formula I according to the invention are expected to be useful for the treatment of a pain disorder such as: acute pain; chronic pain; neuropathic pain such as diabetic neuropathies; inflammatory pain associated with arthritis and rheumatoid diseases; low back pain; post-operative pain; pain associated with various conditions including cancer, angina, renal or billiary colic, menstruation, fibromyalgia, low back pain, post-operative pain, cancer pain, visceral pains such as chronic pelvic pain, cystitis, IBS, pancreatitis, ischeamic pain, or gout.

Still an aspect of the invention is the use of a compound of formula I, for the treatment of a vascular headache such as migraine.

Yet an aspect of the invention is the use of a compound of formula I, for the treatment of pain conditions related to erythermalgia, psoriasis, emesis, urinary incontinence and hyperactive bladder.

Still an embodiment of the present invention is the use of a compound of formula I, for the treatment of epilepsy.

One embodiment of the invention relates to the use of a compound of formula I as hereinbefore defined, for the treatment of pain conditions related to arthritis, fibromyalgia, low back pain, post-operative pain, cancer pain, visceral pains such as chronic pelvic pain, cystitis, IBS, pancreatitis or ischeamic pain.

One embodiment of the invention relates to the use of a compound of formula I as hereinbefore defined, in therapy.

Still an embodiment of the invention relates to the use of a compound of formula I as hereinbefore defined, for the manufacture of a medicament for the treatment of a pain disorder such as: acute pain; chronic pain; neuropathic pain such as diabetic neuropathies; inflammatory pain *associated with* arthritis and rheumatoid diseases; low back pain; post-operative pain; pain *associated with various conditions* including cancer, angina, renal or billiary colic, menstruation, fibromyalgia, low back pain, post-operative pain, cancer pain, visceral pains such as chronic pelvic pain, cystitis, IBS, pancreatitis, ischeamic pain, or gout.

Still an aspect of the invention is the use of a compound of formula I, for the manufacture of a medicament for use in the treatment of a vascular headache such as migraine.

Yet an aspect of the invention is the use of a compound of formula I, for the manufacture of a medicament for use in the treatment of *pain conditions related t*o erythermalgia, psoriasis, emesis, urinary incontinence and hyperactive bladder.

Still an embodiment of the present invention is the use of a compound of formula I, for the manufacture of a medicament for use in the treatment of of epilepsy.

Still an embodiment of the invention relates to a method for the treatment of any one of the following pain disorders such as: acute pain; chronic pain; neuropathic pain such as diabetic neuropathies; inflammatory pain *associated with* arthritis and rheumatoid diseases; low back pain; post-operative pain; pain *associated with various conditions* including cancer, angina, renal or billiary colic, menstruation, fibromyalgia, low back pain, post-operative pain, cancer pain, visceral pains such as chronic pelvic pain, cystitis, IBS, pancreatitis, ischeamic pain, or gout; whereby a compound of formula I as hereinbefore defined, is administered to a subject in need of such treatment.

Still an aspect of the invention is a method for the treatment of a vascular headache such as migraine, whereby a compound of formula I as hereinbefore defined, is administered to a subject in need of such treatment.

Yet an aspect of the invention is a method for the treatment of *pain conditions related to* erythermalgia, psoriasis, emesis, urinary incontinence and hyperactive bladder, whereby a compound of formula I as hereinbefore defined, is administered to a subject in need of such treatment.

Still an embodiment of the present invention is a method for the treatment of epilepsy, whereby a compound of formula I as hereinbefore defined is administered to a subject in need of such treatment.

Yet an embodiment of the invention is a compound of formula I as hereinbefore defined, for use in the treatment of a pain disorder such as: acute pain; chronic pain; neuropathic pain such as diabetic neuropathies; inflammatory pain *associated with* arthritis and rheumatoid diseases; low back pain; post-operative pain; pain *associated with various conditions* including cancer, angina, renal or billiary colic, menstruation, fibromyalgia, low back pain, post-operative pain, cancer pain, visceral pains such as chronic pelvic pain, cystitis, IBS, pancreatitis, ischeamic pain, or gout.

Still an aspect of the invention is a compound of formula I as hereinbefore defined, for use in the treatment of a vascular headache such as migraine.

Yet an aspect of the invention is a compound of formula I as hereinbefore defined, for use in the treatment of *pain conditions related to* erythermalgia, psoriasis, emesis, urinary incontinence and hyperactive bladder.

Still an embodiment of the present invention is a compound of formula I as hereinbefore defined, for use in the treatment of epilepsy.

COMBINATIONS

Pain treatment as defined herein may be applied as a sole therapy or may involve, in addition to a compound according to the invention, administration of other analgesics or adjuvant therapy. Such therapy may for example include in combination with a compound of the present invention, one or more of the following categories of pain-relieving ingredients:

a) opioid analgesics, for example morphine, ketobemidone or fentanyl;
b) analgesics of the NSAID or COX-1/2 class, for example ibuprofene, naproxene, celecoxib or acetylsalicylic acid, and their analogues containing nitric oxide-donating groups;
c) analgesic adjuvants such as amitriptyline, imipramine, duloxetine or mexiletine;
d) NMDA antagonists for example ketamine or dextrometorfan;
e) sodium channel blocking agents, for example lidocaine;
f) anticonvulsants, for example carbamazepine, topiramate or lamotrigine;
g) anticonvulsant/analgesic amino acids such as gabapentin or pregabalin;
h) cannabinoids.

Each active compound of such a combination may be administered simultaneously, separately or sequentiallly.

EXAMPLES

Methods of Preparation

An aspect of the present invention provides a process for preparing a compound of formula I or a salt thereof.

Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Green's Protective Groups in Organic Synthesis" P.G.M. Wuts, T.W. Green, Wiley, New York, 2007. References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3rd ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2nd ed. Longman Scientific and Technical (1992), p. 248-282.

The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

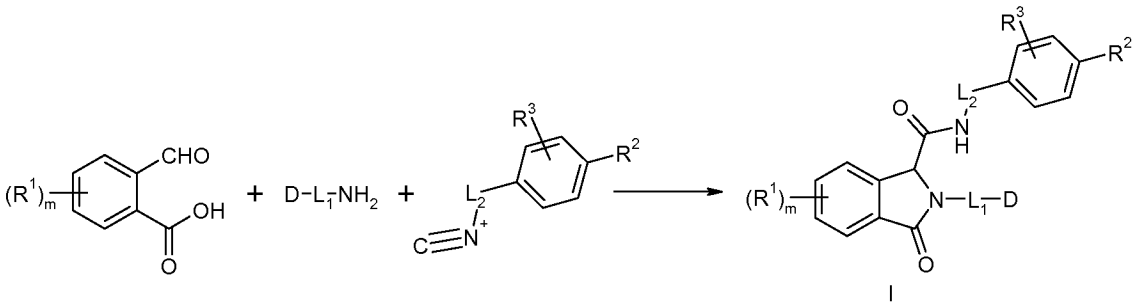
Abbreviations:

DMF	N,N-dimethylformamide
NaOH	sodium hydroxide
HCl	hydrochloric acid
M	molar
PG	protective group

One embodiment of the invention relates to processes for the preparation of a compound of formula I according to Methods A and B, wherein R^1, R^2, R^3, D, L_1, L_2, X^4 and m unless otherwise specified, are defined as in formula I.

Method A

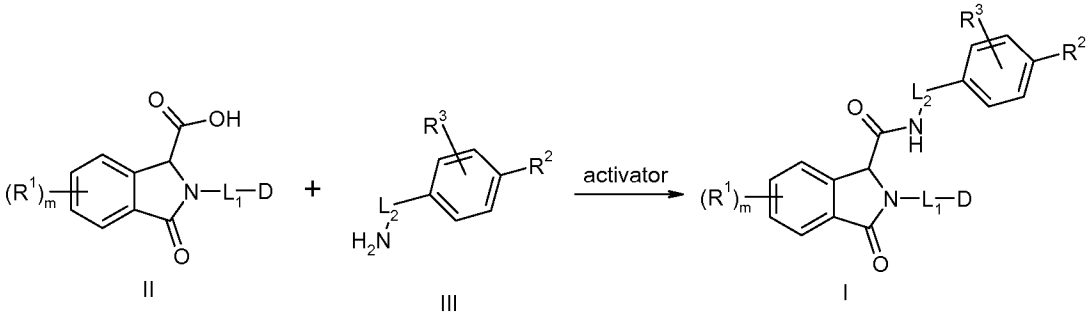
The compound of formula I may be prepared by a 3-component Ugi reaction (Journal of Organic Chemistry (1999), 64(3), 1074-1076) using appropriately substituted 2-formylbenzoic acid, amine and isonitrile reacting in a protic solvent, for example methanol at ambient temperature.



I

Method B

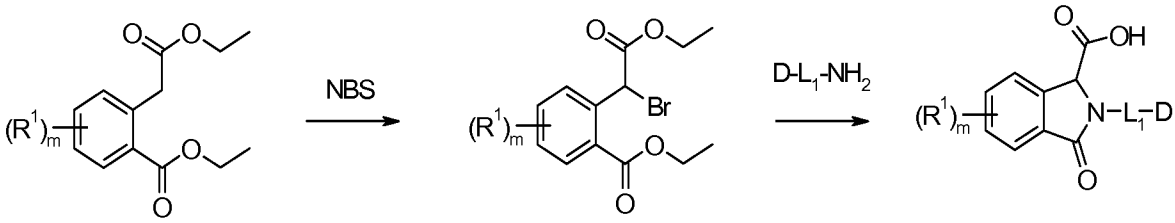
The compound of formula I may be prepared by an amide coupling reaction using appropriately substituted indolone carboxylic acid II and amine III and a suitable activator, for example but not limited to, fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate reacting in precence of an organic base such as triethylamine, N,N-diisopropylamine or 4-(dimethylamino)pyridine in an aprotic solvent such as DMF, acetonitrile, tetrahydrofuran or dioxane at 0-45 °C.



II III I

The carboxylic acids II are available via procedures described in the literature, for example: Othman, M. and Decroix, B., Synthetic communications 1996, 26 (15), 2803-2809 and Othman, M. et. al., Tetrahedron 1998, 54 (30), 8737-8744 where a homophtalic ester is brominated by for example N-bromosuccinimide (NBS) in carbontetrachloride and then ring closed with an amine in precence of an organic base such as triethylamine, N,N-

diisopropylamine or 4-(dimethylamino)pyridine in a solvent such as acetonitrile at 0-25 °C, as shown below.



II

General Methods

Mass spectra were recorded on one of the following instruments:

A) A LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 85 ELS detector and a ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive or negative ion mode. The capillary voltage was set to 3.2 kV and the cone voltage to 30 V, respectively. The mass spectrometer scanned between *m/z* 100-700 with a scan time of 0.3 s. The diode array detector scanned from 200-400 nm. The temperature of the ELS detector was adjusted to 40 °C and the pressure was set to 1.9 bars. Separation was performed on an X-Terra MS C8, 3.0 mm x 50 mm, 3.5 µm (Waters) run at a flow rate of 1 ml/min. A linear gradient was applied starting at 100 % A (A: 10 mM ammonium acetate in 5 % acetonitrile, or 8 mM formic acid in 5 % acetonitrile) ending at 100% B (B: acetonitrile). The column oven temperature was set to 40 °C.

B) A LC-MS system consisting of a Waters sample manager 2777C, a Waters 1525 µ binary pump, a Waters 1500 column oven, a Waters ZQ single quadrupole mass spectrometer, a Waters PDA 2996 diode array detector and a Sedex 85 ELS detector. The mass spectrometer was configured with an atmospheric pressure chemical ionisation (APCI) ion source which was further equipped with atmospheric pressure photo ionisation (APPI) device. The mass spectrometer scanned in the positive mode, switching between APCI and APPI mode. The mass range was set to *m/z* 120-800 using a scan time of 0.3 s.

The APPI repeller and the APCI corona were set to 0.86 kV and 0.80 μA, respectively. In addition, the desolvation temperature (300°C), desolvation gas (400 L/Hr) and cone gas (5 L/Hr) were constant for both APCI and APPI mode. Separation was performed using a Gemini column C18, 3.0 mm x 50 mm, 3 μm, (Phenomenex) and run at a flow rate of 1 ml/min. A linear gradient was used starting at 100 % A (A: 10 mM ammonium acetated in 5 % methanol) and ending at 100% B (methanol). The column oven temperature was set to 40 °C.

C) A LC-MS system consisting of a Waters Alliance 2795 HPLC and a Waters Micromass ZQ detector operating at 120 °C. The mass spectrometer was equipped with an electrospray ion source (ES) operated in a positive or negative ion mode. The mass spectrometer was scanned between *m/z* 100-1000 with a scan time of 0.3 s. The LC system used was 75 % acetonitrile and 25 % of a 0.1 % formic acid solution in water.

Preparative chromatography was run on one of the following instruments:

A) A Waters FractionLynx system with a Autosampler combined Automated Fraction Collector (Waters 2767), Gradient Pump (Waters 2525), Column Switch (Waters CFO) and PDA (Waters 2996). Column; XTerra® Prep MS C8 10 μm OBD™ 19 x 300 mm or XTerra® Prep MS C8 10 μm OBD™ 30 x 150 mm both with the guard column XTerra ® Prep MS C8 10 μm 19 x 10 mm Cartridge. A gradient from 100 % A (95 % 0.1 M ammonium acetate in MilliQ water and 5 % acetonitrile) to 100 % B (100 % acetonitrile) was applied for LC-separation at flow rate 20 ml/min. The PDA was scanned from 210-350 nm. UV triggering determined the fraction collection.

B) A Waters FractionLynx system with a Autosampler combined Automated Fraction Collector (Waters 2767), Gradient Pump (Waters 2525), Regeneration Pump (Waters 600), Make Up Pump (Waters 515), Waters Active Splitter, Column Switch (Waters CFO), PDA (Waters 2996) and Waters ZQ mass spectrometer. Column; XBridge™ Prep C8 5 μm OBD™ 19 x 100 mm, with guard column; XTerra ® Prep MS C8 10 μm 19 x 10 mm

Cartridge. A gradient from 100 % A (95 % 0.1 M ammonium acetate in MilliQ water and 5 % acetonitrile) to 100 % B (100 % acetonitrile) was applied for LC-separation at flow rate 25 ml/min. The PDA was scanned from 210-350 nm. The ZQ mass spectrometer was run with ESI in positive mode. The Capillary Voltage was 3kV and the Cone Voltage was 30V. Mixed triggering, UV and MS signal, determined the fraction collection.

Purity analyses were performed on one of the following instruments:

A) An Agilent HP1100 system consisting of a G1379A Micro Vacuum Degasser, a G1312A Binary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostatted Column Compartment and a G1315C Diode Array Detector. The column used was a Gemini C18 3.0 x 50, 3 μm (Phenomenex) run at a flow rate of 1.0 ml/min. The purity method consisted of three parts: firstly a 3-minute column wash was applied, secondly a blank run was performed and finally the sample was analysed. A linear gradient was used for both the blank and the sample, starting at 100 % A (A: 10 mM ammonium acetate in 5 % acetonitrile) and ending at 100 % B (B: acetonitrile) after 3.5 minutes. The blank run was subtracted from the sample run at the wavelengths 220 nm, 254 nm and 290 nm.

B) A Water Acquity system with PDA (Waters 2996) and Waters ZQ mass spectrometer. Column; Acquity UPLC™ BEH C_8 1.7 μm 2.1 x 50 mm. The column temperature was set to 65 °C. A linear 2 min 15 sec gradient from 100 % A (A: 95 % 0.01 M ammonium acetate in MilliQ water and 5 % acetonitrile) to 100 % B (5 % 0.01 M ammonium acetate in MilliQ water and 95 % acetonitrile) was applied for LC-separation at flow rate 1.0 ml/min. The PDA was scanned from 210-350 nm and 25 4nm was extracted for purity determination. The ZQ mass spectrometer was run with ESI in pos/neg switching mode. The Capillary Voltage was 3kV and the Cone Voltage was 30V.

C) A Waters 600 Controller system with a Waters 717 Plus Autosampler and a Waters 2996 Photodiode Array Detector. The column used was an ACE C_{18}, 5 μm, 60 x 150 mm. A linear gradient was applied, starting at 95 % A (A: 0.1 % H_3PO_4 in water) and ending at

55 % B (B: acetonitrile) in 20 min run. The column was at ambient temperature with the flow rate of 1.0 mL/min. The Diode Array Detector was scanned from 200-400 nm.

NMR spectra were recorded on a Varian Mercury Plus 400 NMR Spectrometer, operating at 400 MHz and equipped with a Varian 400 ATB PFG probe; or on a Varian Unity+ 400 NMR Spectrometer, operating at 400 MHz for proton and 100 MHz for carbon-13, and equipped with a 5 mm BBO probe with Z-gradients; or on a Bruker av400 NMR spectrometer operating at 400 MHz for proton and 100 MHz for carbon-13, and equipped with a 3 mm flow injection SEI $^{1}H/D-^{13}C$ probe head with Z-gradients, using a BEST 215 liquid handler for sample injection; or on a Bruker DPX400 NMR spectrometer, operating at 400 MHz for proton and 100 MHz for carbon-13, and equipped with a 4-nucleus probe with Z-gradients. The following reference signals were used: TMS δ 0.00, or the residual solvent signal of DMSO-d_6 δ 2.49, CD_3OD δ 3.31 or $CDCl_3$ δ 7.25 (unless otherwise indicated). Resonance multiplicities are denoted s, d, t, q, m and br for singlet, doublet, triplet, quartet, multiplet and broad, respectively.

Diastereomers may or may not be denoted in spectra depending upon ease of interpretation of spectra. Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Column chromatography was performed using Merck Silica gel 60 (0.040-0.063 mm), or employing a Combi Flash® Companion™ system using RediSep™ normal-phase flash columns.

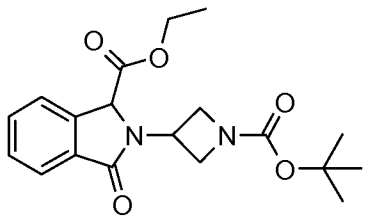
Compounds have been named using ACD/Name, version 8.0 or 9.0, software from Advanced Chemistry Development, Inc. (ACD/Labs), Toronto ON, Canada, www.acdlabs.com, 2004; and ELN version 2.1 software from Cambridgesoft, www.cambridgesoft.com, 2008.

Preparation of intermediates

The invention will now be illustrated by the following non-limiting examples.

Example I-1

Ethyl 2-[1-(*tert*-butoxycarbonyl)azetidin-3-yl]-3-oxoisoindoline-1-carboxylate



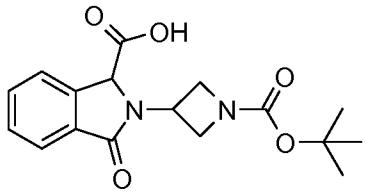
Intermediate 1

A solution of ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (2.5 g, 7.9 mol), prepared according to Othman et al Synth. Comm. 1996, *26*, 2803) in acetonitrile (25 mL) was cooled to 0 °C with ice-bath, and the atmosphere over the solution was exchanged to nitrogen. Triethylamine (2.5 mL, 18 mmol) and 3-amino-azetidine-1-carboxylic acid *tert*-butyl ester (2.0 g, 11.6 mol) were introduced sequentially, and the reaction mixture was allowed to warm up to ambient temperature while stirred over night. The crude was diluted with ethyl acetate (100 ml) and extracted with water, sat. sodium bicarbonate and finally with brine. The organic layer was dried over magnesium sulfate concentrated *in vacuo*. The crude was purified by column chromatography using a gradient of ethyl acetate in heptane (50-80 %). The fractions containing the title compound were pooled and concentrated *in vacuo* to yield 1.8 g (63 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1 H), 7.51 – 7.63 (m, 2 H), 7.49 (d, 1 H), 5.28 (s, 1 H), 4.70 (m, 1 H), 4.29 – 4.38 (m, 1 H), 4.22 – 4.29 (m, 3 H), 4.12 – 4.21 (m, 2 H), 1.41 (s, 9 H), 1.25 (t, 3 H); MS (ESI) *m/z* 359 [M-H].

Example I-2

2-[1-(tert-Butoxycarbonyl)azetidin-3-yl]-3-oxoisoindoline-1-carboxylic acid



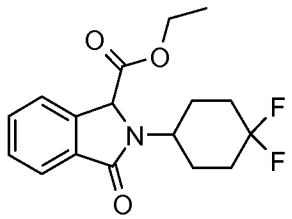
Intermediate 2

To a solution of ethyl 2-(1-(tert-butoxycarbonyl)azetidin-3-yl)-3-oxoisoindoline-1-carboxylate (1.08 g, 3.00 mmol) in methanol (20 mL) NaOH (1 M, 7.5 mL, 7.5 mmol) solution was added, and the reaction was stirred at ambient temperature for 30 min. The reaction mixture was neutralized with HCl (1 M) and concentrated to driness in vacuum. The obatined solid was resolubilized in acetone (25 mL) and the formed solid was filtered off. The filtrate was washed with acetone (10 mL) and the solvent was evaporated to yield the title compound as a yellowish solid, 0.975 g (98 %) .

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.61 - 7.66 (m, 1 H), 7.53 - 7.57 (m, 1 H), 7.49 (td, 1 H), 7.34 - 7.40 (m, 1 H), 4.98 (s, 1 H), 4.54 - 4.68 (m, 1 H), 4.40 (t, 1 H), 4.12 (br. s., 1 H), 3.86 - 4.07 (m, 2 H), 1.39 (s, 9 H); MS (ESI) *m/z* 333 [M+H].

Example I-3

Ethyl 2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxylate



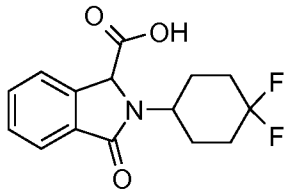
Intermediate 3

The title compound was synthesized according to the procedure described for intermediate 1 from ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (2.0 g, 6.3 mmol), triethylamine (1.3 mL, 9.3 mmol) and 4,4-difluoro-cyclohexylamine (1.0 g, 7.4 mol) in acetonitrile (30 mL) to yield 0.71 g (36 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, 1 H), 7.45 - 7.63 (m, 3 H), 5.16 (s, 1 H), 4.11 – 4.37 (m, 3 H), 2.16 - 2.33 (m, 2 H), 2.05 – 2.16 (m, 1 H), 1.77 – 2.04 (m, 5 H), 1.30 (t, 3 H) ; MS (ESI) *m/z* 324 [M+H].

Example I-4

2-(4,4-Difluorocyclohexyl)-3-oxoisoindoline-1-carboxylic acid



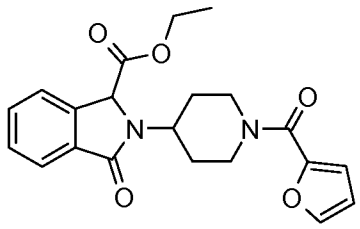
Intermediate 4

To a solution of ethyl 2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxylate (0.70 mg, 2.2 mmol) in methanol (20 mL) NaOH (1 M, 5.4 mL, 5.4 mmol) was added while stirred. The reaction was stirred at ambient temperature for 30 min. and then neutralized with HCl (1 M). The methanol was evaporated in vacuum. The waterphase was acidified to pH 2 with HCl (1 M) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to yield the title compound as a yellowish solid, 0.62 g, (97 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.59 (br. s., 1 H), 7.68 - 7.72 (m, 1 H), 7.51 - 7.67 (m, 3 H), 5.45 (s, 1 H), 4.11 (br. s., 1 H), 3.89 - 4.01 (m, 1 H), 1.87 - 2.15 (m, 7 H); MS (ESI) *m/z* 296 [M+H].

Example I-5

Ethyl 2-[1-(2-furoyl)piperidin-4-yl]-3-oxoisoindoline-1-carboxylate



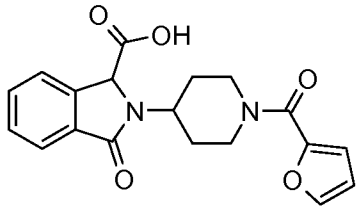
Intermediate 5

The title compound was synthesized according to the procedure described for intermediate 1 from ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (2.5 g, 7.9 mmol), triethylamine (2.2 mL, 15.8 mmol) and1-(2-furoyl)piperidin-4-amine (1.8 g, 9.3 mmol) in acetonitrile (30 mL) to yield 1.2 g (40 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, 1 H), 7.45- 7.62 (m, 4 H), 7.01 (d, 1 H), 6.43-6.54 (m, 1 H), 5.18 (s, 1 H), 4.70 (br s, 2 H), 4.32 – 4.45 (m, 1 H), 4.17 – 4.31 (m, 2 H), 3.01 (br s, 2 H), 2.04 – 2.19 (m, 2 H), 1.76 – 2.04 (m, 2 H), 1.22 – 1.35 (m, 3 H); MS (ESI) *m/z* 383 [M+H].

Example I-6

2-[1-(2-Furoyl)piperidin-4-yl]-3-oxoisoindoline-1-carboxylic acid

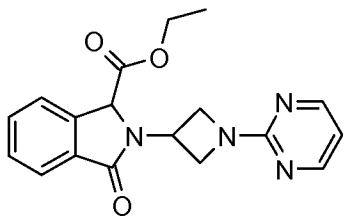


Intermediate 6

The title compound was synthesized according to the procedure described for intermediate 2 from 2-[1-(2-furoyl)piperidin-4-yl]-3-oxoisoindoline-1-carboxylic acid (0.382 g, 1.00 mmol) reacted with NaOH (1 M, 1.5 mL, 1.5 mmol) in methanol (10 mL) to yield a yellowish solid, 0.338 g (95 %). MS (ESI) *m/z* 355 [M+H].

Example I-7

Ethyl 3-oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)isoindoline-1-carboxylate



Intermediate 7

Step 1:

To a solution of ethyl 2-[1-(*tert*-butoxycarbonyl)azetidin-3-yl]-3-oxoisoindoline-1-carboxylate (1.0 g, 2.7 mmol) in anhydrous dichloromethane (10 mL) was added trifluoroacetic acid (2.0 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (10 mL) basified with sodium bicarbonate solution and extracted with ethyl acetate

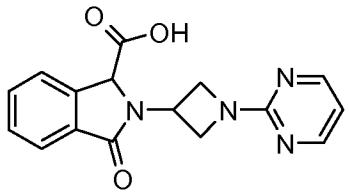
(3 x 30 ml). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo to yield 0.72 g (100 %).

Step 2:

A mixture of 2-bromopyrimidine (500 mg, 3.15 mmol), the deprotected amine from step 1 (722 mg, 2.17 mmol), $Pd_2(dba)_3$ (200 mg, 0.22 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (200 mg, 0.32 mmol) and cesium carbonate (1.1 g, 3.3 mmol) in toluene (115 mL) was degassed while purging with nitrogen and then heated to 80 °C for 19 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography using a gradient of ethyl acetate in hexane (50 – 80 %) to yield 590 mg (63 %) of the desired compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.35 (d, 2 H), 7.85 (d, 1 H), 7.48 – 7.67 (m, 3 H), 6.60 (t, 1 H), 5.38 (s, 1 H), 4.91 – 5.07 (m, 1 H), 4.51 – 4.61 (m, 2 H), 4.40 – 4.51 (m, 2 H), 4.11 – 4.34 (m, 2 H), 1.27 (t, 3 H); MS (ESI) *m/z* 339 [M+H].

Example I-8

3-Oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)isoindoline-1-carboxylic acid

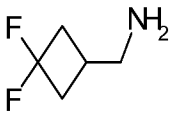


Intermediate 8

The title compound was synthesized according to the procedure described for intermediate 2 from ethyl 3-oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)isoindoline-1-carboxylate (0.338 g, 1.00 mmol) reacted with NaOH (1 M, 2.5 mL, 2.5 mmol) in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL) to yield a yellow solid, 0.301 g (97 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.34 (d, 2 H), 7.60 - 7.66 (m, 1 H), 7.53 - 7.57 (m, 1 H), 7.49 (td, 1 H), 7.38 (t, 1 H), 6.67 (t, 1 H), 5.02 (s, 1 H), 4.80 - 4.90 (m, 1 H), 4.51 - 4.58 (m, 1 H), 4.23 - 4.34 (m, 2 H), 4.18 (t, 1 H); MS (ESI) *m/z* 311 [M+H].

Example I-9

(3,3-Difluorocyclobutyl)methanamine



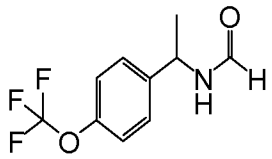
Intermediate 9

3,3-difluorocyclobutanecarbonitrile (113 mg, 0.97 mmol) was dissolved in methanol (20 mL) and hydrogenated in a continuous flow hydrogenating apparatus (H-Cube) using Pd/C (10 % standard cartridge) with 1.0 mL/minute flow at 25°C under full H_2 mode. The solution was runned twice through the system. The solvent was removed under reduced pressure to yield the title compound as an oil (65.0 mg, 55.6 %, 60 % purity). The compound was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.73 (d, 2 H) 2.61 - 2.70 (m, 3 H) 2.17 - 2.27 (m, 2 H).

Example I-10

N-(1-(4-(Trifluoromethoxy)phenyl)ethyl)formamide



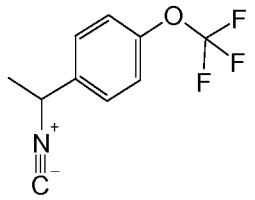
Intermediate 10

1-(4-(trifluoromethoxy)phenyl)ethanamine (0.352 g, 1.72 mmol) was dissolved in dichloromethane (4 mL), set under N_2 atmosphere and was cooled down to 0°C. Phenyl formate (0.187 mL, 1.72 mmol) was added dropwise and the mixture was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was purified on silica column using heptane : ethyl acetate = 100:0 to 0:100 as gradient. Colorless oil, 284 mg (71 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.20 (s, 1 H) 7.36 (d, 2 H) 7.17 - 7.22 (m, 2 H) 5.77 (br. s., 1 H) 5.24 (t, 1 H) 1.53 (d, 3 H). MS (ESI) *m/z* 234 [M+H].

Example I-11

1-(1-Isocyanoethyl)-4-(trifluoromethoxy)benzene



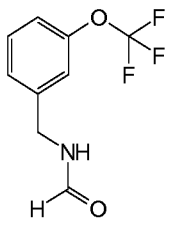
Intermediate 11

N-(1-(4-(Trifluoromethoxy)phenyl)ethyl)formamide (0.275 g, 1.18 mmol) was dissolved in dichloromethane (4 mL) and cooled to -15°C under N_2 atmosphere. N,N-diisopropylethylamine (0.780 mL, 4.72 mmol) followed by phosphorus oxychloride (0.132 mL, 1.42 mmol) were added and the resulting mixture was allowed to slowly reach room temperature (3 hours). Then methanol (1.5 mL) was added to quench the reaction. The mixture was diluted with dichloromethane and washed twice with saturated $NaHCO_3$ solution. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give the product as a brown oil, 284 mg (112 %) which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.41 (d, 2 H) 7.24 - 7.29 (m, 2 H) 4.85 (q, 1 H) 1.70 (d, 2 H). MS (ESI) *m/z* 216 [M+H].

Example I-12

N-(3-(Trifluoromethoxy)benzyl)formamide



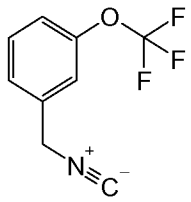
Intermediate 12

The title compound was prepared according to the method described for example 10 using (3-(trifluoromethoxy)phenyl)methanamine (0.2 g, 1.05 mmol) and phenyl formate (0.117 mL, 1.05 mmol). Colorless oil, 120 mg (52 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.31 (s, 1 H) 7.35 - 7.40 (m, 1 H) 7.22 - 7.26 (m, 1 H) 7.15 (br. s., 2 H) 5.92 (br. s., 1 H) 4.53 (d, 2 H). MS (ESI) *m/z* 220 [M+H].

Example I-13

1-(Isocyanomethyl)-3-(trifluoromethoxy)benzene



Intermediate 13

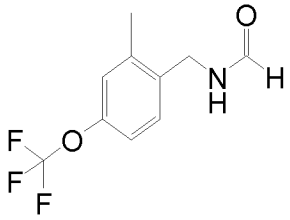
The title compound was prepared according to the method described for example 11 using N-(3-(trifluoromethoxy)benzyl)formamide (120 mg, 0.55 mmol), N,N-diisopropylethylamine (0.362 mL, 2.19 mmol) and phosphorus oxychloride (0.061 mL, 0.66 mmol).

Brown oil, 110 mg (100 %) which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43 - 7.49 (m, 1 H) 7.31 (d, 1 H) 7.21 - 7.25 (m, 2 H) 4.69 (s, 2 H). MS (ESI) *m/z* 202 [M+H].

Example I-14

N-(2-Methyl-4-(trifluoromethoxy)benzyl)formamide



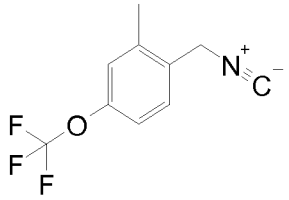
Intermediate 14

The title compound was prepared according to the method described for example 10 using (2-methyl-4-(trifluoromethoxy)phenyl)methanamine (0.35 g, 1.71 mmol) and phenyl formate (0.191 mL, 1.71 mmol). The crude was purified on silica column using dichloromethane : (dichloromethane/methanol/ammonia 90:10:1) = 100:0 to 30:70 as gradient. White solid, 252 mg (63 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.28 (s, 1 H) 7.27 (t, 1 H) 7.06 (br. s., 2 H) 5.68 (br. s., 1 H) 4.49 (d, 2 H) 2.36 (s, 3 H). MS (ESI) *m/z* 232 [M-H].

Example I-15

1-(Isocyanomethyl)-2-methyl-4-(trifluoromethoxy)benzene

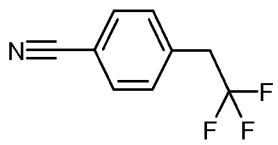


Intermediate 15

The title compound was prepared according to the method described for example 11 using N-(2-methyl-4-(trifluoromethoxy)benzyl)formamide (0.250 g, 1.07 mmol), N,N-diisopropylethylamine (0.742 mL, 4.29 mmol) and phosphorus oxychloride (0.120 mL, 1.29 mmol). Brown oil, 300 mg (130 %) which was used without further purification. MS (ESI) *m/z* 216 [M+H].

Example I-16

4-(2,2,2-Trifluoroethyl)benzonitrile



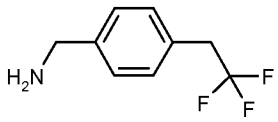
Intermediate 16

To the DMF (25 mL) solution of 1-bromo-4-(2,2,2-trifluoroethyl)benzene (2.15 g, 9.00 mmol) were zinc cyanide (2.11 g, 18.0 mmol) then $Pd(PPh_3)_4$ (0.828 g, 0.720 mmol) added. The mixture was heated at 100°C for 18 hours then cooled to room temperature, diluted with ethyl acetate (50 mL) and filtered through a short bed of celite. The filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using hexane : ethyl acetate = 90:10 as eluent to give the title compound as a white solid, 800 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (d, 2 H) 7.43 (d, 2 H) 3.44 (q, 2 H). ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -65.85, -65.88 and -65.91. MS (ESI) *m/z* 186 [M+H].

Example I-17

(4-(2,2,2-Trifluoroethyl)phenyl)methanamine



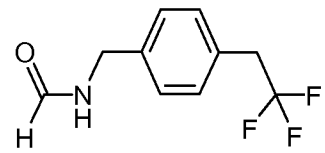
Intermediate 17

1M borane in tetrahydrofuran (9.40 mL, 9.40 mmol) was added to the tetrahydrofuran (15 mL) solution of 4-(2,2,2-trifluoroethyl)benzonitrile (0.580 g, 3.13 mmol). The mixture was heated at 60°C for 18 hours, cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in methanol (15 mL), refluxed for 2 hours and concentrated under reduced pressure. The crude residue was dissolved in dichloromethane (50 mL), washed with 2M NaOH solution (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the title compound as a pale yellow oil, 600 mg (100 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 - 7.34 (m, 4 H) 3.88 (s, 2 H) 3.36 (q, 2H) (NH_2 not shown). ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -66.42, -66.45 and -66.48. MS (ESI) *m/z* 190 [M+H].

Example I-18

N-(4-(2,2,2-Trifluoroethyl)benzyl)formamide



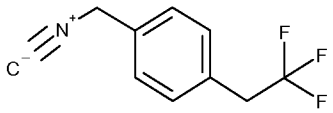
Intermediate 18

A solution of (4-(2,2,2-trifluoroethyl)phenyl)methanamine (0.650 g, 3.40 mmol) in ethylformate (5 mL) was refluxed for 18 hours. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography using hexane: ethyl acetate = 100:0 to 50:50 as eluent to afford the desired compound as a white solid, 620 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (s, 1 H) 7.29 (s, 4 H) 5.77 (m, 1 H) 4.51 (d, 2 H) 3.36 (q, 2 H). ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -66.36, -66.39 and -66.41. MS (ESI) *m/z* 218 [M+H].

Example I-19

1-Isocyanomethyl-4-(2,2,2-trifluoroethyl)benzene



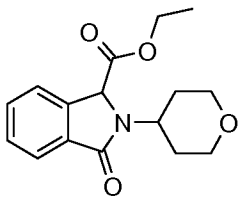
Intermediate 19

Phosphorus oxychloride (0.320 mL, 3.43 mmol) was added dropwise to a solution of N-(4-(2,2,2-trifluoroethyl)benzyl)formamide (0.620 g, 2.86 mmol) and N,N-diisopropylethylamine (1.97 mL, 11.4 mmol) in dichloromethane (20 mL) at -20°C. The mixture was slowly warmed to room temperature and stirred for 16 hours. Afterwards the reaction mixture was concentrated, the residue was dissolved in methanol (3 mL) and triethylamine (2.5 mL) was added. The reaction mixture was stirred for 5 minutes and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography using hexane: ethyl acetate = 100:0 to 80:20 as eluent yielding the title compound as a white solid, 442 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (s, 4 H) 4.66 (s, 2 H) 3.39 (q, 2 H). ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -66.31, -66.34 and -66.37. MS (ESI) *m/z* 200 [M+H].

Example I-20

Ethyl 3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxylate



Intermediate 20

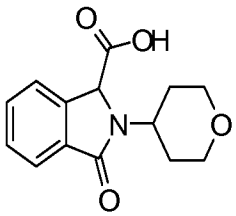
The title compound was prepared according to the procedure described for intermediate 1 from ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (3.15 g, 10.0 mmol), triethylamine

(2.23 mL, 16.0 mmol) and 4-aminotetrahydropyran (1.52 mL, 15.0 mmol) in acetonitrile (25 mL) to yield a white solid, 2.35 g (81 %).

^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 7.76 - 7.81 (m, 1 H) 7.61 - 7.68 (m, 2 H) 7.54 - 7.60 (m, 1 H) 5.51 (s, 1 H) 4.22 - 4.33 (m, 2 H) 4.13 - 4.22 (m, 1 H) 3.98 - 4.06 (m, 2 H) 3.47 - 3.57 (m, 2 H) 1.96 - 2.18 (m, 2 H) 1.86 - 1.94 (m, 2 H) 1.30 (t, 3 H). MS (ESI) *m/z* 290 [M+H].

Example I-21

3-Oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxylic acid



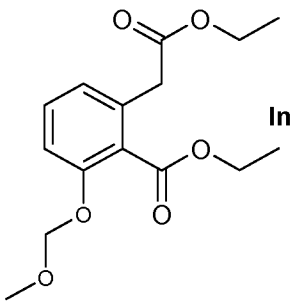
Intermediate 21

The title compound was synthesized according to the procedure described for intermediate 2 from ethyl 3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxylate (1.45 g, 5.00 mmol) reacted with 2 M NaOH (5.0 mL, 10.0 mmol) in methanol (15 mL) to yield a white solid, 0.97 g (75 %)

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.59 (br. s., 1 H) 7.68 - 7.72 (m, 1 H) 7.58 - 7.67 (m, 2 H) 7.51 - 7.57 (m, 1 H) 5.44 (s, 1 H) 4.00 - 4.10 (m, 1 H) 3.87 - 3.95 (m, 2 H) 3.35 - 3.43 (m, 2 H) 1.85 - 2.04 (m, 2 H) 1.76 - 1.85 (m, 2 H). MS (ESI) *m/z* 262 [M+H].

Example I-22

Ethyl 2-(2-ethoxy-2-oxoethyl)-6-(methoxymethoxy)benzoate



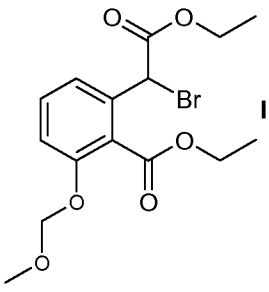
Intermediate 22

At room temperature chloro(methoxy)methane (3.47 g, 43.21 mmol) was added to a stirred solution of ethyl 2-(2-ethoxy-2-oxoethyl)-6-hydroxybenzoate (7.8 g, 30.86 mmol, prepared according to *Journal of the Chemical Society, Chemical Communications* **1977**, *17*, 582) and N,N-diisopropylethylamine (8.0 mL, 45.94 mmol) in dry dichloromethane (50 mL). The reaction mixture was stirred for 3 hours, diluted with dichloromethane (50 mL) and then quenched with water (20 mL). The phases were separated, the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using hexane : ethyl acetate = 90:10 eluent to give the desired product, 7.29 g (79.7 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30 (t, 1 H) 7.09 (d, 1 H) 6.95 (d, 1 H) 5.18 (s, 2 H) 4.38 (q, 2 H) 4.14 (q, 2 H) 3.66 (s, 2 H) 3.48 (s, 3 H) 1.37 (t, 3 H) 1.24 (t, 3 H). MS (ESI) *m/z* 297 [M+H].

Example I-23

Ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)-6-(methoxymethoxy)benzoate



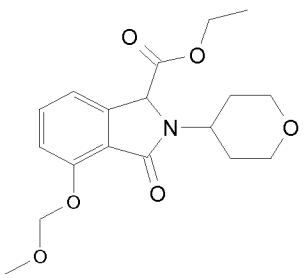
Intermediate 23

N-Bromosuccinamide (6.2 g, 31.47 mmol) and 2,2'-azobis(2-methylpropionitrile) (1.1 g) were sequentially added to a solution of ethyl 2-(2-ethoxy-2-oxoethyl)-6-(methoxymethoxy)benzoate (6.0 g, 20.24 mmol) in carbon tetrachloride (100 ml). The reaction mixture was refluxed for 1.5 hours then was cooled down to room temperature, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography by using hexane : ethyl acetate = 100:0 to 95:5 as gradient yielding the desired product, 4.6 g (79 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 - 7.53 (m, 1 H) 7.38 (t, 1 H) 7.15 (d, 1 H) 5.49 (s, 1 H) 5.19 (s, 2 H) 4.44 (q, 2 H) 4.16 - 4.36 (m, 2 H) 3.48 (s, 3 H) 1.40 (t, 3 H) 1.27 (t, 3 H). MS (ESI) *m/z* 376 [M+H].

Example I-24

Ethyl 4-(methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxylate



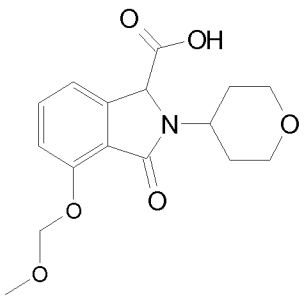
Intermediate 24

The title compound was prepared according to the procedure described for intermediate 1 from ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)-6-(methoxymethoxy)benzoate (1.4 g, 3.73 mmol), 4-aminotetrahydropyran (0.376 g, 3.72 mmol) and triethylamine (1.03 mL, 7.43 mmol) in acetonitrile (20 mL). Solid, 900 mg (69 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (t, 1 H) 7.21 (d, 1 H) 7.15 (d, 1 H) 5.36 (s, 2 H) 5.12 (s, 1 H) 4.13 - 4.40 (m, 3 H) 3.94 - 4.12 (m, 2 H) 3.40 - 3.63 (m, 5 H) 1.75 - 2.02 (m, 4 H) 1.29 (t, 3 H). MS (ESI) *m/z* 350 [M+H].

Example I-25

4-(Methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxylic acid



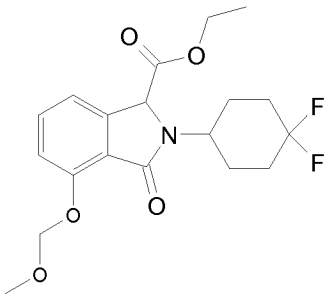
Intermediate 25

A solution of lithium hydroxide (0.113 g, 4.72 mmol) in water (1 mL) was added to a stirred solution of ethyl 4-(methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxylate (1.1 g, 3.15 mmol) in tetrahydrofuran (5 mL) and methanol (5 mL) at room temperature. The reaction mixture was stirred for 3 hours then concentrated *in vacuo*. The crude residue was taken up in water (10 mL), acidified with 6N HCl and extracted with ethyl acetate (3x50 mL). The combined organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, filter and concentrated under reduced pressure to give the desired product, 800 mg (79 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (t, 1 H) 7.21 (d, 1 H) 7.15 (d, 1 H) 5.36 (s, 2 H) 5.21 (s, 1 H) 4.13 - 4.40 (m, 3 H) 3.40 - 3.63 (m, 5 H) 1.75 - 2.02 (m, 4 H). MS (ESI) *m/z* 322 [M+H].

Example I-26

Ethyl 2-(4,4-difluorocyclohexyl)-4-(methoxymethoxy)-3-oxoisoindoline-1-carboxylate



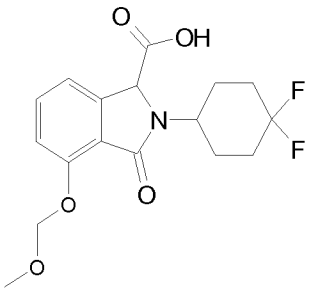
Intermediate 26

The title compound was prepared according to the procedure described for intermediate 1 from ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)-6-(methoxymethoxy)benzoate (2.8 g, 7.47 mmol), 4,4-difluorocyclohexanamine (1.35 g, 10.0 mmol) and triethylamine (2.5 mL, 18.0 mmol) in acetonitrile (20 mL). Solid, 1.67 g (58.6 %).

MS (ESI) *m/z* 384 [M+H].

Example I-27

2-(4,4-Difluorocyclohexyl)-4-(methoxymethoxy)-3-oxoisoindoline-1-carboxylic acid



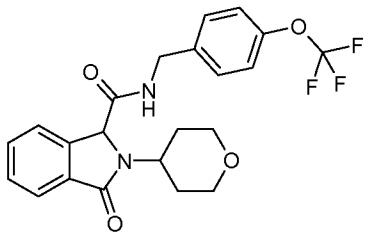
Intermediate 27

The title compound was prepared according to the method described for example 25 using ethyl 2-(4,4-difluorocyclohexyl)-4-(methoxymethoxy)-3-oxoisoindoline-1-carboxylate (650 mg, 1.69 mmol) in tetrahydrofuran/methanol (5/5 mL) and lithium hydroxide (81 mg, 3.37 mmol) in water (1 mL). Solid, 350 mg (60 %).

MS (ESI) *m/z* 356 [M+H].

Example 1 (general procedure 1)

2-(Oxan-4-yl)-3-oxo-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide

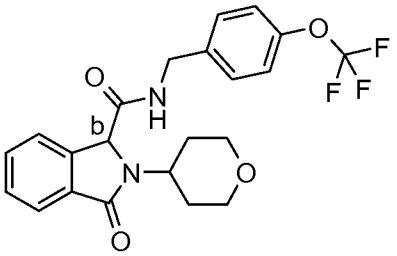


To a solution of 2-formylbenzoic acid (45 mg, 0.3 mmol) in methanol (2 mL) tetrahydro-2H-pyran-4-amine (30 μL, 0.30 mmol) was added followed by addition of 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (57 mg, 0.29 mmol). The mixture was stirred over night at ambient temperature before it was filtered and purified using preparative liquid chromatography. The fractions containing the product were pooled, and the acetonitrile was removed in vacuum. The water solution was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to yield the title compound as white solid, 78 mg (60 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 - 9.19 (m, 1 H), 7.67 - 7.72 (m, 1 H), 7.57 - 7.62 (m, 1 H), 7.51 - 7.55 (m, 1 H), 7.46 - 7.51 (m, 1 H), 7.30 - 7.41 (m, 4 H), 5.32 (s, 1 H), 4.34 (d, 2 H), 4.06 - 4.17 (m, 1 H), 3.86 - 3.92 (m, 1 H), 3.77 - 3.84 (m, 1 H), 3.33 - 3.41 (m, 2 H), 1.77 - 1.91 (m, 1 H), 1.63 - 1.73 (m, 3 H); MS (ESI) *m/z* 435 [M+H], MS (ESI) *m/z* 433 [M-H].

Example 2

2-(Oxan-4-yl)-3-oxo-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide, ISOMER 2



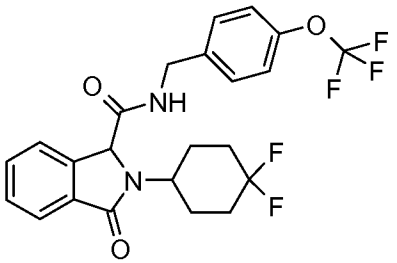
ISOMER 2
b = unknown absolute

The enantiopure compound was obtained by chiral separation of the racemic compound 2-(Oxan-4-yl)-3-oxo-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide using SFC Berger Multigram II system; Column: Chiralpak AD, 21.2x250 mm, 10µm; Mobile phase: 25 % ethanol / 75 % CO_2; Flowrate: 50 mL/min, ~15 mg/inj. The fractions were collected accordind to retention times yielding ISOMER 2 as the second fraction. The fraction were evaporated at 23-25 °C in order to avoid thermo racemisation, and handled separately. Analytical LC analysis were conducted using Berger SFC Analytix; Column: Chiralpak AD-H, 4.6 x 250 mm, 5 µm; Mobilphase: 25 % ethanol / 75 % CO_2; Flowrate: 2 mL/min; ISOMER 2 (6.20 min), 26 mg, enantiopurity: 99 %.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, 1 H), 7.69 (d, 1 H), 7.60 (td, 1 H), 7.46 - 7.55 (m, 2 H), 7.35 - 7.41 (m, 2 H), 7.30 - 7.35 (m, 2 H), 5.32 (s, 1 H), 4.34 (d, 2 H), 4.06 - 4.16 (m, 1 H), 3.89 (dd, 1 H), 3.76 - 3.84 (m, 1 H), 3.33 - 3.40 (m, 2 H), 1.78 - 1.90 (m, 1 H), 1.64 - 1.73 (m, 3 H); MS (ESI) m/z 435[M+H], MS (ESI) m/z 433 [M-H].

Example 3 (general procedure 2)

2-(4,4-Difluorocyclohexyl)-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide

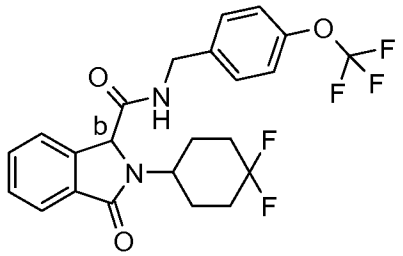


To a solution of 2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxylic acid (74 mg, 0.25 mmol) in DMF (2 mL) under argon atmosphere, triethylamine (139 µL, 1.00 mmol), and fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (99 mg, 0.38 mmol) were added sequentially. The reaction mixture was stirred at ambient temperature for 2 minutes. (4-(trifluoromethoxy)phenyl)methanamine (96 µL, 0.50 mmol) was added and the reaction mixture was stirred at 45 °C over night. The mixture was filtered, and purified using preparative liquide chromatography. The fractions containing the product were pooled and the acetonitrile was removed in vacuum. The water solution was basified with saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over magensium sulfate and concentrated in vacuum to yield the title compound as a white solid, 8 mg (7 %).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.76 (d, 1 H), 7.59 - 7.63 (m, 2 H), 7.48 - 7.54 (m, 1 H), 7.11 (s, 4 H), 6.16 (t, 1 H), 5.12 (s, 1 H), 4.45 (dd, 1 H), 4.29 (dd, 1 H), 4.14 - 4.26 (m, 1 H), 2.04 - 2.23 (m, 2 H), 1.72 - 1.97 (m, 6 H); MS (ESI) m/z 467 [M-H].

Example 4

2-(4,4-Difluorocyclohexyl)-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide, ISOMER 2



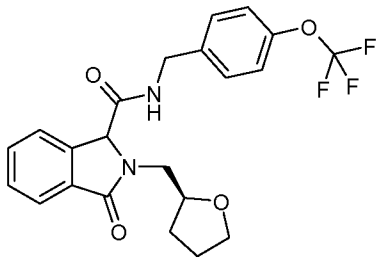
ISOMER 2
b = unknown absolute

The enantiopure compound was obtained by chiral separation of the racemic compound 2-(4,4-difluorocyclohexyl)-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide using SFC Berger Multigram II system; Column: Chiralpak AD, 21.2x250 mm; Mobilephase: 25 % ethanol / 75 % CO_2; Flowrate: 50 ml/min, 40mg/ 900µL/injection. The fractions were collected according to retention times yielding ISOMER 2 as the second fraction eluting at 3.10 min. The fraction was evaporated separately at 23-25 °C in order to avoid thermo racemisation. Analytical LC analysis were conducted with SFC Berger Analytix; Column: Chiralpak AD, 4.6x250 mm, 5µm; Mobilephase: 30 % ethanol / 70 % CO_2; Flowrate: 2 ml/min; ISOMER 2 (2.93 min), 117 mg, enantiopurity: 99 %.

^{1}H NMR (400 MHz, DMSO-d_6) δppm 9.18 (t, 1 H), 7.69 (d, 1 H), 7.60 (td, 1 H), 7.52 (t, 1 H), 7.45 - 7.49 (m, 1 H), 7.36 - 7.41 (m, 2 H), 7.30 - 7.35 (m, 2 H), 5.31 (s, 1 H), 4.27 - 4.41 (m, 2 H), 4.00 - 4.11 (m, 1 H), 1.78 - 2.10 (m, 7 H), 1.61 - 1.76 (m, 1 H); MS (ESI) m/z 469 [M+H], MS (ESI) m/z 467 [M-H].

Example 5

3-Oxo-2-[[(2S)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide

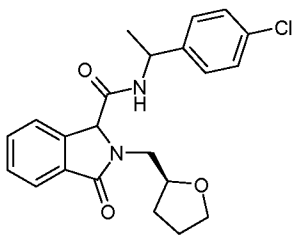


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (38 mg, 0.25 mmol), (*S*)-1-(Tetrahydro-furan-2-yl)-methylamine (27 μL, 0.25 mmol), and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (50 mg, 0.25 mmol). White solid, 63 mg (59 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 - 9.25 (m, 1 H), 7.69 - 7.73 (m, 1 H), 7.59 - 7.64 (m, 1 H), 7.54 - 7.58 (m, 1 H), 7.50 - 7.54 (m, 1 H), 7.36 - 7.41 (m, 2 H), 7.30 - 7.35 (m, 2 H), 5.42 (d, 1 H), 4.29 - 4.43 (m, 2 H), 3.91 - 4.07 (m, 2 H), 3.68 - 3.76 (m, 1 H), 3.54 - 3.67 (m, 1 H), 2.81 - 3.16 (m, 1 H), 1.84 - 2.02 (m, 1 H), 1.71 - 1.84 (m, 2 H), 1.45 - 1.59 (m, 1 H); MS (ESI) *m/z* 435 [M+H], MS (ESI) *m/z* 433 [M-H].

Example 6

N-[1-(4-Chlorophenyl)ethyl]-3-oxo-2-[[(2S)-oxolan-2-yl]methyl]-1H-isoindole-1-carboxamide



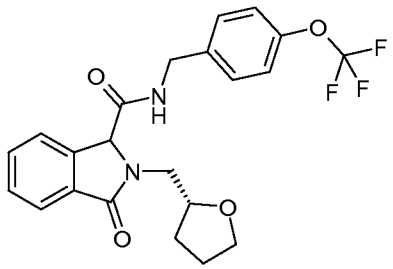
The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (30 mg, 0.20 mmol), (*S*)-1-(Tetrahydro-furan-2-yl)-

methylamine (21 μL, 0.20 mmol), and 1-chloro-4-(1-isocyanoethyl)benzene (33 mg, 0.20 mmol). White solid, 47 mg (59 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 - 9.25 (m, 1 H), 7.64 - 7.74 (m, 1 H), 7.46 - 7.64 (m, 3 H), 7.33 - 7.42 (m, 4 H), 5.32 - 5.52 (m, 1 H), 4.86 - 4.99 (m, 1 H), 3.85 - 4.13 (m, 2 H), 3.55 - 3.83 (m, 2 H), 2.69 - 3.19 (m, 1 H), 1.70 - 2.05 (m, 3 H), 1.45 - 1.61 (m, 1 H), 1.41 (d, 3 H); MS (ESI) *m/z* 499 [M+H].

Example 7

3-Oxo-2-[[(2R)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide

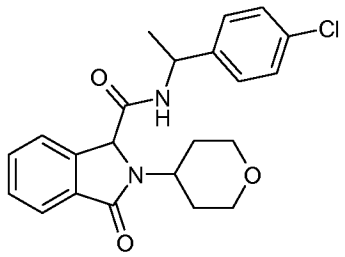


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (38 mg, 0.25 mmol), (*R*)-1-(Tetrahydro-furan-2-yl)-methylamine (27 μL, 0.25 mmol), and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (50mg, 0.25 mmol). White solid, 58 mg (53 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 - 9.25 (m, 1 H), 7.71 (d, 1 H), 7.59 - 7.65 (m, 1 H), 7.50 - 7.58 (m, 2 H), 7.36 - 7.41 (m, 2 H), 7.30 - 7.36 (m, 2 H), 5.42 (d, 1 H), 4.29 - 4.44 (m, 2 H), 3.99 - 4.06 (m, 1 H), 3.91 - 3.99 (m, 1 H), 3.68 - 3.76 (m, 1 H), 3.54 - 3.66 (m, 1 H), 2.82 - 3.18 (m, 1 H), 1.84 - 2.03 (m, 1 H), 1.71 - 1.84 (m, 2 H), 1.45 - 1.59 (m, 1 H); MS (ESI) *m/z* 435 [M+H], MS (ESI) *m/z* 433 [M-H].

Example 8

N-[1-(4-chlorophenyl)ethyl]-2-(oxan-4-yl)-3-oxo-1H-isoindole-1-carboxamide

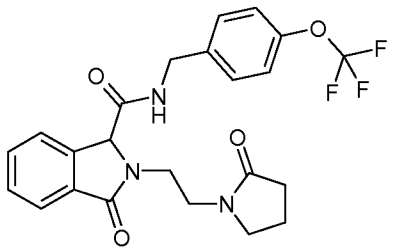


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (45 mg, 0.3 mmol), tetrahydro-2H-pyran-4-amine (30 µL, 0.30 mmol), and 1-chloro-4-(1-isocyanoethyl)benzene (47 mg, 0.29 mmol). White solid, 40 mg (33 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 - 7.82 (m, 1 H), 7.46 - 7.65 (m, 3 H), 7.29 - 7.34, 7.06 - 7.13 (m + m, 2 H), 7.20 - 7.25, 6.72 - 6.79 (m + m , 2 H), 6.00, 5.94 (d + d, 1 H), 5.11, 5.05 (s + s, 1 H), 4.99 - 5.12 (m, 1 H), 4.39 - 4.49, 4.17 - 4.28 (m +m, 1 H), 4.03 - 4.12, 3.99, 3.86 (m + dd + dd, 2 H), 3.53, 3.30 - 3.46 (td + m, 2 H), 1.44 - 2.04 (m, 4 H), 1.41, 1.29 (d + d, 3 H); MS (ESI) *m/z* 399 [M+H], MS (ESI) *m/z* 397 [M-H].

Example 9

3-Oxo-2-[2-(2-oxopyrrolidin-1-yl)ethyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide

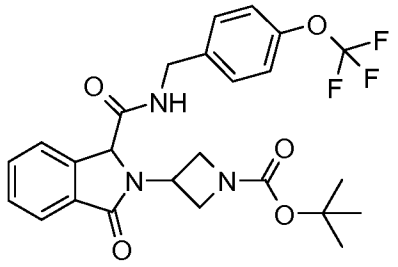


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (45 mg, 0.30 mmol), 1-(2-aminoethyl)pyrrolidin-2-one (38 µL, 0.30 mmol), and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (60 µL, 0.30 mmol). White solid, 71 mg (51 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 - 9.33 (m, 1 H), 7.66 - 7.72 (m, 1 H), 7.58 - 7.63 (m, 1 H), 7.49 - 7.57 (m, 1 H), 7.35 - 7.41 (m, 2 H), 7.29 - 7.34 (m, 2 H), 5.36 (s, 1 H), 4.30 - 4.42 (m, 2 H), 4.06 - 4.16 (m, 1 H), 3.61 - 3.70 (m, 1 H), 3.44 - 3.53 (m, 1 H), 3.15 - 3.31 (m, 2 H), 3.00 - 3.08 (m, 1 H), 2.08 - 2.16 (m, 1 H), 1.93 - 2.03 (m, 1 H), 1.79 - 1.90 (m, 2 H); MS (ESI) *m/z* 462 [M+H], MS (ESI) *m/z* 460 [M-H].

Example 10

***tert*-Butyl 3-(1-oxo-3-{[4-(trifluoromethoxy)benzyl]carbamoyl}-1,3-dihydro-2*H*-isoindol-2-yl)azetidine-1-carboxylate**

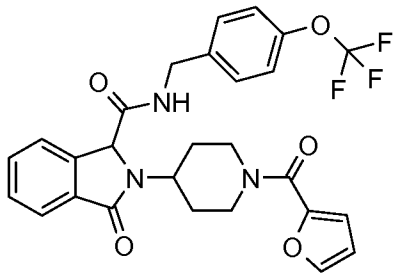


The title compound was prepared according to the general procedure 2, described in example 3, from 2-[1-(tert-butoxycarbonyl)azetidin-3-yl]-3-oxoisoindoline-1-carboxylic acid (83 mg, 0.25 mmol) and (4-(trifluoromethoxy)phenyl)methanamine (96 µL, 0.50 mmol). Solid, 9 mg (7 %).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.64 - 7.68 (m, 1 H), 7.56 - 7.63 (m, 2 H), 7.45 (t, 1 H), 7.09 - 7.16 (m, 4 H), 6.46 - 6.53 (m, 1 H), 5.29 (s, 1 H), 4.85 - 4.95 (m, 1 H), 4.41 - 4.48 (m, 1 H), 4.31 - 4.38 (m, 1 H), 4.18 - 4.27 (m, 2 H), 4.08 - 4.17 (m, 2 H), 1.46 (s, 9 H); MS (ESI) m/z 506 [M+H], MS (ESI) m/z 504 [M-H].

Example 11

2-[1-(2-Furoyl)piperidin-4-yl]-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide

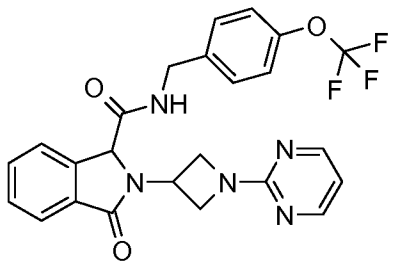


The title compound was prepared according to the general procedure 2, described in example 3, from 2-(1-(furan-2-carbonyl)piperidin-4-yl)-3-oxoisoindoline-1-carboxylic acid (89 mg, 0.25 mmol) and (4-(trifluoromethoxy)phenyl)methanamine (96 μL, 0.50 mmol). White solid, 11 mg (8 %).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.74 - 7.80 (m, 1 H), 7.59 - 7.62 (m, 2 H), 7.48 - 7.55 (m, 2 H), 7.06 - 7.12 (m, 4 H), 7.03 (dd, 1 H), 6.51 (dd, 1 H), 6.14 - 6.20 (m, 1 H), 5.12 (s, 1 H), 4.67 (br. s., 2 H), 4.28 - 4.46 (m, 3 H), 2.97 (br. s., 2 H), 1.82 - 1.94 (m, 3 H), 1.79 (dd, 1 H); MS (ESI) m/z 528 [M+H], MS (ESI) m/z 526 [M-H].

Example 12

3-Oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide

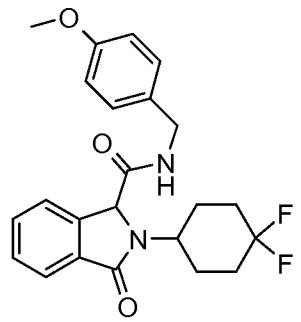


The title compound was prepared according to the general procedure 2, described in example 3, from 3-oxo-2-(1-(pyrimidin-2-yl)azetidin-3-yl)isoindoline-1-carboxylic acid (78 mg, 0.25 mmol) and (4-(trifluoromethoxy)phenyl)methanamine (96 mg, 0.50 mmol). White solid, 10 mg (8 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, 1 H), 8.38 (d, 2 H), 7.71 (d, 1 H), 7.61 - 7.66 (m, 1 H), 7.51 - 7.59 (m, 2 H), 7.29 - 7.35 (m, 2 H), 7.20 - 7.25 (m, 2 H), 6.72 (t, 1 H), 5.57 (s, 1 H), 4.91 - 5.00 (m, 1 H), 4.20 - 4.41 (m, 6 H); MS (ESI) m/z 484 [M+H], MS (ESI) m/z 482 [M-H].

Example 13

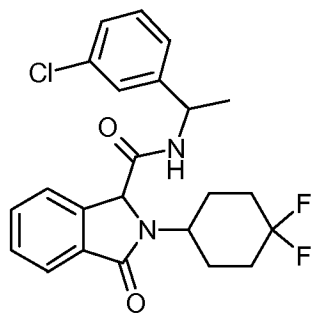
2-(4,4-Difluorocyclohexyl)-*N*-(4-methoxybenzyl)-3-oxoisoindoline-1-carboxamide



The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (35 mg, 0.23 mmol), 4,4-difluorocyclohexanamine (31 mg, 0.23 mmol) and 1-(isocyanomethyl)-4-methoxybenzene (31 mg, 0.21 mmol) to yield 28 mg (29 %). MS (ESI) m/z 415 [M+H].

Example 14

***N*-[1-(3-Chlorophenyl)ethyl]-2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxamide**

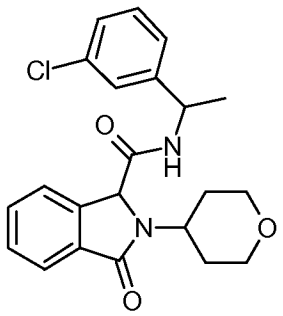


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (35 mg, 0.23 mmol), 4,4-difluorocyclohexanamine

(31 mg, 0.23 mmol) and 1-chloro-3-(1-isocyanoethyl)benzene (35 mg, 0.21 mmol) to yield 20 mg (20 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 9.19, 9.15 (d + d, 1 H), 7.25 - 7.71 (m, 8 H), 5.31 (s, 1 H), 4.85 - 4.95 (m, 1 H), 4.02 - 4.09 (m, 1 H), 1.58 - 2.12 (m, 8 H), 1.44, 1.42 (d + d, 3 H); MS (ESI) m/z 433 [M+H].

Example 15
***N*-[1-(3-Chlorophenyl)ethyl]-3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxamide**

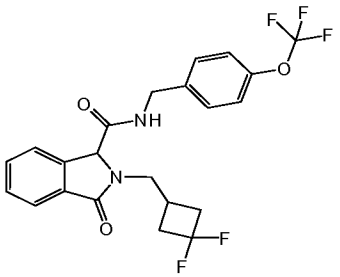


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (35 mg, 0.23 mmo), tetrahydro-2H-pyran-4-amine (23 mg, 0.23 mmol) and 1-chloro-3-(1-isocyanoethyl)benzene (35 mg, 0.21 mmol) to yield 34 mg (37 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 9.16, 9.11 (d + d, 1 H), 7.65 - 7.71 (m, 1 H), 7.54 - 7.64 (m, 1 H), 7.51 - 7.54 (m, 1 H), 7.42 - 7.51 (m, 1 H), 7.26 - 7.42 (m, 4 H), 5.31 - 5.32 (m, 1 H), 4.86 - 4.95 (m, 1 H), 4.05 - 4.15 (m, 1 H), 3.92, 3.78 (dd + dd, 1 H), 3.88 (dd, 1 H), 3.34 - 3.42 (m, 2 H), 1.54 - 1.91 (m, 4 H), 1.44, 1.43 (d + d, 3 H); MS (ESI) m/z 399 [M+H].

Example 16

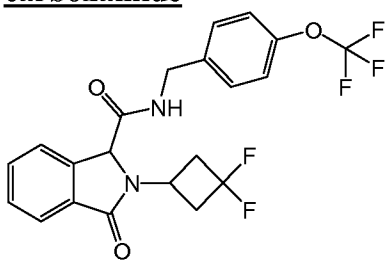
2-((3,3-Difluorocyclobutyl)methyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (66.9 mg, 0.45 mmol), 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.075 mL, 0.45 mmol) and (3,3-difluorocyclobutyl)methanamine (54 mg, 0.45 mmol). White solid, 22 mg (11 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.55 - 7.69 (m, 3 H) 7.46 (t, 1 H) 7.07 - 7.19 (m, 4 H) 6.35 (t, 1 H) 5.07 (s, 1 H) 4.31 - 4.49 (m, 2 H) 4.12 (dd, 1 H) 3.30 (dd, 1 H) 2.55 - 2.77 (m, 2 H) 2.31 - 2.53 (m, 3 H). MS (ESI) *m/z* 455 [M+H].

Example 17 (general procedure 3)

2-(3,3-Difluorocyclobutyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



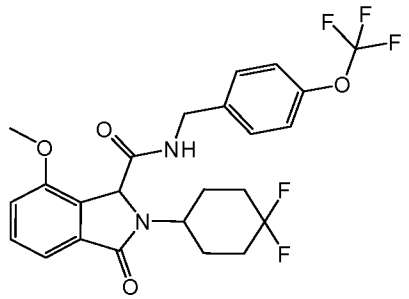
3,3-Difluorocyclobutanaminium chloride (28.7 mg, 0.20 mmol) and triethylamine (0.042 mL, 0.30 mmol, *note that no more than 2.0 equivalent base is recommended to be used in the reaction*) were mixed in methanol (2 mL) and after 5 minutes 2-formylbenzoic acid (30 mg, 0.20 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (40.2 mg, 0.20 mmol) were added. The mixture was stirred for 16 hours at ambient temperature before it was filtered and purified using preparative liquid chromatography. The fractions

containing the product were pooled, and the acetonitrile was removed in vacuum. The water solution was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to yield the title compound as yellowish solid, 21 mg (24 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.63 - 7.68 (m, 1 H) 7.60 (t, 1 H) 7.49 (d, 1 H) 7.42 (t, 1 H) 7.09 - 7.19 (m, 4 H) 6.62 (t, 1 H) 5.16 (s, 1 H) 4.41 - 4.51 (m, 2 H) 4.30 - 4.39 (m, 1 H) 2.87 - 3.08 (m, 3 H) 2.81 (ddd, 1 H). MS (ESI) *m/z* 441 [M+H].

Example 18

2-(4,4-Difluorocyclohexyl)-7-methoxy-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

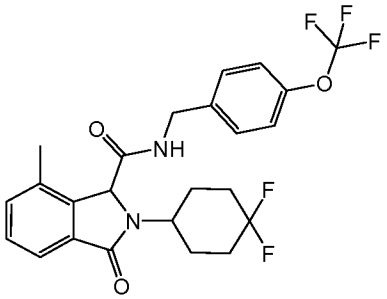


The title compound was synthesized according to the general procedure 3, described in example 17, from 4,4-difluorocyclohexanaminium chloride (57.2 mg, 0.33 mmol), triethylamine (0.056 mL, 0.40 mmol), 3-hydroxy-4-methoxyisobenzofuran-1(3H)-one (60 mg, 0.33 mmol, prepared according to *Journal of Organic Chemistry* **2007**, *72*, 3419), 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (67.0 mg, 0.33 mmol). White solid, 32 mg (19 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 - 7.51 (m, 2 H) 7.21 - 7.30 (m, 2 H) 7.11 - 7.19 (m, 2 H) 7.00 (dd, 1 H) 6.22 (t, 1 H) 5.07 (s, 1 H) 4.32 - 4.56 (m, 2 H) 4.08 - 4.27 (m, 1 H) 3.75 (s, 3 H) 2.00 - 2.26 (m, 3 H) 1.69 - 1.98 (m, 5 H). MS (ESI) *m/z* 499 [M+H].

Example 19

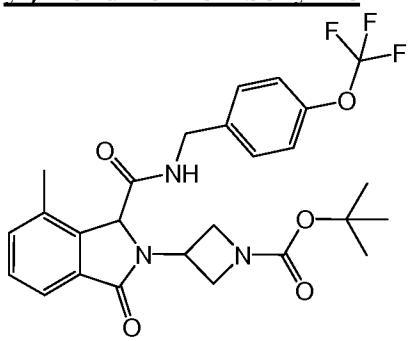
2-(4,4-Difluorocyclohexyl)-7-methyl-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



The title compound was synthesized according to the general procedure 3, described in example 17, from 4,4-difluorocyclohexanaminium chloride (31.4 mg, 0.18 mmol), triethylamine (0.050 mL, 0.36 mmol), 3-hydroxy-4-methylisobenzofuran-1(3H)-one (30 mg, 0.18 mmol, prepared according to the procedure described in *Tetrahedron Letters* **2002**, *43*, 7315 for the unsubstituted analog) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (36.8 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 4 hours, then at 50°C for 40 hours. White solid, 31.9 mg (36 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.25 (t, 1 H) 7.51 (d, 1 H) 7.39 (d, 3 H) 7.27 - 7.37 (m, 3 H) 5.26 (s, 1 H) 4.32 - 4.40 (m, 1 H) 4.23 - 4.31 (m, 1 H) 4.08 (t, 1 H) 2.23 (s, 3 H) 1.85 - 2.09 (m, 5 H) 1.75 (br. s., 1 H) 1.57 - 1.72 (m, 2 H). MS (ESI) *m/z* 483 [M+H].

Example 20

tert-Butyl 3-(4-methyl-1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate



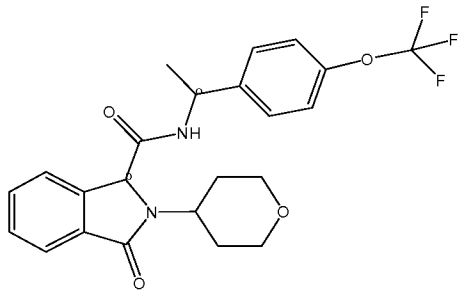
The title compound was synthesized according to the general procedure 1, described in example 1, from 3-hydroxy-4-methylisobenzofuran-1(3H)-one (30 mg, 0.18 mmol,

prepared according to the procedure described in *Tetrahedron Letters* **2002**, *43*, 7315 for the unsubstituted analog), tert-butyl 3-aminoazetidine-1-carboxylate (31.5 mg, 0.18 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (36.8 mg, 0.18 mmol). The reaction mixture was stirred at 50°C for 60 hours. White solid, 33.4 mg (35 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.55 - 7.65 (m, 1 H) 7.38 - 7.45 (m, 2 H) 7.13 (s, 4 H) 5.96 (t, 1 H) 5.25 (s, 1 H) 4.83 - 4.90 (m, 1 H) 4.37 - 4.43 (m, 1 H) 4.28 - 4.35 (m, 1 H) 4.16 - 4.28 (m, 3 H) 4.10 (t, 1 H) 2.40 (s, 3 H) 1.47 (s, 9 H). MS (ESI) *m/z* 418 [M-H].

Example 21

3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethoxy)phenyl)ethyl)isoindoline-1-carboxamide, ISOMER 4



ISOMER 4

The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (0.105 g, 0.70 mmol), 4-aminotetrahydropyran (0.071 g, 0.70 mmol) and 1-(1-isocyanoethyl)-4-(trifluoromethoxy)benzene (0.151 g, 0.70 mmol). White solid, 118 mg (37.6 %). The diasteromeric mixture (118 mg, 0.26 mmol) was separated by chiral chromatography, which was performed on Berger Multigram II SFC system. Column: Reprosil-NR; 20*250 mm, 10µm; Mobilephase: 10% methanol and 90% CO_2; Flow: 50 mL/minute, provided the separated isomers eluting at 8.3 minutes as ISOMER 1, at 9.4 minutes as ISOMER 2, at 11 minutes as ISOMER 3 and at 12.7 minutes as ISOMER 4. The separated isomers were collected, evaporated and handled separately. The samples were analyzed by HPLC using SFC Berger Analytix; Column: Reprosil-NR;

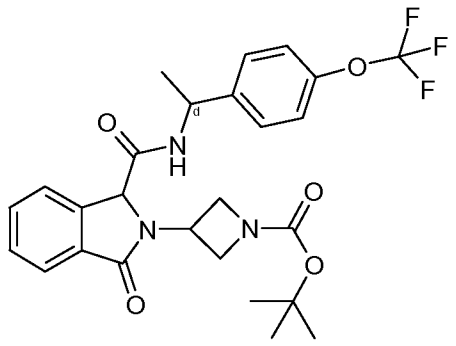
4.6*250 mm; 5µm; Mobilephase: 20% methanol and 80% CO_2; Flow: 2 mL/minute, ISOMER 4 (6.5 minutes), 25 mg, enatiomeric purity: 99 %.

Isomer 4 epimerised slowly to isomer 3 after separation according to NMR and chiral HPLC.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.19 (d, 1 H), 7.65 (m, 2 H), 7.47 (m, 4 H), 7.33 (d, 2 H), 5.30 (s, 1 H), 4.93 (m, 1 H), 4.09 (m, 1 H), 3.86 (dd, 1 H), 3.71 (dd, 1 H), 1.71 (m, 2 H), 1.53 (m, 2 H), 1.45 (m, 3 H). MS (ESI) *m/z* 449 [M+H].

Example 22

tert-Butyl 3-(1-oxo-3-(1-(4-(trifluoromethoxy)phenyl)ethylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate, ISOMER 3&4



ISOMER 3&4
d = unknown absolute

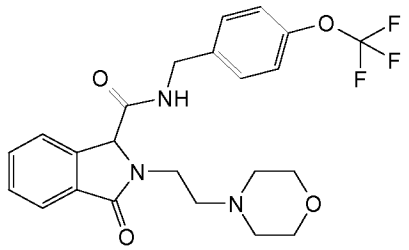
The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (0.105 g, 0.70 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (0.121 g, 0.70 mmol) and 1-(1-isocyanoethyl)-4-(trifluoromethoxy)benzene (0.151 g, 0.70 mmol). White solid, 170 mg (46.7 %). The diastereomeric mixture (0.151 g) was subjected to enantiomeric separation which was performed on Berger Multigram II SFC system. Column: Reprosil-NR; 20*250 mm, 10µm; Mobilephase: 0-7 minutes: 25% isopropanol and 75% CO_2, 7-11 minutes: 35% isopropanol and 65% CO_2, Flow: 50 mL/minute, provided the separated isomers eluting at 5 minutes as ISOMER 1&2 together, at 6.6 minutes as ISOMER 3 and at 9.8 minutes as ISOMER 4. The separated isomers were collected, evaporated and handled separately. The samples were analyzed by HPLC using

SFC Berger Analytix; Column: Reprosil-NR; 4.6*250 mm; 5µm; Mobilephase: 20% methanol and 80% CO_2; Flow: 2 mL/minute. ISOMER 3 was epimerised to ISOMER 4 ,during the time needed to remove the solvent, yielding a 1:1 mixture of ISOMER 3 and 4 (6.2 minutes and 8.9 minutes retention times, respectively), 40 mg, 1:1 diastereomeric mixture.

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.33 (d, 1 H) 7.68 (d, 1 H) 7.59 (m, 1 H) 7.49 (m, 4 H) 7.33 (d, 2 H) 5.47 (s, 1 H) 4.96 (m, 1 H) 4.69 (m, 1 H) 4.10 (m, 4 H) 1.43 (d, 3 H) 1.40 (s, 9 H). MS (ESI) *m/z* 518 [M-H].

Example 23

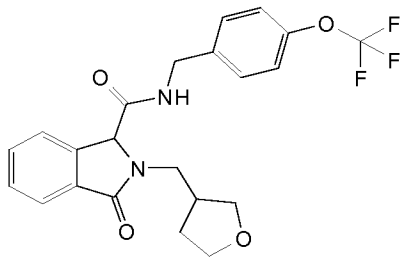
2-(2-Morpholinoethyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (200 mg, 1.33 mmol), 2-morpholinoethanamine (172 mg, 1.33 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (267 mg, 1.33 mmol). The crude was purified by silica gel column chromathography using dichloromethane : methanol = 100:0 to 95:5 as gradient. Solid, 220 mg (32.8 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (t, 1 H) 7.68 (d, 1 H) 7.53 (t, 1 H) 7.27 (t, 1 H) 7.24 - 7.12 (m, 3 H) 7.07 (d, 2 H) 5.29 (s, 1 H) 4.53 - 4.32 (m, 2 H) 3.81 (dt, 1 H) 3.65 - 3.46 (m, 5 H) 2.68 - 2.42 (m, 4 H) 2.38 - 2.21 (m, 2 H). MS (ESI) *m/z* 464 [M+H].

Example 24
3-Oxo-2-((tetrahydrofuran-3-yl)methyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

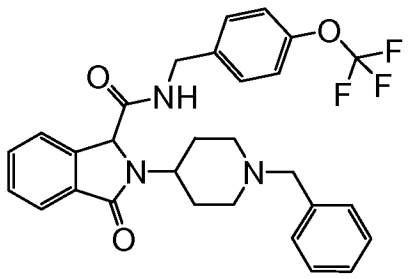


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (150 mg, 1.00 mmol), (tetrahydrofuran-3-yl)methanamine (101 mg, 1.00 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (201 mg, 1.00 mmol). The crude was purified by silica gel column chromathography using dichloromethane : methanol = 100:0 to 95:5 as gradient. Solid, 180 mg (34.6 %). 1:1 mixture of diastereomers, integration was set to 1 proton corresponding to 1 proton in one of the diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (br. s., 2 H) 7.61 (d, 2 H) 7.49 (t, 2 H) 7.21 (dd, 4 H) 7.16 - 7.02 (m, 6 H) 6.84 - 6.68 (m, 2 H) 5.13 (d, 2 H) 4.58 - 4.46 (m, 2 H) 4.46 - 4.34 (m, 2 H) 4.01 - 3.87 (m, 2 H) 3.87 - 3.74 (m, 3 H) 3.74 - 3.59 (m, 3 H) 3.55 - 3.38 (m, 2 H) 3.20 - 3.06 (m, 2 H) 2.67 - 2.47 (m, 2 H) 2.12 - 1.94 (m, 1 H) 1.94 - 1.76 (m, 1 H) 1.64 - 1.42 (m, 2 H). MS (ESI) *m/z* 435 [M+H].

Example 25

2-(1-Benzylpiperidin-4-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

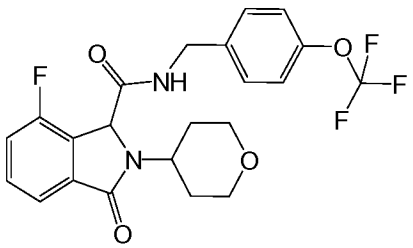


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (65 mg, 0.43 mmol), 4-amino-1-benzylpiperidine (0.089 mL, 0.43 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.087 mL, 0.43 mmol). White solid, 61 mg (27 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.16 (t, 1 H) 7.68 (d, 1 H) 7.59 (dt, 1 H) 7.51 (t, 1 H) 7.48 - 7.42 (m, 1 H) 7.41 - 7.35 (m, 2 H) 7.35 - 7.22 (m, 7 H) 5.30 (s, 1 H) 4.40 - 4.28 (m, 2 H) 3.93 - 3.84 (m, 1 H) 3.45 (s, 2 H) 2.85 (d, 1 H) 2.78 (d, 1 H) 2.03 - 1.92 (m, 2 H) 1.80 (qd, 1 H) 1.72 - 1.62 (m, 3 H). MS (ESI) *m/z* 524 [M+H].

Example 26

7-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

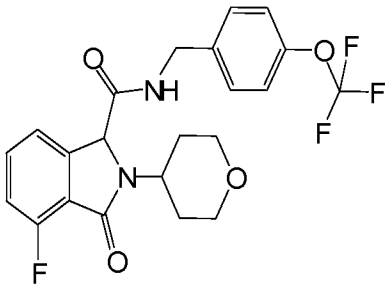


The title compound was synthesized according to the general procedure 1, described in example 1, from 4-fluoro-3-hydroxyisobenzofuran-1(3H)-one (40 mg, 0.24 mmol), tetrahydro-2H-pyran-4-amine (0.024 mL, 0.24 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.048 mL, 0.24 mmol). White solid, 4 mg (4 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (m, 1 H) 7.51 (m, 1 H) 7.26 (m, 3 H) 7.16 (d, 2 H) 6.14 (br. s., 1 H) 5.20 (s, 1 H) 4.38 - 4.52 (ddd, 2 H) 4.26 - 4.39 (m, 1 H) 4.03 (dd, 1 H) 3.94 (dd, 1 H) 3.44 - 3.48 (m, 2 H) 1.99 - 2.09 (m, 1 H) 1.80 - 1.92 (m, 1 H) 1.70 - 1.76 (m, 2 H). MS (ESI) *m/z* 453 [M+H].

Example 27

4-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

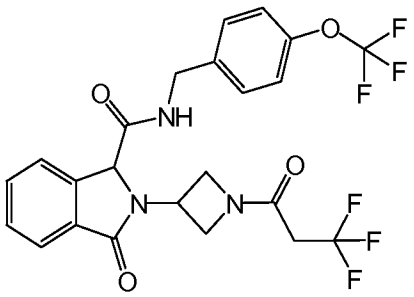


The title compound was synthesized according to the general procedure 1, described in example 1, from 7-fluoro-3-hydroxyisobenzofuran-1(3H)-one (35 mg, 0.21 mmol), tetrahydro-2H-pyran-4-amine (0.021 mL, 0.21 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.042 mL, 0.21 mmol). White solid, 36 mg (38 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (m, 1 H) 7.42 (d, 1 H) 7.33 (t, 1 H) 7.18 (d, 2 H) 7.10 (m, 2 H) 5.12 (s, 1 H) 4.41 - 4.47 (dd, 1 H) 4.30 - 4.36 (dd, 1 H) 4.17 (m, 1 H) 3.89 - 3.97 (m, 2 H) 3.31 - 3.37 (m, 2 H) 1.77 - 1.84 (m, 3 H) 1.63 - 1.76 (m, 2 H). MS (ESI) *m/z* 453 [M+H].

Example 28

3-Oxo-N-(4-(trifluoromethoxy)benzyl)-2-(1-(3,3,3-trifluoropropanoyl)azetidin-3-yl)isoindoline-1-carboxamide



Step 1:

tert-Butyl 3-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate (76 mg, 0.15 mmol) was dissolved in dichloromethane (2 mL) and trifluoroacetic acid (0.070 mL, 0.90 mmol) was added. The mixture was stirred for 16 hours. To the mixture extra trifluoroacetic acid (0.03 mL) was added and stirred for 2 hour at 40°C. Then toluene (2 mL) was added and the volatiles were removed *in vacuo*. This procedure was repeated one more time resulting a grey oil (78 mg, 100 %) which was used without further purification at the next step. MS (ESI) *m/z* 406 [M+H].

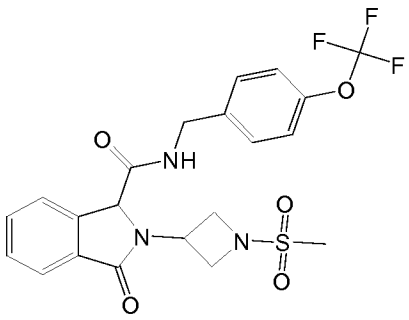
Step 2:

3-(1-Oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidinium 2,2,2-trifluoroacetate (78 mg, 0.15 mmol) and triethylamine (0.084 mL, 0.60 mmol) were mixed in dichloromethane (2 mL) and after 5 minutes 3,3,3-trifluoropropanoyl chloride (33.0 mg, 0.23 mmol) was added. The mixture was stirred for 16 hours at room temperature. The solvent was removed in vacuo and purified by preparative HPLC. The fractions containing the product were pooled, and the acetonitrile was removed in vacuum. The water solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to yield the title compound as yellowish foam /2:1 mixture of rotamers/, 37 mg (48 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 - 7.65 (m, 3 H) 7.35 - 7.46 (m, 1 H) 7.22 (t, 2 H) 7.10 - 7.18 (m, 3 H) 5.27 (d, 1 H) 4.85 (d, 1 H) 4.34 - 4.62 (m, 5 H) 4.21 - 4.33 (m, 1 H) 2.93 (qd, 2 H). MS (ESI) *m/z* 516 [M+H].

Example 29

2-(1-(Methylsulfonyl)azetidin-3-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



Step 1:

tert-Butyl 3-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate (example 10, 530 mg, 1.05 mmol) was dissolved in dichloromethane (10 mL), trifluoroacetic acid (2 mL) was added and the resulting reaction mixture was stirred for 3 hours at room temperature. The mixture was diluted with dichloromethane (30 mL) and water (10 mL) then 2M aqueous sodium hydroxide solution (10 mL) was carefully added during vigorous stirring (pH~12). The phases were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic phase was washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated to give the amine as dry film, 332 mg (78 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 - 7.66 (m, 3 H) 7.45 (t, 1 H) 7.15 (d, 2 H) 7.09 (d, 2 H) 6.87 (br.s., 1 H) 5.35 (d, 1 H) 4.99 - 5.07 (m, 1 H) 4.44 (dd, 1 H) 4.30 (dd, 1 H) 4.09 (t, 1 H) 4.01 (t, 1 H) 3.87 (t, 1 H) 3.80 (t, 1 H) 2.23 (br.s., 1 H). MS (ESI) *m/z* 406 [M+H].

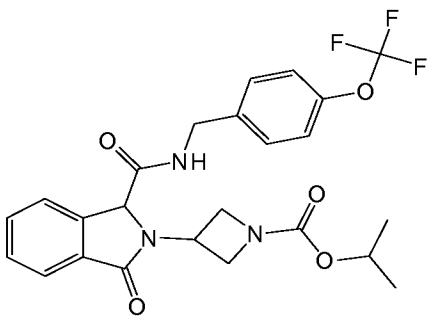
Step 2:

2-(Azetidin-3-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide (66mg, 0.16 mmol) was dissolved in dry dichloromethane (2 mL), N,N-diisopropylethylamine (0.057 mL, 0.33 mmol) and methanesulfonyl chloride (0.019 mL, 0.24 mmol) were added. The resulting solution was allowed to stir for 16 hours at room temperature. The reaction was quenched by the addition of diethylamine (0.120 mL). The fractions containing the product were pooled, and the acetonitrile was removed in vacuum. The water solution was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated to yield the title compound as dry film, 25 mg (32 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, 2 H) 7.40 (d, 2 H) 7.21 (d, 2 H) 7.13 (d, 2 H) 6.84 (br.s., 1 H) 5.22 (d, 1 H) 4.74 - 4.82 (m, 1 H) 4.38 - 4.50 (m, 4 H) 4.06 (dt, 2 H) 2.96 (s, 3 H). MS (ESI) *m/z* 484 [M+H].

Example 30

Isopropyl 3-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate

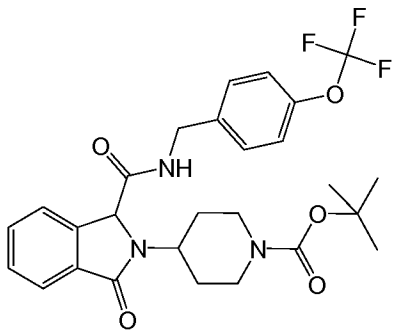


The title compound was prepared according to the method given for example 29 employing 2-(azetidin-3-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide (0.066 g, 0.16 mmol), dry pyridine (0.1 mL), isopropyl carbonochloridate (1M solution in toluene, 0.244 mL, 0.24 mmol). Dry film, 34 mg (42 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (d, 1 H) 7.59 (d, 1 H) 7.36 - 7.42 (m, 2 H) 7.12-7.18 (m, 4 H) 6.75 (br.s., 1 H) 5.28 (s, 1 H) 4.85 - 4.95 (m, 2 H) 4.35 - 4.48 (m, 2 H) 4.14 - 4.31 (m, 4 H) 1.24 (d, 6 H). MS (ESI) *m/z* 492 [M+H].

Example 31

tert-Butyl 4-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)piperidine-1-carboxylate

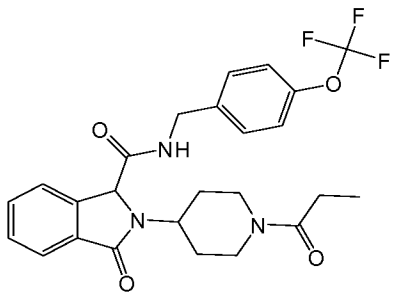


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (315 mg, 2.10 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (420 mg, 2.10 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.422 mL, 2.10 mmol). The crude was purified by silica gel chromathography using heptane : ethyl acetate = 80:20 to 50:50 as gradient. White solid, 773 mg (69 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57 - 7.64 (m, 3 H) 7.46 (t, 1 H) 7.10 (s, 4 H) 6.39 (br. s., 1 H) 5.10 (s, 1 H) 4.27 - 4.39 (m, 2 H) 4.17 - 4.24 (m, 3 H) 2.70 - 2.80 (m, 2 H) 1.70 - 1.77 (m, 4 H) 1.48 (s, 9 H). MS (ESI) *m/z* 534 [M+H].

Example 32

3-Oxo-2-(1-propionylpiperidin-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



Step 1:

tert-Butyl 4-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)piperidine-1-carboxylate (620 mg, 1.16 mmol) was dissolved in acetic acid (10 mL) and water (2 mL) mixture and the solution was heated to 80°C and stirred for 16 hours. Then the reaction mixture was evaporated, the residue was taken up in dichloromethane and was washed with saturated aqueous $NaHCO_3$ solution. The organic phase was extracted with brine and dried over anhydrous magnesium sulphate, filtered and concentrated to give the amine intermediate 3-oxo-2-(piperidin-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide as solid (485 mg, 96 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 - 7.61 (m, 3 H) 7.41 (t, 1 H) 7.06 - 7.13 (m, 4 H) 6.69 (br. s., 1 H) 5.13 (s, 1 H) 4.30 - 4.43 (m, 2 H) 4.17 - 4.24 (m, 1 H) 3.11 (t, 2 H) 2.60 - 2.69 (m, 2 H) 2.5 (br. s., 2 H) 1.70 - 1.80 (m, 4 H). MS (ESI) *m/z* 434 [M+H].

Step 2:

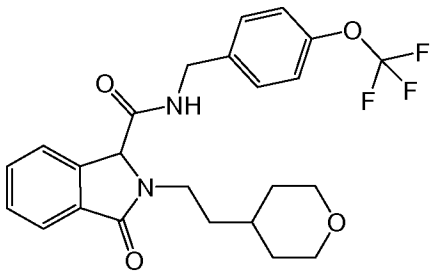
The amine intermediate (56 mg, 0.13 mmol) was dissolved in dry dichloromethane (2 mL) and stirred for 2 minutes then dry pyridine (0.013 mL, 0.16 mmol) and propionic anhydride (0.020 mL, 0.16 mmol) were added and the resulting solution was stirred at room temperature for 1 hour. The reaction was quenched by addition of diethylamine (0.10 mL). The crude reaction mixture was evaporated, the residue was taken up in methanol and was purified by preparative liquid chromatography. Appropriate fractions were pooled and

concentrated to approx. 10 mL volume and extracted with dichloromethane. The organic phase was dried over anhydrous magnesium sulphate, filtered and concentrated to give the product amide as white solid, 39 mg (62 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.13 (m, 1 H), 7.70 (d, 1 H) 7.60 (t, 1 H) 7.52 (d, 1 H) 7.48 (t, 1 H) 7.36 (d, 2 H) 7.30 (d, 2 H) 5.30 (d, 1 H) 4.25 - 4.52 (m, 3 H) 4.00 - 4.21 (m, 1 H) 3.86 (dd, 1 H) 3.04 (t, 1 H), 2.52 (m, 1 H) 2.25 - 2.37 (m, 2 H) 2.72 - 2.90 (d, 2 H) 1.45 - 1.70 (m, 2 H) 0.98 (t, 3 H). MS (ESI) *m/z* 490 [M+H].

Example 33

3-Oxo-2-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide

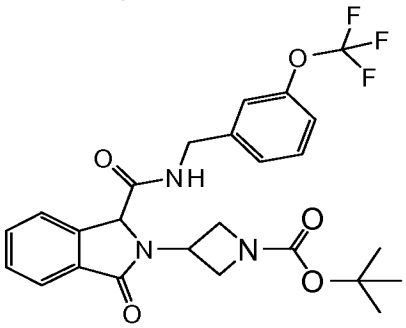


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (0.038 g, 0.25 mmol), 2-(tetrahydro-2H-pyran-4-yl)ethanamine (0.032 mL, 0.25 mmol) and 1-(isocyanomethyl)-4-(trifluoromethoxy)benzene (0.048 mL, 0.24 mmol). White solid, 81 mg (70 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.19 (t, 1 H) 7.67 - 7.73 (m, 1 H) 7.58 - 7.64 (m, 1 H) 7.50 - 7.57 (m, 2 H) 7.36 - 7.41 (m, 2 H) 7.30 - 7.36 (m, 2 H) 5.27 (s, 1 H) 4.35 (d, 2 H) 3.83 - 3.93 (m, 1 H) 3.75 - 3.82 (m, 2 H) 3.16 - 3.27 (m, 2 H) 2.95 - 3.06 (m, 1 H) 1.52 - 1.64 (m, 2 H) 1.36 - 1.52 (m, 3 H) 1.02 - 1.21 (m, 2 H). MS (ESI) *m/z* 463 [M+H].

Example 34

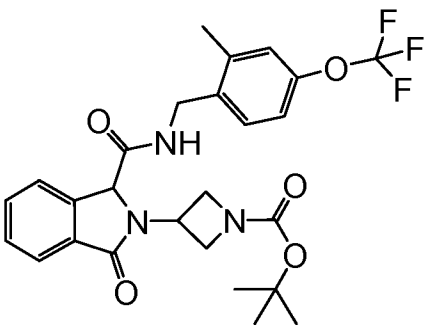
tert-Butyl 3-(1-oxo-3-(3-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate



The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (0.060 g, 0.40 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (0.069 mL, 0.40 mmol) and 1-(isocyanomethyl)-3-(trifluoromethoxy)benzene (0.080 g, 0.40 mmol). White solid, 21.4 mg (10 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 9.25 (t, 1 H) 7.71 (d, 1 H) 7.62 (dt, 1 H) 7.59 - 7.52 (m, 2 H) 7.45 (t, 1 H) 7.26 (t, 2 H) 7.18 (s, 1 H) 5.51 (s, 1 H) 4.66 (m, 1 H) 4.36 (d, 2 H) 4.20 (dd, 1 H) 4.07 - 3.95 (m, 2 H) 1.38 (s, 9 H). MS (ESI) *m/z* 504 [M-H].

Example 35

tert-Butyl 3-(1-(2-methyl-4-(trifluoromethoxy)benzylcarbamoyl)-3-oxoisoindolin-2-yl)azetidine-1-carboxylate

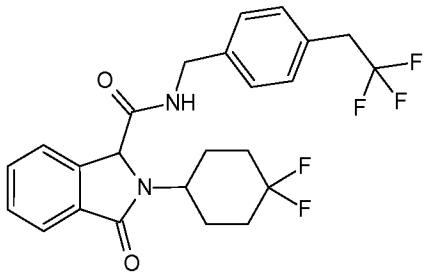


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (37.5 mg, 0.25 mmol), tert-butyl 3-aminoazetidine-

1-carboxylate (43.1 mg, 0.25 mmol) and 1-(isocyanomethyl)-2-methyl-4-(trifluoromethoxy)benzene (53.8 mg, 0.25 mmol). White solid, 0.5 mg (0.4 %).
^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 7.80 (d, 1 H) 7.65 (m, 1 H) 7.57 (m, 2 H) 7.29 (d, 1 H) 7.12 (s, 1 H) 7.07 (d, 1 H) 5.43 (s, 1 H) 4.75 (m, 1 H) 4.45 (s, 2 H) 4.37 (dd, 2 H) 4.19 (m, 2 H) 2.36 (s, 3 H) 1.46 (s, 9 H). MS (ESI) *m/z* 518 [M-H].

Example 36

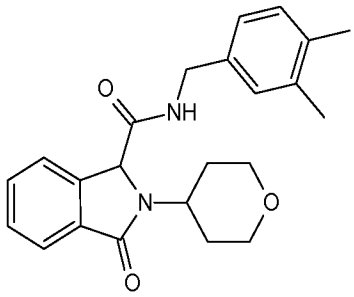
2-(4,4-Difluorocyclohexyl)-3-oxo-N-(4-(2,2,2-trifluoroethyl)benzyl)isoindoline-1-carboxamide



The title compound was synthesized according to the general procedure 3, described in example 17, from 4,4-difluorocyclohexanaminium chloride (51.5 mg, 0.30 mmol), triethylamine (0.05 mL, 0.36 mmol), 2-formylbenzoic acid (45 mg, 0.30 mmol) and 1-isocyanomethyl-4-(2,2,2-trifluoroethyl)benzene (60 mg, 0.30 mmol). The crude was purified by silica gel column chromatography using dichloromethane : methanol = 100:0 to 95:5 as gradient. Pale yellow solid, 88 mg (63 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (d, 1H) 7.56 - 7.63 (m, 2 H) 7.47 - 7.52 (m, 1 H) 7.19 (d, 2 H) 7.08 (d, 2 H) 6.12 (m, 1H) 5.10 (s, 1 H) 4.48 (dd, 1 H) 4.25 (dd, 1 H) 4.11 - 4.21 (m, 1 H) 3.32 (q, 2 H) 2.03 - 2.20 (m, 2 H) 1.70 - 1.96 (m, 6 H). ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -66.33, -66.36, -66.39, -93.93, -94.57. MS (ESI) *m/z* 467 [M+H].

Example 37

N-(3,4-Dimethylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide

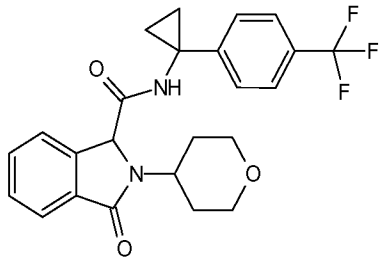


1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg, 0.785 mmol) and 1-hydroxybenzotriazole hydrate (105 mg, 0.785 mmol) were added to a solution of (3,4-dimethylphenyl)methanamine (60 mg, 0.44 mmol) and 3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxylic acid (100 mg, 0.383 mmol) in dry tetrahydrofuran (10 mL) at room temperature. The reaction mixture was stirred for 16 hours then concentrated *in vacuo*. The crude residue was taken up in ethyl acetate (30 mL), washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography using heptane : ethyl acetate = 50:50 to 30:70% affording the title compound as solid, 63 mg (69 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 - 7.72 (m, 1 H) 7.53 - 7.62 (m, 2 H) 7.42 (t, 1 H) 6.99 (d, 1 H) 6.74 - 6.89 (m, 2 H) 6.42 (t, 1 H) 5.12 (s, 1 H) 4.32 - 4.48 (m, 1 H) 4.17 - 4.32 (m, 2 H) 3.97 (td, 2 H) 3.31 - 3.52 (m, 2 H) 2.19 (s, 3 H) 2.14 (s, 3 H) 1.80 - 2.00 (m, 2 H) 1.62 - 1.80 (m, 2 H). MS (ESI) *m/z* 379 [M+H].

Example 38

3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)isoindoline-1-carboxamide

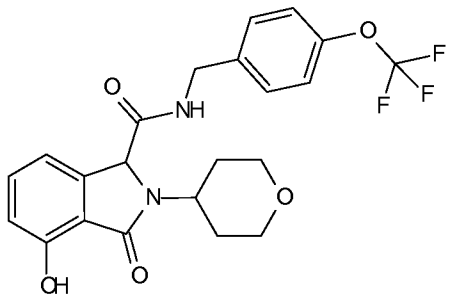


The title compound was synthesized according to the method described for example 37 from 3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxylic acid (100 mg, 0.383 mmol), 1-(4-(trifluoromethyl)phenyl)cyclopropanamine (60 mg, 0.407 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.523 mmol) and 1-hydroxybenzotriazole hydrate (100 mg, 0.74 mmol) in dry tetrahydrofuran (5 mL). Solid, 33 mg (22 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (d, 1 H) 7.65 - 7.47 (m, 3 H) 7.40 (d, 2 H) 7.06 - 6.93 (m, 3 H) 5.10 (s, 1 H) 4.45 - 4.28 (m, 1 H) 4.06 - 3.89 (m, 2 H) 3.51 - 3.37 (m, 2 H) 1.94 - 1.68 (m, 4 H) 1.44 - 1.32 (m, 1 H) 1.32 - 1.23 (m, 1 H) 1.23 - 1.08 (m, 2 H). MS (ESI) *m/z* 445 [M+H].

Example 39

4-Hydroxy-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide



Step 1:

4-(Methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide was synthesized according to the method described for example 37 from 4-(methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxylic acid (200 mg, 0.623 mmol), (4-(trifluoromethoxy)phenyl)methanamine (170 mg, 0.889 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (200 mg, 1.04 mmol) and 1-hydroxybenzotriazole hydrate (100 mg, 0.74 mmol) in tetrahydrofuran (10 mL). Solid, 110 mg (35.8 %).

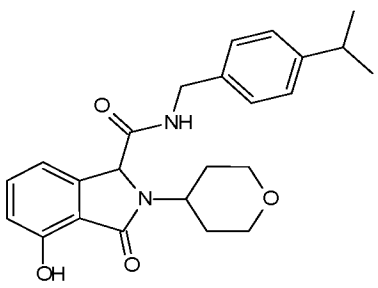
Step 2:

The anhydrous tetrahydrofuran (10 mL) solution of 4-(methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide (110 mg, 0.22 mmol) was set under nitrogen atmosphere and cooled down to 0°C. HCl gas was bubbled into the reaction mixture for 5 minutes then was allowed to stir for 1 hour at room temperature. The solvent was removed *in vacuo* and the crude was purified by silica gel column chromatography using hexane : ethyl acetate = 100:0 to 30:70 as gradient to give the desired compound, 40 mg (40 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (s, 1 H) 7.42 - 7.61 (m, 3 H) 7.20 (d, 2 H) 7.07 (d, 1 H) 6.93 (d, 1 H) 6.13 (br. s., 1 H) 5.13 (s, 1 H) 4.32 - 4.56 (m, 2 H) 4.23 (t, 1 H) 3.86 - 4.10 (m, 2 H) 3.43 (q, 2 H) 1.76 - 2.06 (m, 2 H) 1.69 (br. s., 2 H). MS (ESI) *m/z* 451 [M+H].

Example 40

4-Hydroxy-N-(4-isopropylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide

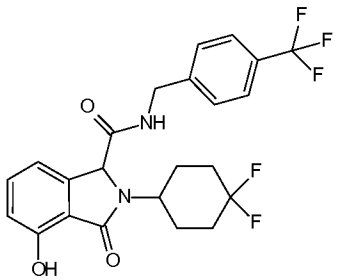


The title compound was synthesized according to the method described for example 39 from 4-(methoxymethoxy)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxylic acid (150 mg, 0.466 mmol), (4-isopropylphenyl)methanamine (100 mg, 0.669 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg, 0.785 mmol) and 1-hydroxybenzotriazole hydrate (75 mg, 0.555 mmol) in tetrahydrofuran (7 mL). Solid, 71 mg (78.9 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.33 (s, 1 H) 7.46 (t, 1 H) 7.08 - 7.19 (m, 3 H) 6.99 - 7.08 (m, 2 H) 6.92 (d, 1 H) 5.81 - 5.95 (m, 1 H) 5.10 (s, 1 H) 4.47 (dd, 1 H) 4.10 - 4.29 (m, 2 H) 3.88 - 4.08 (m, 2 H) 3.41 (q, 2 H) 2.87 (dt, 1 H) 1.76 - 2.06 (m, 2 H) 1.66 (td, 2 H) 1.22 (d, 6 H). MS (ESI) *m/z* 407 [M-H].

Example 41

2-(4,4-Difluorocyclohexyl)-4-hydroxy-3-oxo-N-(4-(trifluoromethyl)benzyl)isoindoline-1-carboxamide

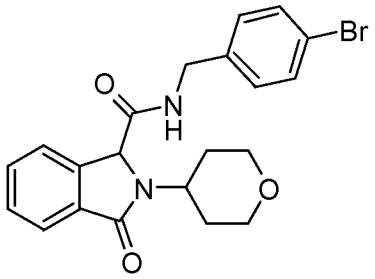


The title compound was synthesized according to the method described for example 39 from 2-(4,4-difluorocyclohexyl)-4-(methoxymethoxy)-3-oxoisoindoline-1-carboxylic acid (130 mg, 0.366 mmol), (4-(trifluoromethyl)phenyl)methanamine (100 mg, 0.571 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg, 0.785 mmol) and 1-hydroxybenzotriazole hydrate (100 mg, 0.740 mmol) in tetrahydrofuran (10 mL). Solid, 47.7 mg (58 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (s, 1 H) 7.41 - 7.60 (m, 3 H) 7.15 - 7.35 (m, 2 H) 7.06 (d, 1 H) 6.94 (d, 1H) 6.02 (br. s., 1 H) 5.10 (s, 1 H) 4.31 - 4.57 (m, 2 H) 4.10 (br. s., 1 H) 2.03 - 2.20 (m, 2 H) 1.70 - 1.96 (m, 6 H). MS (ESI) *m/z* 469 [M+H].

Example 42

N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide

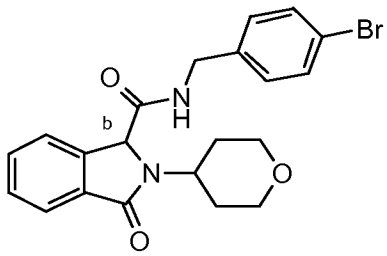


The title compound was synthesized according to the general procedure 1, described in example 1, from 2-formylbenzoic acid (0.113 g, 0.75 mmol), tetrahydro-2H-pyran-4-amine (0.076 mL, 0.75 mmol) and 1-bromo-4-(isocyanomethyl)benzene (0.140 g, 0.71 mmol). White solid, 128 mg (40 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.16 (t, 1 H) 7.67 - 7.72 (m, 1 H) 7.57 - 7.63 (m, 1 H) 7.49 - 7.55 (m, 3 H) 7.45 - 7.49 (m, 1 H) 7.18 - 7.25 (m, 2 H) 5.32 (s, 1 H) 4.29 (d, 2 H) 4.06 - 4.17 (m, 1 H) 3.89 (dd, 1 H) 3.78 - 3.86 (m, 1 H) 3.35 - 3.41 (m, 2 H) 1.76 - 1.92 (m, 1 H) 1.63 - 1.74 (m, 3 H). MS (ESI) *m/z* 430 [M+H].

Example 43

N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide, ISOMER 2



ISOMER 2
b = unknown absolute

The racemic N-(4-bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide (128 mg, 0.3 mmol) was subjected to enantiomeric separation, which was performed on Berger Multigram II system. Column: Chiralpak AD; 21.2*250 mm Mobilephase: 40% ethanol and 60% CO_2; Flow: 50 mL/minute, provided two separated

isomers eluting at 4.2 minutes as ISOMER 1 and ISOMER 2 at 6.8 minutes. The separated isomers were collected, evaporated and handled separately. The samples were analyzed by HPLC using SFC Berger Analytix; Column: Reprosil-AM (AD); 4.6*250 mm; 5µm; Mobilephase: 40% ethanol and 60% CO_2; Flow: 2 mL/minute, ISOMER 2 (6.2 minutes), 41 mg, enatiomeric purity: 99 %.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.16 (t, 1 H) 7.67 - 7.72 (m, 1 H) 7.57 - 7.63 (m, 1 H) 7.49 - 7.55 (m, 3 H) 7.45 - 7.49 (m, 1 H) 7.18 - 7.25 (m, 2 H) 5.32 (s, 1 H) 4.29 (d, 2 H) 4.06 - 4.17 (m, 1 H) 3.89 (dd, 1 H) 3.78 - 3.86 (m, 1 H) 3.35 - 3.41 (m, 2 H) 1.76 - 1.92 (m, 1 H) 1.63 - 1.74 (m, 3 H). MS (ESI) *m/z* 430 [M+H].

BIOLOGICAL TESTS

Expression of voltage-gated sodium channel in cell lines:

Gene(s) encoding the full-length protein of the voltage-gated sodium channel of interest are cloned and expressed under a suitable promoter in a suitable cell line, as well known in the art. The so constructed stable cell lines are used in screening assays to identify suitable compounds active on voltage-gated sodium channels. Suitable screening assays are as follows.

Li+ influx assay

The cell line expressing the voltage-gated sodium channel of interest is plated in conventional 96 or 384 well tissue plates at a suitable cell density (for example 40000 cells/well in 96 well plate, or 20000 cells/well in 384 well plate). The cells are then repeatedly washed with a suitable Na free buffer using a suitable commercially available washer (for example EL-405 washer) until all tissue culture medium is removed from the wells. A suitable Na-free buffer could have the composition (mM) Choline chloride 137, KCl 5.4, $MgSO_4$ 0.81, $CaCl_2$ 0.95, glucose 5.55 and HEPES 25 at pH 7.4, but may also have other suitable composition. After completion of all wash steps, cells are incubated in the suitable Na free buffer for 15 min. Then, the Na free buffer is removed and cells are incubated with a buffer rich in LiCl for 60 min at 37°C. The LiCl buffer is also enriched in

potassium ions, causing a depolarizing stimulus to the cells. Such a buffer may have the composition (mM): LiCl 100, KCl 50, $MgSO_4$ 0.81, $CaCl_2$ 0.95, glucose 5.55 and HEPES 25 at pH 7.4, but may also have other suitable composition. To enhance signal–to-noise ratio, an effective concentration (for example 100 μM) of the voltage-gated sodium channel opener veratridine, or any other suitable voltage-gated sodium channel opener, may be added to the medium to enhance signal detection. Furthermore, and also to enhance signal-to-noise ratio, an effective concentration (for example 10 μg/ml) of suitable scorpion venom may also be added to the medium to delay channel inactivation. In order to find a modulator of the voltage-gated sodium channel of interest, the assay can be complemented with compounds from a compound library. Compounds of interest are added to the Li-rich solution, one in each well. At the end of the incubation period cells are repeatedly washed with Na free buffer until all extracellular LiCl is removed. Cell lysis is obtained through incubation of cells with triton (1%) for 15 min, or any other suitable method. The resulting cell lysate is then introduced into an atomic absorption spectrophotometer, thus quantifying the amount of Li-influx during the procedure described above.

The described assay can be run with any atomic absorption spectrophotometer using plates of 96-well format, 384-well format, or any other conventional plate format. The described assay can be applied to cell lines expressing any given one or more of the voltage-gated sodium channel alpha subunits, as well as any given combination of one of the voltage-gated alpha subunits with any one or more beta subunit.

If needed the cell line of choice can be further hyperpolarised by expression of a suitable potassium leak ion channel, for example TREK-1, either by transient co-transfection or through establishment of a stable co-transfected cell line. The successful expression of a leak K current can be verified using traditional intracellular electrophysiology, either in whole cell patch-clamp, perforated patch-clamp or conventional two-electrode voltage-clamp. A cell line of choice modified to successfully express a voltage-gated sodium channel of interest together with a suitable potassium leak ion channel transfected can then be used for screening using atomic absorptions spectrometry, as described above.

Whole-cell voltage clamp electrophysiology assay

Electrophysiological recordings of sodium currents in cells stably expressing the voltage-gated sodium channel of interest confirms activity and provides a functional measure of the potency of compounds that specifically affect such channels.

Electrophysiological studies can be performed using automated patch-clamp electrophysiology platforms, like IonWorks HT, IonWorks Quattro, PatchXpress, or any other suitable platform. The cell line expressing the voltage-gated sodium channel of interest is plated in appropriate well tissue plates, as provided by the manufacturer of the automated patch-clamp platforms. Suitable extracellular and intracellular buffer for such experiments are applied according to the instructions given by the manufacturer of the automated patch-clamp platforms. Cells that express the voltage-gated sodium channel protein of interest are exposed to drugs through the pipetting system integrated in the platforms. A suitable voltage stimulus protocol is used to activate the voltage-gated sodium channel proteins of interest. A suitable stimulus protocol may consist of eight voltage pulses, each to –20 mV and 50 ms in length, and separated from each other by 330 ms intervals at a potential of –90 mV or –65 mV, but may also have other suitable parameters.

Electrophysiological studies can also be performed using the whole cell configuration of the standard patch clamp technique as described in the literature. In this assay, cells that express the human voltage-gated sodium channel protein of interest are exposed to the drugs by conventional microperfusion systems and a suitable voltage stimulus protocol is used to activate the voltage-gated sodium channels.

In vivo experiments

A compound of the invention when given by systemic injection to mice or rats, may specifically reduce pain behavior in the formalin test. This test is an accepted model of clinical pain in man, involving elements of nociceptor activation, inflammation, peripheral sensitization and central sensitization *(*A Tjølsen et al. *Pain 1992*, 51, 5*)*. It can therefore be inferred that a compound of the present invention is usefulas a therapeutic agent to relieve pain of various origins.

Compounds of formula I may showin analgesic activity in the intraarticular FCA (Freund's complete adjuvant) test in the rat, a model of inflammatory pain *(Iadarola et al. Brain Research 1988, 455, 205-12)* and in the Chung nerve lesion test in the rat, a model for neuropathic pain *(Kim and Chung. Pain 1992, 50, 355)*. The analgesic effects in the animal models may be obtained after doses that do not produce tissue concentrations leading to conduction block in nerve fibers. Thus, the analgesic effects can not be explained by the local anesthetic properties of the compounds mentioned in the publication by Kornet and Thio. Analgesic efficacy after systemic administration is not a general property of drugs with local anesthetic effects *(Scott et al. British Journal of Anaesthesia 1988, 61, 165-8)*.

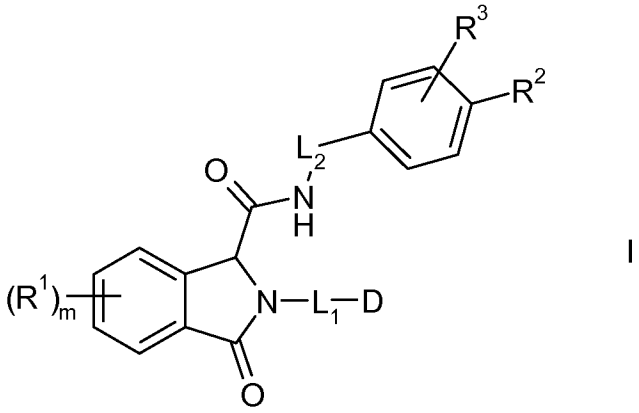
Generally, compounds of the invention are active in the Whole-cell voltage clamp electrophysiology assay above with IC_{50} values less than 10 μM. In one aspect of the invention, the IC_{50} value is less than 1 μM.

Title compounds of the above Examples were tested in the Whole-cell voltage clamp electrophysiology assay mentioned above. IC50 represents the compound concentration required for 50% inhibition. Specimen results are shown in the following table as pIC50 values, i.e. -log (IC50). Thus the larger the pIC50 the more potent the compound. For example, a pIC50 of 6.4 indicates an IC50 of $10^{-6.4}$ M.

Ex no.	NaV1.7 pIC50	Ex no.	NaV1.7 pIC50
1	6.4	**23**	6.1
2	6.6	**24**	5.9
3	6.9	**25**	6.2
4	7.4	**26**	6.3
5	6.3	**27**	5.5
6	6.3	**28**	5.9
7	6	**29**	5.9
8	5.7	**30**	6.3
9	5.9	**31**	6.5
10	7	**32**	5.7
11	6	**33**	6.5
12	5.9	**34**	6.4
13	6.1	**35**	5.5
14	6.7	**36**	6.4
15	6.3	**37**	6.0
16	6.3	**38**	5.8
17	6.7	**39**	6.4
18	6.2	**40**	6.3
19	6.4	**41**	6.2
20	7.0	**42**	5.7
21	5.6	**43**	6.0
22	6.3		

CLAIMS

1. A compound of formula I



I

wherein

R^1 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, cyano, hydroxy or halo; *and wherein said C_{1-3}alkyl is optionally substituted by one or more substituents independently selected from hydroxy, C_{1-3}alkoxy and fluoro; and said C_{1-3}alkoxy is optionally substituted by one or more fluoro;*

m is 1 or 2;

R^2 and R^3 is each and independently selected from hydrogen, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, halo, C_{1-4}alkoxy, C_{1-4}alkyl and C_{3-7}cycloalkyloxy; *wherein said C_{3-7}cycloalkyloxy is optionally substituted by one or more fluoro;* and R^2 and R^3 may not both be hydrogen;

D is C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl; *and wherein said C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl may optionally be substituted by one or more **X^4***;

X^4 is halo, C_{1-3}alkyl, C_{1-3}alkylOC_{1-3}alkyl, C_{1-3}alkoxy, benzyl, C_{1-4}alkylsulfonyl, oxo, $R^4O(C=O)$, $R^5(C=O)$, or C_{5-6} heteroaryl; *wherein said C_{1-3}alkyl, C_{1-3}alkylOC_{1-3}alkyl, C_{1-3}alkoxy and C_{1-4}alkylsulfonyl is optionally substituted by one or more fluoro;*

R^4 is C_{1-4}alkyl, C_{1-4}alkylOC_{1-4}alkyl, C_{5-6}cycloalkyl, or aryl;
R^5 is C_{1-4}alkyl, C_{1-4}fluoroalkyl or C_{5-6} heteroaryl;

L_1 is C_{1-4}alkylene or a bond;
L_2 is C_{1-3}alkylene;

with the exception of the compound
2-(cyclohexylmethyl)-3-oxo-N-[2-(trifluoromethyl)benzyl]isoindoline-1-carboxamide;

as well as a pharmaceutically acceptable salt, or isomer thereof, or a salt of said isomer.

2. A compound according to claim 1, wherein
R^1 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, halo, or hydroxy;
m is 1;

R^2 is selected from hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, halo, C_{1-4}alkoxy, and C_{1-4}haloalkoxy;
R^3 is hydrogen, C_{1-4}alkyl, halo, or C_{1-4}haloalkoxy;
and R^2 and R^3 may not both be hydrogen;

D is C_{4-6}cycloalkyl or C_{4-6}heterocycloalkyl; *wherein C_{4-6}cycloalkyl or C_{4-6}heterocycloalkyl is optionally substituted with one or more X^4;*
X^4 is halo, oxo, $R^4O(C=O)$, $R^5(C=O)$ or C_{5-6}heteroaryl;
R^4 is C_{1-4}alkyl;
R^5 is C_{5-6} heteroaryl;
L_1 is C_{1-2}alkylene or a bond; and
L_2 is C_{1-2}alkylene.

3. A compound acording to claim 1 or 2, wherein **m** is 1.

4. A compound acording to any one claims 1-3, wherein $\mathbf{R^1}$ is hydrogen.

5. A compound acording to any one claims 1-3, wherein $\mathbf{R^1}$ is methyl

6. A compound acording to any one claims 1-3, wherein $\mathbf{R^1}$ is methoxy.

7. A compound acording to any one claims 1-3, wherein $\mathbf{R^1}$ is fluoro.

8. A compound acording to any one claims 1-3, wherein $\mathbf{R^1}$ is hydroxy.

9. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is–O-CF_3.

10. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is chloro or bromo.

11. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is methoxy.

12. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is CF_3 or -CH_2-CF_3.

13. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is methyl.

14. A compound acording to any one of claims 1-8, wherein $\mathbf{R^2}$ is iso-propyl.

15. A compound acording to any one of claims 1-14, wherein $\mathbf{R^3}$ is hydrogen.

16. A compound acording to any one of claims 1-14, wherein $\mathbf{R^3}$ is methyl.

17. A compound acording to any one of claims 1-14, wherein $\mathbf{R^3}$ is chloro.

18. A compound acording to any one of claims 1-14, wherein $\mathbf{R^3}$ is –OCF_3.

19. A compound acording to any one of claims 1-18, wherein $\mathbf{L_1}$ is a bond.

20. A compound acording to any one of claims 1-18, wherein $\mathbf{L_1}$ is methylene.

21. A compound acording to any one of claims 1-18, wherein $\mathbf{L_1}$ is ethylene.

22. A compound acording to any one of claims 1-21, wherein $\mathbf{L_2}$ is methylene.

23. A compound acording to any one of claims 1-21, wherein $\mathbf{L_2}$ is $-CH(CH_3)-$.

24. A compound acording to any one of claims 1-21, wherein $\mathbf{L_2}$ is cyclopropylene.

25. A compound acording to any one of claims 1-24, wherein **D** is selected from any one of azetidinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl , pyrrolidinyl-2-on, piperidinyl, and morpholinyl.

26. A compound acording to any one of claims 1-24, wherein **D** is cyclobutyl or cyclohexyl.

27. A compound acording to any one of claims 1-24, wherein **D** is di-substituted by X^4.

28. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is fluoro.

29. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is $-C(O)-O-C(CH_3)_3$.

30. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is $-C(O)-O-CH(CH_3)_2$.

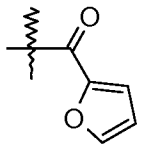
31. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is $-C(O)-CH_2-CH_3$.

32. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is $-C(O)-CH_2-CF_3$.

33. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is $-SO_2-CH_3$.

34. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is pyrimidinyl.

35. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is



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36. A compound acording to any one of claims 1-27, wherein $\mathbf{X^4}$ is benzyl.

37. A compound according to any one of the preceding claims, selected from any one of:

2-(Oxan-4-yl)-3-oxo-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

3-Oxo-2-[[(2S)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

N-[1-(4-Chlorophenyl)ethyl]-3-oxo-2-[[(2S)-oxolan-2-yl]methyl]-1H-isoindole-1-carboxamide;

3-Oxo-2-[[(2R)-oxolan-2-yl]methyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

N-[1-(4-chlorophenyl)ethyl]-2-(oxan-4-yl)-3-oxo-1H-isoindole-1-carboxamide;

3-Oxo-2-[2-(2-oxopyrrolidin-1-yl)ethyl]-N-[[4-(trifluoromethoxy)phenyl]methyl]-1H-isoindole-1-carboxamide;

tert-Butyl 3-(1-oxo-3-{[4-(trifluoromethoxy)benzyl]carbamoyl}-1,3-dihydro-2*H*-isoindol-2-yl)azetidine-1-carboxylate;

2-[1-(2-Furoyl)piperidin-4-yl]-3-oxo-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

3-Oxo-2-(1-pyrimidin-2-ylazetidin-3-yl)-*N*-[4-(trifluoromethoxy)benzyl]isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-*N*-(4-methoxybenzyl)-3-oxoisoindoline-1-carboxamide;

N-[1-(3-Chlorophenyl)ethyl]-2-(4,4-difluorocyclohexyl)-3-oxoisoindoline-1-carboxamide;

N-[1-(3-Chlorophenyl)ethyl]-3-oxo-2-(tetrahydro-2*H*-pyran-4-yl)isoindoline-1-carboxamide;

2-((3,3-Difluorocyclobutyl)methyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(3,3-Difluorocyclobutyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-7-methoxy-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(4,4-Difluorocyclohexyl)-7-methyl-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

tert-Butyl 3-(4-methyl-1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;

3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethoxy)phenyl)ethyl)isoindoline-1-carboxamide, ISOMER 4;

tert-Butyl 3-(1-oxo-3-(1-(4-(trifluoromethoxy)phenyl)ethylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate, ISOMER 3&4;

2-(2-Morpholinoethyl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

3-Oxo-2-((tetrahydrofuran-3-yl)methyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

2-(1-Benzylpiperidin-4-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

7-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

4-Fluoro-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;

3-Oxo-N-(4-(trifluoromethoxy)benzyl)-2-(1-(3,3,3-trifluoropropanoyl)azetidin-3-yl)isoindoline-1-carboxamide;
2-(1-(Methylsulfonyl)azetidin-3-yl)-3-oxo-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;
Isopropyl 3-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;
tert-Butyl 4-(1-oxo-3-(4-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)piperidine-1-carboxylate;
3-Oxo-2-(1-propionylpiperidin-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;
3-Oxo-2-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;
tert-Butyl 3-(1-oxo-3-(3-(trifluoromethoxy)benzylcarbamoyl)isoindolin-2-yl)azetidine-1-carboxylate;
tert-Butyl 3-(1-(2-methyl-4-(trifluoromethoxy)benzylcarbamoyl)-3-oxoisoindolin-2-yl)azetidine-1-carboxylate;
2-(4,4-Difluorocyclohexyl)-3-oxo-N-(4-(2,2,2-trifluoroethyl)benzyl)isoindoline-1-carboxamide;
N-(3,4-Dimethylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide;
3-Oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)isoindoline-1-carboxamide;
4-Hydroxy-3-oxo-2-(tetrahydro-2H-pyran-4-yl)-N-(4-(trifluoromethoxy)benzyl)isoindoline-1-carboxamide;
4-Hydroxy-N-(4-isopropylbenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide;
2-(4,4-Difluorocyclohexyl)-4-hydroxy-3-oxo-N-(4-(trifluoromethyl)benzyl)isoindoline-1-carboxamide;
N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide; and
N-(4-Bromobenzyl)-3-oxo-2-(tetrahydro-2H-pyran-4-yl)isoindoline-1-carboxamide, ISOMER 2.

38. A compound according to any one of the preceding claims, for use in therapy.

39. Use of a compound according to any one of claims 1-37 for the manufacture of a medicament for use in the treatment of a pain disorder.

40. A method for the treatment of a pain disorder, whereby a compound according to any one of claims 1-37 is administered to a subject in need of such pain treatment.

41. A compound according to any one of claims 1-37, for use in the treatment of a pain disorder.

42. A pharmaceutical composition comprising a compound according to any one of claims 1-37, in admixture with a pharmaceutically and pharmacologically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050618

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA, MARPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008008022 A1 (ASTRAZENECA AB), 17 January 2008 (17.01.2008), page 5, line 10 - line 11; page 238, line 3 - line 6, claims 1, 59 --	1-42
A	WO 2006020879 A1 (ASTRAZENECA AB), 23 February 2006 (23.02.2006), claim 1 --	1-42
A	WO 2008008020 A1 (ASTRAZENECA AB), 17 January 2008 (17.01.2008), claims 1, 6, 8, 9, page 24, example 19 --	1-42

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2009	25 -08- 2009
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Håkan Yildirim / Eö Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050618

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007007057 A1 (VERNALIS (R&D) LIMITED), 18 January 2007 (18.01.2007), claims 1, 16, page 47, examples 116 and 125	1-42
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A	US 20040167224 A1 (OZAKI, FUMIHIRO ET AL), 26 August 2004 (26.08.2004), claims 1, 38, page 61, example 54, page 78, example 185	1-42
	--	
P,A	WO 2008116814 A1 (GLAXO GROUP LIMITED), 2 October 2008 (02.10.2008), claims 1, 3, 16, table 1, all of the examples	1-42
	--	
A	Ilyn, A. P. et al. (2006) Synthesis of novel carbamoyl-substituted derivatives of isoindole and benzo[f][1,4]oxazepine using a modified Ugi reaction. Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya i Khimicheskaya Tekhnologiya (2006), Vol. 49(5), pages 13-19, table 1, compounds 4, 10, 17 and 18	1-42
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050618

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 40
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 40 relates to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.1

methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.

International patent classification (IPC)
C07D 405/04 (2006.01)
A61K 31/4035 (2006.01)
A61K 31/4523 (2006.01)
A61K 31/506 (2006.01)
A61P 25/04 (2006.01)
C07D 209/46 (2006.01)
C07D 403/04 (2006.01)
C07D 403/06 (2006.01)
C07D 403/14 (2006.01)
C07D 405/06 (2006.01)
C07D 405/14 (2006.01)

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Cited literature, if any, will be enclosed in paper form.

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