Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2582507 A1 2006/03/30

(21) 2 582 507

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2005/09/22
(87) Date publication PCT/PCT Publication Date: 2006/03/30
(85) Entrée phase nationale/National Entry: 2007/03/21
(86) N° demande PCT/PCT Application No.: SE 2005/001402
(87) N° publication PCT/PCT Publication No.: 2006/033630
(30) Priorités/Priorities: 2004/09/24 (GBPCT/GB2004/004124); 2004/12/30 (US60/640,804)

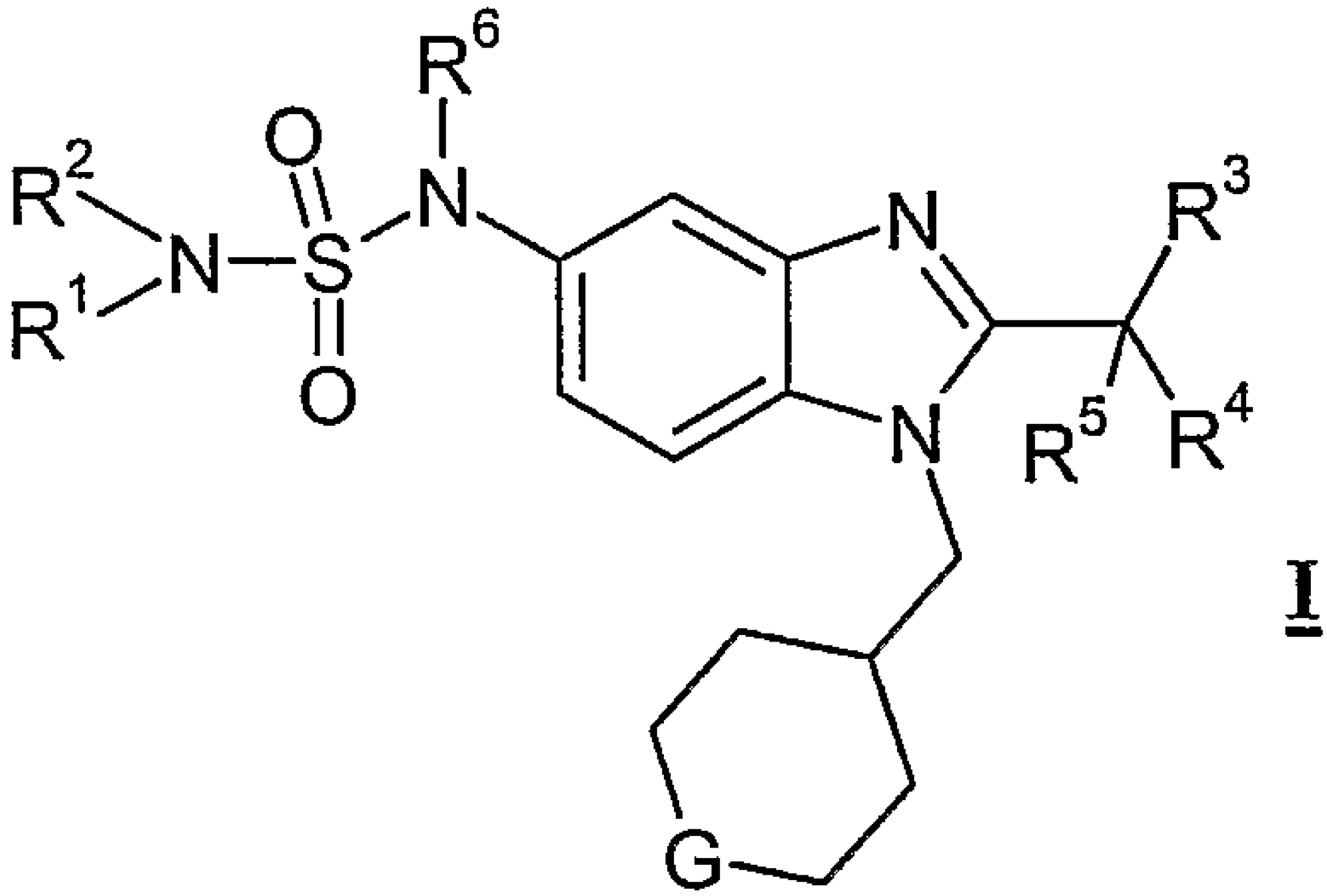
(51) Cl.Int./Int.Cl. *C07D 405/06* (2006.01), *A61K 31/4184* (2006.01), *A61P 1/00* (2006.01), *A61P 25/00* (2006.01), *A61P 25/16* (2006.01), *A61P 25/22* (2006.01), *A61P 25/28* (2006.01), *A61P 35/00* (2006.01), *A61P 9/00* (2006.01), *C07D 235/08* (2006.01)

(71) Demandeur/Applicant:
ASTRAZENECA AB, SE

(72) Inventeurs/Inventors:
MILBURN, CLAIRE, US;
DESFOSSES, HELENE, CA;
PAGE, DANIEL, CA;
WALPOLE, CHRISTOPHER, CA;
...

(54) Titre : DERIVES DE BENZIMIDAZOLE, COMPOSITIONS CONTENANT CES DERIVES, PREPARATION ET UTILISATIONS DE CES DERNIERS

(54) Title: COMPOUNDS, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF III



I

(57) Abrégé/Abstract:
Compounds of Formula I, or pharmaceutically acceptable salts thereof: I (chemical formula to be inserted here - please see paper copy) wherein R1, R2, R3, R4, R5, R6 and G are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

CA 2582507 A1 2006/03/30

(21) 2 582 507

(13) A1

(72) Inventeurs(suite)/Inventors(continued): WEI, ZHONG-YONG, CA; YANG, HUA, CA

(74) Agent: MCCARTHY TETRAULT LLP

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/033630 A1

(51) International Patent Classification:
C07D 405/06 (2006.01) *A61P 25/22* (2006.01)
A61K 31/4184 (2006.01) *A61P 25/28* (2006.01)
A61P 1/00 (2006.01) *A61P 35/00* (2006.01)
A61P 25/00 (2006.01) *A61P 9/00* (2006.01)
A61P 25/16 (2006.01) *C07D 235/08* (2006.01)

(21) International Application Number:
PCT/SE2005/001402

(22) International Filing Date:
22 September 2005 (22.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/GB2004/004124
24 September 2004 (24.09.2004) GB
60/640,804 30 December 2004 (30.12.2004) US

(71) Applicant: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WEI, Zhong-Yong** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA). **MILBURN, Claire** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA). **DESFOSSES, Helene** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA). **PAGÈ, Daniel** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA). **WALPOLE, Christopher** [GB/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA). **YANG, Hua** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Québec H4S 1Z9 (CA).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

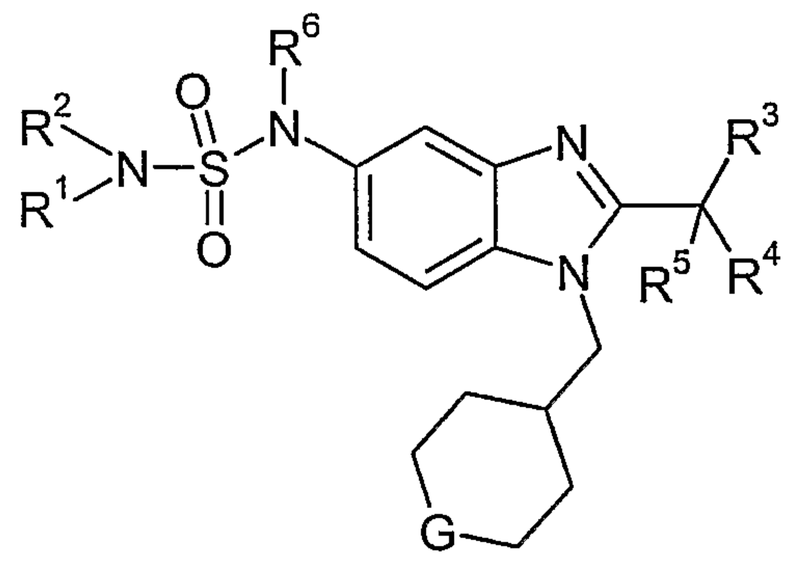
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF III



I

(57) Abstract: Compounds of Formula I, or pharmaceutically acceptable salts thereof: I *(chemical formula to be inserted here - please see paper copy)* wherein R1, R2, R3, R4, R5, R6 and G are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

WO 2006/033630 A1

Benzimidazole derivatives, compositions containing them, preparation thereof and uses thereof III

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB_1 receptor, CB_2 receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB_1 receptor agonists, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB_1 receptors located in CNS. There are lines of evidence, however, suggesting that CB_1 agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB_1 receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB_1 receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-4}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, butyl, isobutyl, t-butyl.

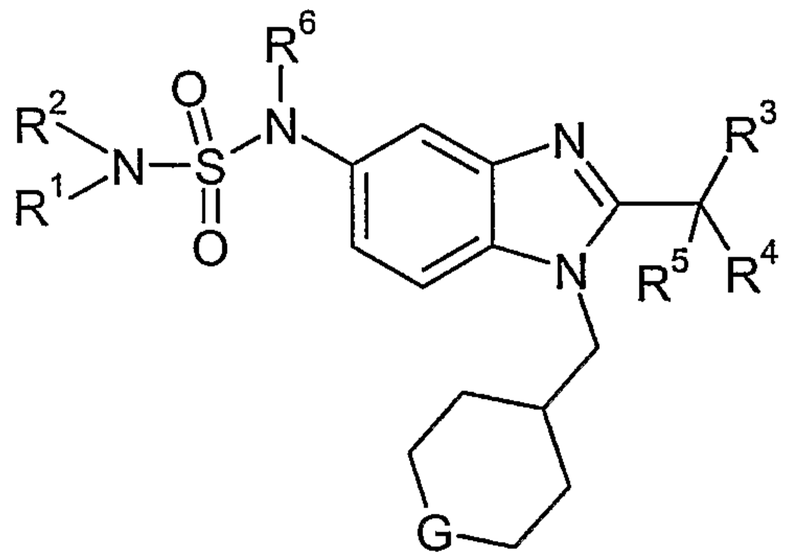
The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is an alkyl. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and isobutoxy.

Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 and R^2 are each independently –H, C_{3-6}cycloalkyl, and C_{1-6}alkyl, wherein said C_{3-6}cycloalkyl and C_{1-6}alkyl used in defining R^1 and R^2 is optionally substituted

by C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{6-10}aryl, -C(=O)-)R^7, C(=O)-NHR^7, wherein R^7 is selected from C_{1-6}alkyl and C_{3-6}cycloalkyl;

G is selected from $-CH_2-$, -O-, -CHF-, and $-CF_2-$;

R^6 is selected from –H and methyl and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

In another embodiment, R^1 and R^2 of formula I are each independently C_{1-4}alkyl.

In another embodiment, R^1 and R^2 of formula I are independently selected from –H, methyl, ethyl, 2-methoxylethyl, benzyl, cyclopropylmethyl, isopropyl, butyl, isobutyl and propyl with a proviso that R^1 and R^2 are not both -H.

In another embodiment, G of formula I is selected from -O-, -CHF-, and $-CF_2-$

In a further embodiment, G of formula I is selected from -CHF- and $-CF_2-$.

In an even further embodiment, the invention provides a compound selected from:

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide;

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-diethyl-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-diethyl-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-bis(2-methoxyethyl)-*N*-methylsulfamide;

N-Butyl-*N*'-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*'-(cyclopropylmethyl)-*N*,*N*'-dimethylsulfamide;

N-Benzyl-*N*'-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N'-Benzyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*,*N*',*N*'-trimethylsulfamide;

N'-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*-dimethylsulfamide;

Methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate;

N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-ethyl-N^2-methylglycinamide;

N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-cyclopropyl-N^2-methylglycinamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*'-ethyl-*N*-methylsulfamide;

N-[1-(cyclohexylmethyl)-2-(1,1-difluoroethyl)-1*H*-benzimidazol-5-yl]-*N*'-isobutyl-*N*,*N*'-dimethylsulfamide; and pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB_1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson´s disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

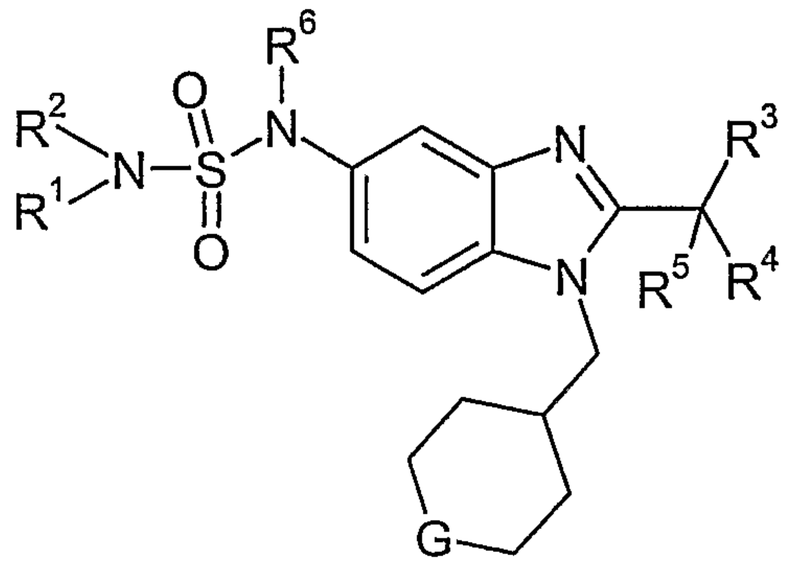
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

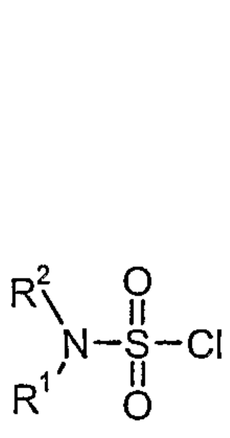
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula I, comprising:

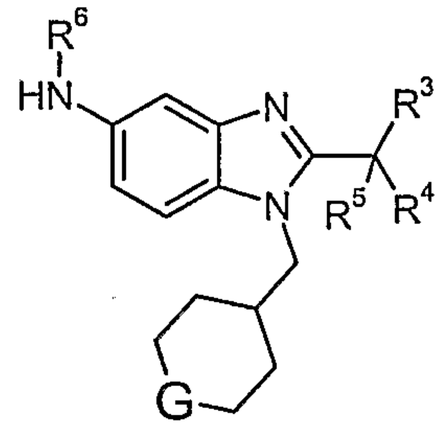


I

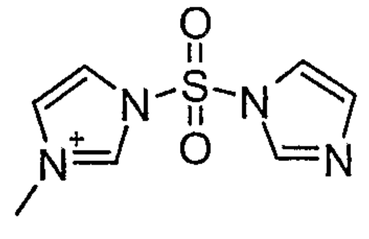
reacting a compound of Formula II with a compound of formula III,



II



III

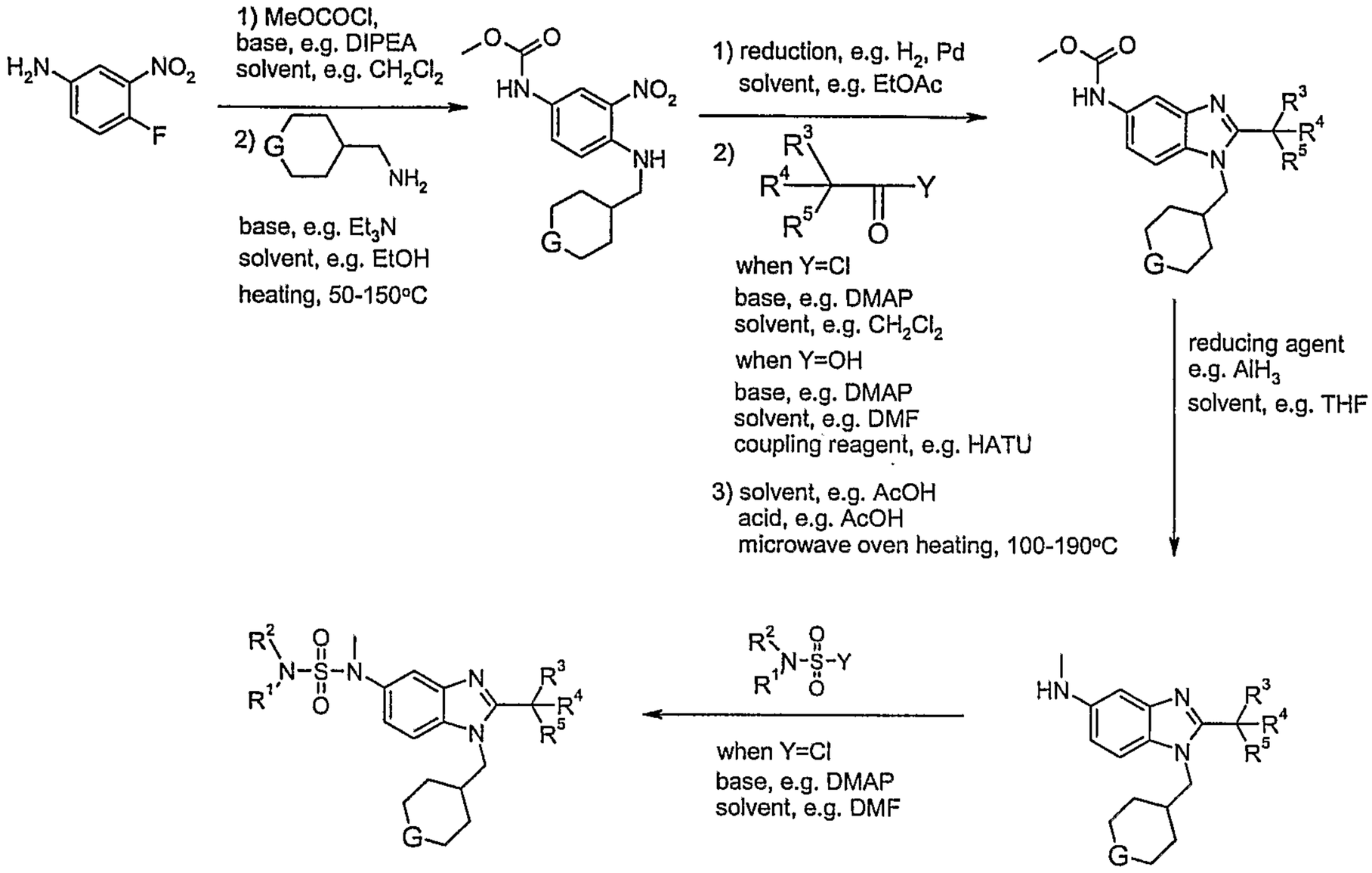


IV

alternatively, reacting a compound of formula III with compound IV followed by reacting with TMSOTf and $R^2(R^1)NH$. wherein R^1, R^2, R^3, R^4, R^5, R^6 and G are as defined above.

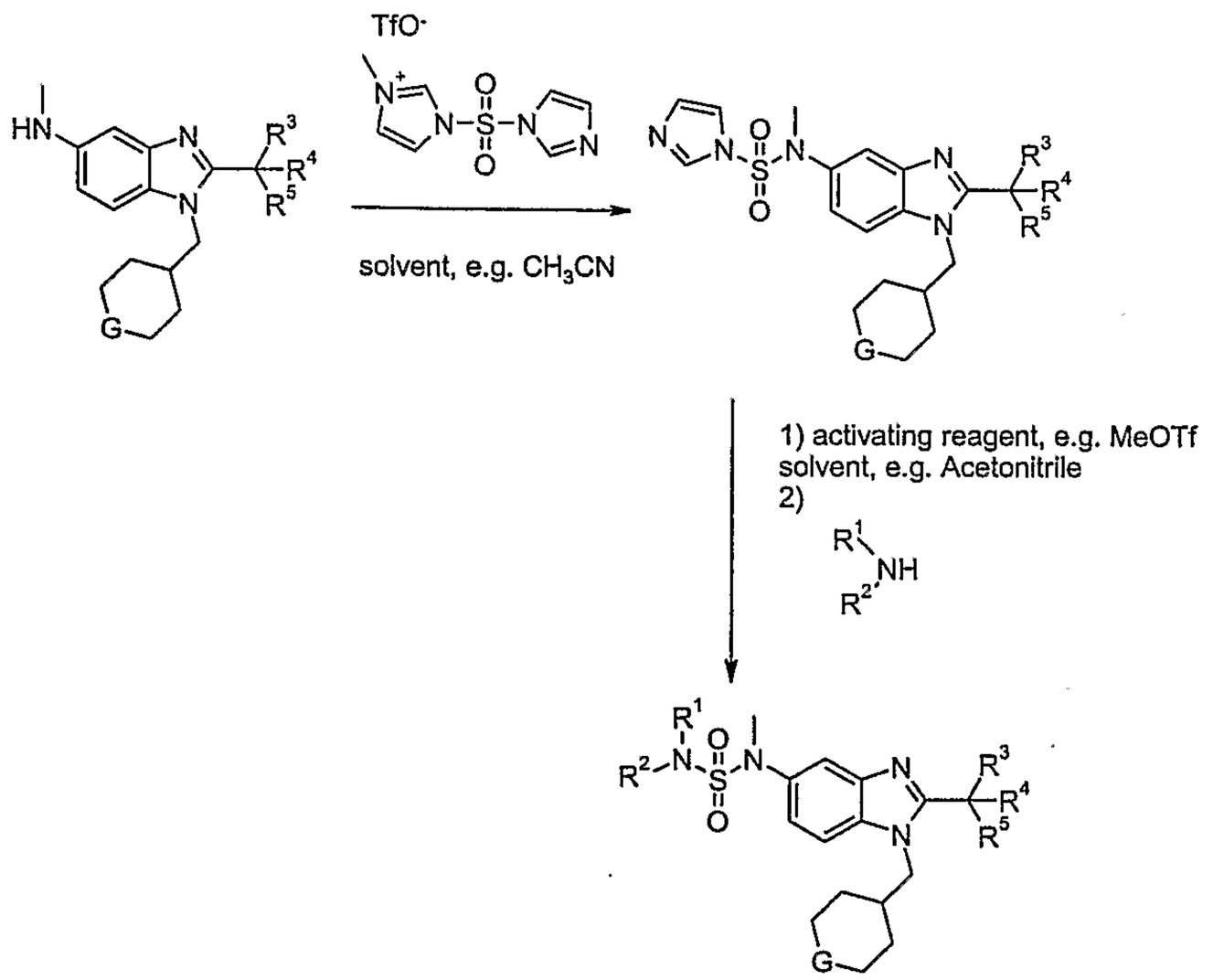
Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1-4.

Scheme 1



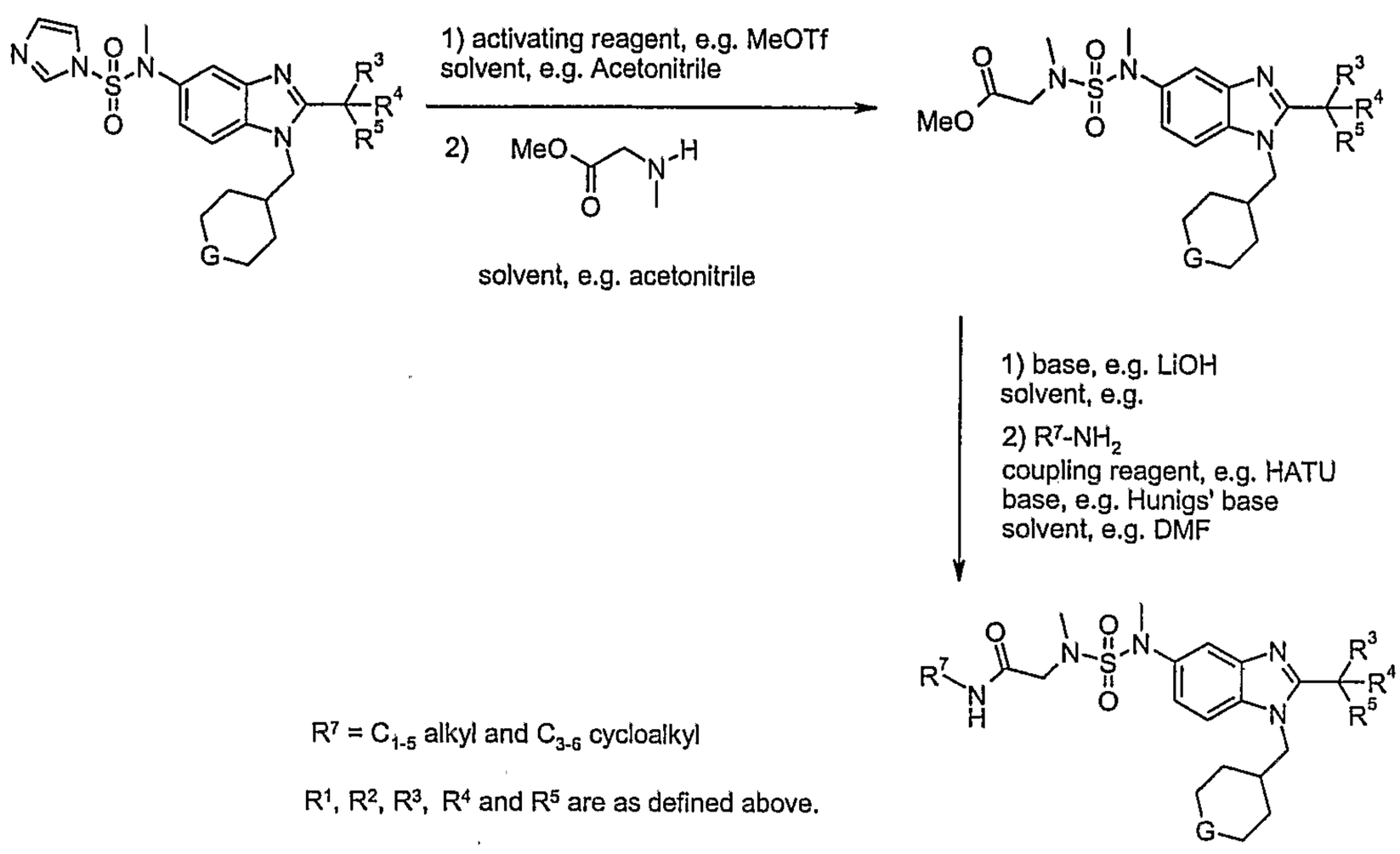
R^1, R^2, R^3, R^4 and R^5 are as defined above.

Scheme 2



R^1, R^2, R^3, R^4 and R^5 are as defined above.

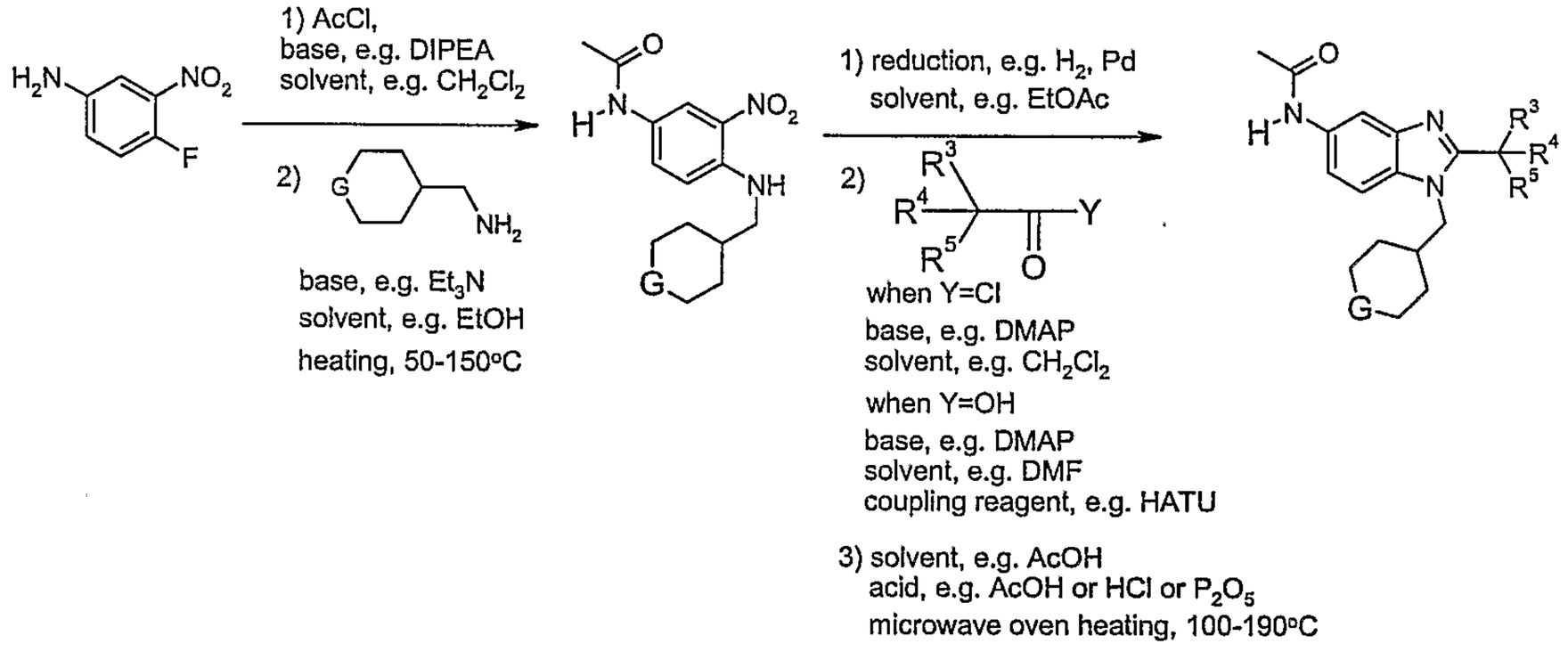
Scheme 3



R^7 = C_{1-5} alkyl and C_{3-6} cycloalkyl

R^1, R^2, R^3, R^4 and R^5 are as defined above.

Scheme 4



G, R^3, R^4 and R^5 are as defined above.

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor from BioSignal (hCB_2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point

dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

<u>hCB_1 and hCB_2 GTPγS binding</u>

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The EC_{50} and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPg^{35}S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB_2) or 10 µM (hCB_1) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB2) or 112.5 µM (hCB_1) GDP prior to distribution in plates (15 µM (hCB_2) or 30 µM (hCB_1) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

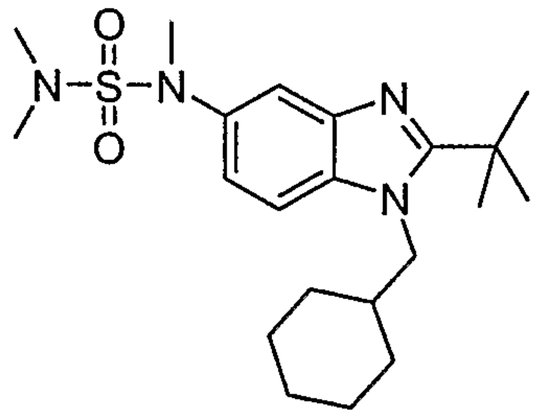
Using the above-mentioned assays, the Ki towards human CB_1 receptors for certain compounds of the invention are in the range of between 2.98 nM and 495 nM. EC_{50} for these compounds are in the range of between 4.5 nM and 350 nM. Emax for these compounds are in the range of between 73% and 142%.

EXAMPLES

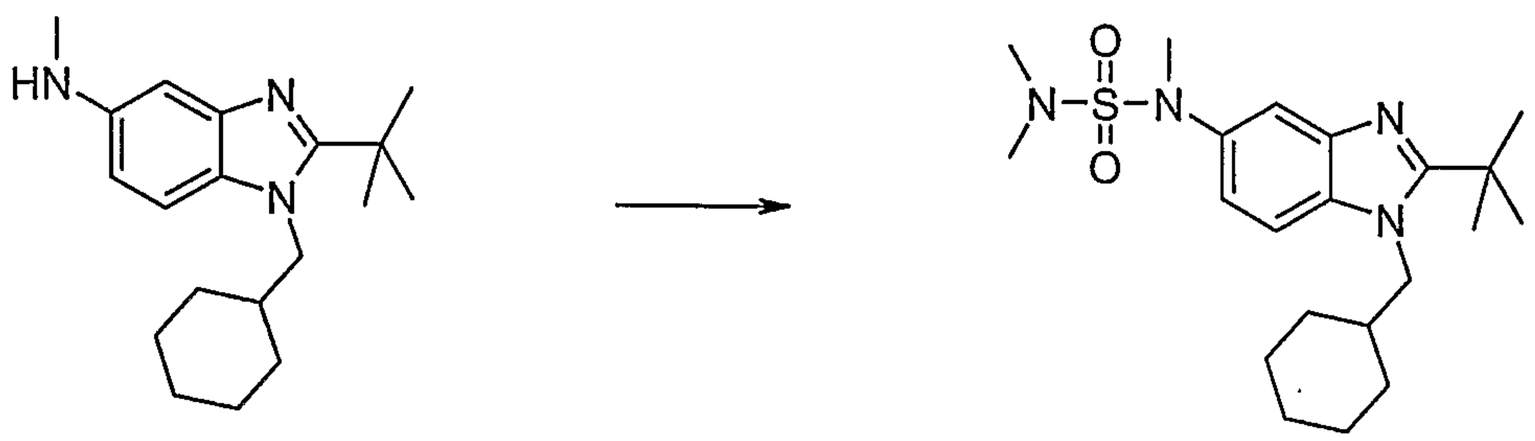
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide**

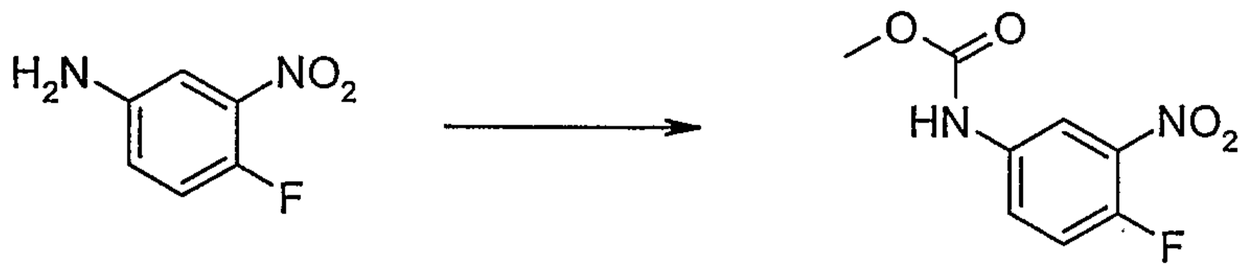


Step A. *N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide



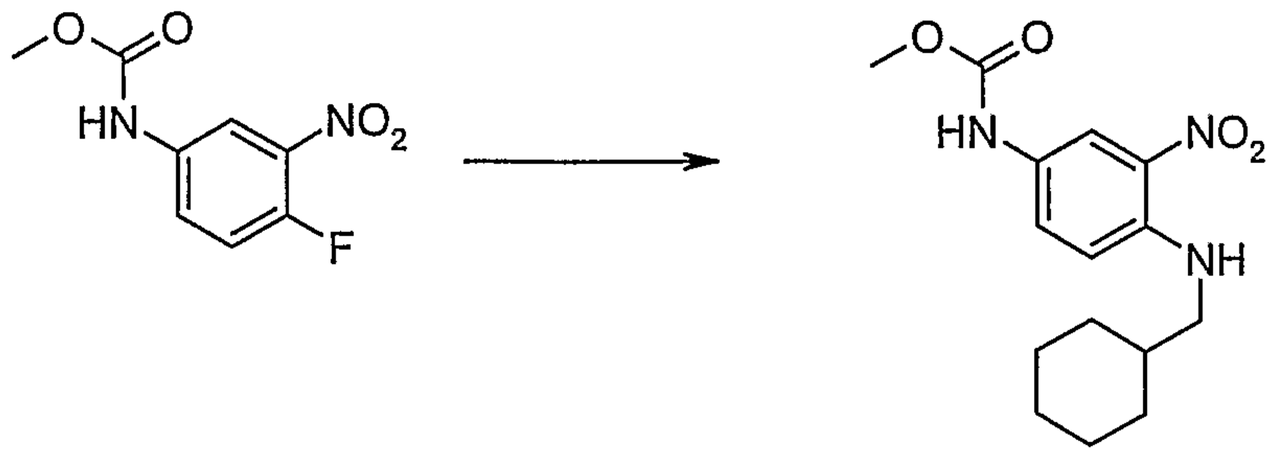
2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (40 mg, 0.133 mmol) (for preparation, see the following steps B, C, D, E and F) and dimethylsulfamoyl chloride (0.020 mL, 0.173 mmol) were stirred in 3 mL of dichloromethane containing a catalytic amount of DMAP overnight at rt. The solvent was evaporated. The product was purified by reversed-phase HPLC using 20-80% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. Yield: 36 mg (52%); ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.22 (m, 5H), 1.62 (m, 2H), 1.65 (s, 9H), 1.67 (m, 1H), 1.75 (m, 2H), 2.10 (m, 1H), 2.81 (s, 6H), 3.29 (s, 3H), 4.44 (d, J = 7.62 Hz, 2H), 7.64 (dd, J = 9.08, 2.05 Hz, 1H), 7.78 (d, J = 1.95 Hz, 1H), 7.90 (d, J = 8.98 Hz, 1H); MS (ESI) $(M+H)^+$ 407.3; Anal. Calcd for $C_{21}H_{34}N_4O_2S$ + 1.3 TFA + 0.3 H_2O: C, 50.60; H, 6.46; N, 10.00. Found: C, 50.64; H, 6.47; N, 10.15.

Step B. Methyl (4-fluoro-3-nitrophenyl)carbamate



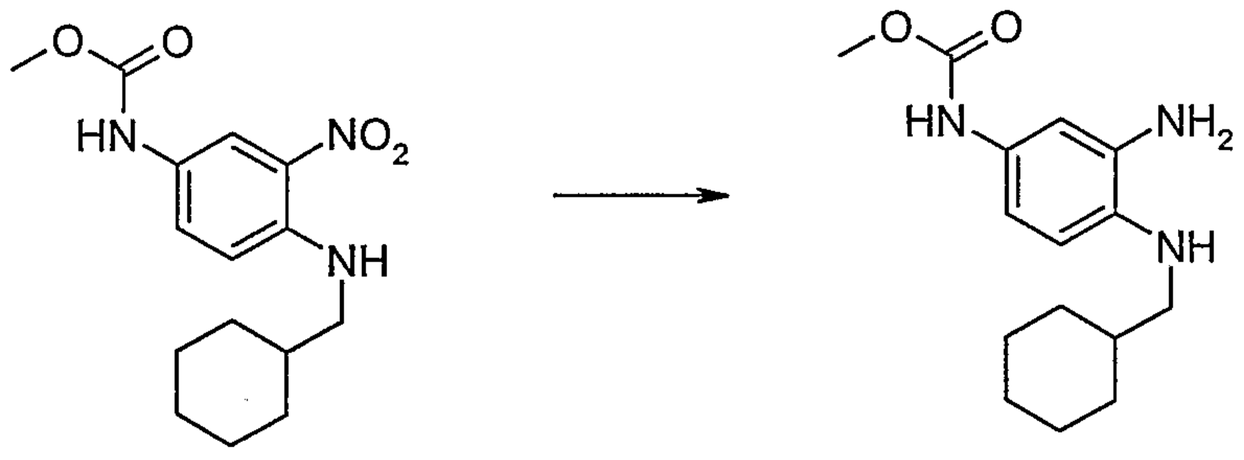
Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59 Hz, 1H), 8.17 (dd, J = 6.35, 2.64 Hz, 1H).

Step C. Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate



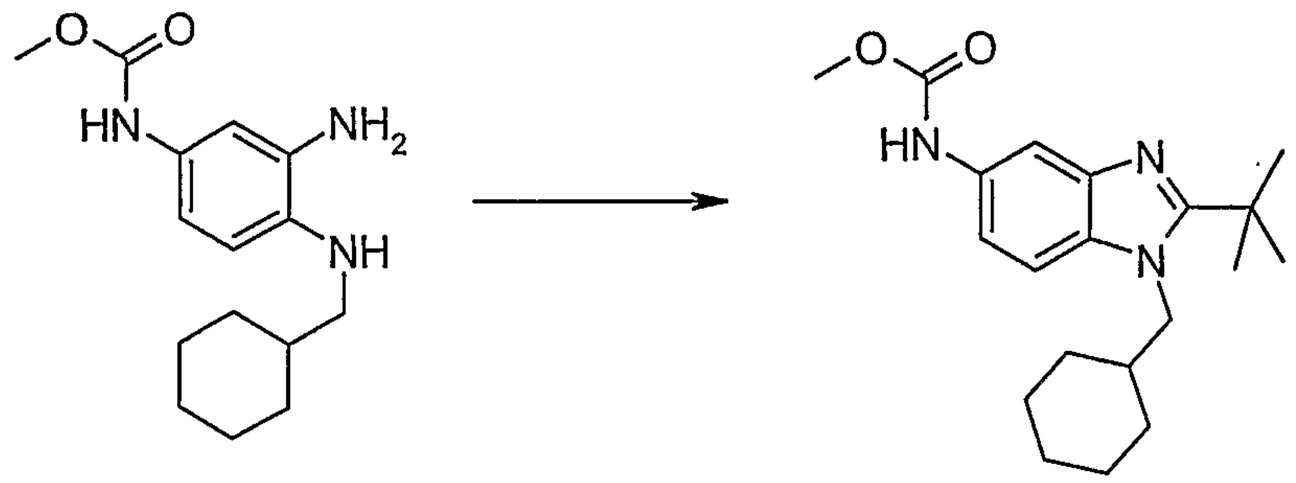
Methyl (4-fluoro-3-nitrophenyl)carbamate (1.00 g, 4.67 mmol) and cyclohexylmethyl amine (0.730 mL, 5.60 mmol) were stirred in EtOH (20 mL) containing TEA (1.0 mL, 7.00 mmol) at 75°C for 24h. The solvent was concentrated. The residue was dissolved in EtOAc and washed with 5% $KHSO_4$ solution, saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by flash chromatography using 4:1/hex:EtOAc on silica gel. Yield: 1.05 g (73%); ^1H NMR (400 MHz, CHLOROFORM-D) δ 1.04 (ddd, J = 24.02, 12.11, 2.93 Hz, 2H), 1.25 (m, 3H), 1.69 (m, 2H), 1.76 (m, 1H), 1.79 (m, 1H), 1.83 (m, 1H), 1.86 (m, 1H), 3.14 (dd, J = 6.44, 5.66 Hz, 2H), 3.78 (s, 3H), 6.46 (m, 1H), 6.84 (d, J = 9.37 Hz, 1H), 7.63 (m, 1H), 8.05 (d, J = 2.54 Hz, 1H), 8.09 (m, 1H).

Step D. Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate



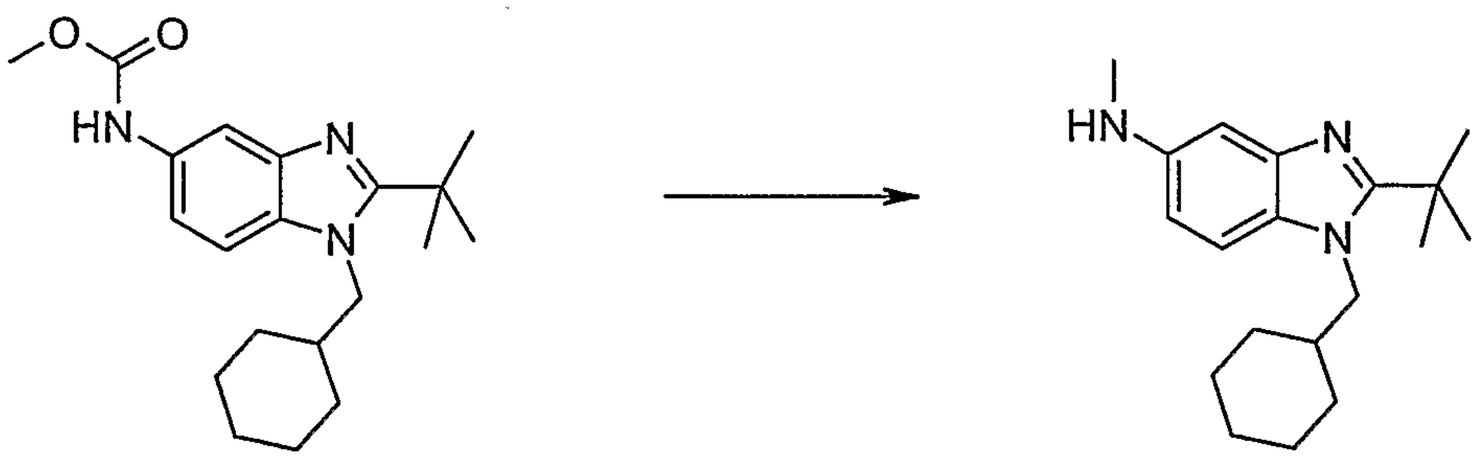
Methyl {4-[(cyclohexylmethyl)amino]-3-nitrophenyl}carbamate (1.05 g, 3.42 mmol) was dissolved in 30 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken in a Parr hydrogenation apparatus under H_2 atmosphere (40 psi) at rt overnight. The solution was filtered through Celite and the solvent evaporated. The product was directly used for the next step without further purification. Yield: 950 mg (99%). MS (ESI) $(M+H)^+$ 277.9.

Step E. Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(cyclohexylmethyl)amino]phenyl}carbamate (950 mg, 3.43 mmol) and DMAP (100 mg, 0.858 mmol) were dissolved in 25 mL of dichloromethane. Trimethylacetyl chloride (0.460 mL, 3.77 mmol) was added in dropwise and the solution was stirred at rt for 1h. The solvent was concentrated. The residue was divided in two portions and each of them was dissolved in 3 mL of glacial AcOH in a sealed tube. The solutions were heated at 150°C using a Personal Chemistry Smith Synthesizer microwave instrument for three intervals of 30 min (3 X 30 min). The contents of the two tubes were combined and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by flash chromatography using 3:1/dichloromethane:diethyl ether. Yield: 656 mg (56%); ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (m, 2H), 1.18 (m, 3H), 1.54 (s, 9H), 1.65 (m, 1H), 1.69 (m, 2H), 1.73 (dd, J = 5.96, 3.22 Hz, 2H), 2.02 (m, 1H), 3.78 (s, 3H), 4.10 (d, J = 7.42 Hz, 2H), 6.64 (m, 1H), 7.25 (d, J = 8.79 Hz, 1H), 7.39 (m, 1H), 7.59 (d, J = 1.76 Hz, 1H).

Step F. 2-*tert*-Butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine

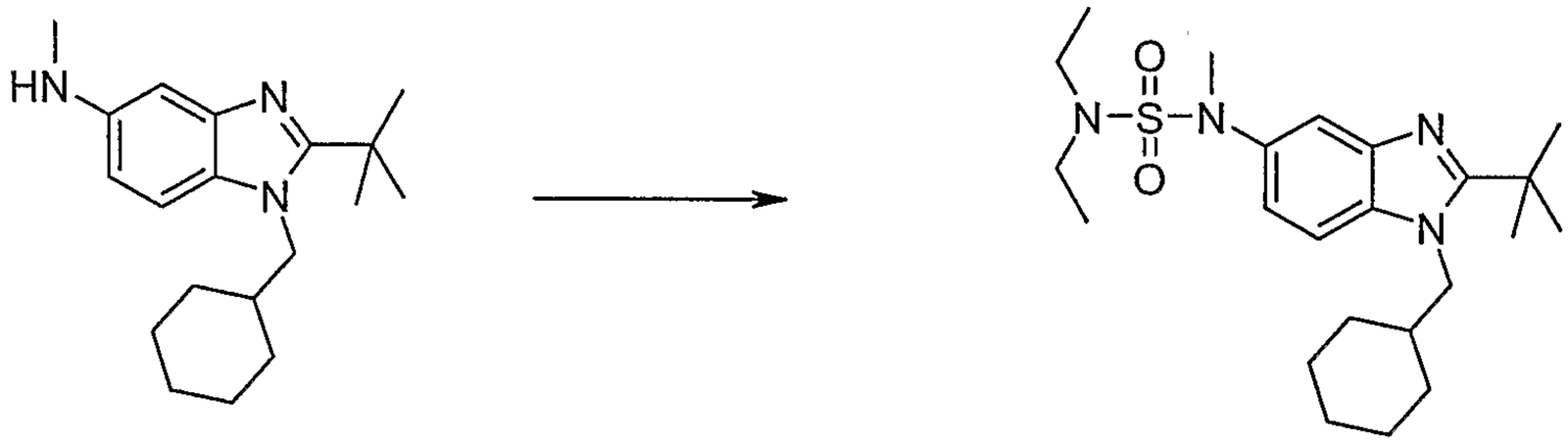


Methyl [2-*tert*-butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]carbamate (650 mg, 1.89 mmol) was dissolved in 20 mL of THF at 0°C under nitrogen. 1M HCl/ether (2.65 mL, 2.65 mmol) was added dropwise and the solution was stirred at 0°C for 15min. $LiAlH_4$ (360 mg, 9.45 mmol) was then slowly added and the solution was

stirred at rt overnight. The reaction mixture was quenched at 0°C by addition of MeOH (5 mL) followed by water (10 mL). The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was used directly for Step A without further purification. Yield: 544 mg (96%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.08 (s, 2H), 1.17 (m, 3H), 1.54 (s, 9H), 1.64 (m, 2H), 1.67 (m, 2H), 1.72 (m, 2H), 2.02 (m, 1H), 2.87 (s, 3H), 4.06 (d, J = 7.62 Hz, 2H), 6.60 (dd, J = 8.69, 2.25 Hz, 1H), 7.00 (d, J = 1.76 Hz, 1H), 7.12 (d, J = 8.59 Hz, 1H).

Example 2

***N*-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N'*,*N'*-diethyl-*N*-methylsulfamide**

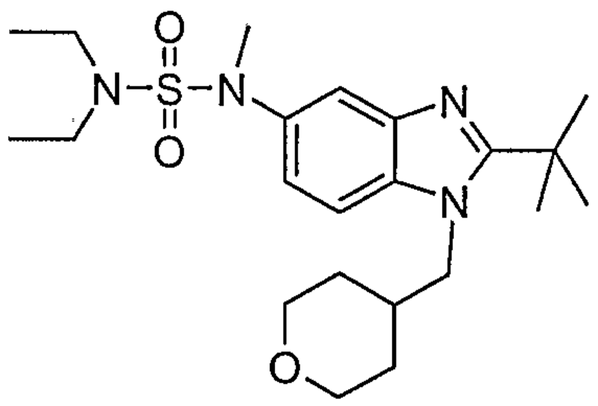


A solution of diethylamine (0.103 mL, 1.00 mmol) in 1 mL dichloromethane and TEA (0.140 mL, 1.00 mmol) were added sequentially to a cold (0°C) solution of SO_2Cl_2 (0.160 mL, 2.00 mmol) in dichloromethane (1 mL) under a nitrogen atmosphere. The solution was then stirred at rt for 3h. The solution was washed with 5% $KHSO_4$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was then dissolved in 1 mL of dichloromethane, to which a solution of 2-*tert*-butyl-1-(cyclohexylmethyl)-*N*-methyl-1*H*-benzimidazol-5-amine (25 mg, 0.0835 mmol, for preparation, see steps B to F in Example 1) and DMAP (catalytic) in 1 mL of dichloromethane was added dropwise. The solution was stirred at rt for 24h. The product was purified by reversed-phase HPLC using 30-80% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 15 mg (33%); ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.13 (t, J = 7.13Hz, 6H), 1.24 (m, 5H), 1.63 (m, 2H), 1.67 (s, 9H), 1.70 (m, 1H), 1.77 (m, 2H), 2.12 (m, 1H), 3.26 (s, 3H), 3.30 (m, 4H), 4.46 (d, J = 7.62Hz, 2H), 7.61 (dd, J = 8.98,

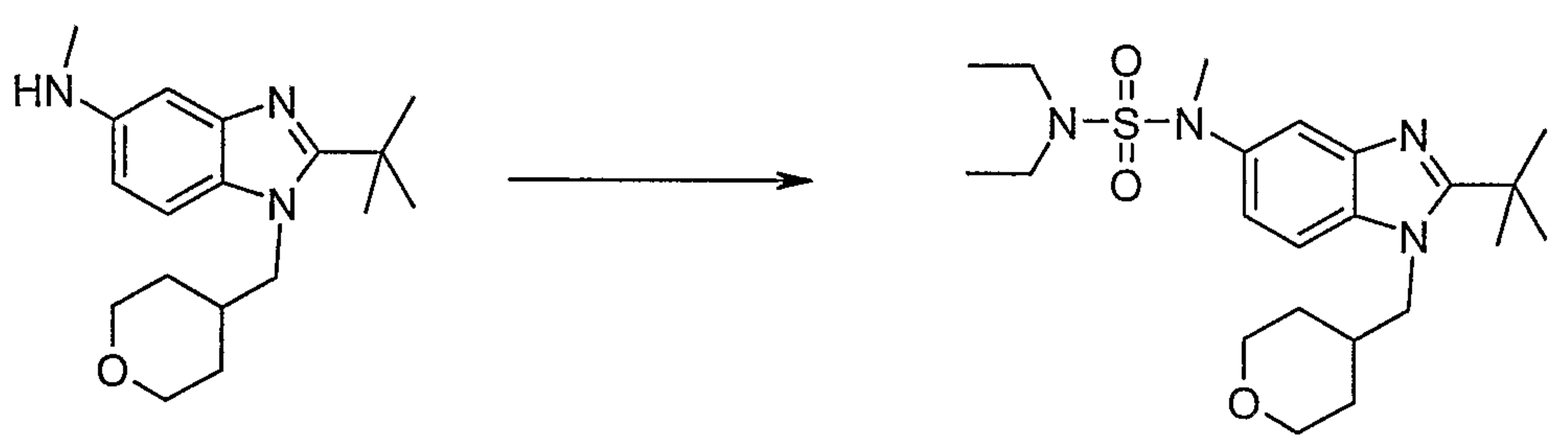
2.15Hz, 1H), 7.78 (d, J = 1.95 Hz, 1H), 7.89 (d, J = 8.98Hz, 1H); MS (ESI) $(M+H)^+$ 435.2; Anal. Calcd for $C_{23}H_{38}N_4O_2S$ + 1.2 TFA + 0.8 H_2O: C, 52.07; H, 7.02; N, 9.56. Found: C, 52.00; H, 7.01; N, 9.55.

Example 3

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N'*,*N'*-diethyl-*N*-methylsulfamide**



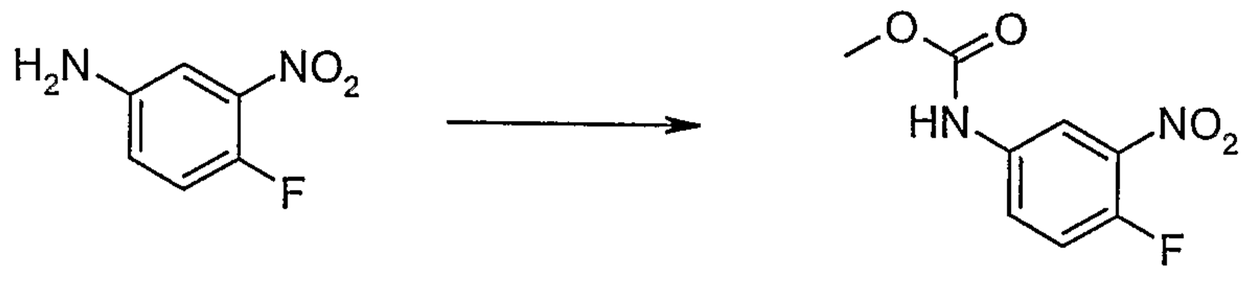
Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N'*,*N'*-diethyl-*N*-methylsulfamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (46 mg, 0.153 mmol) (for preparation, see steps B to F) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (51 mg, 0.168 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was evaporated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was dissolved in 3 mL of DMF at 0°C and NaH (60% dispersion in oil) (18 mg, 0.459 mmol) was added. The solution was stirred at 0°C for 10 min. Iodoethane (0.060 mL, 0.765 mmol) was added and the solution was stirred at rt overnight. The reaction was quenched with MeOH at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$.

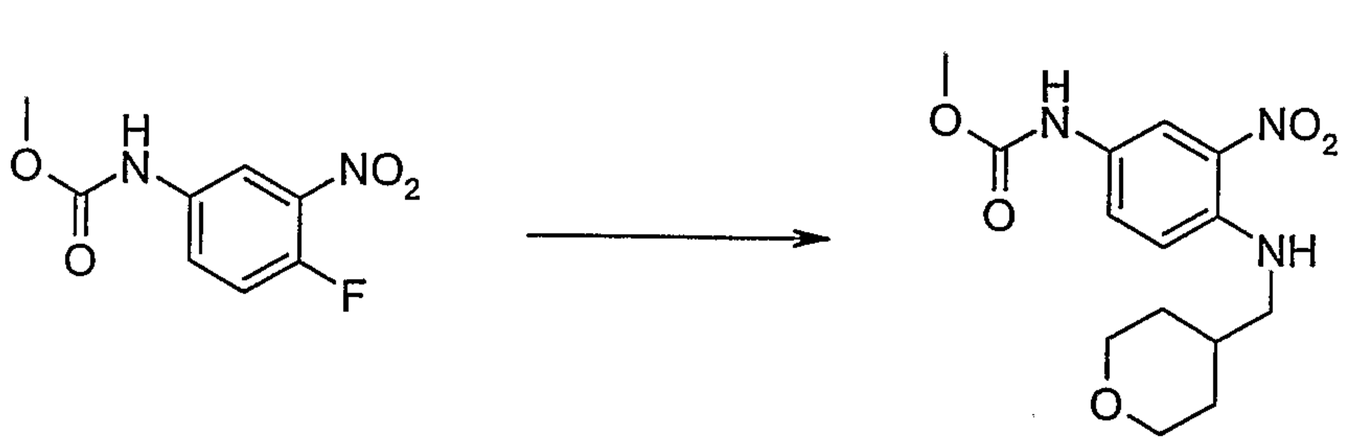
The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 32 mg (38%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.14 (t, J=7.13 Hz, 6 H), 1.52 - 1.57 (m, 2 H), 1.58 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.43 (m, 1 H), 3.26 (s, 3 H), 3.28 - 3.31 (m, 4 H), 3.35 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.95 (d, J=3.91 Hz, 1 H), 4.54 (d, J=7.62 Hz, 2 H), 7.64 (dd, J=8.98, 1.95 Hz, 1 H), 7.79 (d, J=1.95 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 437.0; Anal. Calcd for $C_{22}H_{36}N_4O_3S$ + 1.3 TFA + 0.9 H_2O: C, 49.16; H, 6.56; N, 9.32. Found: C, 49.05; H, 6.46; N, 9.50.

Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate



Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59Hz, 1H), 8.17 (dd, J = 6.35, 2.64Hz, 1H).

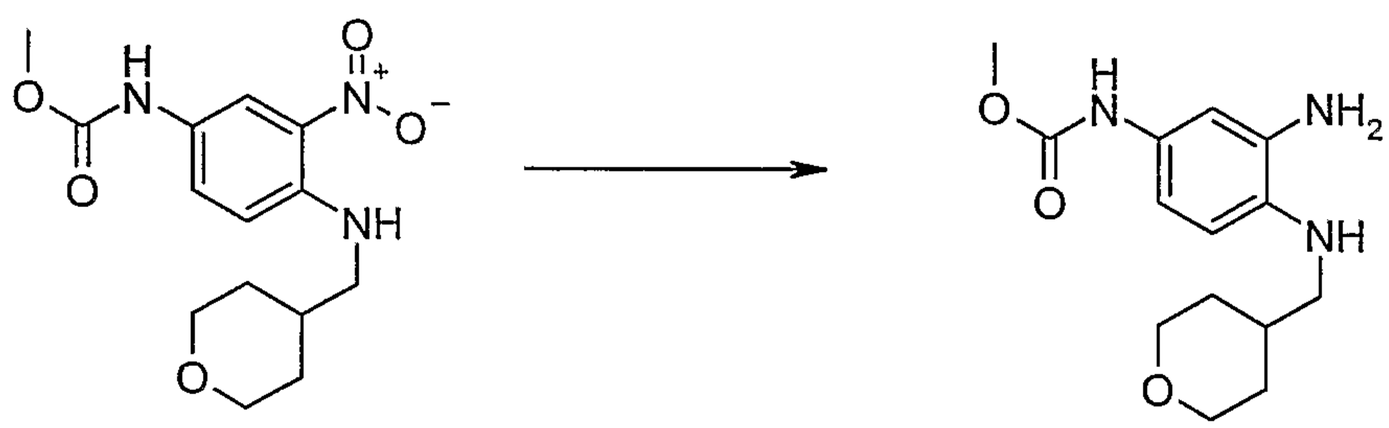
Step C: Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48h. The solvent was evaporated. The residue was

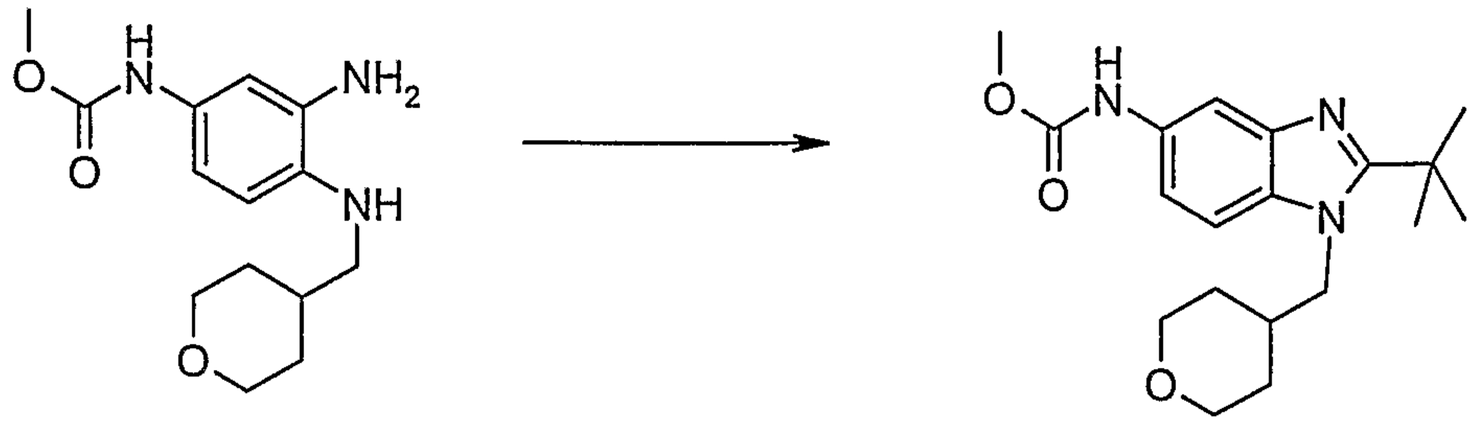
dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53g (88%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ1.42 (m, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, *J*=6.74, 5.57 Hz, 2 H), 3.42 (m, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

Step D: Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate



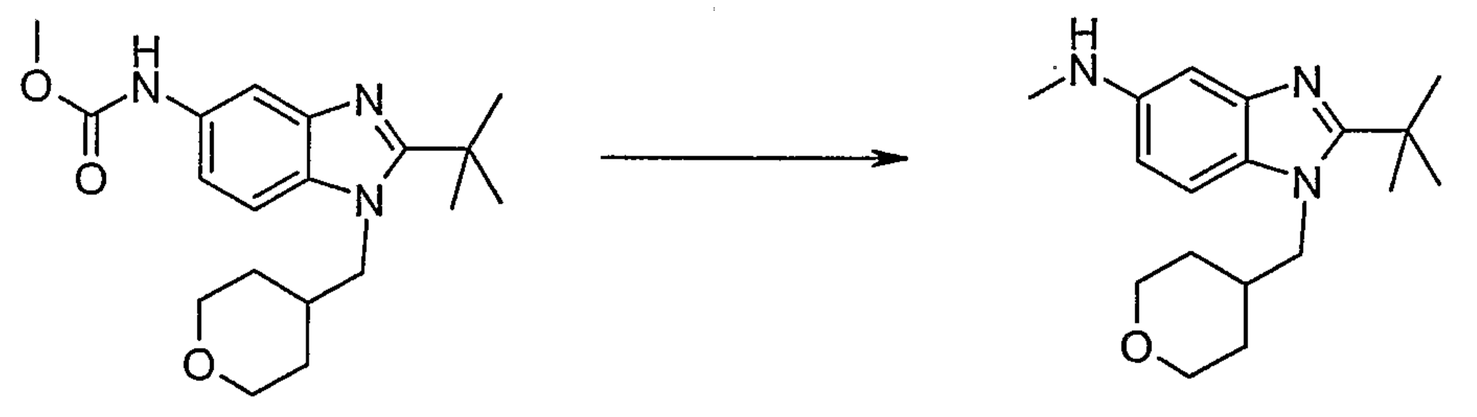
Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29g (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.40 (m, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (m, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

Step E: Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate (2.29 g, 8.20 mmol) and DMAP (0.20g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81g (64%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, *J*=2.93 Hz, 1 H) 3.99 (t, *J*=3.03 Hz, 1 H) 4.18 (d, *J*=7.42 Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, *J*=1.95 Hz, 1 H).

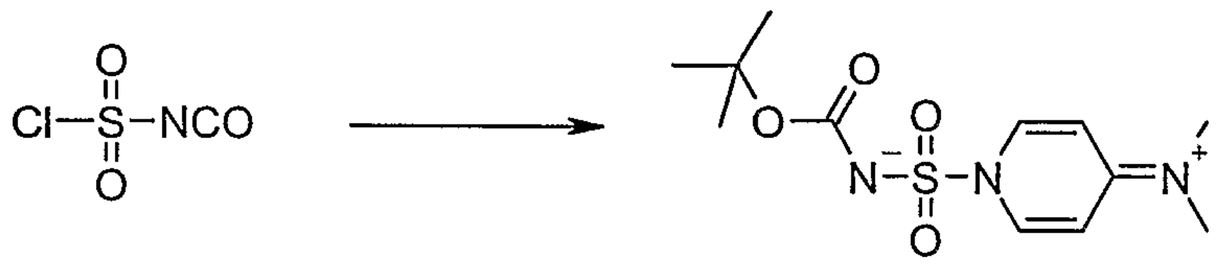
Step F: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80g, 5.21 mmol) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min.

Anhydrous Na_2SO_4 (10g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 1.54g (98%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

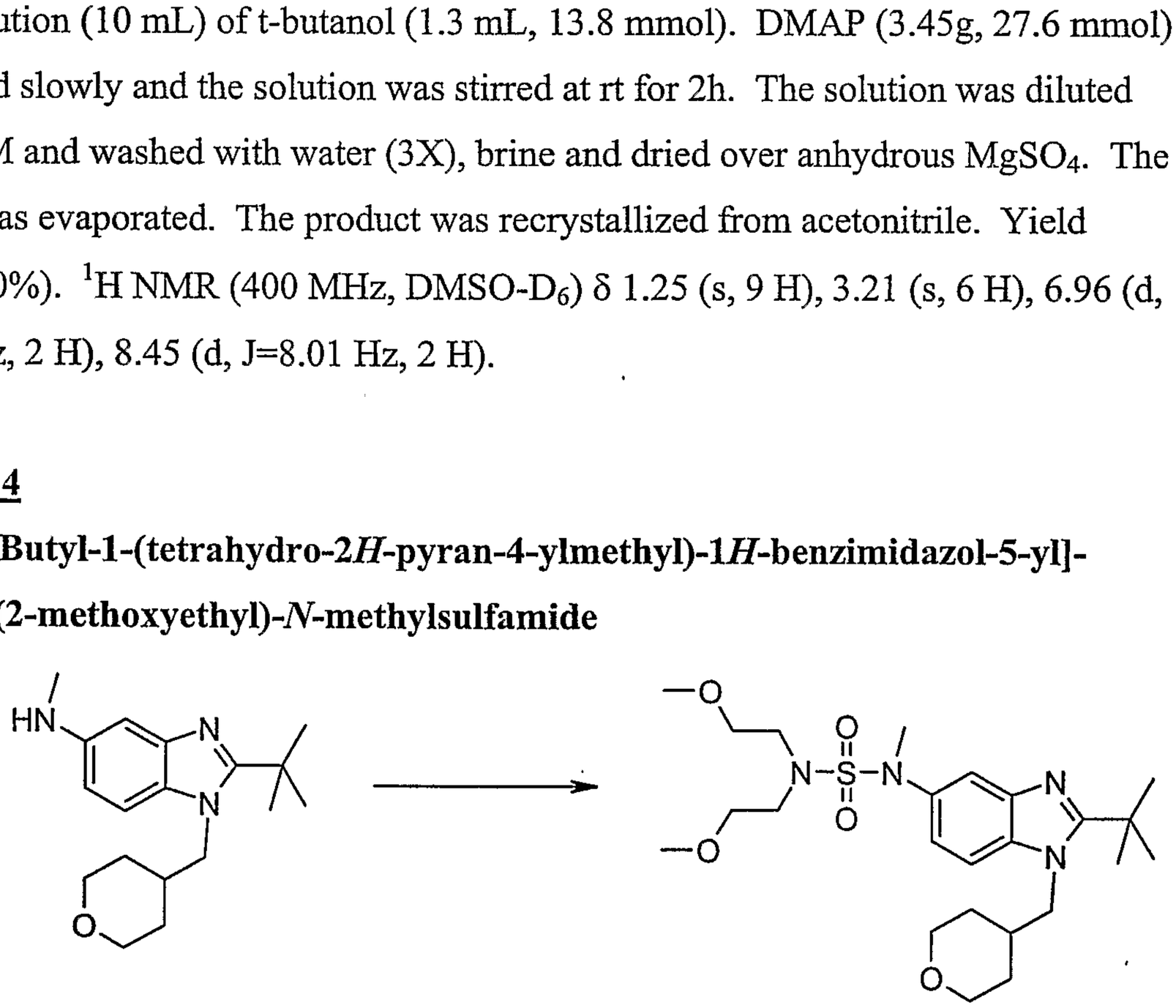
Step G: (*tert*-Butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide



Chlorosulfonyl isocyanate (1.2 mL, 13.8 mmol) was added dropwise to a stirring DCM solution (10 mL) of t-butanol (1.3 mL, 13.8 mmol). DMAP (3.45g, 27.6 mmol) was added slowly and the solution was stirred at rt for 2h. The solution was diluted with DCM and washed with water (3X), brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The product was recrystallized from acetonitrile. Yield (1.68g (40%). ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.25 (s, 9 H), 3.21 (s, 6 H), 6.96 (d, J=8.20 Hz, 2 H), 8.45 (d, J=8.01 Hz, 2 H).

Example 4

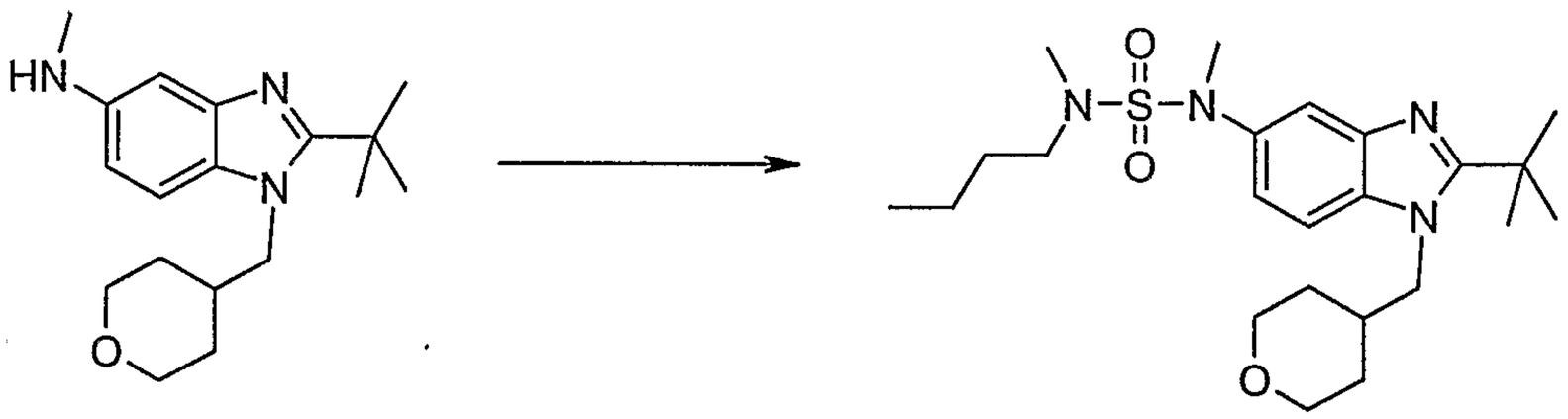
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N'*,*N'*-bis(2-methoxyethyl)-*N*-methylsulfamide**



Following Step A in Example 3 using 2-tert-butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (60 mg, 0.199 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (66 mg, 0.219 mmol) in 3 mL of DCE. 2-Bromoethyl methyl ether (0.056 mL, 0.597 mmol) and NaH (60% dispersion in oil) (25 mg, 0.597 mmol) in 5 mL of DMF were used in the subsequent step. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 39 mg (32%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.51 - 1.58 (m, 2 H), 1.59 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.35 - 2.43 (m, 1 H), 3.28 (s, 3 H), 3.31 - 3.39 (m, 8 H), 3.43 - 3.48 (m, 4 H), 3.50 - 3.54 (m, 4 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=3.91 Hz, 1 H), 4.55 (d, J=7.42 Hz, 2 H), 7.67 (dd, J=8.98, 1.95 Hz, 1 H), 7.80 (d, J=1.76 Hz, 1 H), 7.97 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 497.0; Anal. Calcd for $C_{24}H_{40}N_4O_5S$ + 2.2 TFA + 1.1 H_2O: C, 44.45; H, 5.83; N, 7.29. Found: C, 44.56; H, 6.02; N, 6.89.

Example 5

***N*-Butyl-*N'*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N'*-dimethylsulfamide**

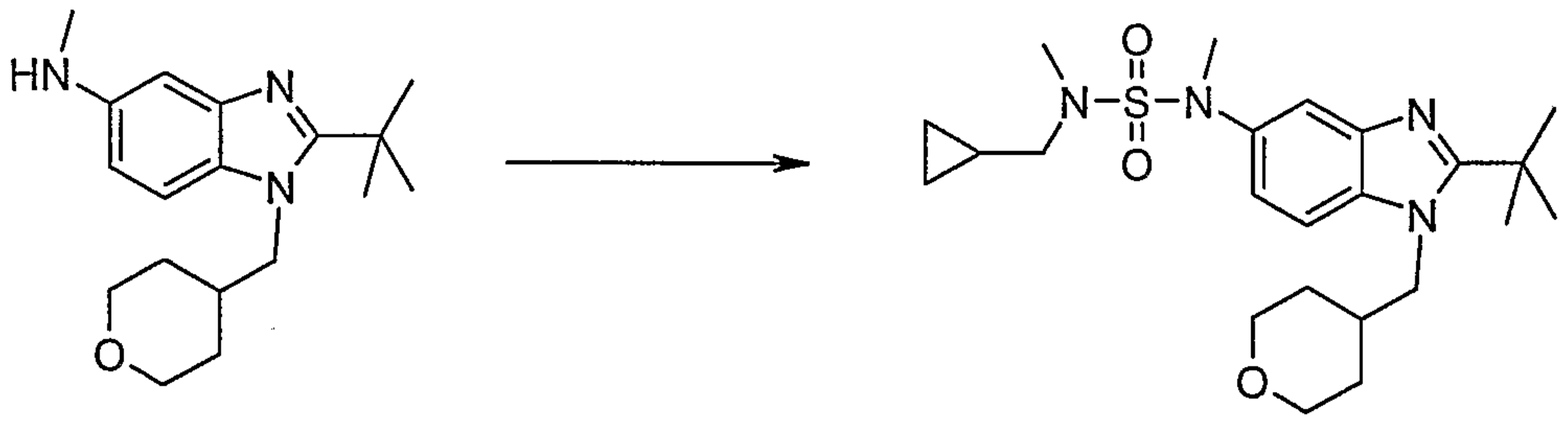


2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (75 mg, 0.249 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (82 mg, 0.274 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was concentrated. The residue was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (15 mg, 0.373 mmol) was added followed by iodomethane (0.031 mL, 0.498 mmol). The solution was stirred at rt for 3h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed

with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (15 mg, 0.373 mmol) was added. The solution was stirred at 0°C for 10 min. 1-iodobutane (0.085 mL, 0.747 mmol) was added and the solution was stirred at rt for 3h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 58 mg (41%). ^1H NMR (400 MHz, METHANOL-D_4) δ 0.90 (t, J=7.32 Hz, 3 H), 1.28 (m, 2 H), 1.47 - 1.58 (m, 4 H), 1.58 - 1.67 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.44 (m, 1 H), 2.84 (s, 3 H), 3.14 - 3.19 (m, 2 H), 3.28 (s, 3 H), 3.35 (m, 2 H), 3.93 (d, J=3.32 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.55 (d, J=7.62 Hz, 2 H), 7.67 (dd, J=9.08, 2.05 Hz, 1 H), 7.80 (d, J=1.76 Hz, 1 H), 7.97 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 451.0; Anal. Calcd for $C_{23}H_{38}N_4O_3S$ + 1.9 TFA + 0.2 H_2O: C, 47.98; H, 6.05; N, 8.35. Found: C, 47.98; H, 5.89; N, 8.62.

Example 6

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N'*-(cyclopropylmethyl)-*N*,*N'*-dimethylsulfamide**

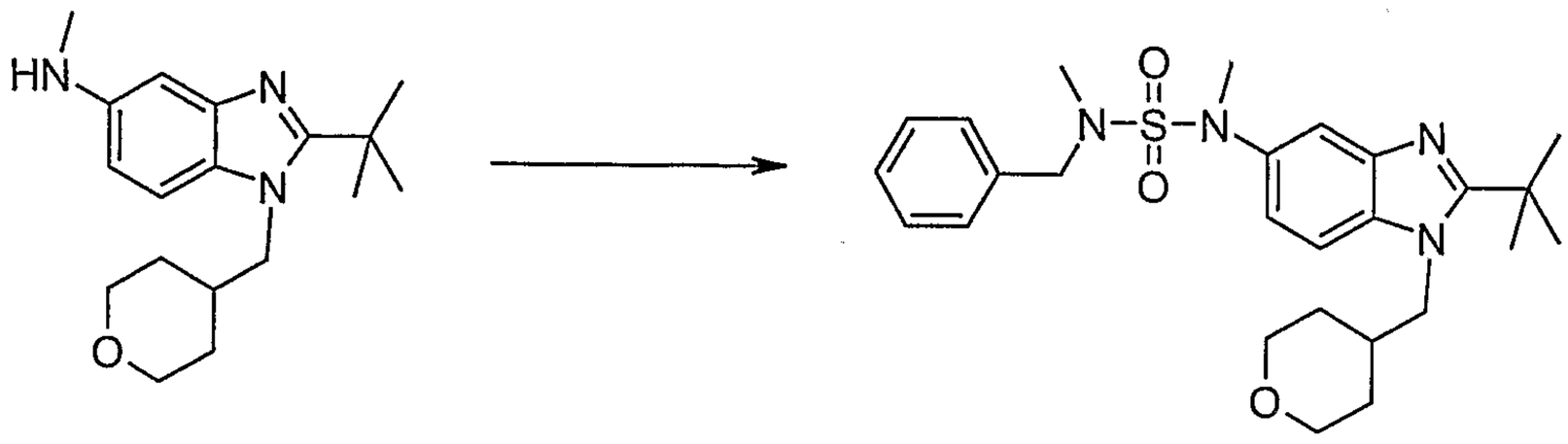


2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (65 mg, 0.216 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (71 mg, 0.238 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent.

The solvent was concentrated. The residue was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (13 mg, 0.324 mmol) was added followed by iodomethane (0.025 mL, 0.432 mmol). The solution was stirred at rt for 3h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (13 mg, 0.324 mmol) was added. The solution was stirred at 0°C for 10 min. Bromomethyl cyclopropane (0.031 mL, 0.324 mmol) was added and the solution was stirred at rt overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 36 mg (30%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 0.17 - 0.23 (m, 2 H), 0.49 - 0.56 (m, 2 H), 0.91 - 1.01 (m, 1 H), 1.51 - 1.58 (m, 2 H), 1.59 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.43 (m, 1 H), 2.93 (s, 3 H), 3.05 (d, J=7.03 Hz, 2 H), 3.27 (s, 3 H), 3.35 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.95 (d, J=3.71 Hz, 1 H), 4.54 (d, J=7.42 Hz, 2 H), 7.65 (dd, J=8.98, 1.95 Hz, 1 H), 7.79 (d, J=1.95 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 449.0; Anal. Calcd for $C_{23}H_{36}N_4O_3S$ + 1.3 TFA + 0.8 H_2O: C, 50.30; H, 6.41; N, 9.17. Found: C, 50.37; H, 6.45; N, 9.01.

Example 7

***N*-Benzyl-*N'*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N'*-dimethylsulfamide**

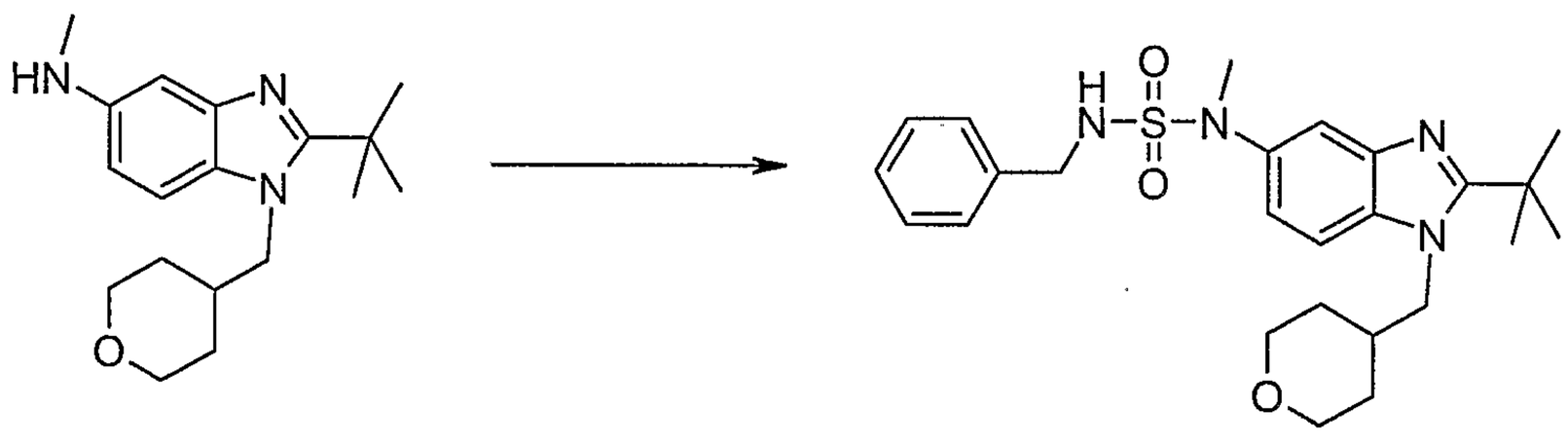


2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (50 mg, 0.116 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (60 mg, 0.199 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was concentrated. The residue was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (10 mg, 0.249 mmol) was added followed by iodomethane (0.016 mL, 0.249 mmol). The solution was stirred at rt for 1h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was dissolved in 5 mL of DMF at 0°C and NaH (60% dispersion in oil) (10 mg, 0.249 mmol) was added. The solution was stirred at 0°C for 10 min. Benzyl bromide (0.030 mL, 0.249 mmol) was added and the solution was stirred at rt overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 45 mg (45%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.53 - 1.59 (m, 2 H), 1.59 - 1.67 (m, 2 H), 1.70 (s, 9 H, 2.36 - 2.44 (m, 1 H), 2.75 (s, 3 H), 3.36 (m, 2 H), 3.34 (s, 3 H), 3.93 (d, J=3.32 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.32 (s, 2 H), 4.56 (d, J=7.42 Hz, 2 H), 7.24 - 7.32 (m, 5 H), 7.71 (dd, J=9.08, 2.05 Hz, 1 H), 7.83 (d, J=1.76 Hz, 1 H), 7.99 (d, J=9.18 Hz, 1 H); MS (ESI) $(M+H)^+$ 485.2; Anal. Calcd

for $C_{26}H_{36}N_4O_3S$ + 1.9 TFA + 0.8 H_2O: C, 50.01; H, 5.56; N, 7.83. Found: C, 50.05; H, 5.53; N, 7.86.

Example 8

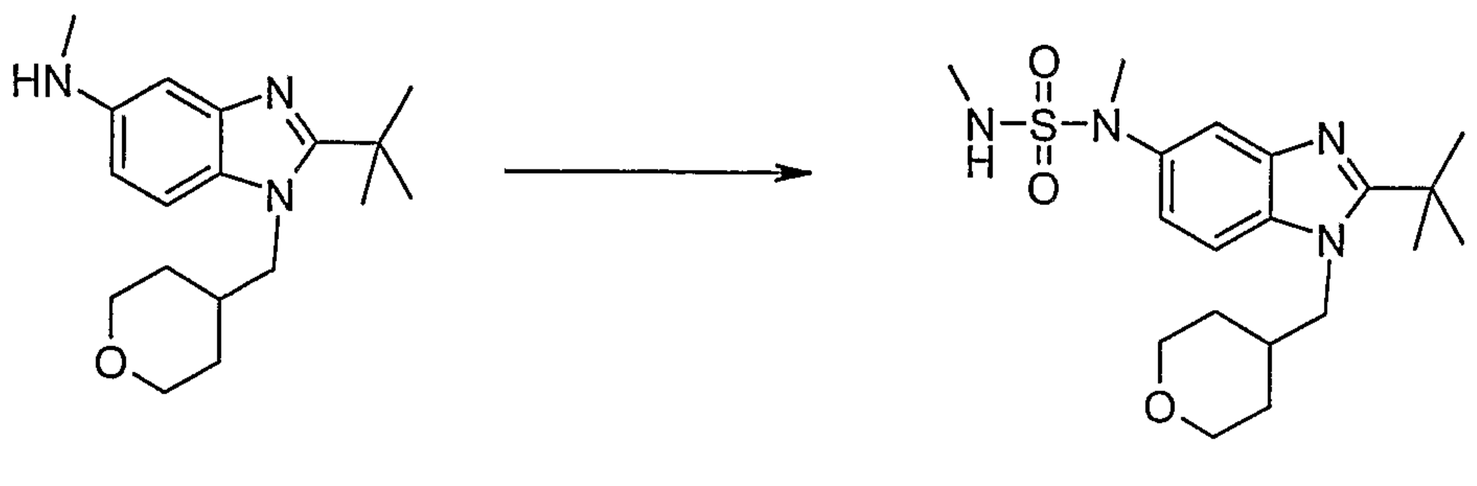
***N'*-Benzyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylsulfamide**



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (50 mg, 0.166 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (60 mg, 0.199 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was concentrated. The residue was dissolved in 3 mL of DMF at 0°C and NaH (60% dispersion in oil) (10 mg, 0.249 mmol) was added followed by benzyl bromide (0.030 mL, 0.249 mmol). The solution was stirred at rt overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 21 mg (22%). ^1H NMR (400 MHz, METHANOL-D_4) δ1.50 - 1.56 (m, 2 H), 1.57 - 1.62 (m, 2 H), 1.67 (s, 9 H), 2.33 - 2.41 (m, 1 H), 3.22 (s, 3 H), 3.34 (m, 2 H), 3.92 (d, J=3.12 Hz, 1 H), 3.95 (d, J=2.34 Hz, 1 H), 4.16 (s, 2 H), 4.51 (d, J=7.62 Hz, 2 H), 7.22 - 7.26 (m, 1 H), 7.27 (s, 3 H), 7.28 (br.s, 1 H), 7.57 (dd, J=8.98, 2.15 Hz, 1 H), 7.71 (d, J=2.15 Hz, 1 H), 7.87 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 471.0.

Example 9

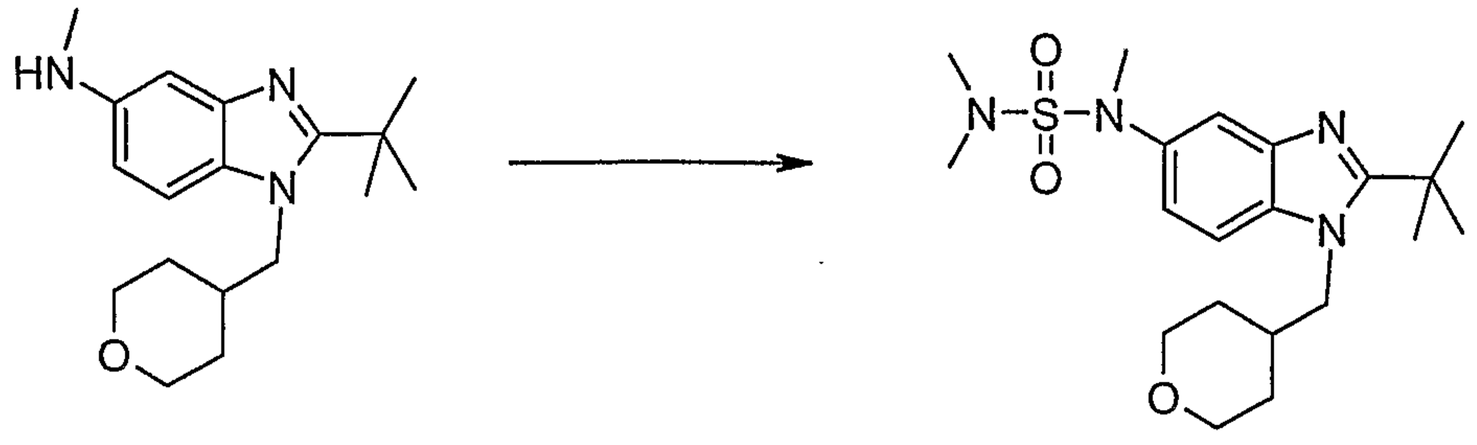
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (40 mg, 0.133 mmol) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (48 mg, 0.160 mmol) were stirred in 3 mL of DCE at 70°C for 1h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was concentrated. The residue was dissolved in 3 mL of DMF at 0°C and NaH (60% dispersion in oil) (8 mg, 0.200 mmol) was added followed by iodomethane (0.012 mL, 0.200 mmol). The solution was stirred at rt for 1h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0°C and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 20 mg (30%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.50 - 1.55 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.34 - 2.41 (m, 1 H), 2.66 (s, 3 H), 3.27 (s, 3 H), 3.34 (m, 2 H), 3.92 (d, J=3.12 Hz, 1 H), 3.95 (d, J=3.71 Hz, 1 H), 4.53 (d, J=7.42 Hz, 2 H), 7.66 (dd, J=8.98, 1.95 Hz, 1 H), 7.78 (d, J=1.76 Hz, 1 H), 7.94 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 395.0; Anal. Calcd for $C_{19}H_{30}N_4O_3S$ + 1.8 TFA + 0.6 H_2O:C, 44.46; H, 5.45; N, 9.18. Found: C, 44.42; H, 5.46; N, 9.31.

Example 10

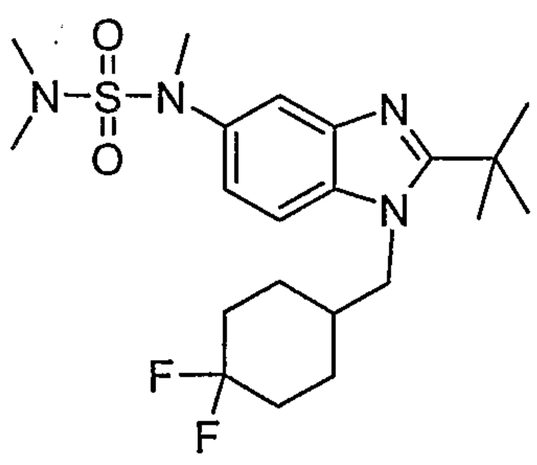
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide



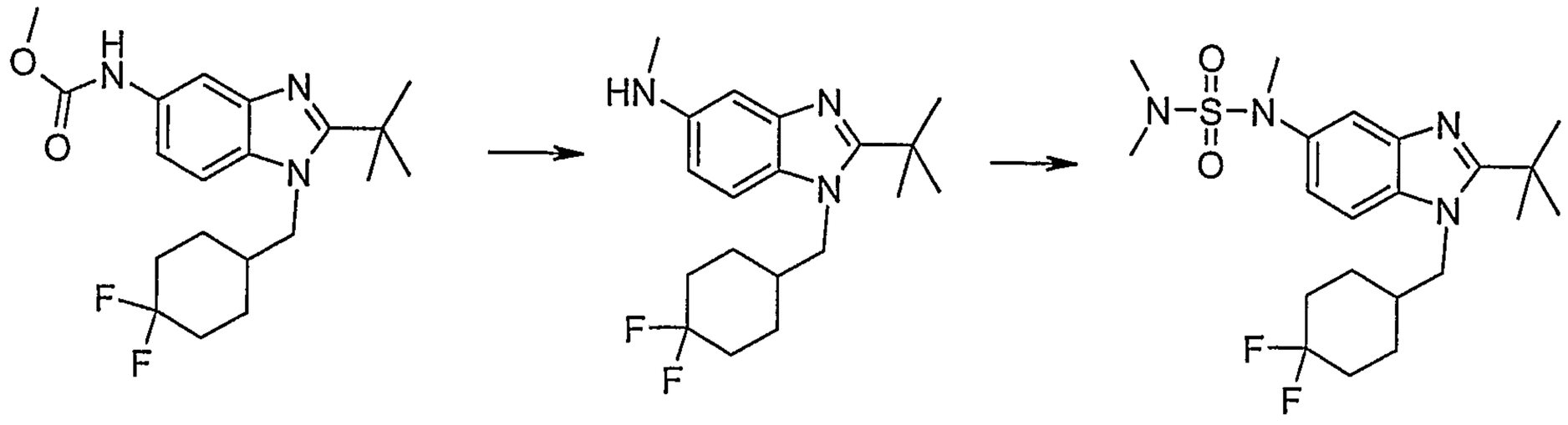
2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (32 mg, 0.106 mmol), DMAP (19 mg, 0.159 mmol) and dimethylsulfamoyl chloride (0.017 mL, 0.159 mmol) were stirred in 2 mL of DCE at 70°C for 3h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 43 mg (78%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.52 - 1.58 (m, 2 H), 1.58 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.44 (m, 1 H), 2.84 (s, 6 H), 3.30 - 3.32 (s, 3 H), 3.36 (m, 2 H), 3.93 (d, J=2.93 Hz, 1 H), 3.96 (d, J=3.91 Hz, 1 H), 4.55 (d, J=7.62 Hz, 2 H), 7.68 (dd, J=9.08, 2.05 Hz, 1 H), 7.81 (d, J=1.76 Hz, 1 H), 7.97 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 409.0; Anal. Calcd for $C_{20}H_{32}N_4O_3S$ + 1.4 TFA + 2.1 H_2O: C, 45.19; H, 6.25; N, 9.24. Found: C, 45.16; H, 6.19; N, 9.19.

Example 11

_N_-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1_H_-benzimidazol-5-yl}-_N_,_N'_,_N'_-trimethylsulfamide

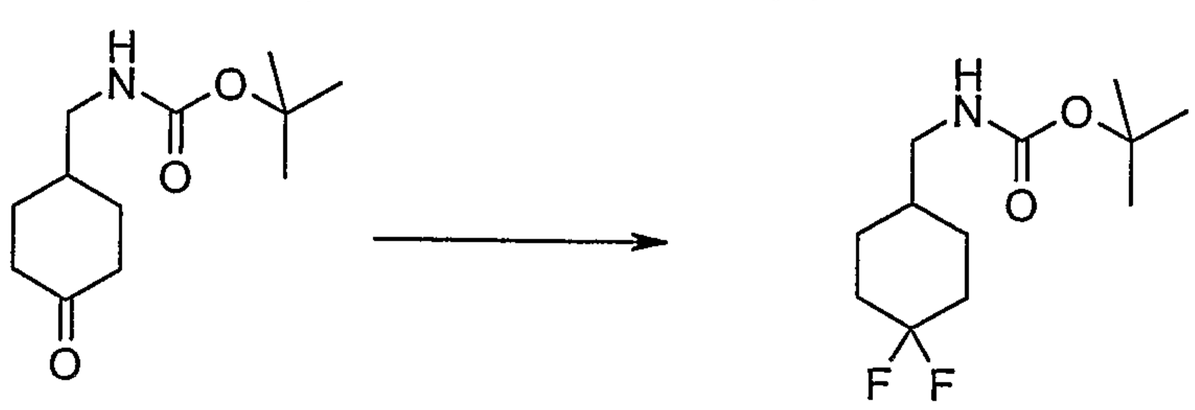


Step A. _N_-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1_H_-benzimidazol-5-yl}-_N_,_N'_,_N'_-trimethylsulfamide



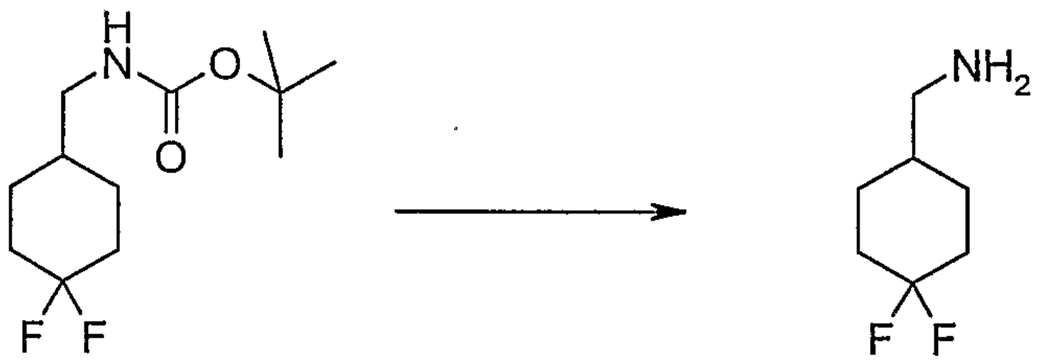
Methyl (3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate (for preparation, see the following steps B, C, D, E and F) (11 mg, 0.0290 mmol) was dissolve in 3 mL of THF at 0°C. 1M HCl/ether (0.040 mL, 0.0406 mmol) was added and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (5 mg, 0.145 mmol) was adde and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (1 mL) and water (1 mL) and then stirred at rt for 30 min. The solution was extracted with EtOAc (2X). The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The product was dissolved in 2 mL of DCE and DMAP (5 mg, 0.0435 mmol) followed by dimethylsulfamoyl chloride (0.005 mL, 0.0435 mmol) were added. The solution was stirred at 70°C for 3h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 5 mg (39%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.54 - 1.63 (m, 2 H), 1.68 (s, 9 H), 1.71 - 1.78 (m, 3 H), 1.78 - 1.85 (m, 1 H), 2.02 - 2.12 (m, 2 H), 2.20 - 2.32 (m, 1 H), 2.84 (s, 6 H), 3.31 (s, 3 H), 4.56 (d, J=7.62 Hz, 2 H), 7.67 (dd, J=8.98, 2.15 Hz, 1 H), 7.81 (d, J=1.56 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); (ESI) $(M+H)^+$ 443.0.

Step B. *tert*-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate



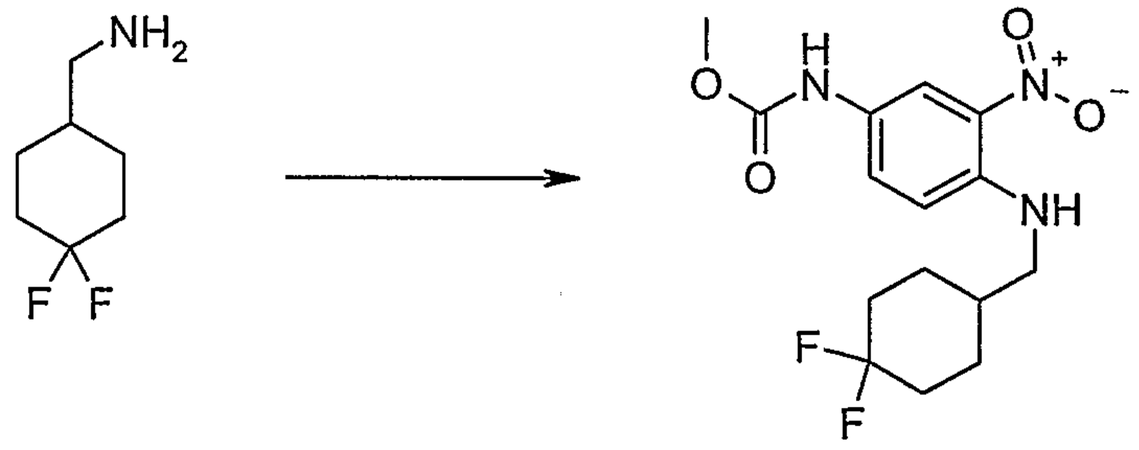
4-N-Boc-aminomethyl cyclohexanone (1.00g, 4.4 mmol) was dissolved in 30 mL of DCM at 0°C. DAST (1.45 mL, 11.0 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 3:1 / hexanes : EtOAc as eluent. Yield: 508mg (46%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.19 - 1.36 (m, 2 H), 1.44 (s, 9 H), 1.51 - 1.56 (m, 1 H), 1.59 - 1.75 (m, 2 H), 1.75 - 1.84 (m, 2 H), 2.01 - 2.16 (m, 2 H), 3.03 (t, *J*=6.54 Hz, 2 H), 4.62 (br.s, 1 H).

Step C. [(4,4-Difluorocyclohexyl)methyl]amine hydrochloride



tert-Butyl [(4,4-difluorocyclohexyl)methyl]carbamate (505 mg, 2.03 mmol) was stirred in 5 mL of 1M HCl/AcOH at rt for 2h. The solvent was evaporated. The residue was washed with ether, filtered and dried. Yield: 330 mg (88%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.28 - 1.40 (m, 2 H), 1.71 - 1.82 (m, 2 H), 1.84 (d, *J*=3.12 Hz, 2 H), 1.86 - 1.89 (m, 1 H), 2.03 - 2.15 (m, 2 H), 2.85 (d, *J*=7.03 Hz, 2 H).

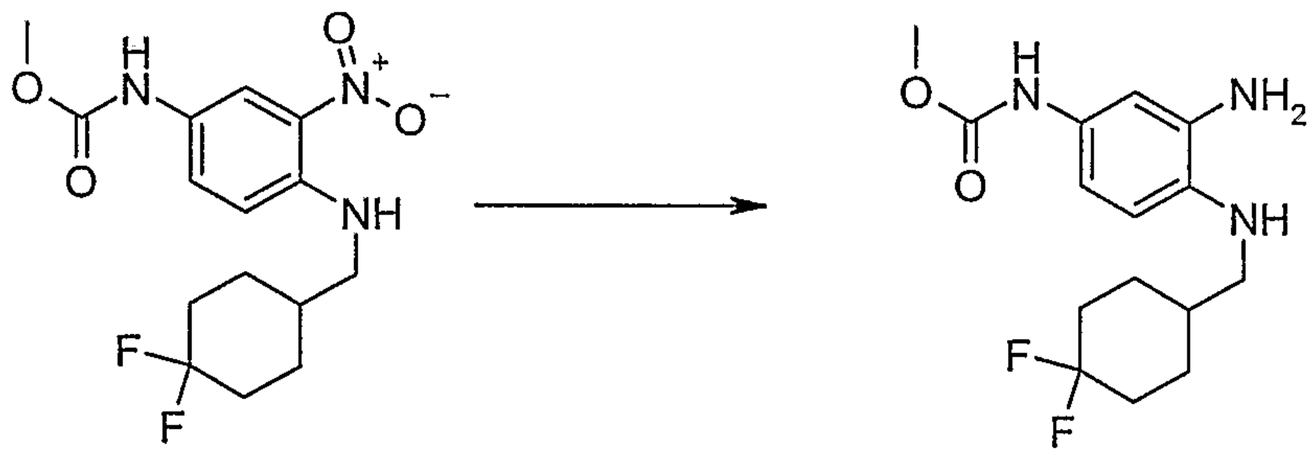
Step D. Methyl (4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate



Following the same procedure as in Step C of Example 1 using [(4,4-difluorocyclohexyl)methyl]amine hydrochloride (210 mg, 1.12 mmol), methyl (4-fluoro-3-nitrophenyl)carbamate (200 mg, 0.934 mmol) and TEA (0.390 mL, 2.80 mmol) in 10 mL of EtOH. The crude product was purified by silica gel flash chromatography using 5% ether/DCM as eluent. Yield: 200 mg (62%). ^{1}H NMR

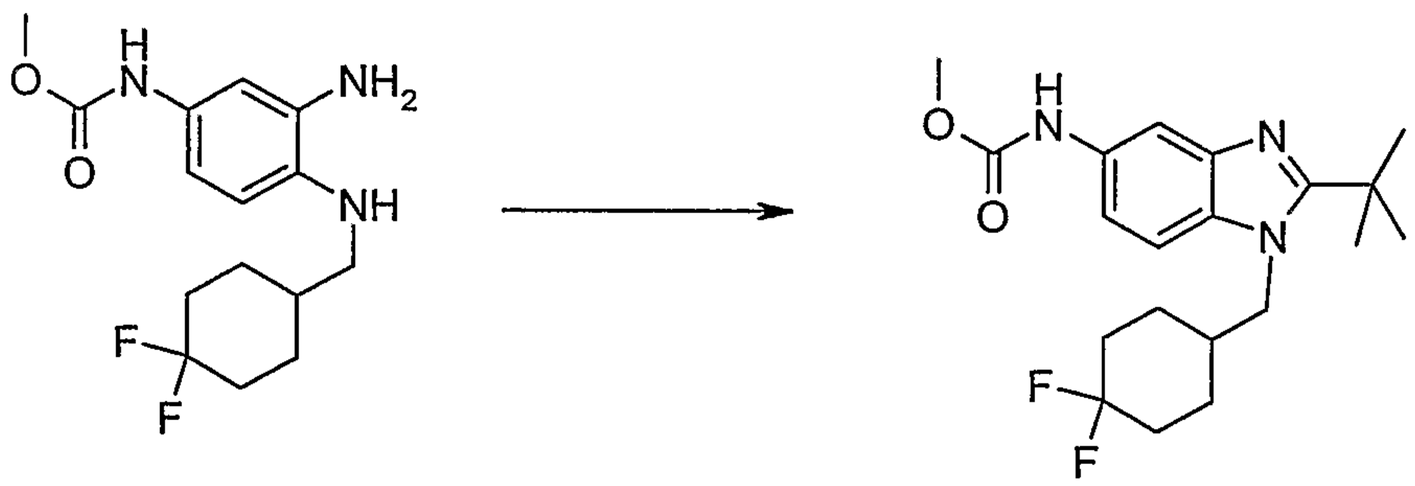
(400 MHz, CHLOROFORM-D) δ 1.34 - 1.47 (m, 2 H), 1.65 - 1.75 (m, 2 H), 1.78 - 1.85 (m, 1 H), 1.90 - 1.93 (m, 1 H), 1.94 - 1.97 (m, 1 H), 2.10 - 2.21 (m, 2 H), 3.23 (dd, *J*=6.64, 5.66 Hz, 2 H), 3.78 (s, 3 H), 6.48 (br.s, 1 H), 6.83 (d, *J*=9.18 Hz, 1 H), 7.66 (br.s, 1 H), 8.05 (br.s, 1 H), 8.07 (d, *J*=2.54 Hz, 1 H).

Step E. Methyl (3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate



Following the same procedure as in Step D of Example 1 using methyl (4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)carbamate (200 mg, 0.583 mmol) and a catalytic amount of 10% Pd/C in 20 mL of EtOAc. Yield: 185 mg (99%). MS (ESI) $(M+H)^+$ 314.29.

Step F. Methyl {2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}carbamate

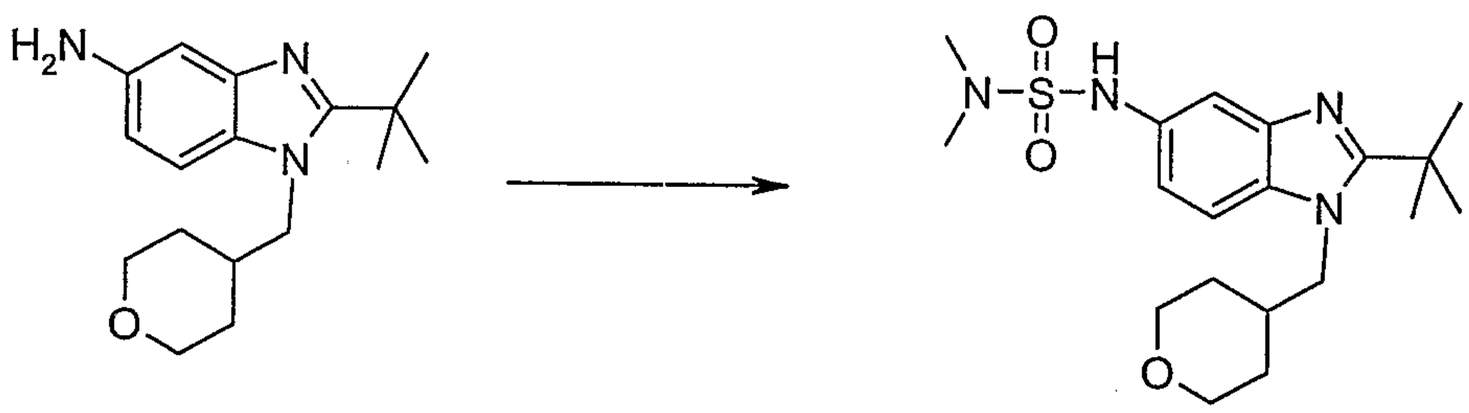


Methyl (3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)carbamate (185 mg, 0.590 mmol) and DMAP (15 mg, 0.118 mmol) were dissolved in 10 mL of DCM. Trimethylacetyl chloride (0.080 mL, 0.649 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated. The residue was dissolved in 4 mL of DCE and P_2O_5 (catalytic) was added and the solution was heated at 125°C for 1h using a Personal Chemistry microwave apparatus.

The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 50 to 75% EtOAc / hexanes. Yield: 122 mg (54%); ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.43 - 1.52 (m, 2 H), 1.55 (s, 9 H), 1.57 - 1.66 (m, 2 H), 1.67 - 1.74 (m, 2 H), 2.08 - 2.18 (m, 3 H), 3.79 (s, 3 H), 4.19 (d, *J*=7.42 Hz, 2 H), 6.63 (br.s, 1 H), 7.23 (d, *J*=8.79 Hz, 1 H), 7.37 - 7.46 (m, 1 H), 7.62 (d, *J*=1.76 Hz, 1 H).

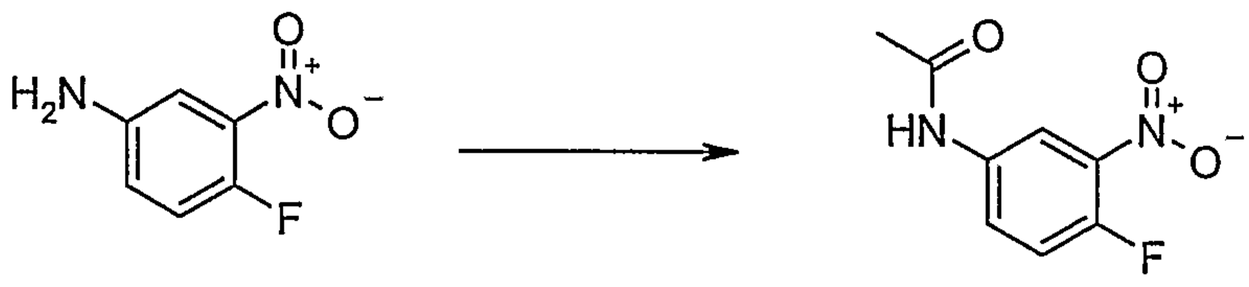
Example 12

Step A: *N'*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*-dimethylsulfamide



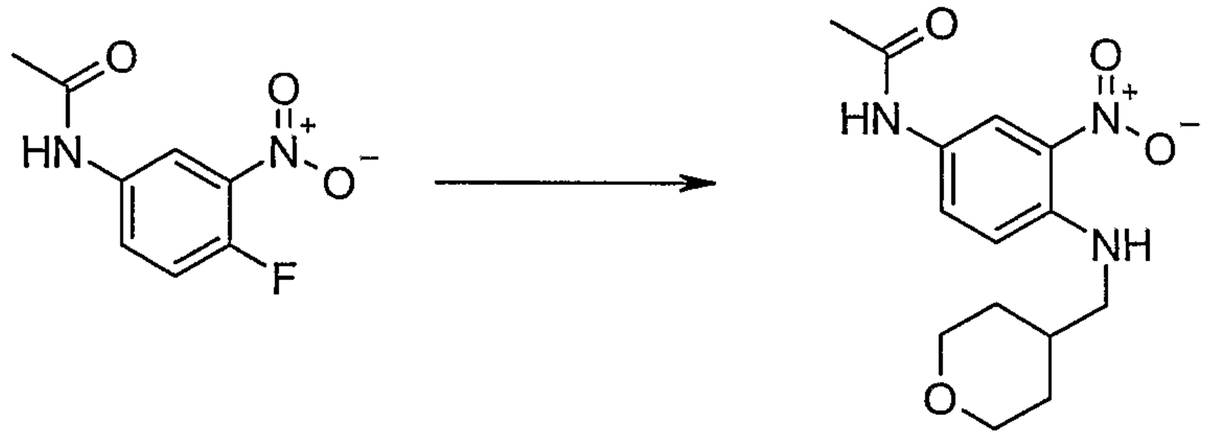
2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (for preparation see following Steps B, C, D, E and F) (30 mg, 0.104 mmol) and DMAP (13 mg, 0.104 mmol) were dissolved in 2 mL of DCE. Dimethylsulfamoyl chloride (0.035 mL, 0.312 mmol) was added and the solution was stirred at 70°C for 3h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 43 mg (81%); ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.50 - 1.55 (m, 2 H), 1.56 - 1.64 (m, 2 H), 1.66 (s, 9 H), 2.32 - 2.40 (m, 1 H), 2.80 (s, 6 H), 3.34 (m, 2 H), 3.92 (d, J=2.93 Hz, 1 H), 3.94 (d, J=3.91 Hz, 1 H), 4.50 (d, J=7.42 Hz, 2 H), 7.36 (dd, J=8.98, 2.15 Hz, 1 H), 7.68 (d, J=1.76 Hz, 1 H), 7.86 (d, J=9.18 Hz, 1 H); MS (ESI) $(M+H)^+$ 395.0; Anal. Calcd for $C_{19}H_{30}N_4O_3S$ + 1.7 TFA + 0.6 H_2O: C, 44.90; H, 5.53; N, 9.50. Found: C, 44.80; H, 5.30; N, 9.87.

Step B. *N*-(4-Fluoro-3-nitrophenyl)acetamide



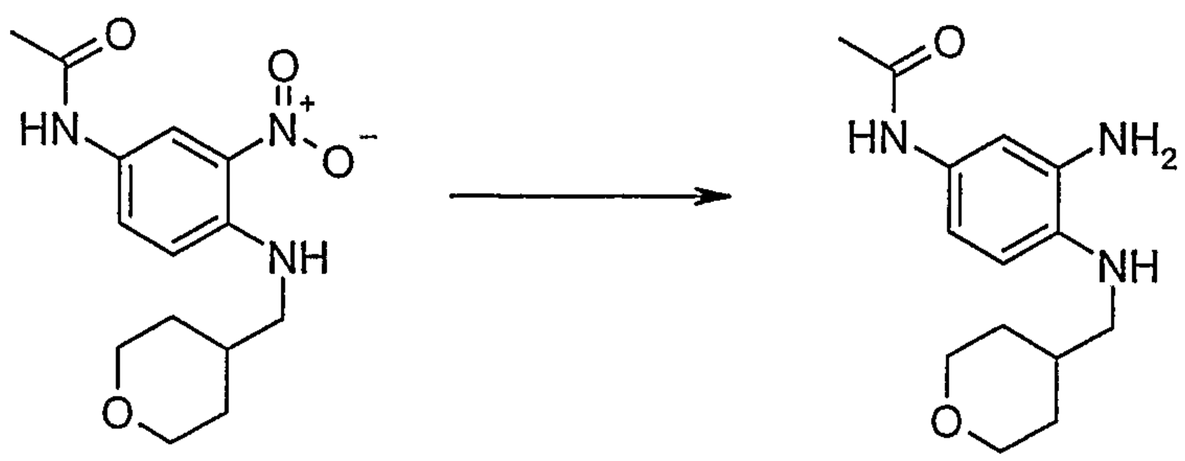
4-Fluoro-3-nitroaniline (5.0g, 32.0 mmol) was dissolved in 50 mL of DCM at 0°C containing TEA (6.7 mL, 48.0 mmol). Acetyl chloride (2.75 mL, 38.4 mmol) was added dropwise and the solution was stirred at rt overnight. The solution was washed with aqueous 5% $KHSO_4$ solution, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was crystallized from DCM. Yield: 5.3g (84%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 2.04 (s, 3 H), 7.51 (dd, J=11.23, 9.08 Hz, 1 H), 7.80 (ddd, J=9.08, 4.00, 2.93 Hz, 1 H), 8.47 (dd, J=7.03, 2.73 Hz, 1 H), 10.38 (s, 1 H).

Step C. *N*-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



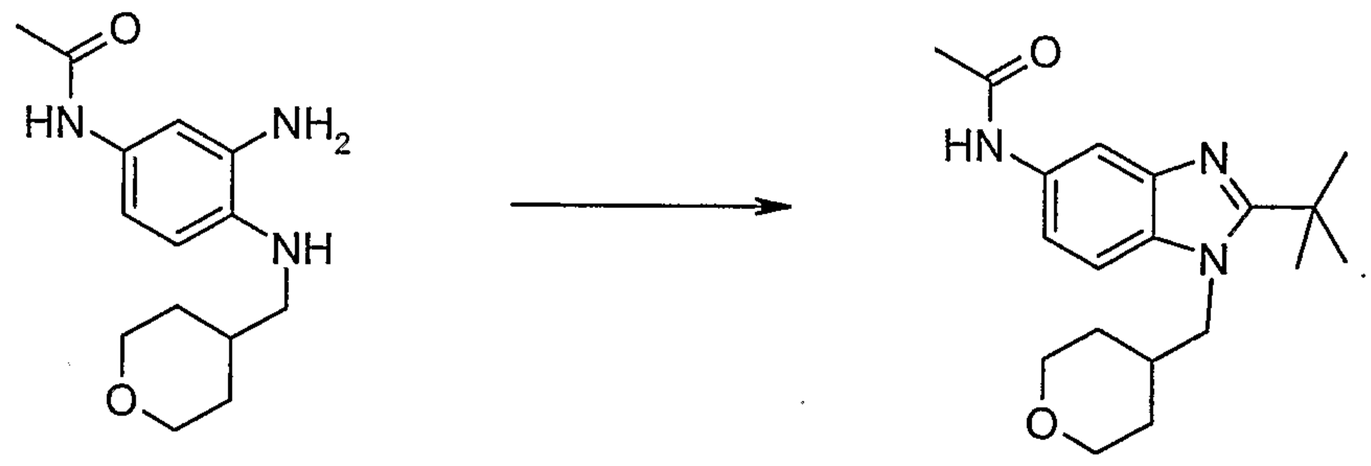
N-(4-Fluoro-3-nitrophenyl)acetamide (500 mg, 2.52 mmol) and 4-aminomethyl tetrahydropyran (350 mg, 3.02 mmol) were stirred in 20 mL of EtOH containing TEA (0.525 mL, 3.78 mmol) at 75°C overnight. The solvent was concentrated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 611 mg (83%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.42 (m, 2 H), 1.74 (m, 2 H), 1.89 – 2.00 (m, 1H), 2.18 (s, 3 H), 3.22 (dd, J=6.44, 5.66 Hz, 2 H), 3.42 (m, 2 H), 4.02 (m, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 – 8.12 (m, 1 H).

Step D. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



N-{3-Nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (605mg, 2.06 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 315mg (58%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.40 (m, 2 H), 1.74 (m, 2 H), 1.82 – 1.91 (m, 1H), 2.13 (s, 3 H), 2.99 (d, J=6.64, 2 H), 3.42 (m, 2 H), 4.02 (m, 2 H), 6.84 (d, J=9.37 Hz, 1 H), 7.20 (br.s, 1 H), 7.81 (dd, J=9.37, 2.54 Hz, 1 H), 8.09 (d, J=2.54 Hz, 1 H), 8.10 – 8.12 (m, 1 H).

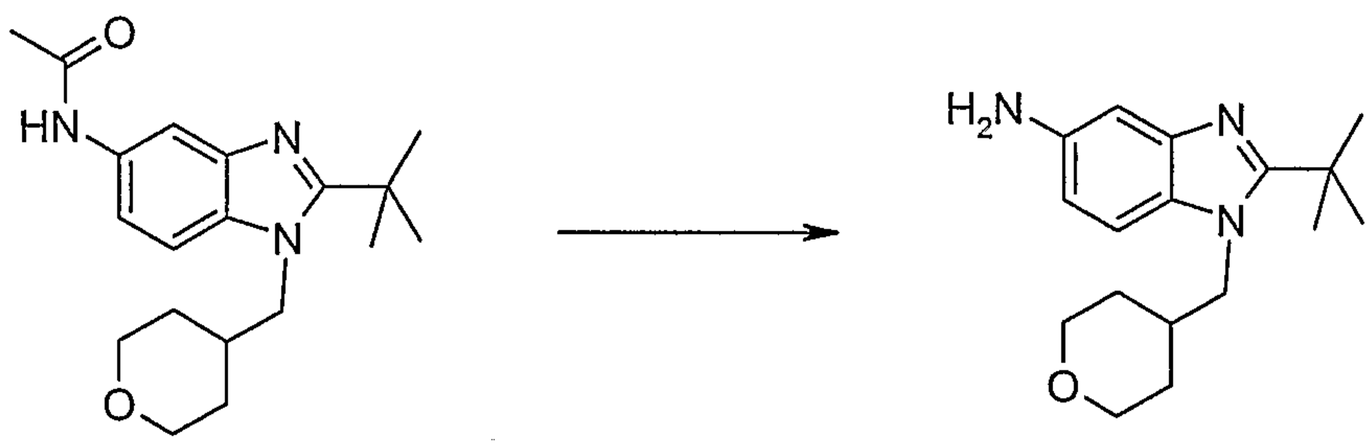
Step E. ***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide**



N-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (315 mg, 1.20 mmol) and DMAP (30 mg, 0.240 mmol) were dissolved in 20 mL of DCM. Trimethylacetyl chloride (0.160 mL, 1.32 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 3 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : acetone as eluent. Yield: 135 mg (34%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.48 –

1.54 (m, 4 H), 1.56 (s, 9 H), 2.20 (s, 3 H), 2.24 – 2.35 (m, 1 H), 3.28 – 3.35 (m, 2 H), 3.96 (t, J= 2.83 Hz, 1 H), 3.99 (t, J= 3.03 Hz, 1 H), 4.19 (d, J=7.42 Hz, 2 H), 7.27 (d, J=8.59 Hz, 1 H), 7.34 (br.s, 1 H), 7.57 (dd, J=8.79, 1.95 Hz, 1 H), 7.67 (d, J=1.95 Hz, 1 H).

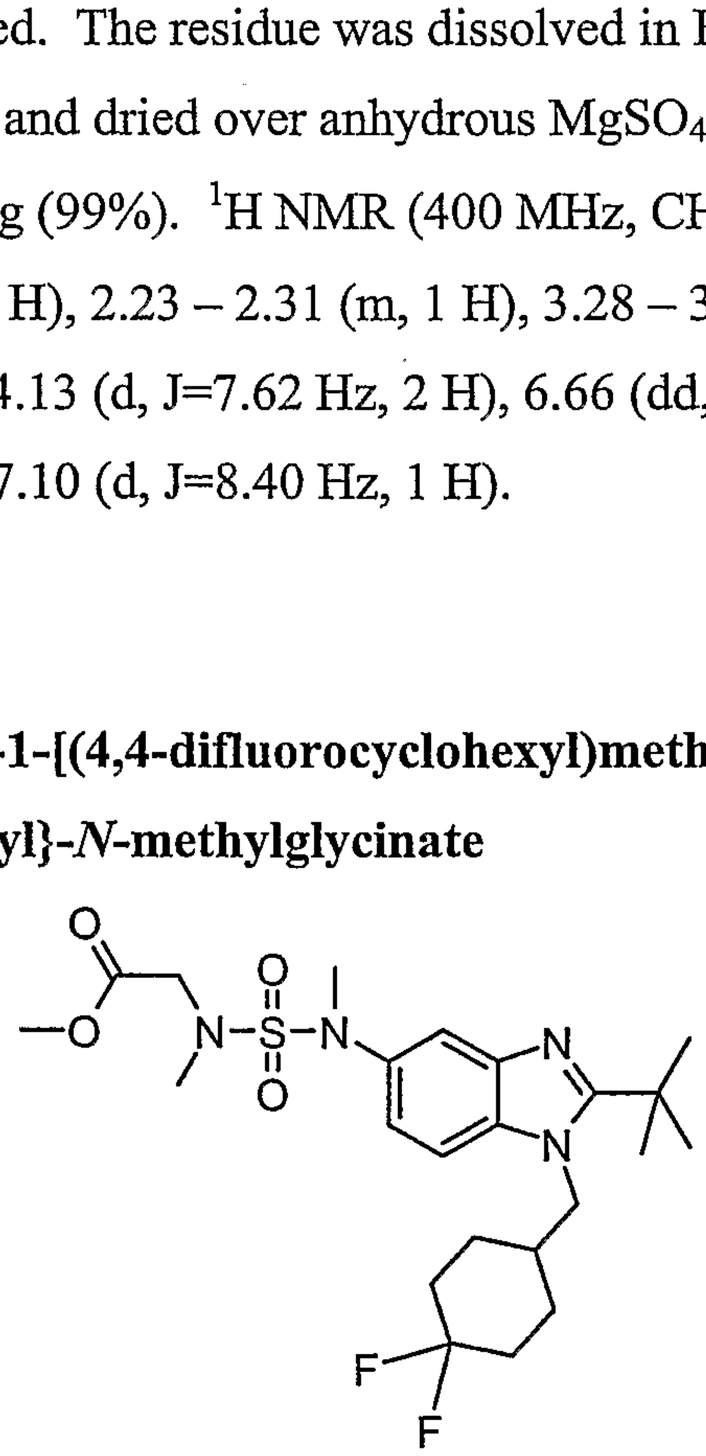
Step F. 2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



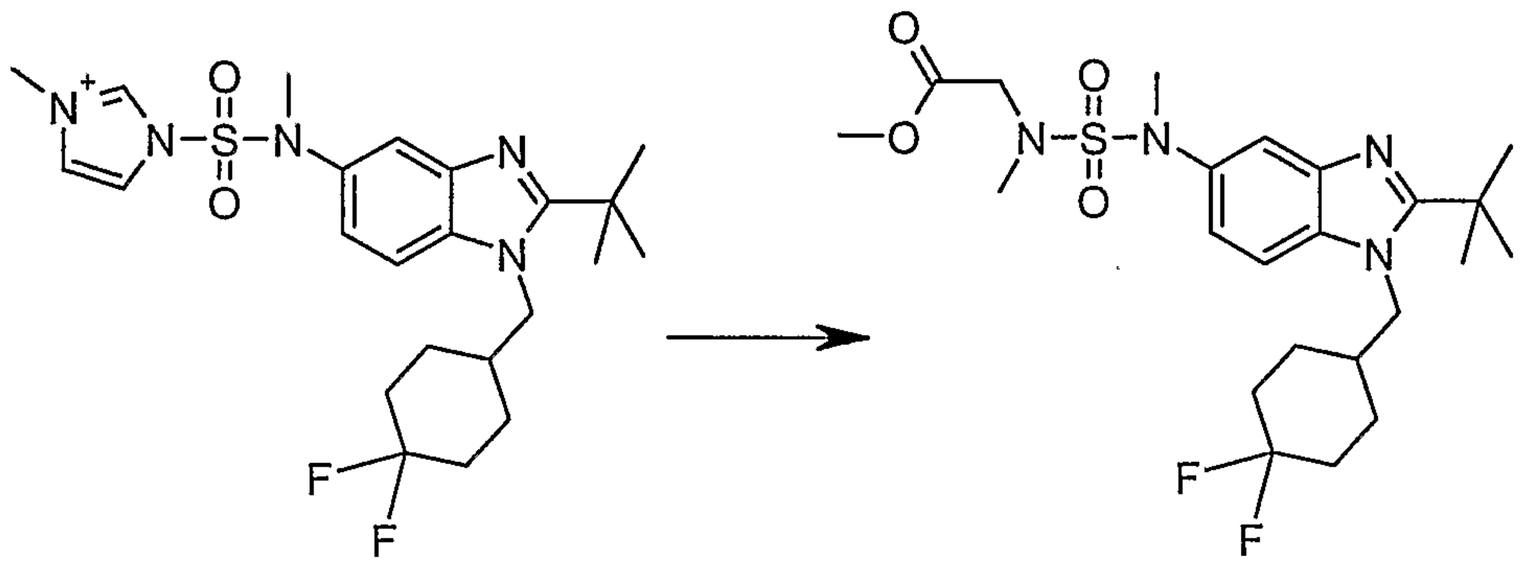
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]acetamide (135 mg, 0.409 mmol) was dissolved in 4 mL of 1:1 / EtOH:2M HCl. The solution was heated at 120°C for 30 min using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with 2M NaOH solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 117 mg (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.47 – 1.52 (m, 4 H), 1.54 (s, 9 H), 2.23 – 2.31 (m, 1 H), 3.28 – 3.36 (m, 2 H), 3.96 (m, 1 H), 3.97 – 4.00 (m, 1 H), 4.13 (d, J=7.62 Hz, 2 H), 6.66 (dd, J=8.40, 2.15 Hz, 1 H), 7.06 (d, J=2.15 Hz, 1 H), 7.10 (d, J=8.40 Hz, 1 H).

Example 13

Methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate

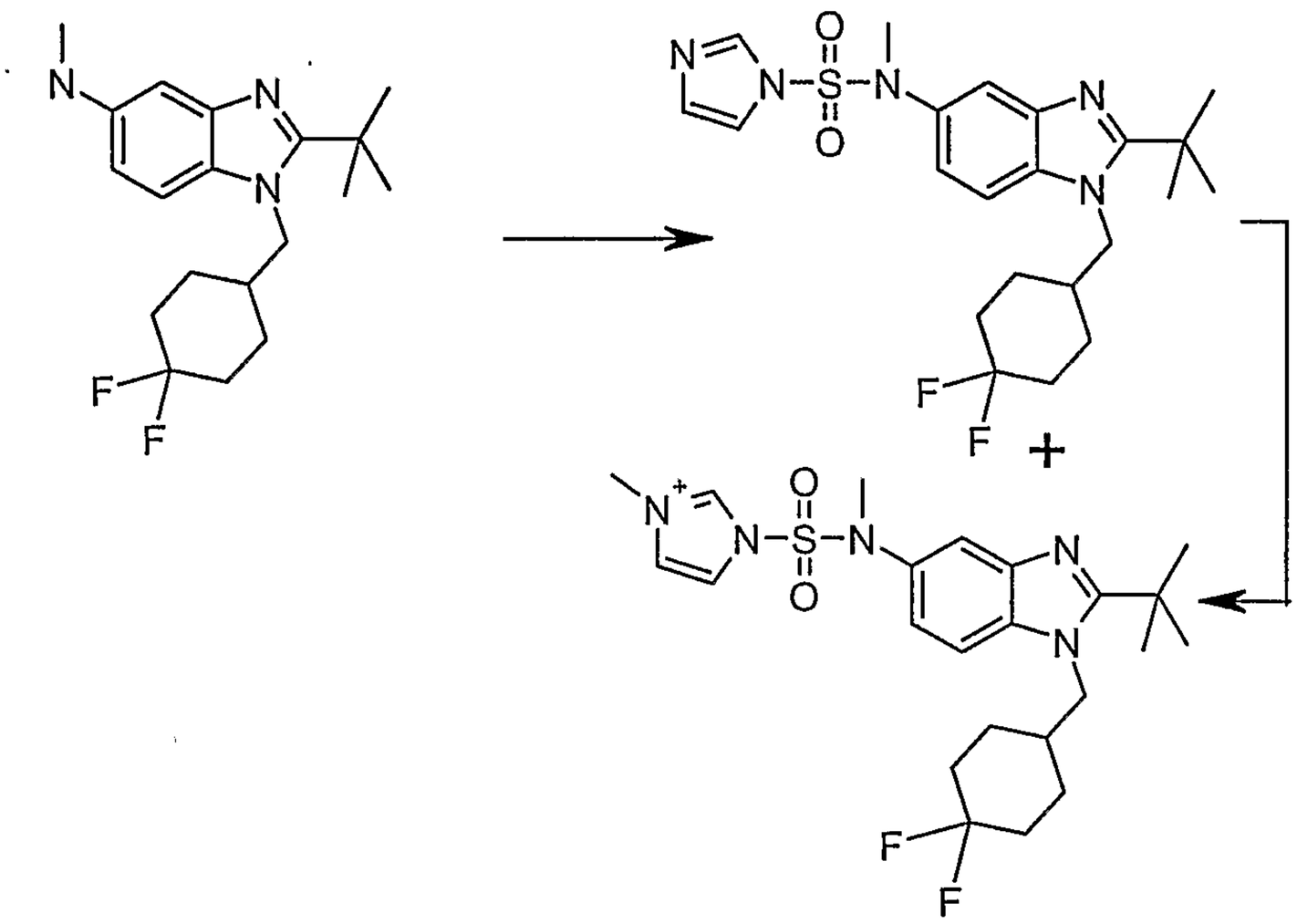


Step A. Methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate



Sarcosine methyl ester hydrochloride (100 mg, 0.71 mmol) and Hunig's base (0.3 mL) were added to a solution of 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (crude product from Step B, 0.3 mmol) in MeCN. The reaction mixture was stirred for 12 hr at r.t., and then concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography to provide methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate (85 mg, 57 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.56 (m, 2H), 1.67 (s, 9H), 1.75 (m, 4H), 2.04 (m, 2H), 2.26 (m, 1H), 2.93 (s, 3H), 3.29 (s, 3H), 3.71 (s, 3H), 4.01 (s, 2H), 4.55 (d, J = 7.4 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.82 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$500.8.

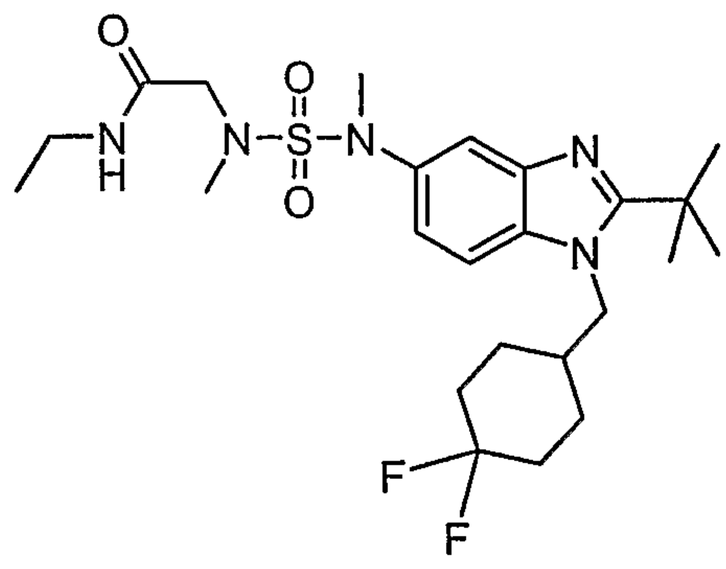
Step B. 1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate



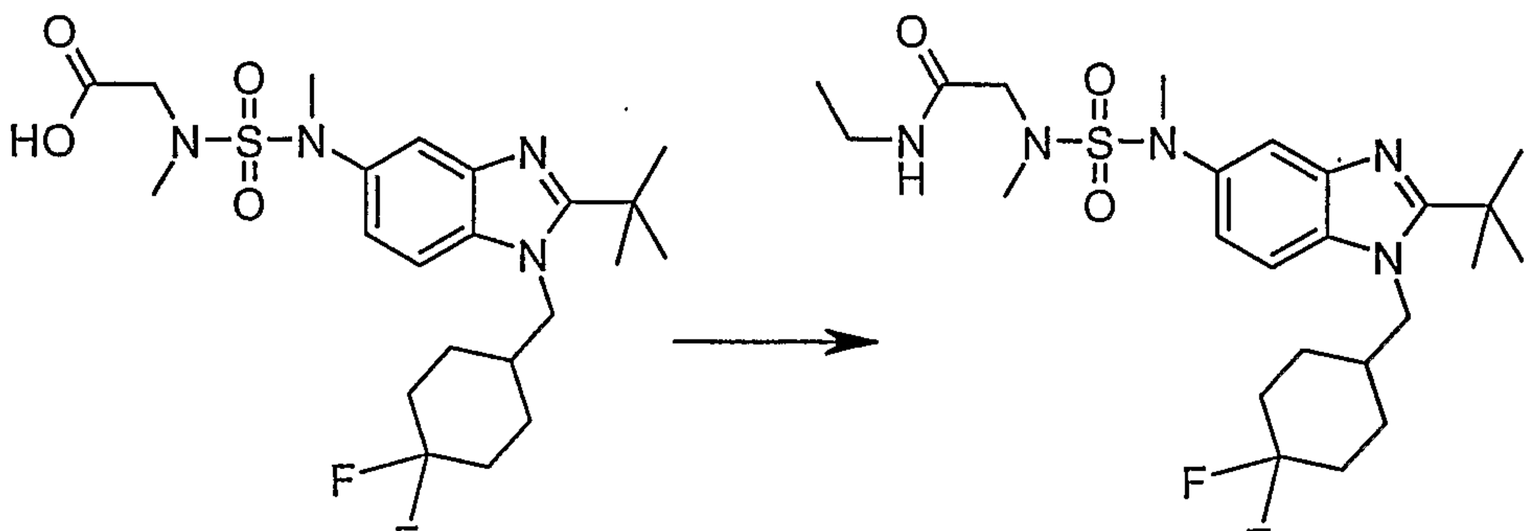
3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium triflate (217 mg; 0.6 mmol) was added into a solution of 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (100 mg, 0.3 mmol) (for preparation, see Example 11) in acetonitrile (10 mL). After being stirred at room temperature for 12 hr, the reaction mixture was treated with methyl trifluoromethanesulfonate (98 mg, 0.6 mmol) at r.t for 2 hr. The resulting MeCN solution of 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate was then used in the Step A directly.

Example 14

N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-ethyl-N^2-methylglycinamide

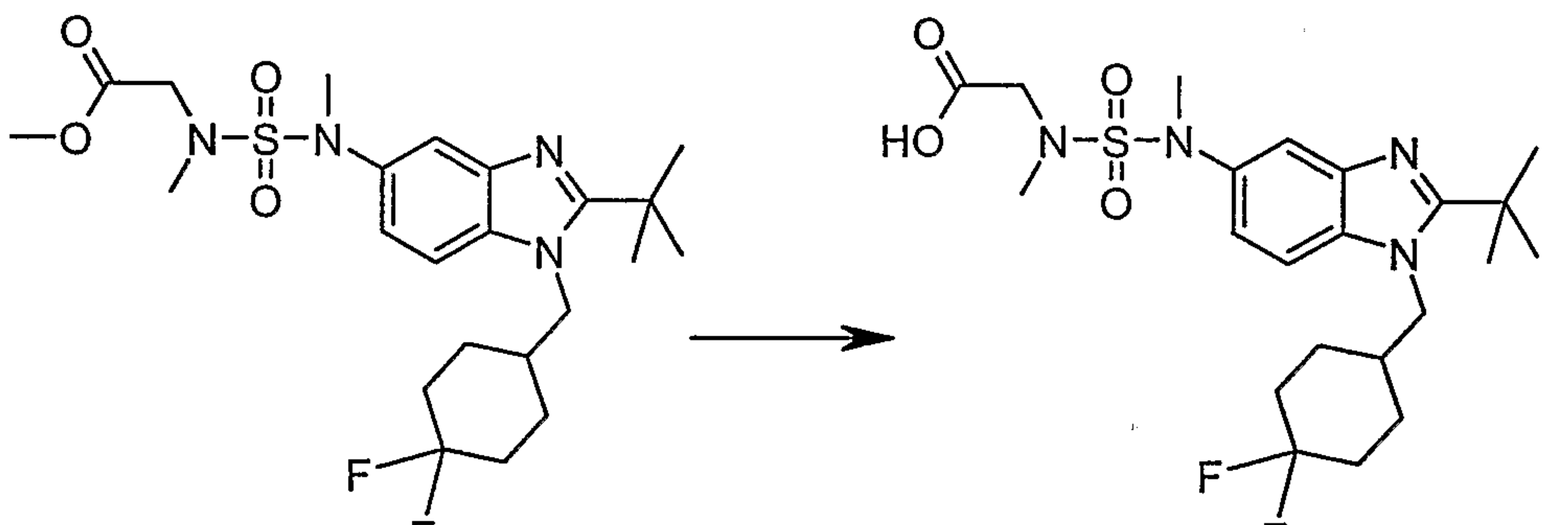


Step A. N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-ethyl-N^2-methylglycinamide



HATU (150 mg, 0.4 mmol) was added to a solution of *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycine (50 mg, 0.10 mmol), ethylamine hydrochloride (81 mg, 1.0 mmol) and DIPEA (0.2 mL) in DMF (1.5 mL) at r.t. After 1 hr, the reaction mixture was condensed to give a residue, which was purified by reverse phase HPLC to provide N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-ethyl-N^2-methylglycinamide (TFA salt, 48 mg, 75%). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.09 (t, J=7.4 Hz, 3H), 1.57 (m, 2H), 1.67 (s, 9H), 1.75 (m, 4H), 2.05 (m, 2H), 2.25 (m, 1H), 2.90 (s, 3H), 3.20 (q, J=7.4 Hz, 2H), 3.32 (s, 3H), 3.80 (s, 2H), 4.54 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.85 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$513.7.

Step B: *N*-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycine

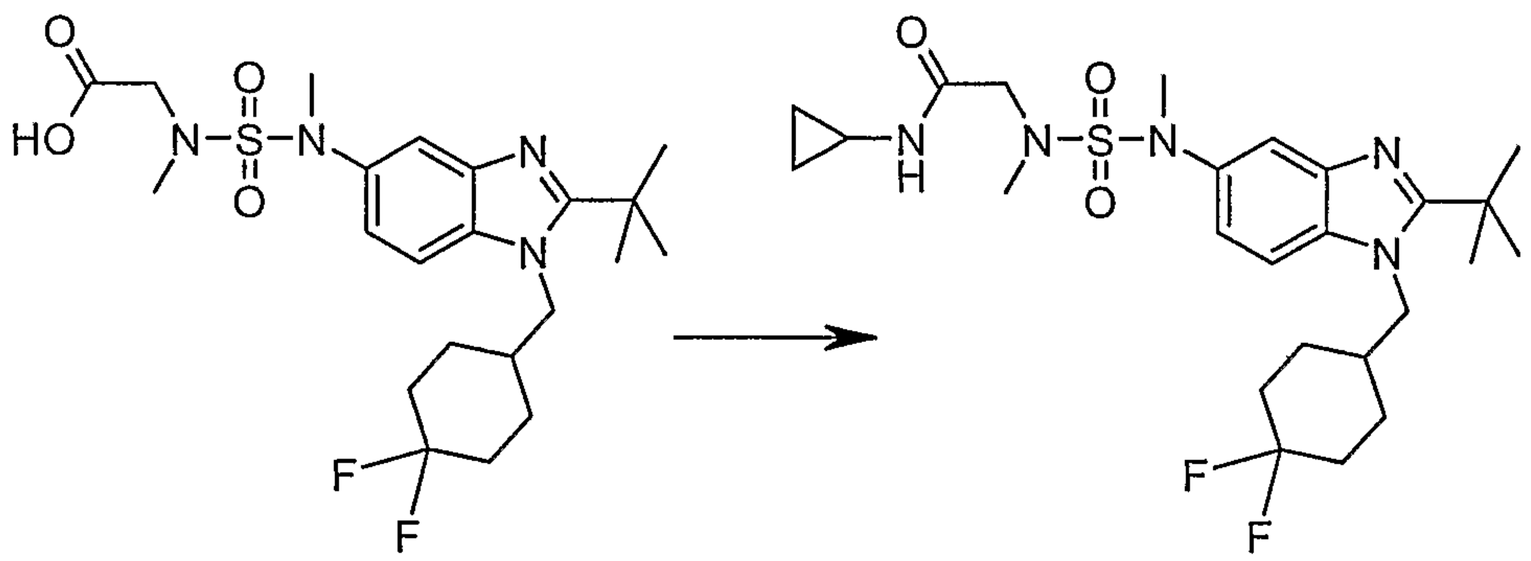


LiOH (120 mg, 5.0 mmol) was added to a solution of methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate (80 mg, 0.16 mmol) in MeOH (6 mL) and H_2O (2 mL) at r.t. The reaction mixture was stirred overnight, and then was neutralized to pH at 7.0 with hydrochloric acid. After removal of MeOH, the residue was extracted by CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Removal of solvents provided *N*-{[{2-*tert*-

butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycine (65 mg, 84 %), which was used in Step A without further purification.

Example 15

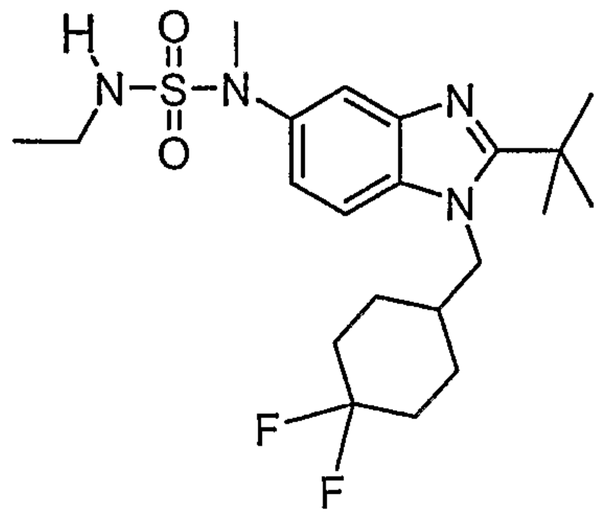
N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-cyclopropyl-N^2-methylglycinamide



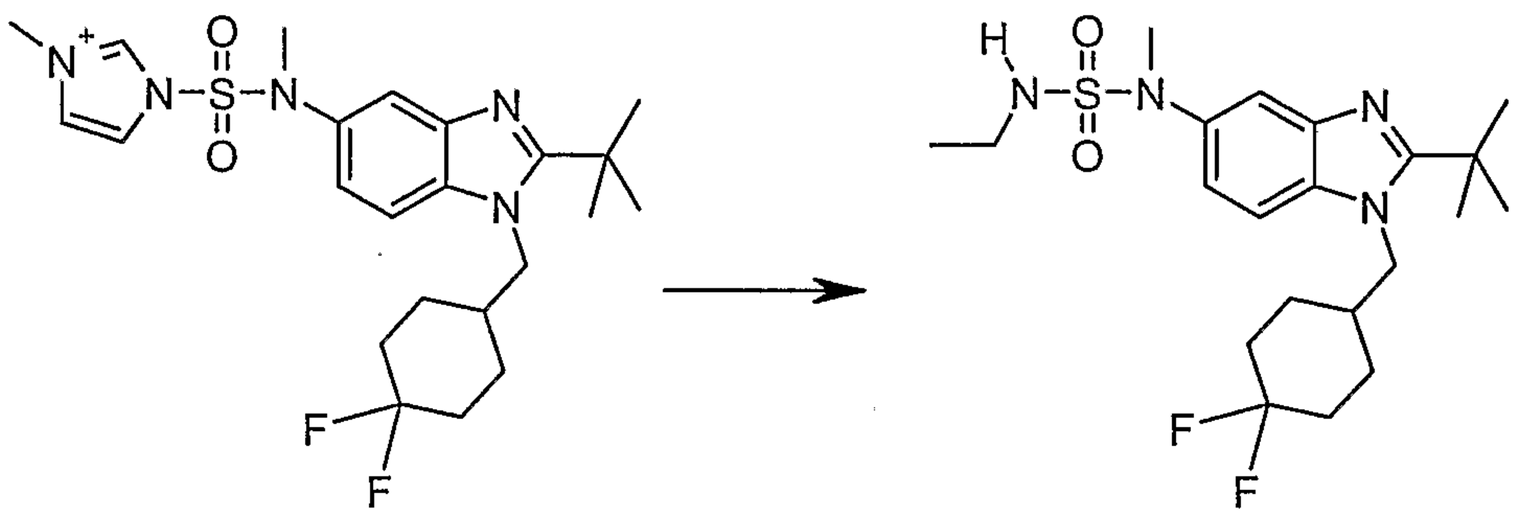
HATU (150 mg, 0.4 mmol) was added to a solution of *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycine (15 mg, 0.03 mmol), cyclopropylamine (57 mg, 1.0 mmol) and DIPEA (0.2 mL) in DMF (1.0 mL) at r.t. After 1 hr, the reaction mixture was condensed to give a residue, which was purified by reverse phase HPLC to provide N^2-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-cyclopropyl-N^2-methylglycinamide (TFA salt, 6 mg, 31 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 0.46 (m, 2H), 0.70 (m, 2H), 1.59 (m, 2H), 1.67 (s, 9H), 1.75 (m, 4H), 2.05 (m, 2H), 2.25 (m, 1H), 2.64 (m, 1H), 2.89 (s, 3H), 3.32 (s, 3H), 3.80 (s, 2H), 4.54 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 9.0 Hz, 1H), 7.86 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$525.8.

Example 16

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N'*-ethyl-*N*-methylsulfamide**

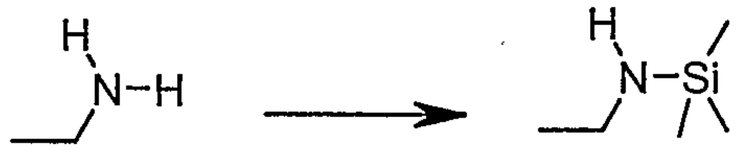


Step A. *N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N'*-ethyl-*N*-methylsulfamide



N-Ethyl-1,1,1-trimethylsilanamine (from Step B, 1.0 mmol) and Hunig's base (0.3 mL) were added to the solution of 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (64 mg, 0.1 mmol) in MeCN. The reaction mixture was stirred for 12 hr at r.t., and then concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N'*-ethyl-*N*-methylsulfamide (4 mg, 7 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.13 (t, J=7.2 Hz, 3H), 1.55 (m, 2H), 1.67 (s, 9H), 1.75 (m, 4H), 2.05 (m, 2H), 2.25 (m, 1H),3.04 (q, J=7.2 Hz, 2H), 3.33 (s, 3H), 4.55 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.78 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$443.0.

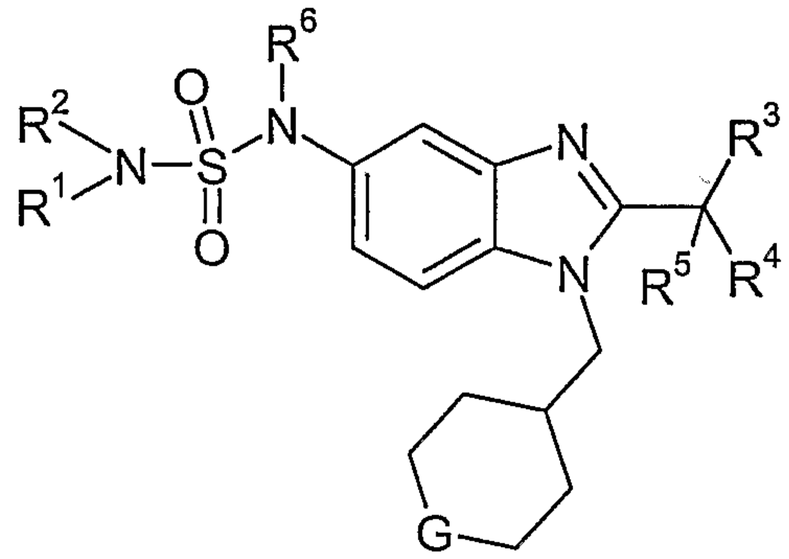
Step B: *N*-Ethyl-1,1,1-trimethylsilanamine



Trimethylsilyl chloride (109 mg, 1.0 mmol) was added to a solution of ethylamine (45 mg, 1.0 mmol) and Hunig's base (0.3 mL) in THF at 0^0C. The reaction mixture was stirred for 1 hr at r.t., and was used in Step A directly.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

R^1 and R^2 are each independently –H, C_{3-6}cycloalkyl, and C_{1-6}alkyl, wherein said C_{3-6}cycloalkyl and C_{1-6}alkyl used in defining R^1 and R^2 is optionally substituted by C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{6-10}aryl, -C(=O)-)R^7, C(=O)-NHR^7, wherein R^7 is selected from C_{1-6}alkyl and C_{3-6}cycloalkyl;

G is selected from $–CH_2$-, -O-, -CHF-, and $-CF_2$-;

R^6 is selected from –H and methyl and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

2. A compound as claimed in claim 1, wherein

R^1 and R^2 are each independently C_{1-4}alkyl.

3. A compound as claimed in claim 1, wherein

R^1 and R^2 are independently selected from –H, methyl, ethyl, 2-methoxylethyl, benzyl, cyclopropylmethyl, isopropyl, butyl, isobutyl and propyl with a proviso that R^1 and R^2 are not both -H.

4. A compound as claimed in claim 1, wherein

G is selected from -O-, -CHF-, and $-CF_2$-.

5. A compound as claimed in claim 1, wherein

G is selected from -CHF- and $-CF_2$-.

6. A compound selected from:

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide;

N-[2-*tert*-Butyl-1-(cyclohexylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-diethyl-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-diethyl-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*',*N*'-bis(2-methoxyethyl)-*N*-methylsulfamide;

N-Butyl-*N*'-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*'-(cyclopropylmethyl)-*N*,*N*'-dimethylsulfamide;

N-Benzyl-*N*'-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N'-Benzyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*'-dimethylsulfamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*',*N*'-trimethylsulfamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*,*N*',*N*'-trimethylsulfamide;

N'-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*,*N*-dimethylsulfamide;

Methyl *N*-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylglycinate;

N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-ethyl-N^2-methylglycinamide;

N^2-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-N^1-cyclopropyl-N^2-methylglycinamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N'*-ethyl-*N*-methylsulfamide; and pharmaceutically acceptable salts thereof.

7. A compound according to any one of claims 1-6 for use as a medicament.

8. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the therapy of pain.

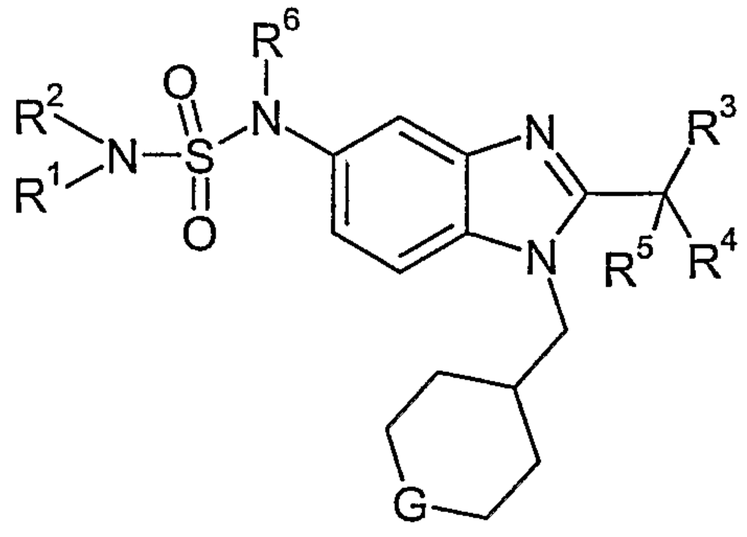
9. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of anxiety disorders.

10. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-6 and a pharmaceutically acceptable carrier.

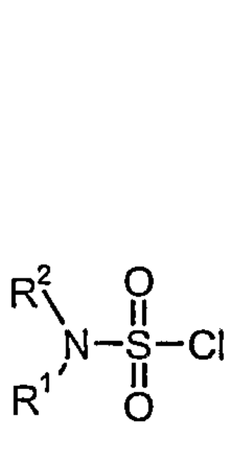
12. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-6.

13. A method for preparing a compound of Formula I, comprising:

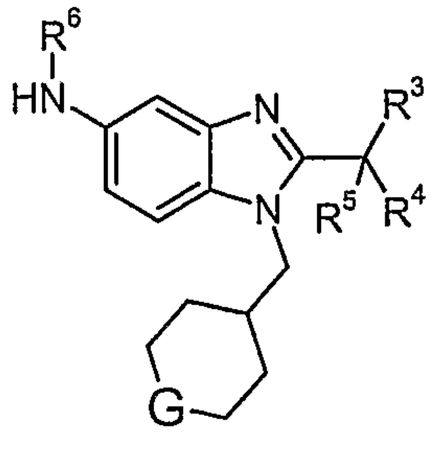


I

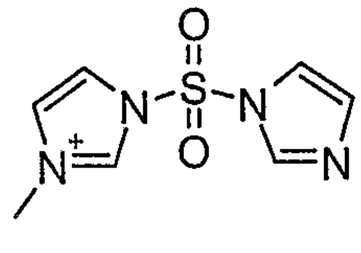
reacting a compound of Formula II with a compound of formula III,



II



III



IV

alternatively, reacting a compound of formula III with compound IV followed by reacting with TMSOTf and $R^2(R^1)NH$.

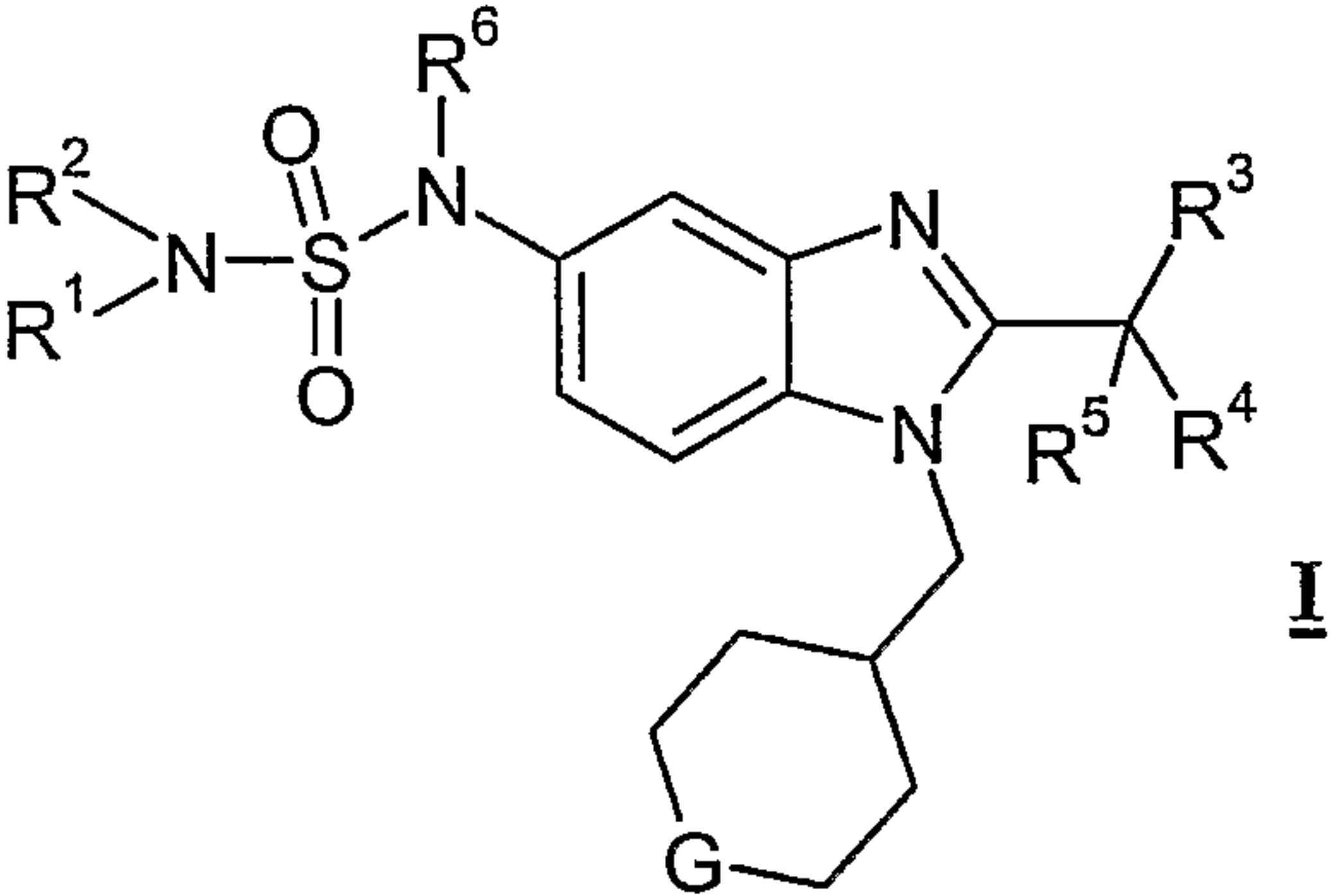
wherein

R^1 and R^2 are each independently –H, C_{3-6}cycloalkyl, and C_{1-6}alkyl, wherein said C_{3-6}cycloalkyl and C_{1-6}alkyl used in defining R^1 and R^2 is optionally substituted by C_{1-6}alkoxy, C_{3-6}cycloalkyl, C_{6-10}aryl, -C(=O)-)R^7, C(=O)-NHR^7, wherein R^7 is selected from C_{1-6}alkyl and C_{3-6}cycloalkyl;

G is selected from –CH_2-, -O-, -CHF-, and -CF_2-;

R^6 is selected from –H and methyl and

R^3, R^4 and R^5 are independently selected from fluoro and methyl..



I