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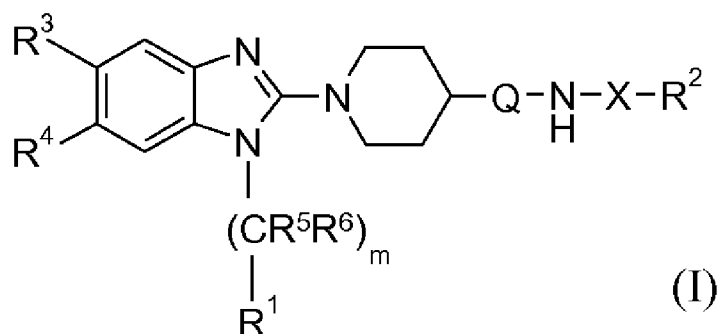
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(54) Title: MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (MPGES1) INHIBITORS



(57) Abstract: A compound of formula (I): as well as pharmaceutically acceptable salts thereof, and a pharmaceutical composition comprising the compound. The compound is useful for the treatment of disorder selected from inflammatory diseases, nociceptive pain, auto-immune disease, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular diseases.

MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (MPGES1) INHIBITORSFIELD OF THE INVENTION

The present invention relates to piperidinyl benzoimidazole derivatives and to the use thereof in disease therapy. Particularly, the present invention relates to compounds useful in the treatment or prevention of diseases in which inhibition of the activity of microsomal prostaglandin E synthase-1 (accession number "O14684" at <http://www.uniprot.org/>) is desired and/or required and, more particularly, in the treatment of diseases such as inflammatory diseases, nociceptive pain, auto-immune disease, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular disease.

BACKGROUND OF THE INVENTION

The following is provided as background information only and represents the current state-of-art in the scientific literature. Furthermore, this background information should not be taken as an admission that any subject matter discussed or that any reference mentioned is prior art to the instant invention.

Prostaglandin (PG) E₂ is produced in a sequential action including liberation of arachidonic acid, conversion into PGG₂/PGH₂ by cyclooxygenase (Cox) -1 or Cox-2, and finally prostaglandin E synthase converts PGH₂ into PGE₂. There exist three known enzymes that catalyze the latter reaction, i.e. microsomal prostaglandin E synthase-1 (mPGEs-1), cytosolic prostaglandin E synthase (cPGEs), and microsomal prostaglandin E synthase-2 (mPGEs-2). The latter two enzymes are constitutively expressed whereas mPGEs-1 is inducible. Initially, mPGEs-1 was regarded as the enzyme predominantly coupled with Cox-2 activity. However; later results demonstrate that mPGEs-1 can also catalyze the conversion of Cox-1 derived PGH₂ into PGE₂. mPGEs-1 possesses the highest catalytic efficiency of the known PGE synthases. The role of PGE₂ as one of the most potent mediators of inflammation together with many *in vitro* reports on the presence of mPGEs-1 in different models of inflammation suggested this enzyme to be an attractive drug target for development of new anti inflammatory drugs with fewer side effects than the currently available NSAIDs and selective Cox-2 inhibitors [Samuelsson, B.; Morgenstern, R.; Jakobsson, P.-J. Membrane Prostaglandin E Synthase-1: A Novel Therapeutic Target. *Pharmacol. Rev.* **2007**, 59,207-224; Jachak, S. M. PGE synthase inhibitors as an alternative to COX-2 inhibitors. *Curr. Opin. Investig. Drugs*, **2007**, 8, 411-415]. The rationale is that mPGEs-1 is predominantly expressed during inflammation and that other enzymes exist as mediating "house keeping functions".

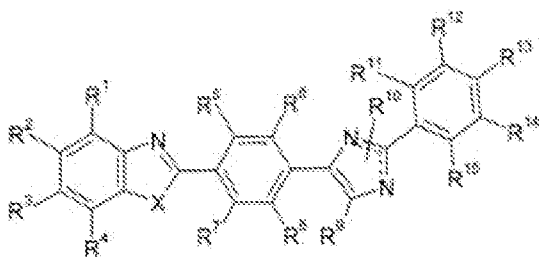
Furthermore, mPGEs-1-derived PGE₂ has been implicated in a range of diseases, not confined to inflammation, and it is suggested that inhibitors of mPGEs-1 are effective for the treatment or prevention of these diseases also. Consequently, examples of treatable diseases of the invention include inflammatory diseases, nociceptive pain, auto-immune disease, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular disease. More specifically, non-limiting examples of these diseases include the treatment or prevention of rheumatoid arthritis [Murakami, M.; Nakashima, K.; Kamei, D.; Masuda, S.; Ishikawa, Y.; Ishii, T.; Ohmiya, Y.; Watanabe, K.; Kudo, I. Cellular prostaglandin E₂ production by membrane-bound prostaglandin E synthase-2 via both cyclooxygenases-1 and -2. *J. Biol. Chem.* **2003**, 278, 37937–37947; Westman, M.; Korotkova, M.; af Klint, E.; Stark, A.; Audoly, L. P.; Klareskog, L.; Ulfgren, A. K.; Jakobsson, P. J. Expression of microsomal prostaglandin E synthase 1 in rheumatoid arthritis synovium. *Arthritis Rheum.* **2004**, 50, 1774–1780] or other inflammatory diseases related to arthritis [Kojima, F.; Kato, S.; Kawai, S. Prostaglandin E synthase in the pathophysiology of arthritis. *Fundam. Clin. Pharmacol.* **2005**, 19, 255–261; Fahmi, H. mPGEs-1 as a novel target for arthritis. *Curr. Opin. Rheumatol.* **2004**, 16, 623–627] inflammatory bowel disease [Dey, I.; Giembycz, M. A.; Chadee, K. Prostaglandin E(2) couples through EP(4) prostanoid receptors to induce IL-8 production in human colonic epithelial cell lines. *Br. J. Pharmacol.* **2009**, 156, 475–85], osteoarthritis [Kojima, F.; Naraba, H.; Miyamoto, S.; Beppu, M.; Aoki H, and Kawai S (2004) Membraneassociated prostaglandin E synthase-1 is upregulated by proinflammatory cyto-kines in chondrocytes from patients with osteoarthritis. *Arthritis Res. Ther.* **2004**, R355–R365; Masuko-Hongo, K.; Berenbaum, F.; Humbert, L.; Salvat, C.; Goldring, M. B.; Thirion, S. Up-regulation of microsomal prostaglandin E synthase 1 in osteoarthritic human cartilage: critical roles of the ERK-1/2 and p38 signaling pathways. *Arthritis Rheum.* **2004**, 50, 2829–2838], dermatitis including psoriasis [Stark, K.; Törmä, H.; Oliw, E. H. Co-localization of COX-2, CYP4F8, and mPGEs-1 in epidermis with prominent expression of CYP4F8 mRNA in psoriatic lesions. *Prostaglandins Other Lipid Mediat.* **2006**, 79, 114–125] and eczema, swelling, inflammatory pain [Trebino, C. E.; Stock, J. L.; Gibbons, C. P.; Naiman, B. M.; Wachtmann, T. S.; Umland, J. P.; Pandher, K.; Lapointe, J. M.; Saha, S.; Roach, M. L., Carter, D.; Thomas, N. A.; Durtschi, B. A.; McNeish, J. D.; Hambor, J. E.; Jakobsson, P. J.; Carty, T. J.; Perez, J. R.; Audoly, L. P. Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. *Proc. Natl. Acad. Sci. USA*, **2004**, 100, 9044–9049], post-operative pain [Shavit, Y.; Fridel, K.; Beilin, B. Postoperative pain management and proinflammatory cytokines: animal and human studies. *J. Neuroimmune Pharmacol.* **2006**, 443–451], fibromyalgia, dysmenorrhea [Proctor, M.; Farquhar, C. Dysmenorrhoea. *Clin. Evid.*, **2002**,

7,1639-1653], migraine, arthrotic and arthritic pain [Schaible, H. G.; Ebersberger, A.; von Banchet, G. S. Mechanisms of pain in arthritis. *Ann. N Y Acad. Sci.* **2002**, 966, 343-354], pain in connection with osteoarthritis, cephalgia (headache) [Wienecke, T.; Olesen, J.; Oturai, P. S.; Ashina, M. Prostaglandin E2 (PGE2) induces headache in healthy subjects. *Cephalalgia*, **2009**, 29, 509-519], pain due to gall-stones, pain due to metastasis, familial adenomatous polyposis (FAP) condition [Takeda, H.; Sonoshita, M.; Oshima, H.; Sugihara, K.; Chulada, P. C.; Langenbach, R.; Oshima, M.; Taketo, M. M. Cooperation of cyclooxygenase 1 and cyclooxygenase 2 in intestinal polyposis. *Cancer Res.* **2003**, 63, 4872-4877], colorectal cancer [Kamei, D.; Murakami, M.; Nakatani, Y.; Ishikawa, Y.; Ishii, T.; Kudo, I. Potential role of microsomal prostaglandin E synthase-1 in tumorigenesis. *J. Biol. Chem.*, **2003**, 278, 19396-19405; Yoshimatsu, K.; Golijanin, D.; Paty, P. B.; Soslow, R. A.; Jakobsson, P.-J.; DeLellis, R. A.; Subbaramaiah, K.; Dannenberg, A. J. Inducible microsomal prostaglandin E synthase is overexpressed in colorectal adenomas and cancer. *Clin. Cancer Res.* **2001**, 7, 3971-3976; Elander, N.; Ungerback, J.; Olsson, H.; Uematsu, S.; Akira, S.; Söderkvist, P. Genetic deletion of mPGEs-1 accelerates intestinal tumorigenesis in APC(Min/+) mice. *Biochem. Biophys. Res. Commun.* **2008**, 372, 249-253], epithelial ovarian cancer [Rask, K.; Zhu, Y.; Wang, W.; Hedin, L.; Sundfeldt, K. Ovarian epithelial cancer: a role for PGE2-synthesis and signalling in malignant transformation and progression. *Mol. Cancer*, **2006**, 16, 62], breast cancer [Mehrotra, S.; Morimiya, A.; Agarwal, B.; Konger, R.; Badve, S. Microsomal prostaglandin E2 synthase-1 in breast cancer: a potential target for therapy. *J. Pathol.* **2006**, 208, 356-363], gastric tumorigenesis [Oshima, H.; Matsunaga, A.; Fujimura, T.; Tsukamoto, T.; Taketo, M. M.; Oshima, M. Carcinogenesis in mouse stomach by simultaneous activation of the Wnt signaling and prostaglandin E2 pathway. *Gastroenterology*, **2006**, 131, 1086-1095], multiple sclerosis, atherosclerosis such as myocardial infarction and stroke [Ikeda-Matsuo, Y.; Ota, A.; Fukada, T.; Uematsu, S.; Akira, S.; Sasaki, Y. Microsomal prostaglandin E synthase-1 is a critical factor of stroke-reperfusion injury. *Proc. Natl. Acad. Sci. USA.* **2006**, 103, 11790-11795], apnea or other respiratory distress symptoms in adults and children [Hofstetter, A. O.; Saha, S.; Siljehav, V.; Jakobsson, P. J.; Herlenius, E. The induced prostaglandin E2 pathway is a key regulator of the respiratory response to infection and hypoxia in neonates. *Proc. Natl. Acad. Sci. USA.* **2007**, 104, 9894-9899], sudden infant death syndrome (SIDS), asthma, fever [Engblom, D.; Saha, S.; Engström, L.; Westman, M.; Audoly, L. P.; Jakobsson, P. J.; Blomqvist, A. Microsomal prostaglandin E synthase-1 is the central switch during immune-induced pyresis. *Nat. Neurosci.* **2003**, 6, 1137-1138; Saha, S.; Engström, L.; Mackerlova, L.; Jakobsson, P. J.; Blomqvist, A. Impaired febrile responses to immune challenge in mice deficient in microsomal prostaglandin E synthase-1. *Am. J. Physiol.* **2005**, 288, R1100-R1107], inflammation related anorexia

[Samuelsson, B.; Morgenstern, R.; Jakobsson, P.-J. Membrane Prostaglandin E Synthase-1: A Novel Therapeutic Target. *Pharmacol. Rev.* **2007**, *59*, 207-224], Alzheimer's disease [Satoh, K.; Nagano, Y.; Shimomura, C.; Suzuki, N.; Saeki, Y.; Yokota, H. Expression of prostaglandin E synthase mRNA is induced in beta-amyloid treated rat astrocytes. *Neurosci. Lett.* **2000**, *283*, 221-223; Licastro, F.; Davis, L.J.; Pedrini, S.; Galasko, D.; Masliah, E. Prostaglandin E2 induced polymerization of human alpha-1-antichymotrypsin and suppressed its protease inhibitory activity: implications for Alzheimer's disease. *Biochem. Biophys. Res. Commun.* **1998**, *249*, 182-186; Chaudhry, U. A.; Zhuang, H.; Crain, B. J.; Doré, S. Elevated microsomal prostaglandin-E synthase-1 in Alzheimer's disease. *Alzheimers Dement.* **2008**, *4*, 6-13; Hoozemans, J. J.; Veerhuis, R.; Janssen, I.; van Elk, E. J.; Rozemuller, A. J.; Eikelenboom, P. The role of cyclooxygenase 1 and 2 activity in prostaglandin E(2) secretion by cultured human adult microglia: implications for Alzheimer's disease. *Brain Res.* **2002**, *951*, 218-226; Scali, C.; Prosperi, C.; Bracco, L.; Piccini, C.; Baronti, R.; Ginestroni, A.; Sorbi, S.; Pepeu, G.; Casamenti, F. Neutrophils CD11b and fibroblasts PGE(2) are elevated in Alzheimer's disease. *Neurobiol. Aging*, **2002**, *23*, 523-30], as well as the use of the said compounds in the manufacture of medicaments for the treatment of those disorders [For a reviews discussing most of the therapeutic indications mentioned above see: Samuelsson, B.; Morgenstern, R.; Jakobsson, P.-J. Membrane Prostaglandin E Synthase-1: A Novel Therapeutic Target. *Pharmacol. Rev.* **2007**, *59*, 207-224; Murakami M, Kudo I. Prostaglandin E synthase: a novel drug target for inflammation and cancer. *Curr Pharm Des.* **2006**, *12*, 943-954; Kojima, F.; Kato, S.; Kawai, S. Prostaglandin E synthase in the pathophysiology of arthritis. *Fundam. Clin. Pharmacol.* **2005**, *19*, 255-261].

Other examples of medical conditions associated with mPGES-1 are pain in connection to ankylosing spondylitis, gout, or rheumatic fever, toothache, cellular neoplastic transformations and metastatic tumor growth, endometriosis, hemophilic arthropathy, Parkinson's disease, mPGES-1-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor angiogenesis, symptoms associated with viral infections, and premature labor.

WO 2008/084218 discloses benzazole derivatives of the general formula



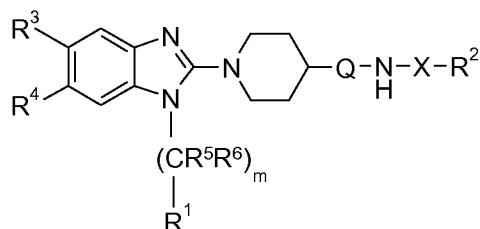
as useful in the treatment of diseases in which it is desired and/or required to inhibit the activity of a member of the MAPEG family, e.g. microsomal prostaglandin E synthase-1 (mPGEs-1).

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SUMMARY OF THE INVENTION

There still is a large unmet need for drugs that are as effective as NSAID inhibitors but having significantly improved side effect profile, for the treatment of conditions such as inflammatory diseases, nociceptive pain, auto-immune diseases, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular diseases. One object of the present invention is to provide compounds having said desired improved properties. The present inventors now have surprisingly found certain piperidinyl benzoimidazoles that are capable of efficiently blocking mPGEs-1.

Consequently, in one aspect the present invention provides a compound of formula (I)



15

(I)

wherein:

R^1 is selected from branched or unbranched C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl or C_2 - C_{10} alkynyl; C_3 - C_{10} cycloalkyl; C_4 - C_{10} cycloalkenyl; C_8 - C_{10} cycloalkynyl; C_1 - C_9 heterocyclyl; and C_6 - C_{10} aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or cycloalkynyl moiety optionally is substituted with 1, 2 or 3 groups R^a ; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b ;

R^2 is selected from branched or unbranched C_1 - C_9 alkyl, C_2 - C_9 alkenyl, or C_2 - C_9 alkynyl; C_3 - C_6 cycloalkyl; C_4 - C_6 cycloalkenyl; C_8 - C_{10} cycloalkynyl; C_1 - C_9 heterocyclyl; and C_6 - C_{10} aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or cycloalkynyl moiety optionally

is substituted with 1, 2 or 3 groups R^a; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b;

R³ and R⁴ are each independently selected from C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₄ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; halogen; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; and C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; wherein any alkyl, alkenyl, alkynyl or cycloalkyl moiety optionally is substituted with 1, 2, or 3 groups R^c;

R⁵ and R⁶ are independently selected from hydrogen; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; and halogen; wherein any alkyl; alkenyl or alkynyl moiety optionally is substituted with 1, 2, or 3 groups R^c;

X represents a bond or branched or unbranched C₁-C₃ alkyl, C₂-C₃ alkenyl or C₂-C₃ alkynyl;

Q represents carbonyl, sulfonyl or sulfinyl;

m is an integer of 0, 1 or 2;

each R^a is independently selected from halogen; hydroxy; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^b is independently selected from halogen; carboxy; hydroxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₃-C₅ cycloalkyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; amino carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl sulfonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary sulphonamido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy, C₂-C₄ alkenyloxy, or C₂-C₄ alkynyloxy carbonyl; C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl, alkynyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^c is independently selected from fluorine and chlorine;

and pharmaceutically acceptable salts thereof.

- 5 Another aspect of the present invention is to provide a compound of formula (I) for use as a medicament.

Another aspect of the present invention is to provide a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable
10 salt thereof, in admixture with at least one pharmaceutically acceptable adjuvant, diluent or carrier.

Another aspect of the present invention is to provide a method of medical treatment by use of said pharmaceutical compositions.

15 Another aspect of the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined herein above, for use in the treatment of a disorder in which inhibition of the activity of microsomal prostaglandin E synthase-1 is desired and/or required.

20 Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of a disorder in which inhibition of the activity of microsomal prostaglandin E synthase-1 is desired and/or required.

25 Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of an inflammatory disease, said disease preferably being selected from rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, psoriasis, eczema, swelling and periodontitis.

30 Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of nociceptive pain, said pain preferably being selected from inflammatory pain, post-operative pain, fibromyalgia, dysmenorrhea, migraine, arthrotic pain, arthritic pain, pain in connection with osteoarthritis, cephalalgia, pain due to gall-stones and pain due to metastasis, ankylosing spondylitis, gout, or rheumatic fever, and toothache. The compound
35 of formula (I) also may be used in preemptive treatment of surgical pain.

Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of an autoimmune disease, said autoimmune disease preferably being selected from rheumatoid arthritis and multiple sclerosis.

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Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of a breathing disorder, said disorder preferably being selected from apnea or other respiratory distress symptoms in adults and children, sudden infant death syndrome (SIDS), asthma and other chronic obstructive lung-diseases and sarcoidosis.

10

Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of cancer, said cancer preferably being selected from familial adenomatous polyposis (FAP) condition, colorectal cancer, breast cancer, gastric tumorigenesis and epithelial ovarian cancer, as well as cellular neoplastic transformations and metastatic tumor growth.

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Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of cardiovascular diseases due to atherosclerosis such as myocardial infarction and stroke.

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Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of fever- or inflammation-related anorexia.

Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of Alzheimer's disease.

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Another aspect of the present invention provides a compound of formula (I), for use in the treatment and/or prevention of endometriosis, hemophilic arthropathy, Parkinson's disease, mPGES-1-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor angiogenesis, symptoms associated with viral infections, and premature labor.

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Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of an inflammatory disease, said disease preferably being selected from rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, psoriasis, eczema, swelling and periodontitis.

Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of nociceptive pain, said pain preferably being selected from inflammatory pain, post-operative pain, fibromyalgia, dysmenorrhea, migraine, arthrotic pain, arthritic pain, pain in connection with osteoarthritis, cephalalgia, pain due to gall-stones and pain due to metastasis, pain due to ankylosing spondylitis, pain due to gout, toothache and pain due to rheumatic fever, or for the preemptive treatment of surgical pain.

- 10 Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of an autoimmune disease, said autoimmune disease preferably being selected from rheumatoid arthritis and multiple sclerosis.

- 15 Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of a breathing disorder, said disorder preferably being selected from apnea or other respiratory distress symptoms in adults and children, sudden infant death syndrome (SIDS), asthma and other chronic obstructive lung-diseases and sarcoidosis.

- 20 Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of cancer, said cancer preferably being selected from familial adenomatous polyposis (FAP) condition, colorectal cancer, breast cancer, gastric tumorigenesis and epithelial ovarian cancer, as well as cellular neoplastic transformations and metastatic tumor growth.

- 25 Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of cardiovascular diseases due to atherosclerosis such as myocardial infarction and stroke.

- 30 Another aspect of the present invention provides the use of a compound of formula (I), in preparation of a medicament for the treatment and/or prevention of fever- or inflammation-related anorexia.

Another aspect of the present invention provides the use of a compound of formula (I), in the preparation of a medicament for the treatment and/or prevention of Alzheimer's disease.

Another aspect of the present invention provides a method of treatment of a disease in which inhibition of the activity of mPGEs-1 is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

Another aspect of the present invention provides a method of treatment of an inflammatory disease, said disease preferably being selected from rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, psoriasis, eczema, swelling and periodontitis, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of nociceptive pain, said pain preferably being selected from inflammatory pain, post-operative pain, fibromyalgia, dysmenorrhea, migraine, arthrotic pain, arthritic pain, pain in connection with osteoarthritis, cephalalgia, pain due to gall-stones and pain due to metastasis, pain due to ankylosing spondylitis, gout, toothache and pain due to rheumatic fever, as well as preemptive treatment of surgical pain, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of an autoimmune disease, said autoimmune disease preferably being selected from rheumatoid arthritis and multiple sclerosis, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of a breathing disorder, said disorder preferably being selected from apnea or other respiratory distress symptoms in adults and children, sudden infant death syndrome (SIDS), asthma and other chronic obstructive lung-diseases and sarcoidosis, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of cancer, said cancer preferably being selected from familial adenomatous polyposis (FAP) condition, colorectal cancer, breast cancer, gastric tumorigenesis and epithelial ovarian cancer, as well as cellular neoplastic transformations and metastatic tumor growth, which method comprises administration
5 of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of cardiovascular diseases due to atherosclerosis such as myocardial infarction and stroke, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or
10 a pharmaceutically-acceptable salt thereof, to a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of fever- or inflammation-related anorexia, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to
15 a patient in the need of such treatment.

Another aspect of the present invention provides a method of treatment of Alzheimer's disease, which method comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, to a patient in the need of such
20 treatment.

In another aspect of the invention, methods for preparing a compound of formula (I) are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar diagram showing results of a carrageenan-induced paw edema assay in Wistar rats using the compound synthesised in Example 41. The compound at 10, 30 and 100 mg/kg, as well as vehicle was administered intraperitoneally immediately before carrageenan challenge. Hind paw edema, a measure of inflammation, was recorded 6 hours after carrageenan
30 administration. Volume increase is paw volume at 6 hours after carrageenan administration minus paw volume before carrageenan administration. The bars represent average $\pm$ standard error of the mean (n=8).

Figure 2 is a bar diagram showing inhibition of CFA-induced paw swelling by the compound synthesised in Example 41 compared to vehicle control. Data represent average inhibition of paw swelling $\pm$ standard error of the mean for acute (A) or delayed (B) phase (n=5). Inhibition of paw swelling = (paw volume (vehicle) – paw volume (treatment))/paw volume (vehicle).

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DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise indicated or apparent from the context, any alkyl, alkenyl or alkynyl group as referred to herein may be branched or unbranched. This also applies to said groups when present in moieties such as alkoxy groups, and the like.

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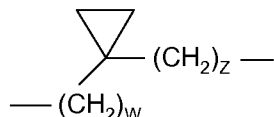
The term “alkyl” as employed herein, alone or as part of another group, refers to an acyclic straight or branched chain radical, unless otherwise specified containing 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbons in the normal chain, which includes methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl and *n*-octyl. Examples of branched chain radicals, not excluding any of the possible isomers not mentioned, are *iso*-propyl, *sec*-butyl, *iso*-pentyl, 3-methylpentyl, 2,3-dimethylhexyl, 3-ethylhexyl, and the like. Alkyl also includes a straight or branched alkyl group that contains or is interrupted by a carbocyclyl group, exemplified by cyclopropane, as exemplified below:

15



20

wherein, w and z are 1 to 8, the sum of w and z is not more than 9. The alkyl portions can be attached at any variable point of attachment to the carbocyclyl, including the same ring carbon, as exemplified below:



25

When substituted alkyl is present, this refers to a straight or branched alkyl group, substituted with 1, 2, 3 groups of R^a, which groups may be the same or different at any available point, as defined with respect to each variable.

30

The term “alkenyl” as used herein, alone or as part of another group, refers to a straight or branched chain radical, unless otherwise specified containing 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, containing at least one carbon to carbon double bond, which includes in the normal chain vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, and the like. Examples of branched chain radicals, not excluding

any of the possible isomers not mentioned, are 2-buten-2-yl, 4-methyl-2-pentenyl, 6-methylene-2-octenyl, and the like. All possible (*E*)- and (*Z*)-isomers is contemplated within the scope of the invention. As described above with respect to the “alkyl”, the straight or branched portion of the alkenyl group may be optionally substituted when a substituted alkenyl group is provided, and the chain may be interrupted by a carbocyclyl group. When substituted alkenyl is present, this refers to a straight or branched alkyl group, substituted with 1, 2, 3 groups of R^a, which groups may be the same or different at any available point, as defined with respect to each variable.

The term “alkynyl” as used herein by itself or as part of another group refers to a straight or branched chain radical, unless otherwise specified containing 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbons, which contains at least one carbon to carbon triple bond, which in the normal chain such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, and the like. Examples of branched chain radicals, not excluding any of the possible isomers not mentioned, are 3-methyl-1-butynyl, 2-methyl-4-pentynyl, 6-methyl-4-octynyl, 6-methyl-3-propyl-4-octynyl, and the like. The alkynyl can in addition to carbon to carbon triple bonds also include a to carbon double bond. Examples of such radicals, not excluding any of the possible not mentioned, are 3-buten-1-ynyl, 1-buten-3-ynyl, 6-methylene-2-octynyl, 3-allyl-6-methyl-1-octen-4-ynyl, and the like. As described above with respect to the “alkyl”, the straight or branched portion of the alkynyl group may be optionally substituted when a substituted alkynyl group is provided, and the chain may be interrupted by a carbocyclyl group. When substituted alkynyl is present, this refers to a straight or branched alkyl group, substituted with 1, 2, 3 groups of R^a, which groups may be the same or different at any available point, as defined with respect to each variable.

As used herein, the term “carbocyclyl” refers to a cyclic moiety containing only carbon atoms.

As used herein with respect to any carbocyclyl, heterocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl the term “monocyclic” refers to a cyclic moiety containing only one ring. The term “bicyclic” refers to a cyclic moiety containing two rings. A bicyclic group may, for example, be fused or bridged.

The concept of fused and bridged rings are well known to the one skilled in the art, and for example is explained in “Fused Ring and Bridged Fused Ring Nomenclature, FR-1 from IUPAC Recommendations 1998”

As used herein, the terms “(E)- and (Z)-isomers” refer to the terms “Entgegen” and “Zusammen”, respectively. Whether a molecular configuration is designated as Entgegen or Zusammen is determined by the “Cahn-Ingold-Prelog” priority rules, which is well known for the one skilled in the art.

5

As used herein, the terms “heterocyclyl” mean a mono- or bicyclic, saturated or unsaturated cyclic group, possibly aromatic, containing one or more heteroatom(s) preferably selected from N, O and S, such as, but not limited to, aziridinyl, azetidiny, dihydropyranyl, dihydropyridyl, dihydropyrrolyl, dioxolanyl, dioxanyl, dithianyl, dithiolanyl, imidazolidinyl, imidazoliny, morpholiny, oxetanyl, oxiranyl, pyrrolidinyl, pyrrolidinonyl, piperidyl, piperaziny, piperidinyl, pyrazolidinyl, quinuclidiny, sulfalonyl, 3-sulfolenyl, tetrahydrofuranyl tetrahydropyranyl, tetrahydropyridyl, thietanyl, thiiranyl, thiolanyl, thiomorpholiny, trithianyl, tropanyl, 1*H*-indazolyl, monosaccharide, pyridyl, quinoliny, furanyl, thienyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, isoquinoliny, naphthyridiny, imidazolyl, phenaziny, phenothiaziny, phthalaziny, indolyl, pyridaziny, quinazoliny, quinoliziny, quinoxaliny, tetrahydroisoquinoliny, pyraziny, indazolyl, indoliny, pyrimidinyl, thiophenetyl, pyranyl, carbazolyl, chromanyl, cinnoliny, acridiny, benzimidazolyl, benzodioxanyl, benzodioxepiny, benzodioxolyl, benzofuranyl, benzothiazolyl, benzobenzoxadiazolyl, benzoxaziny, benzoxazolyl, benzomorpholiny, benzoselenadiazolyl, benzothienyl, puriny, pteridinyl, and the like.

20

The term “halogen” refers to fluorine, chlorine, bromine and iodine, where the preferred halogen radicals are fluoro and chloro.

As used herein, the term “aryl” means an aromatic group, monocyclic or bicyclic such as, but not limited to phenyl or naphthyl, and the like. The aryl group is preferably a monocyclic C₆ aryl (phenyl).

25

The term “cycloalkyl” as employed herein alone or as part of another group includes saturated cyclic hydrocarbyl groups, mono- or bicyclic rings(s), having a total of 3, 4, 5, 6, 7, 8, 9 or 10 carbons forming the ring(s), which includes cyclopropyl, cyclobutyl, cyclohexyl, cycloheptyl, cyclodecane, bicyclo[4.1.0]heptane, bicyclo[4.3.3]dodecane, cyclopentyl, decahydronaphthalene, bicyclo[2.2.2]octane, and the like, optionally substituted with 1, 2 or 3 groups of R^a.

30

The term "cycloalkenyl" as employed herein alone or as part of another group includes unsaturated cyclic rings(s), mono- or bicyclic, having a total of 4, 5, 6, 7, 8, 9 or 10 carbons forming the ring(s), which includes cyclohexene, cyclobutene, bicyclo[4.2.0]-3-octene, 1,3-cyclodecadiene and the like, optionally substituted with 1, 2 or 3 groups of R^a.

5

The term "cycloalkynyl" as employed herein alone or as part of another group includes mono- or bicyclic, rings having one carbon to carbon triple bond, and having a total of 8, 9 or 10 carbons forming the ring, which includes cyclooctyne, cyclodecyne, bicyclo[6.2.0]-4-decyne and the like, optionally substituted with 1, 2 or 3 groups of R^a. The cycloalkynyl can in addition to carbon to carbon triple bonds also contain a carbon to carbon double bond, which includes 1-cyclodecen-5-yne and the like.

10

The term "carbocyclyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbyl groups or unsaturated (at least one carbon to carbon double bond) cyclic hydrocarbyl groups, containing one ring and a total of 3, 4, 5, 6, 7, 8, 9 or 10 carbons forming the ring, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, cycloheptyl, and the like. The cyclic hydrocarbyl may be mono- or bicyclic.

15

By the term "unsaturated", when referring to a bicyclic system, is meant a ring system comprising at least one double or triple bond in at least one ring. Thus, it is contemplated that both rings may be unsaturated or only one ring may be unsaturated, the other one being saturated. Furthermore, the term "unsaturated bicyclic" also is intended to refer to a non-aromatic bicyclic system comprising a ring that is either unsaturated or saturated fused to a ring that by itself would be aromatic, such as in indane or 4,5-dihydro-1-indole.

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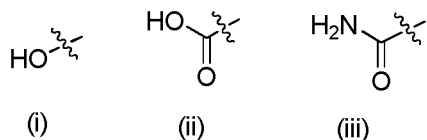
The term "aromatic", as used herein, refers to an unsaturated cyclic moiety that has an aromatic character, while the term "non-aromatic", as used herein, refers to a cyclic moiety, that may be unsaturated, but that does not have an aromatic character.

In a bicyclic ring system, as referred to herein, the rings may be both saturated or both unsaturated, e.g. both aromatic. The rings may also be of different degrees of saturation, and one ring may be aromatic whereas the other is non-aromatic. The rings also may comprise different numbers of atoms, e.g. one ring being 5-membered and the other one being 6-membered.

30

In a bicyclic heterocyclyl, as referred to herein, one or both of the rings may contain one or several heteroatoms.

The terms hydroxy (i), carboxy (ii) and aminocarbonyl (iii), refer to radicals of the type:



5

The terms alkyloxy, alkenyloxy, alkynyloxy and cycloalkyloxy refer to a radical of the type:



wherein R is an alkyl, alkenyl, alkynyl or cycloalkyl moiety.

10

The terms alkylthio, alkenylthio, and alkynylthio refer to a radical of the type:



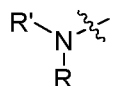
wherein R is an alkyl, alkenyl or alkynyl moiety.

15 The terms alkyl, alkenyl and alkynyl secondary amino refer to a radical of the type:



wherein R is an alkyl, alkenyl or alkynyl moiety.

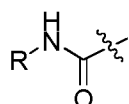
The terms alkyl, alkenyl and alkynyl tertiary amino refer to a radical of the type:



20

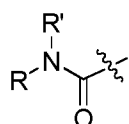
wherein R and R' are each an independently selected alkyl, alkenyl or alkynyl moiety.

The terms alkyl, alkenyl and alkynyl secondary amido refer to a radical of the type:



25 wherein R is an alkyl, alkenyl or alkynyl moiety.

The terms alkyl, alkenyl and alkynyl tertiary amido refer to a radical of the type:



wherein R and R' are each an independently selected alkyl, alkenyl or alkynyl moiety.

The terms alkyl, alkenyl and alkynyl carbonyl refer to a radical of the type:



5 wherein R is an alkyl, alkenyl or alkynyl moiety.

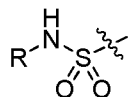
The terms alkyl, alkenyl and alkynyl sulfonyl refer to a radical of the type:



wherein R is an alkyl, alkenyl or alkynyl moiety.

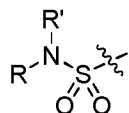
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The terms alkyl, alkenyl and alkynyl secondary sulphonamido refer to a radical of the type:



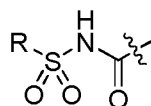
wherein R is an alkyl, alkenyl or alkynyl moiety.

15 The terms alkyl, alkenyl and alkynyl tertiary sulphonamido refer to a radical of the type:



wherein R and R' are each independently selected from alkyl, alkenyl or alkynyl moiety.

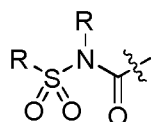
The terms alkyl, alkenyl and alkynyl secondary acylsulphonamido refer to a radical of the type:



20

wherein R is an alkyl, alkenyl or alkynyl moiety.

The terms alkyl, alkenyl and alkynyl tertiary acylsulphonamido refer to a radical of the type:



25 wherein each R is independently selected from an alkyl, alkenyl or alkynyl moiety.

The terms alkyl, alkenyl and alkynyl alkynyloxy carbonyl refer to a radical of the type:



wherein R is an alkyl, alkenyl or alkynyl moiety.

The terms carbonyl (i), sulfonyl (ii) and sulfinyl (iii), when used to define the scope of Q, refer to di-radicals of the type:



(i)



(ii)



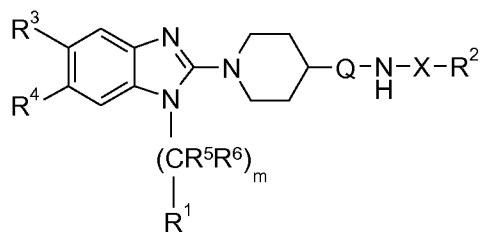
(iii)

The term “cyclic”, as used herein in respect of an atom, refers to an atom that is a member of at least one ring in a carbocycle or heterocycle.

A cyclyl according to the invention may comprise 1-10 carbons, it being understood that in case the cyclyl comprises less than 3 carbons, it must necessarily also comprise at least one heteroatom.

Unless otherwise indicated or apparent from the context, in a bicyclic moiety according to the invention, each constituent monocycle may independently be selected from aromatic or non-aromatic carbo- and heterocycles.

In a first aspect of the invention, there is provided a compound of formula (I):



(I)

as defined herein above.

R^1 in formula (I) is selected from branched or unbranched C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl or C_2 - C_{10} alkynyl; C_3 - C_{10} cycloalkyl; C_4 - C_{10} cycloalkenyl; C_8 - C_{10} cycloalkynyl; C_1 - C_9 heterocyclyl; and C_6 - C_{10} aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or cycloalkynyl moiety optionally is substituted with 1, 2 or 3 groups R^a ; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b , as defined herein.

In one embodiment, R¹ in formula (I) is selected from branched or unbranched C₁-C₁₀ alkyl; C₃-C₁₀ cycloalkyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; said alkyl and cycloalkyl optionally being substituted with 1, 2 or 3 groups R^a; and said heterocyclyl and aryl optionally being substituted with 1, 2, 3, 4 or 5 groups R^b.

In one embodiment of the invention, R¹ in formula (I) is optionally substituted branched or unbranched C₁-C₁₀ alkyl, e.g. C₁-C₈ alkyl, i.e. methyl, ethyl and branched or unbranched propyl, butyl, pentyl, hexyl, heptyl, and octyl, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, pentan-2-yl, pentan-3-yl, *n*-hexyl, *n*-heptyl, and *n*-octyl. More specifically, in this embodiment, R¹ in formula (I) may be selected from optionally substituted branched or unbranched C₁-C₆ alkyl, e.g. methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, pentan-2-yl, pentan-3-yl, *n*-hexyl, or from optionally substituted branched or unbranched C₁-C₄ alkyl. For example, in this embodiment, R¹ may be optionally substituted *iso*-propyl.

In one embodiment of the invention, when R¹ in formula (I) is selected from optionally substituted branched or unbranched C₁-C₁₀ alkyl, m is 0.

In another embodiment, R¹ in formula (I) is optionally substituted C₃-C₁₀ cycloalkyl, in particular C₃-C₆ cycloalkyl, or C₃-C₅ cycloalkyl.

R¹ in formula (I) also may be optionally substituted C₁-C₉ heterocyclyl, in particular C₁-C₅ heterocyclyl, such as a 6-membered C₁-C₅ heterocyclyl, C₂-C₅ heterocyclyl, C₃-C₅ heterocyclyl, C₄-C₅ heterocyclyl or C₅ heterocyclyl, e.g. tetrahydropyryl or pyridyl, such as pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or tetrahydropyran-4-yl; or 5-membered C₁-C₄ heterocyclyl, C₂-C₄ heterocyclyl, or C₃-C₄ heterocyclyl, e.g. thiazolyl or tetrahydrofuryl, such as thiazol-4-yl and tetrahydrofuran-2-yl.

R¹ in formula (I) also may be optionally substituted C₆-C₁₀ aryl, preferably phenyl.

When R¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, it optionally is substituted with 1, 2 or 3 groups, e.g. 1 or 2 independently selected groups R^a, e.g. 1 group R^a, as defined herein, i.e. selected from halogen; hydroxy; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄

alkynyl secondary or tertiary amino; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

In one embodiment, when R¹ is substituted with R^a, each R^a is independently selected from hydroxy, C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; and C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino, in particular from hydroxy, C₁-C₄ alkoxy, such as methoxy, or C₁-C₄ alkyl secondary or tertiary amino, e.g. such as ethyl secondary or tertiary amino, e.g. diethylamino.

10 In one embodiment, R¹ is not substituted with any R^a.

When R¹ is heterocyclyl or aryl, it optionally is substituted with 1, 2, 3, 4 or 5 independently selected groups R^b, as defined herein, i.e. selected from halogen; carboxy; hydroxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; amino carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl sulfonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary sulphonamido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy, C₂-C₄ alkenyloxy, or C₂-C₄ alkynyloxy carbonyl; C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

In one embodiment, when R¹ is substituted with R^b, R^b is selected from halogen; carboxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; amino carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy, C₂-C₄ alkenyloxy, or C₂-C₄ alkynyloxy carbonyl; and C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl and alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

30 In one particular embodiment, when R¹ is substituted with R^b, R^b is selected from halogen, i.e. F, Cl and Br, in particular F; carboxy; cyano; 5- or 6-membered C₁-C₅ heteroaryl, in particular 5-membered C₁-C₄ heteroaryl, such as triazole; C₁-C₄ alkyl, such as methyl; amino carbonyl; C₁-C₄ alkyl secondary or tertiary amido, such as methyl secondary or tertiary amido; C₁-C₄ alkyl secondary or tertiary acylsulphonamido, such as methyl secondary or tertiary acylsulphonamido;

C₁-C₄ alkyloxy carbonyl, such as methoxy carbonyl; and C₁-C₅ heterocyclyl, such as 5- or 6-membered heterocyclyl, e.g. 5-membered C₁-C₄ heterocyclyl, e.g. tetrazole.

5 In one embodiment, R¹ is substituted with 1-3 groups R^b as defined herein, e.g. with 1 or 2 groups, in particular with 1 group R^b. In another embodiment, R¹ is not substituted with any R^b.

10 In one embodiment, when R¹ is a 6-membered heterocyclyl or aryl, it is substituted with at least one group R^b in *para*-position relative to the linking bond or chain attaching R¹ to the benzimidazol moiety.

15 R² in formula (I) is selected from branched or unbranched C₁-C₉ alkyl, C₂-C₉ alkenyl or C₂-C₉ alkynyl; C₃-C₆ cycloalkyl, C₄-C₆ cycloalkenyl; C₈-C₁₀ cycloalkynyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl optionally being substituted with 1, 2 or 3 groups R^a; and said heterocyclyl or aryl optionally being substituted with 1, 2, 3, 4 or 5 groups R^b.

20 In one embodiment, R² is optionally substituted branched or unbranched C₁-C₉ alkyl, C₂-C₉ alkenyl or C₂-C₉ alkynyl. In this embodiment, R² more particularly may be C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, e.g. C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl. In particular, R² may be branched or unbranched C₁-C₉ alkyl, or C₁-C₆ alkyl, e.g. C₁-C₄ alkyl, e.g. C₂-C₄ alkyl.

In one embodiment, when R² is optionally substituted branched or unbranched C₁-C₉ alkyl, C₂-C₉ alkenyl or C₂-C₉ alkynyl, X is a bond.

25 In another embodiment, R² is optionally substituted C₃-C₆ cycloalkyl or C₄-C₆ cycloalkenyl, and then more particularly may be C₃-C₆ cycloalkyl, in particular pentyl.

30 In still another embodiment, R² is optionally substituted C₁-C₉ heterocyclyl. In this embodiment, R² may in particular be C₁-C₅ heterocyclyl, e.g. 5-membered C₁-C₄ heterocyclyl or 6-membered C₁-C₅ heterocyclyl, in particular 5-membered C₁-C₄ heterocyclyl, e.g. 5-membered C₃-C₄ heterocyclyl. For example, R² may be selected from tetrahydrofuryl and thiazolyl.

In another embodiment, R² is optionally substituted C₆-C₁₀ aryl, and then preferably is phenyl.

When R² is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or cycloalkynyl, it optionally is substituted with 1, 2 or 3 groups, e.g. 1 or 2 groups, R^a, as defined herein, i.e. selected from halogen; hydroxy; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

In one embodiment, when R² is substituted with R^a, each R^a is independently selected from C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; and C₂-C₄ alkynyloxy, in particular C₁-C₄ alkyloxy, such as C₁-C₃ alkyloxy, more particularly methoxy and iso-propoxy. In one embodiment, R² is substituted with 1 group R^a and in another embodiment, R² is not substituted with any group R^a. In one embodiment, when R² is cycloalkyl, cycloalkenyl, or cycloalkynyl, it is not substituted with any group R^a.

When R² is heterocyclyl or aryl, it optionally is substituted with 1, 2, 3, 4 or 5 groups R^b, as defined herein above. In one embodiment, R² is substituted with 1, 2, 3, 4 or 5 groups R^b each independently selected from halogen, e.g. F, Cl and Br, in particular F or Br; cyano; and C₁-C₅ heterocyclyl, e.g. five-membered C₁-C₄ heterocyclyl. For example, R² may be 6-membered heterocyclyl or aryl, such as phenyl, substituted with at least one R^b in *para*-position in relation to the bond attaching R² to X or - in case X is a bond - in *para*-position in relation to the bond X. In one embodiment, R² is substituted with 1-3 groups R^b, e.g. 1 or 2 groups R^b, in particular 1 group R^b.

In a compound of formula (I), R³ and R⁴ are each independently selected from C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₄ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; halogen; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; and C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; wherein any alkyl, alkenyl, alkynyl or cycloalkyl moiety optionally is substituted with 1, 2, or 3 groups R^c.

In one embodiment, R³ and R⁴ are each independently selected from C₁-C₄ alkyl and halogen, in particular from methyl and chloro. For example, R³ and R⁴ may be both halogen or both C₁-C₄ alkyl, e.g. both are Cl or both are methyl, or one may be halogen, e.g. Cl, and the other one C₁-C₄ alkyl, e.g. methyl.

In one embodiment, R³ is selected from C₁-C₄ alkyl, e.g. methyl, and R⁴ is selected from halogen and C₁-C₄ alkyl, e.g. Cl and methyl. In another embodiment, R³ is selected from halogen, e.g. Cl, and R⁴ is selected from halogen and C₁-C₄ alkyl, e.g. Cl and methyl.

- 5 In still another embodiment, R³ is selected from halogen and C₁-C₄ alkyl, e.g. Cl and methyl, and R⁴ is selected from C₁-C₄ alkyl, e.g. methyl. In still another embodiment, R³ is selected from halogen and C₁-C₄ alkyl, e.g. Cl and methyl, and R⁴ is selected from halogen, e.g. Cl.

- 10 R⁵ and R⁶ in formula (I) are independently selected from hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl and halogen; whereby any alkyl; alkenyl; or alkynyl is optionally substituted with 1, 2, or 3 groups R^c.

- 15 In one embodiment, R⁵ and R⁶ are independently selected from hydrogen and C₁-C₄ alkyl, more particularly from H and methyl, for example, R⁵ and R⁶ may both be H; or R⁵ may be H and R⁶ methyl.

- 20 In formula (I), X represents a bond (i.e. a single, covalent bond) or branched or unbranched C₁-C₃ alkyl, C₂-C₃ alkenyl or C₂-C₃ alkynyl. Preferably X represents a bond or C₁-C₃ alkyl, more preferably a bond or methylene (-CH₂-).

Q in formula (I) is selected from carbonyl, sulfonyl and sulfinyl and preferably is carbonyl.

- 25 In formula (I), m is an integer of 0, 1 or 2, preferably 0 or 1. In one particular embodiment, m is 0. In another embodiment, m is 1.

- Each R^a is independently selected from halogen; hydroxy; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

- 30 In one embodiment, each R^a is independently selected from hydroxy; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; and C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; wherein any alkyl, alkenyl and alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c.

35

In another embodiment, each R^a is independently selected from hydroxy; C₁-C₄ alkyloxy, e.g. methoxy and *iso*-propoxy; and C₁-C₄ alkyl secondary or tertiary amino, e.g. diethylamino.

Each R^b in formula (I) is independently selected from halogen; carboxy; hydroxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₃-C₅ cycloalkyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; C₃-C₅ cycloalkylthio; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; amino carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl sulfonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary sulphonamido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy, C₂-C₄ alkenyloxy, or C₂-C₄ alkynyloxy carbonyl; C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl, alkynyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^c as defined herein.

In one embodiment, each R^b is independently selected from halogen; carboxy; hydroxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₃-C₅ cycloalkyloxy; C₁-C₄ alkylthio; C₁-C₄ alkyl secondary or tertiary amino; amino carbonyl; C₁-C₄ alkyl secondary or tertiary amido; C₁-C₄ alkyl carbonyl; C₁-C₄ alkyl sulfonyl; C₁-C₄ alkyl secondary or tertiary sulphonamido; C₁-C₄ alkyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy carbonyl; C₁-C₅ heterocyclyl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^c as defined herein.

In another embodiment, each R^b is independently selected from halogen; carboxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₃-C₅ cycloalkyloxy; C₂-C₄ alkynyl; aminocarbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy carbonyl; and C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl and alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c as defined herein.

In still another embodiment, each R^b is independently selected from halogen; carboxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₃-C₅ cycloalkyloxy; aminocarbonyl; C₁-C₄ alkyl secondary or tertiary amido; C₁-C₄ alkyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy carbonyl; and C₁-C₅ heterocyclyl; wherein any alkyl, moiety optionally is substituted with 1, 2 or 3 groups R^c as defined herein.

In still another embodiment, each R^b is independently selected from halogen; carboxy, cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; amino carbonyl; C₁-C₄ alkyl secondary or tertiary amido; C₁-C₄ alkyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy carbonyl; and C₁-C₅ heterocyclyl; wherein any alkyl, moiety optionally is substituted with 1, 2 or 3 groups R^c as defined herein.

When R^b is C₁-C₅ heterocyclyl, it may be C₁-C₄ heterocyclyl, and preferably is 6-membered C₁-C₅ heterocyclyl or 5-membered C₁-C₄ heterocyclyl, more preferably 5-membered C₁-C₄ heterocyclyl. When R^b is C₁-C₅ heteroaryl, it may be C₁-C₄ heteroaryl, and preferably is 6-membered C₁-C₅ heteroaryl or 5-membered C₁-C₄ heteroaryl.

R^c in formula (I) is selected from fluorine and chlorine. In one embodiment, R^c is absent. In another embodiment, R^c is fluorine.

In a particular embodiment of the invention, X represents methylene or a bond and R^2 represents C₃-C₆ cycloalkyl or heterocyclyl.

In another embodiment of the invention, X represents a bond and R^2 represents cyclopentyl.

In one embodiment of the invention, in a compound of formula (I)

R^1 is selected from branched or unbranched C₁-C₁₀ alkyl; C₃-C₁₀ cycloalkyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^a ; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b ;

R^2 is selected from branched or unbranched C₁-C₉ alkyl; C₃-C₆ cycloalkyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^a ; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b ;

R^3 and R^4 are each independently selected from C₁-C₄ alkyl and halogen;

R^5 and R^6 are each selected from H and methyl;

m is 0 or 1;

Q is carbonyl;

5 X represents a bond or methylene;

each R^a is independently selected from hydroxy; C₁-C₄ alkyloxy; C₁-C₄ alkyl secondary or tertiary amino;

10 each R^b is independently selected from halogen; cyano; C₁-C₅ heteroaryl, carboxy, C₁-C₄ alkyl; C₁-C₄ alkyl secondary or tertiary amido; C₁-C₄ alkyl carbonyl; C₁-C₄ alkyloxy carbonyl; C₁-C₄ alkyl secondary or tertiary acylsulphonamido; and C₁-C₅ heterocyclyl; and R^c is absent.

15 In one embodiment of the invention, in a compound of formula (I)

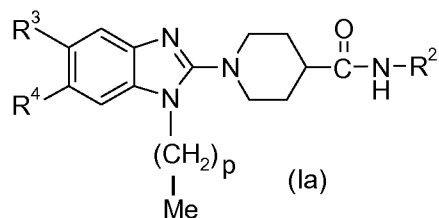
R¹ is selected from branched or unbranched C₁-C₁₀ alkyl; C₃-C₆ cycloalkyl; 5- or 6-membered C₃-C₅ heterocyclyl; and phenyl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a; and any heterocyclyl or phenyl moiety optionally is substituted with 1 or 2 groups R^b;

20 R² is selected from branched or unbranched C₁-C₆ alkyl; C₃-C₆ cycloalkyl; 5- or 6-membered C₃-C₅ heterocyclyl; and phenyl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a; and any heterocyclyl or phenyl moiety optionally is substituted with 1 or 2 groups R^b;

25 R³ and R⁴ are each independently selected from methyl and chloro; and

R⁵ and R⁶ are each selected from H.

30 In yet another embodiment of the invention, R¹ represents C₁-C₁₀ alkyl, e.g. C₁-C₈ alkyl, or C₁-C₆ alkyl; R² represents C₄-C₆ cycloalkyl or C₄-C₅ heterocyclyl, e.g. C₄-C₆ cycloalkyl or 5- or 6-membered C₄-C₅ heterocyclyl; R³ and R⁴ are independently selected from methyl and chlorine; R⁵ and R⁶ are hydrogen; X represents a bond; and Q represents carbonyl. Thus, in this embodiment, the compound of formula (I) may be represented by the formula (Ia):

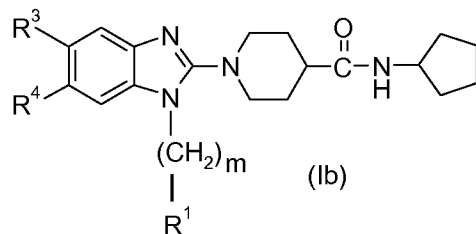


wherein the integer p is 0-11, e.g. 0-9, or 0-7.

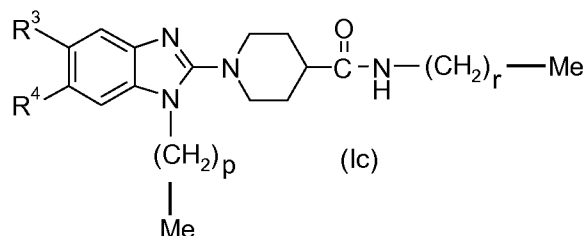
In yet another embodiment of the invention, R^1 represents C_3 - C_6 cycloalkyl; R^2 represents C_4 - C_6 cycloalkyl or C_4 - C_5 heterocyclyl; R^3 and R^4 are independently selected from methyl and chlorine; X represents a bond; and Q represents carbonyl.

In yet another embodiment of the invention, R^1 represents phenyl or C_4 - C_5 heterocyclyl; R^2 represents C_4 - C_6 cycloalkyl or C_4 - C_5 heterocyclyl; R^3 and R^4 are independently selected from methyl and chlorine; X represents a bond; and Q represents carbonyl.

In yet another embodiment of the invention, R^1 represents phenyl or C_4 - C_5 heterocyclyl, e.g. 5- or 6-membered C_4 - C_5 heterocyclyl, optionally substituted with one or more R^b ; R^2 represents cyclopentyl; R^3 and R^4 are independently selected from methyl and chlorine; the integer m is equal to 1 or 0 (zero); R^5 and R^6 are hydrogen; X represents a bond; and Q represents carbonyl. Thus, in this embodiment, the compound of formula (I) may be represented by the formula (Ib):

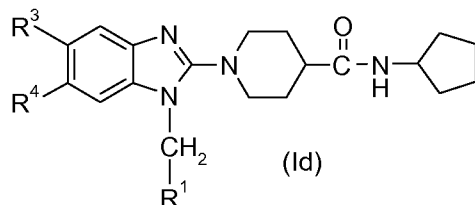


In yet another embodiment of the invention, R^1 represents C_1 - C_{10} alkyl, e.g. C_1 - C_8 alkyl, or C_1 - C_6 alkyl; R^2 represents C_1 - C_9 alkyl, e.g. C_1 - C_6 alkyl, or C_1 - C_4 alkyl; R^3 and R^4 are independently selected from methyl and chlorine, R^5 and R^6 are hydrogen; and Q represents carbonyl. Thus, in this embodiment, the compound of formula (I) may be represented by the formula (Ic):

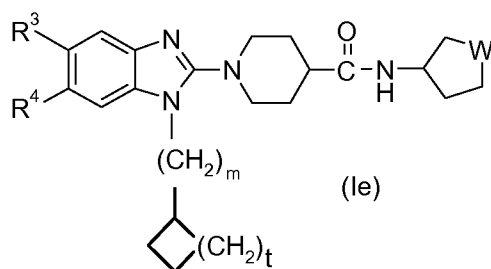


wherein the integer p is 0-11, e.g. 0-9, or 0-7; and the integer r is 0-12, e.g. 0-10, or 0-8.

In yet another embodiment of the invention, R^1 represents C_4 - C_5 saturated heterocyclyl, e.g. 5- or 6-membered C_4 - C_5 heterocyclyl; R^2 represents cyclopentyl; R^3 and R^4 are independently selected from methyl and chlorine; the integer m is equal to 1; R^5 and R^6 are hydrogen; X represents a bond; and Q represents carbonyl. Thus, in this embodiment, the compound of formula (I) may be represented by the formula (Id):



In yet another embodiment of the invention, R^1 represents C_3 - C_5 cycloalkyl; R^2 represents cyclopentyl or tetrahydrofuranyl; R^3 and R^4 are independently selected from methyl and chlorine; the integer m is equal to either 0 (zero) or 1; R^5 and R^6 are hydrogen; X represents a bond and Q represents carbonyl. Thus, in this embodiment, the compound of formula (I) may be represented by the formula (Ie):



wherein the integer t is 0, 1 or 2, and W is oxygen or methylene.

Unless otherwise specified, or apparent from the context, in preferred embodiments of the compounds of formulae (Ia), (Ib), (Ic), (Id), and (Ie), the identity of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , m , X , Q , R^a , R^b , and R^c , is as defined herein above in relation to the inventive compound of the general formula (I).

In another embodiment of the invention, there is provided a compound selected from:

N-cyclopentyl-1-(1-ethyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-propyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
 1-(1-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(1-heptyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-octyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- N*-cyclopentyl-1-(1-hexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(1-(2-(diethylamino)ethyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-4-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-sec-butyl-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 15 *N*-cyclopentyl-1-(5,6-dichloro-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(1-phenylethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 20 *N*-cyclopentyl-1-(5,6-dichloro-1-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-ethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(1-(3,5-difluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
methyl 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoate;
- 30 *N*-cyclopentyl-1-(5,6-dimethyl-1-((2-methylthiazol-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopropyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 35 *N*-cyclobutyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide;
1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-methoxyethyl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(isopropoxymethyl)piperidine-4-carboxamide;
5 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
N-(cyclohexylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
10 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-(cyclopentylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
15 *N*-cyclopentyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-cyanobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(1-(cyclopropylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
20 *N*-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
25 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
30 *N*-cyclopentyl-1-(1-(4-(dimethylcarbamoyl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-carbamoylbenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;

- N*-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 15 *N*-cyclopentyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 20 carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(5,6-dichloro-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-carbamoylbenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 30 carboxamide;
- N*-cyclopentyl-1-(1-cyclopentyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-chlorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;

- 1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 *N*-butyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-
- 10 4-carboxamide;
1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-
- 20 3-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 30 1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(2-methoxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 35 carboxamide;

- N*-cyclopentyl-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(cyclobutylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-(prop-2-ynyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(2-ethylbutyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-neopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 10 carboxamide;
- 1-(1-cyclohexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-sec-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentyl-piperidine-4-carboxamide;
- 15 *N*-cyclopentyl-1-(5,6-dichloro-1-(2-hydroxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1,5,6-trimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-isobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-benzyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 20 *N*-cyclopentyl-1-(1-(2-methoxyethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5-chloro-1-cyclobutyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 25 carboxamide;
- 1-(6-chloro-1-cyclobutyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 30 *N*-butyl-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- N*-butyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-benzyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(4-fluorobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 5 carboxamide;
- N*-(3-isopropoxypropyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(3,3-dimethylbutyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 *N*-(4-bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclohexyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(4-cyanobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 15 (S)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoic acid
- 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-
- 20 carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide;
- N*-(4-(1*H*-tetrazol-5-yl)benzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 30 carboxamide;
- 1-(1-(4-bromophenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- 1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 *N*-cyclopentyl-1-(5,6-dimethyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 30 *N*-cyclopentyl-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-(quinoxalin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(4-(methylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 35

- (R)-1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 10 carboxamide;
(R)-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(5,6-dichloro-1-(3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(4-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(1-(4-*tert*-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(5,6-dichloro-1-(4-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-
- 20 (tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-chloro-3-methoxyphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-
- 30 (tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(5,6-dichloro-1-(4-chloro-3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(1-(2,3-dihydrobenzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(2,3-dihydrobenzofuran-5-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3,5-diethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(5,6-dichloro-1-(cyclobutylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- (R)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 30 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- (R)-1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]-imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
(R)-1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]-imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;:
(R)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (S)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
N-butyl-1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide; *N*-butyl-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-
- 20 4-carboxamide;
1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5-chloro-1-(cyclobutylmethyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 30 1-(6-chloro-1-(cyclobutylmethyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
1-(5-chloro-6-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
1-(6-chloro-5-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;

- 1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-butyl-1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 10 carboxamide;
- N*-butyl-1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (*R*)-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dimethyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 20 yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (*R*)-1-(5,6-dichloro-1-(3-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(4-fluoro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3,5-difluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 30 yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(5-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dichloro-1-(3-isopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5,6-dichloro-1-(3-(difluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(4-isobutylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3,4-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(5,6-dichloro-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(5-fluoropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(1-(4-isobutylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-chloro-3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 (R)-1-(5,6-dichloro-1-(4-chloro-3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3,5-diethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(1-(3-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-tert-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-
- 10 carboxamide;
- (R)-1-(5,6-dichloro-1-(3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(6-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-isopropoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 20 yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-propoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-fluoro-3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5,6-dichloro-1-(4-chloro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-chloro-4-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-
- 30 carboxamide;
- (R)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(1-(3-cyanophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(1-(4-chloro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-chloro-4-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(benzo[d]thiazol-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(1-(benzo[d]thiazol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(3,4-dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(6-chloro-1-(3,4-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (S)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (S)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (S)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;
- 30 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;
- (R)-1-(1-(benzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(4-fluoro-3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-fluoro-5-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dichloro-1-(3-fluoro-5-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(1-(benzofuran-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(6-chloro-1-(4-ethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-tert-butylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(1-(4-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5,6-dichloro-1-(3-(cyclopentyloxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-cyclobutoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-6-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 30 carboxamide;
- 1-(6-chloro-5-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(5-chloro-1-ethyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;

- 1-(6-chloro-1-ethyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(5-chloro-6-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 1-(6-chloro-5-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-butyl-5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-butyl-6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
- 1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (*R*)-1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(6-chloro-5-methyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5-chloro-6-methyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 20 yl)piperidine-4-carboxamide;
- (*R*)-1-(5-chloro-6-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(6-chloro-5-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-
- 30 propoxycyclopentyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;

- 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide;
- 5 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(furan-2-ylmethyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide;
- (*R*)-1-(1-(5-bromopyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (*R*)-1-(1-(5-ethylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-chloro-5-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (*R*)-1-(5,6-dichloro-1-(3-chloro-5-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (*S*)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (*R*)-1-(5,6-dichloro-1-(5-chloropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 (*R*)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(5-chloropyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(5-fluoro-6-methylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(4-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-methoxy-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide; and
- (R)-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) of the invention can be prepared according to the synthetic routes outlined herein and by following the methods described herein below and illustrated in the

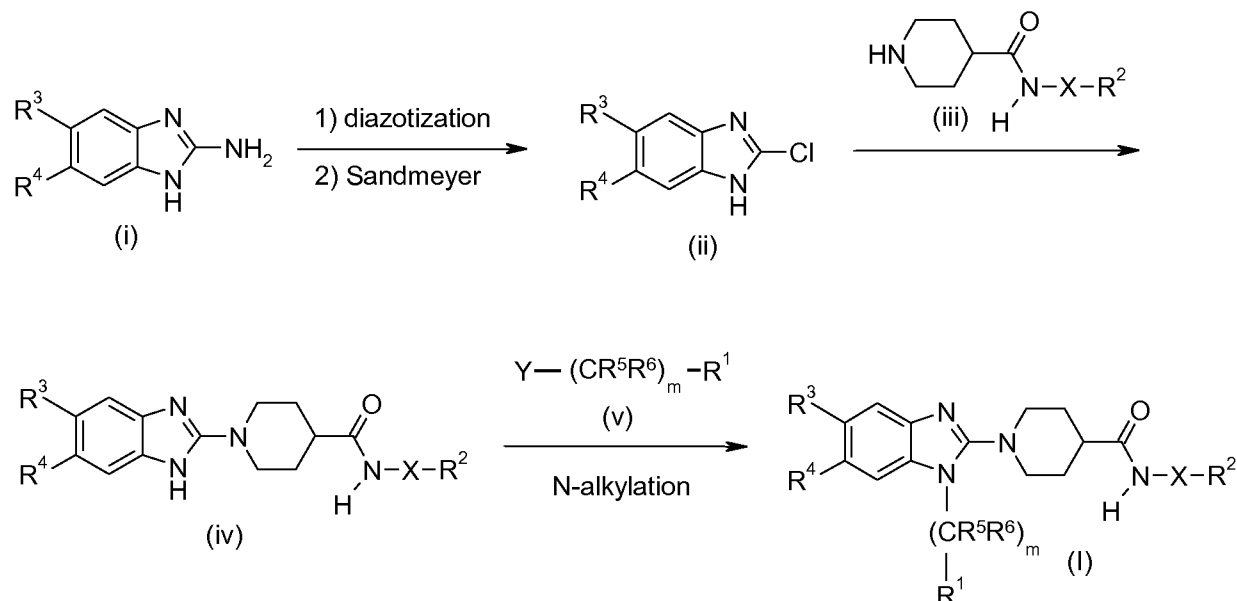
25 Examples. Alternative synthetic routes to these compounds can easily be visualized by any person skilled in the art and the present synthetic routes are not limiting for the invention. With respect to the reaction schemes below, although the various R¹, R², R³, R⁴, R⁵, R⁶, Q and X moieties sometimes are specifically defined, unless otherwise indicated, it is to be understood that R¹, R², R³, R⁴ and X may be any of the groups encompassed thereby.

30 As a non-limiting example, a compound of formula (I) as defined herein may be formed in a three step procedure wherein, first, a suitable substituted 2-aminobenzoimidazol (i) is diazotized and subjected to the Sandmeyer reaction, or any suitable modification of this method, the formed chloro intermediate (ii) is coupled with a piperidine-4-carboxamide derivative (iii) to form the product (iv), which subsequently is *N*-alkylated or arylated by Y-

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(CR⁵R⁶)_m-R¹ (v) to yield the final compound of formula (I). The entire synthetic route is depicted below in Reaction Scheme 1.

Reaction Scheme 1



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The process of forming diazonium compounds from aromatic or heteroaromatic amines has been known for more than 150 years and involves an amine that reacts with a nitrite salt such as sodium nitrite to form a diazonium salt at low temperature, a procedure that should be well known for the one skilled in the art. Typically diazonium compounds are not isolated, but used immediately in further reactions as described below in the Sandmeyer reaction. Diazonium compounds can, however, also be isolated as tetrafluoroborate salts. Conditions suitable for the Sandmeyer reaction are well known to the person skilled in the art and comprise an diazonium salt of an aromatic or heterocyclic kept at low temperature, which is decomposed in the presence of copper(I) salts, such as copper(I) chloride or copper(I) bromide, to form the desired chloro or bromo derivative. Several modifications to the standard procedures above have been made and are exemplified by the use of t-butyl nitrite and anhydrous copper(II) chloride or copper(II) bromide at elevated temperatures [Doyle, M. P.; Siegfried, B.; Dellaria Jr, J. F. Alkyl nitrite-metal halide deamination reactions. 2. Substitutive deamination of arylamines by alkyl nitrites and copper(II) halides. A direct and remarkably efficient conversion of arylamines to aryl halides. *J. Org. Chem.* **1977**, *42*, 2426-2431], t-butyl thionitrite and copper(II) chloride or copper(II) bromide employed at room temperature [Oae, A.; Shinhama, K.; Kim, Y. H. Direct conversion of arylamines to the corresponding halides, biphenyls and sulfides with t-butyl thionitrate. *Chem. Lett.*, 1979, 939-942] and mixtures of Cu(I) and Cu(II) chloro and bromo salts, used in catalytic amounts in the presence of the bidentate ligand phenanthroline and phase-

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transfer catalyst dibenzo-18-crown-6 [Beletskaya, I. P.; Sigeev, A. S.; Peregodov, A. S.; Petrovskii, P. V. Catalytic Sandmeyer Bromination. *Synthesis*, **2007**, 2534–2538]. In this context, it should be contemplated that a wide variety of methods exists for the transformation of (i) into (ii) and several exhaustive review articles on the topic can be found in the literature.

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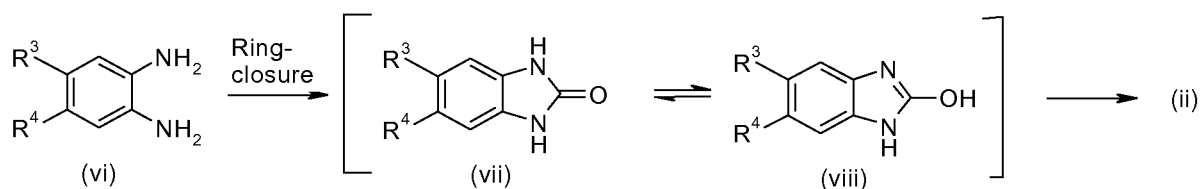
Conditions suitable for the coupling of aromatic and heteroaromatic halides, such as chlorides, with aliphatic amine chains or secondary amine aliphatic ring structures such as piperidine derivatives as (iii) are well known for the one skilled in the art, and there exists a wealth of different methods in the scientific literature, summarized in for example: “*Advanced Organic Chemistry*”, 4th edition, Jerry March, Wiley-Interscience publication, 1992, p 656-657, including the references cited therein. In the present invention the chloro intermediate (ii) is reacted with the piperidine-4-carboxamide derivative (iii) to form the coupled product (iv) in the presence of a base, such as as *N,N*-diisopropylethylamine (Hünig’s base, DIEA, CAS Registry Number: 7087-68-5), in a suitable solvent, such as 1,4-dioxane. Obviously other alternative good bases that are poor nucleophiles can be employed, such as, but not limited to 2,2,6,6-tetramethylpiperidine (TMP, CAS Registry Number: 768-66-1).

In the transformation of (iv) into the final compound of formula (I), *N*-alkylation or *N*-arylation by $Y-R^1$ (v) is employed. For the *N*-alkylation, (iv) is treated with a chloro-, bromo or iodoalkyl electrophile in the presence of a base such as caesium carbonate in a solvent such as acetonitrile and/or *N,N*-dimethylformamide. A palladium catalyst, such as, but not limited to [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2(dppf)$, CAS Registry Number: 72287-26-4) can also be employed in this reaction. Possible use of alternative bidentate palladium-catalysts for a successful *N*-alkylation might involve [1,2-bis(diphenylphosphino)-ethane]dichloro-palladium(II) ($PdCl_2(dppe)$, CAS Registry Number: 19978-61-1), [1,4-bis(diphenylphosphino)-butane] dichloropalladium(II), $PdCl_2(dppb)$, and the like, all well known for the one skilled in the art. For the *N*-arylation, (iv) is treated with a haloaryl in the presence of a base such as caesium carbonate, and an agent as 1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline or 8-hydroxyquinoline, polyethylene glycol and copper(I) oxide in a solvent such as dimethylsulfoxide. Yet other combinations of bases, catalysts, solvents and agents can be appropriately employed and are well known for those skilled in the art [eg. Preston, P. N. Synthesis, reactions, and spectroscopic properties of benzimidazoles. *Chem. Rev.*, **1974**, 74, 279–314], and are well within the scope of the invention.

An alternative preparation of (ii) is depicted in Reaction Scheme 2 and involves the treatment of a suitable substituted diamine (vi) with excess stoichiometric amounts of the carbonyl source

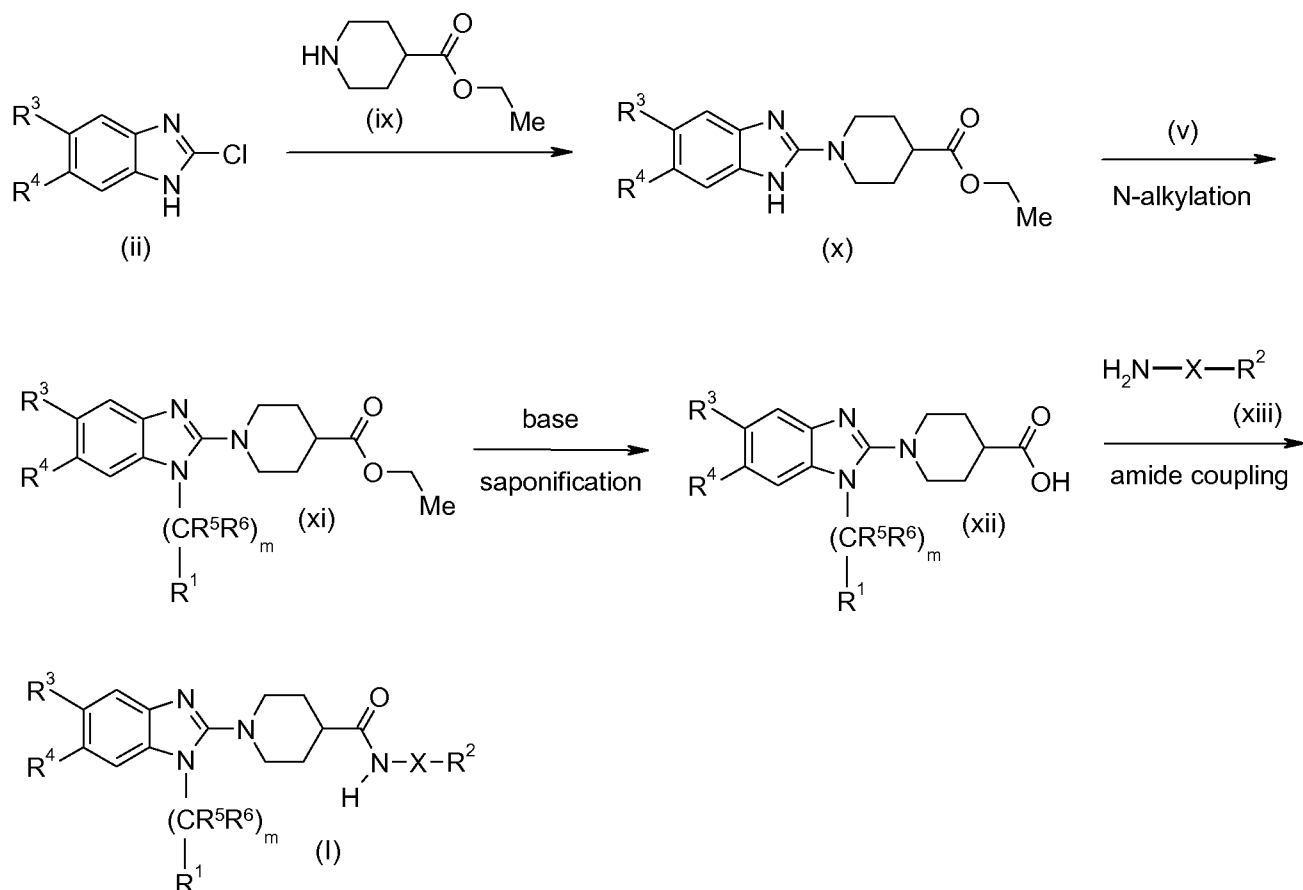
N,N-carbonyl dimidazole (CDI, CAS Registry Number: 530-62-1) in a solvent such as tetrahydrofuran, in order to achieve ring-closure to the corresponding tautomeric most stable benzoimidazol-2-one (vii). The ring-closure of aromatic or heteroaromatic diamines is well-known in the literature and might involve the use of alternative of carbonyl sources exemplified by the usage of carbon monoxide in the presence of catalytic amounts of tungsten hexacarbonyl (CAS Registry Number: 14040-11-0). Subsequently, the tautomeric -ol form (viii) can be transformed to the intermediary (ii) via treatment with phosphoryl trichloride (CAS Registry Number: 10025-87-3), as exemplified in the invention. Alternative reagents include phosphorus pentachloride (CAS Registry Number: 10026-13-8) or phosphorus trichloride (CAS Registry Number: 7719-12-2), the former also, alone or as mixtures in various ratios, or any other chlorination agent, all that exists in abundance in the scientific literature, for the purpose of transforming a hydroxyl group to a chlorine group. In this context, it should be contemplated that the corresponding bromo derivative of (ii) also can be useful as an intermediate in the reaction schemes, leading to the target compounds of the invention, and could be prepared by the action of phosphoryl bromide (CAS Registry Number: 7789-59-5) phosphorus tribromide (CAS Registry Number: 7789-60-8) and/or phosphorus pentabromide (CAS Registry Number: 7789-69-7), or any other brominating agent, all that exists in abundance in the scientific literature, for the purpose of transforming a hydroxyl group to a bromine group.

Reaction Scheme 2



Alternative synthetic strategies for the preparation of a compound of formula (I) are shown in Scheme 3. For example, the chloro intermediate (ii), can be coupled with piperidine-4-carboxylic acid derivative (ix) to form the coupled product (x), which subsequently is N-alkylated by Y-(CR⁵R⁶)_m-R¹ (v), the ethyl ester saponificated to give the carboxylic acid derivative, which can be subjected to amide coupling with H₂N-X-R², to yield the final compound of formula (I). This method is foremost useful when the R²-position needs to be varied, while the R¹-substituent is kept constant during the preparation.

Reaction Scheme 3



The carboxylic acid ester (xi) is saponified with a base such as aqueous sodium hydroxide and a solvent such as ethanol. Acidification of the completed reaction mixture is followed by standard work-up and crystallization or chromatography, to yield the carboxylic acid (xii). A wide variety of other protecting groups for the carboxylic acid can be employed, and their usage is known to those skilled in the art (references describing protecting group strategy include, for example, *"Protecting Groups in Organic Chemistry"*, J. F. W. McOmie, Plenum Press, London, New York, 1973, and *"Protective Groups in Organic Synthesis"*, T. W. Greene, Wiley, New York, 1984).

Conditions suitable for amide coupling, as exemplified herein by the acid derivative (xii) and the amine H_2N-X-R^2 (xiii), are well-known to the person of ordinary skill in the art, and may be e.g. obtained by performing the reaction of acid and amine in the presence of a suitable amide coupling reagent, such as 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; CAS Registry Number: 148893-10-1) and *N,N*-diisopropylethylamine in a suitable solvent, such as dichloromethane, or by reacting the acid derivative in the presence of e.g. triethylamine in a suitable solvent, such as chloroform or in the presence of *N,N*-diisopropylethylamine in a suitable solvent, such as dichloromethane.

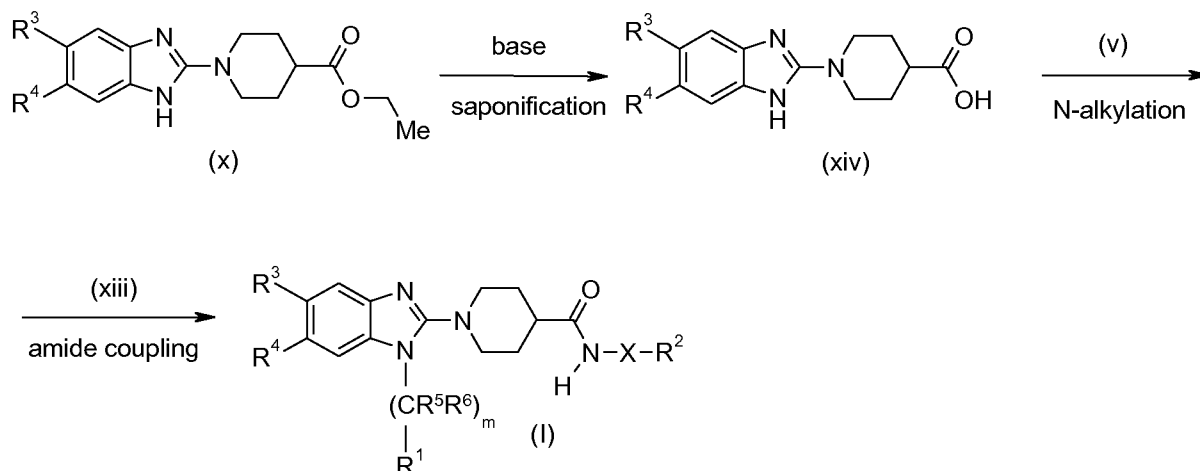
A number of other chemical transformations may also be used within the present invention, all which readily could be modified and improved by the one skilled in the art.

Apart from traditional heating, such as the use of heating blocks, heat transfer via oil baths or the like, the present invention also involve the use of microwave irradiation for heating purposes, which today is well known for the one skilled in the art, as witnessed by a large number of book chapters and published books [eg. Strauss, C. R., Application of microwaves for environmentally benign organic chemistry, In *Handbook of Green Chemistry and Technology*, Clark, J.; Macquarrie, D., Eds. Blackwell Science Ltd: Oxford, 2002, pp 297-415; Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**; Watley, B.; Tierney, J.; Lidström, P.; Westman, J. The impact of microwave assisted organic chemistry on drug discovery. *Drug Discov. Today*, **2002**, 7, 373-380].

All reaction mixtures are purified by standard purification procedures as extraction, washing, recrystallization, and column chromatography employing silica gel, alumina or reverse phase and the like, employing the appropriate eluents for the purification of the Examples described herein.

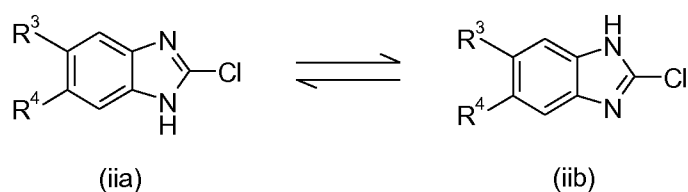
The compounds of the invention can also be prepared by the application of combinatorical and/or parallel chemistry techniques eg. methods of making libraries of compounds, techniques well known for the one skilled in the art, which can include solution phase synthesis, and solid phase synthesis including design of resins, linkers and the like. For example (Scheme 4), (x) can be saponificated to give the intermediate (xiv) that can serve as a suitable scaffold for further manipulation. It can then be contemplated that *N*-alkylation with (v), followed by amide coupling with (xiii) can be conducted in one pot (in the same reaction vessel) if the two reactions are selective in terms of regioselectivity (a term that is well known for the one skilled in the art), which also includes the reverse reaction order eg. amide coupling followed by *N*-alkylation, or alternatively both reactions acting at the same time. This can lead to compounds of formula (I) of the invention in a shorter time than traditional consecutive synthesis, albeit an approach not excluded from the present invention.

Reaction Scheme 4



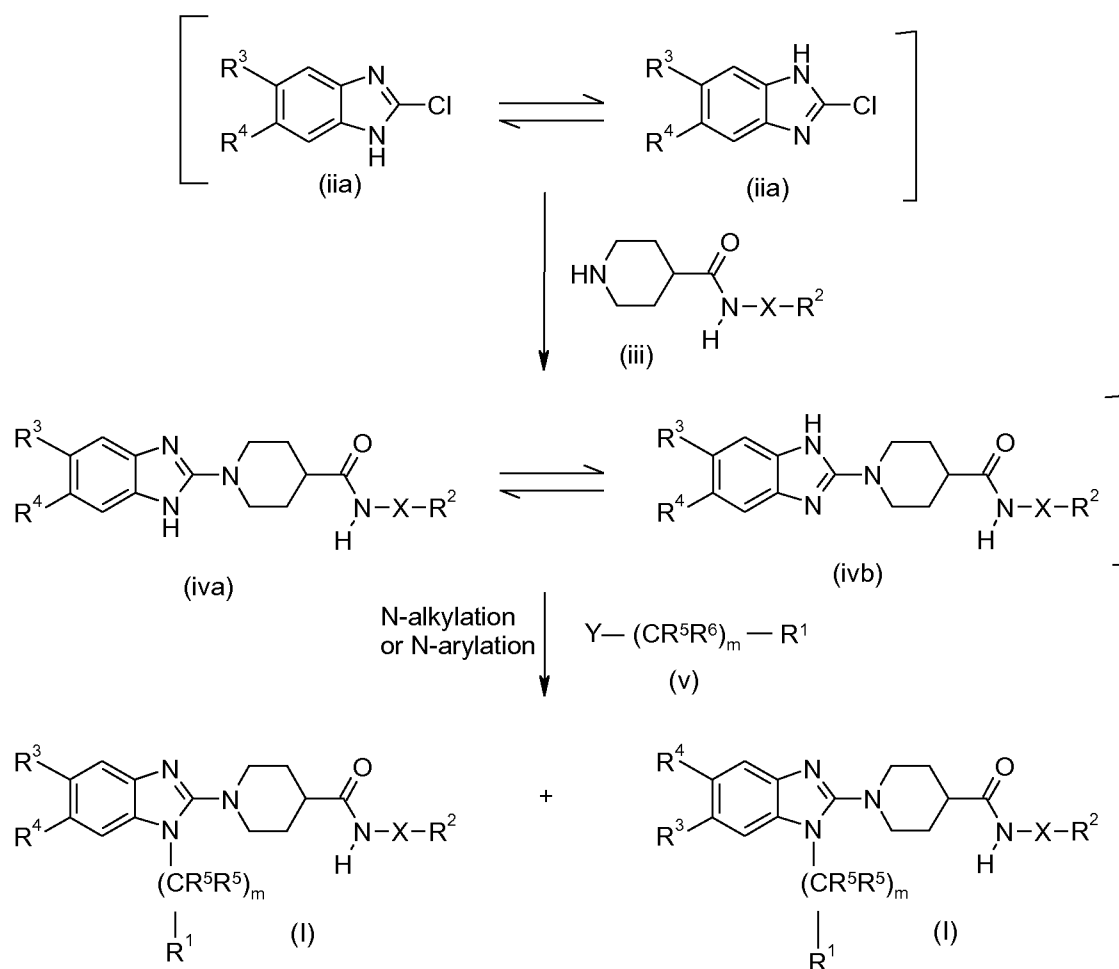
All above is provided when R³ and R⁴ is the same atom or group. On the other hand, when R³ and R⁴ is dissimilar, for instance when R³ is methyl and R⁴ is chlorine, then two tautomeric forms of (ii) will exist as shown in Reaction Scheme 6 (iia and iib). The knowledge of tautomers is well known for the one skilled in the art, and numerous scientific book chapters, reviews and papers have examined various aspects of this phenomenon. [eg. The Chemistry of Heterocyclic Compounds, Benzimidazoles and Cogeneric Tricyclic Compounds (Chemistry of Heterocyclic Compounds: A Series Of Monographs), Preston, P. N. Smith, D. M. and Tennant, G. (Eds), John Wiley & Sons Inc, 1981].

10 Reaction Scheme 5



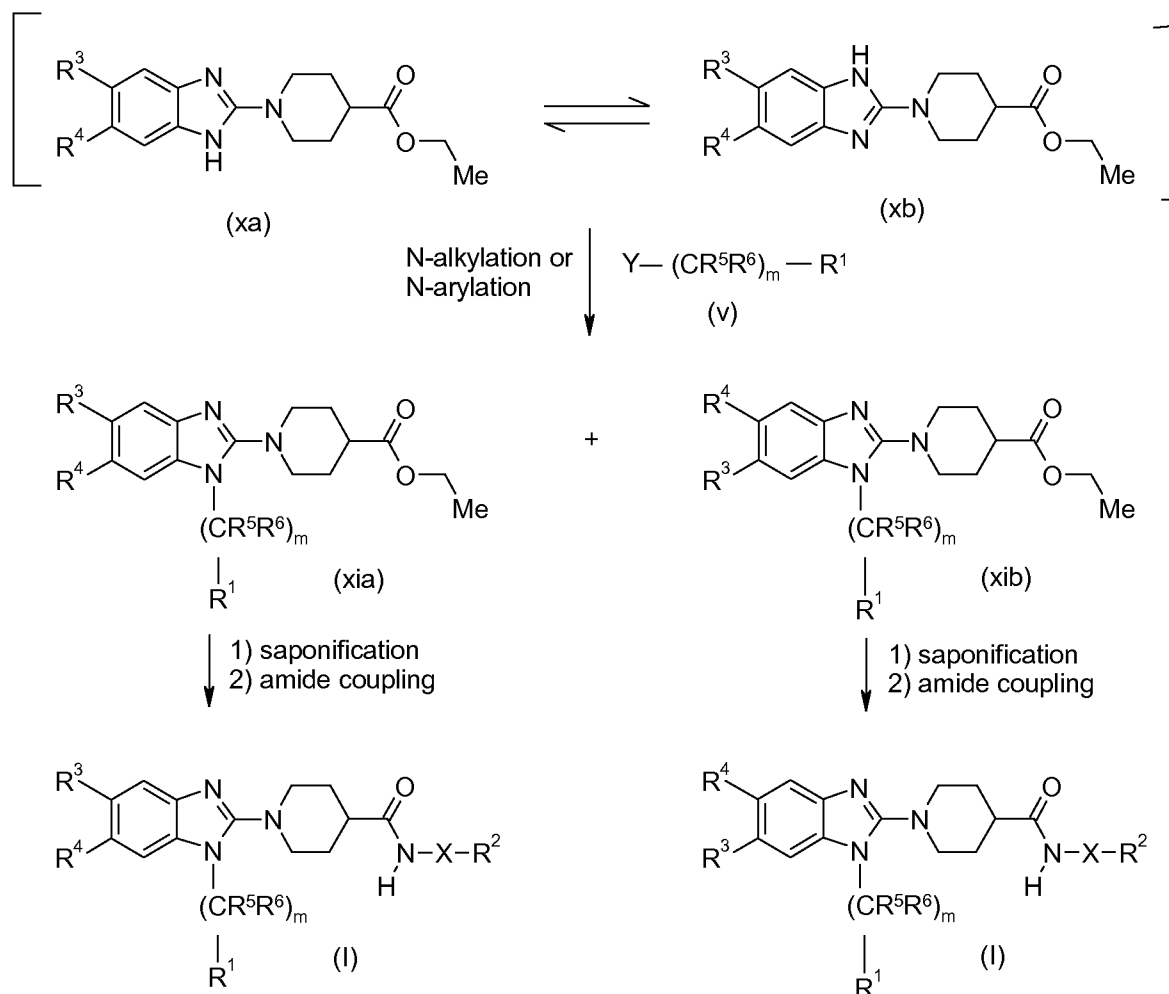
Outlined in Reaction Scheme 7 is the one of the synthetic strategies of the invention that involves tautomeric forms of the intermediate compounds. Accordingly, the tautomeric mixture of (iia) and (iib) is treated with a nucleophilic agent, as exemplified by (iii), but not restricted to, then yet two tautomeric compounds (iva) and (ivb) are formed. In the final step an N-alkylating agent (v) is employed and a regioisomeric mixture of end products (I) is formed, which might be tested directly in biological assays. Alternatively, the regioisomers of the mixture can be separated before biological testing, using for instance column chromatography, recrystallization, sublimation or any other methods available for the one skilled in the art of chemical separation. In the present method the final purification can only take place after the final synthetic step, since all previous intermediates are tautomers.

Reaction Scheme 6



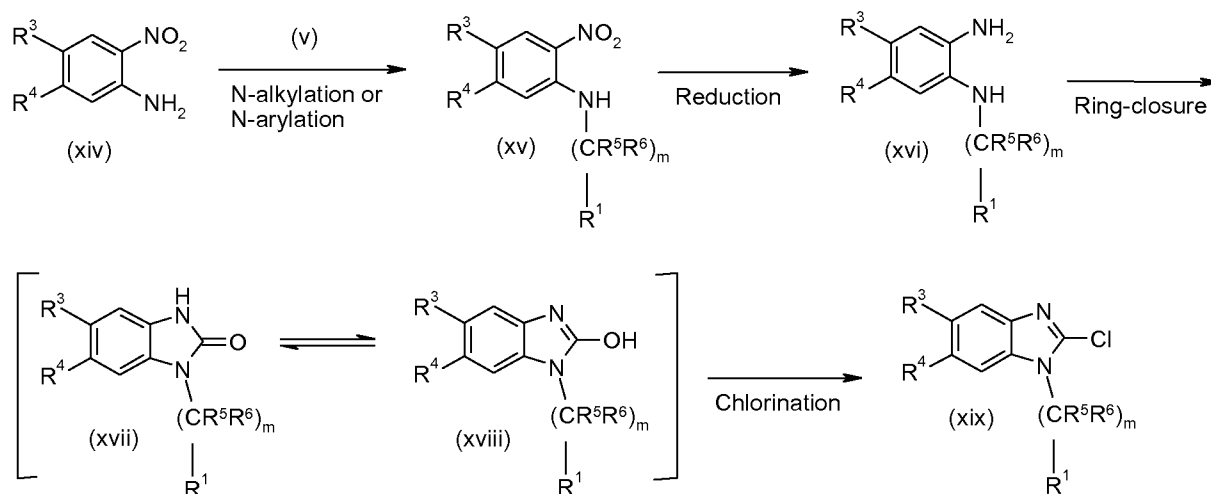
Alternatively, and also within the scope of the invention, N-alkylation or N-arylation can be introduced at an earlier stage in the synthetic procedure, as exemplified shown in Reaction Scheme 7. This will provide the compounds (xia) and (xib), which already at this stage can be separated using any of the techniques mentioned above. As exemplified in Reaction Scheme 7, this strategy will ultimately lead to the end products (I). This synthetic strategy can, for example, be considered when the final Examples are difficult to separate, or because of any other advantageous reason.

10 Reaction Scheme 7



Furthermore, the invention at hand also comprises a synthetic method that is strictly regioselective when R^4 and R^5 are dissimilar. This is outlined in Reaction Scheme 8 and the synthetic strategy involves the introduction of the N-arylating agent (v) at an early stage in the synthesis in order to obtain control over regioselectivity. The ortho-nitroaniline (xiv) is arylated at the amine to give (xv), the nitro group reduced to the diamine (xvi), ring-closed to the tautomers (xvii) and (xviii) and finally chlorinated to give (xix). The resulting compound (xix) can then be transformed to the appropriate end-product by any of the methods described above.

Reaction Scheme 8

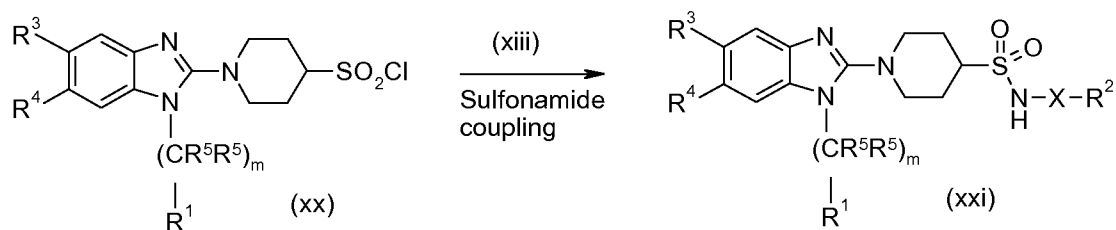


In this context it should be understood that when N-alkylation is mentioned in the text or in the Reaction Schemes, then the N-arylation of the available -NH- or -NH_2 group is not excluded, but an important aspect of the present invention. Also, when only N-arylation is mentioned, then should neither N-alkylation be excluded.

The present invention also comprises stereoisomers that, for example, are prepared with the available methods described above. A large number of available single enantiomers are available commercially or in the literature. The single enantiomers can be amines that are used in the amide coupling of present invention, such as, but not limited to, (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (CAS Registry Number: 111769-27-8), (S)-(-)-tetrahydrofuran-3-amine hydrochloride (CAS Registry Number: 204512-95-8), (1*S*,2*S*)-*trans*-2-aminocyclopentanol hydrochloride (CAS Registry Number: 68327-04-8), (1*R*,2*R*)-*trans*-2-aminocyclopentanol hydrochloride (CAS Registry Number: 68327-11-7).

When Q is sulfonyl, this results in compounds of the invention that are sulfonamides, which can be prepared employing reaction conditions that are very well known from the scientific literature (see for example: "Advanced Organic Chemistry", 4th edition, Jerry March, Wiley-Interscience publication, 1992, p 499). For example, if a suitable substituted piperidine sulfonyl chloride (xv) is reacted with a suitable substituted amine derivative (xiii), a sulfonamide derivative of formula (I) can be formed as shown in Reaction Scheme 9.

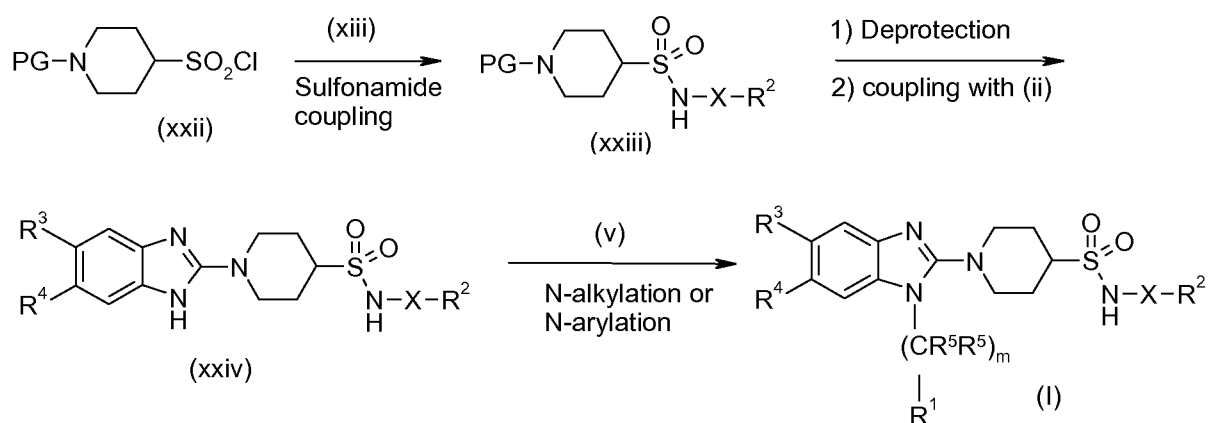
Reaction Scheme 9



Compounds wherein Q is sulfinyl can be prepared using an analogous method as described in Reaction Scheme 9, as well as treatment of sulfonamides with reductive agents, procedures well known for the one skilled in the art.

- 5 Alternatively, and within the scope of the invention, (xxii), which includes a protection group PG, is coupled with an amine (xiii) to give the sulphonamide (xxiii), that can be coupled, after de-protection with a suitable halobenzimidazole (ii), and finally N-alkylated or N-arylated with (v) to the end products (I). The synthetic procedure is shown in Reaction Scheme 10.

Reaction Scheme 10

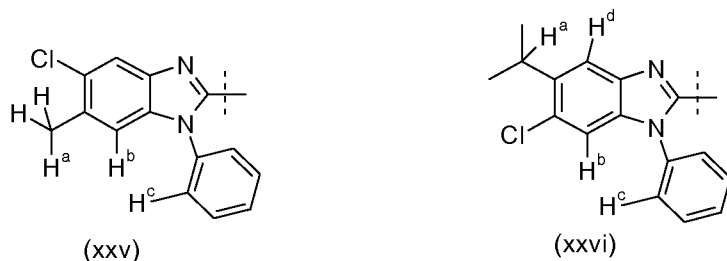


The above methods, as outlined in Schemes 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 are only exemplary and it is contemplated that the skilled person will be able to modify them in view of the particular compound according to formula (I) that is to be prepared, or even to identify other equally suitable methods.

- 15 It should be contemplated that several spectroscopic methods are available for the structural determination of regioisomers. For example, when R^3 is dissimilar to R^4 , the Nuclear Overhauser effect (NOE) can be utilized to determine the exact structure of the Example, since the NOE is observed through space, and not through bonds. Consequently, all atoms that are in proximity to each other give a NOE. For example, and utilized in the present invention, the NMR technique
- 20 NOESY (Nuclear Overhauser Effect Spectroscopy) is used for determination of the nature of the

R³ and R⁴ substituents. For example, A NOE effect can be seen between the H^a, H^b and H^c protons in (xxv), and reveals that H^b correlates with both H^a and H^c in the 2-dimensional plot. On the other hand, in (xxvi) H^a and H^d correlates as a pair, as H^b and H^c.

Reaction Scheme 11



The compounds according to formula (I) will be useful for treating various diseases such as inflammatory diseases, nociceptive pain, auto-immune disease, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular disease. The treatment may be preventive, palliative or curative.

- 10 Examples of pharmaceutically acceptable addition salts for use in the pharmaceutical compositions of the present invention include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, and arylsulphonic acids. The pharmaceutically acceptable excipients described herein, for
- 15 example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. The pharmaceutically acceptable carrier may be one that is chemically inert to the active compounds and that has no detrimental side effects or toxicity under the conditions of use. Pharmaceutical formulations are found e.g. in Remington: The Science and Practice of Pharmacy, 19th ed., Mack Printing Company, Easton, Pennsylvania
- 20 (1995).

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents.

- 25 Consequently, compounds of formula (I) can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared,

they can be separated by conventional methods, which for example is chromatographic or fractional crystallization.

Prodrugs of the compounds of formula (I) may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, in vivo when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesizing the parent compound with a prodrug substituent. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group in a compound of formula (I) is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, *N*-acyl derivatives, *N*-Mannich bases. General information on prodrugs may be found in the scientific literature [eg. Bundegaard, H. "Design of Prodrugs" p 1-92, Elsevier, New York-Oxford, 1985; *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., chapter 31, Academic Press, 1996; *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. chapter 5, pgs 113 – 191, Harwood Academic Publishers, 1991). Said references are incorporated herein by reference. All prodrugs of the compounds of the invention are included within the scope of the invention.

The compounds of the formula (I) can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, aqueous or oily suspensions or solutions, elixirs, syrups, capsules, granules or powders; sublingually; buccally; ocular; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions). Also, the compounds of the formula (I) may be applied as gargles and mouth washes. For parenteral administration, a parenterally acceptable aqueous or oily suspension, emulsion or solution is employed, which is pyrogen free and has requisite pH, isotonicity and stability. Those skilled in the art are well able to prepare suitable formulations and numerous methods are described in the literature. A brief review of methods of drug delivery is also found in the scientific literature [eg. Langer, *Science* 249:1527-1533 (1990)]. Furthermore, the compounds of the formula (I) can be administered nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a gel, cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended release.

Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally. The precise nature of the carrier or other material will
5 depend on the route of administration and those skilled in the art are well able to prepare suitable solutions and numerous methods are described in the literature.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a
10 suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula (I) can also be delivered through the oral cavity by
15 sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also
20 include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions, emulsions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, oil or other suitable dispersing or wetting and suspending agents, including
35 synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the mammal over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including the potency of the specific compound, the age, condition and body weight of the patient, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration, as well as the stage and severity of the disease. The dose will also be determined by the route (administration form), timing and frequency of administration. Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 mg per kg of body weight per day (mg/kg/day) to 20 mg/kg/day, and most preferably 0.1 to 10 mg/kg/day, for adult humans. For oral administration, the compositions are preferably provided in the form of tablets or other forms of presentation provided in discrete units containing 0.5 to 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated, for example 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 200, 400, 500, 600 and 800 mg..

Parenterally, especially intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. A nasal, sublingual or buccal administration

typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from about 1 mg to about 100 mg of active ingredient, per dose.

5 The compounds of the present invention may be also be used or administered in combination with one or more additional drugs useful in the treatment of inflammatory diseases, nociceptive pain, auto-immune diseases, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular diseases. The components may be in the same formulation or in separate formulations for administration simultaneously or sequentially. The compounds of the present invention may also be used or administered in combination with other
10 treatment such as irradiation for the treatment of cancer.

Accordingly, in a further aspect of the invention, there is provided a combination product comprising:

- (A) a compound of the invention, as hereinbefore defined; and
15 (B) another therapeutic agent that is useful in the treatment of inflammatory diseases, nociceptive pain, auto-immune disease, breathing disorders, fever, cancer, inflammation related anorexia, Alzheimer's disease and cardiovascular diseases., wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier. Such combination products provide for the administration of a compound of the invention in
20 conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

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Thus, there is further provided:

- (1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and
30 (2) a kit of parts comprising components:
(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

- 5 Compounds of the formula (I) will be useful as partial or complete substitute for cyclooxygenase-2 inhibitors and conventional NSAIDs in preparations wherein they are presently co-administered with other agents or ingredients.
- Examples of such agents for the administration in combination with compounds of the invention, include suitable anti-inflammatory, anti-pain, anti-autoimmune, anti-fever, anti-cancer and anti-anorexia (inflammatori) agents, and agents for the treatment or prevention of breathing
- 10 disorders, cardiovascular diseases and Alzheimer's disease. a potentiator including caffeine, an H₂ antagonist, aluminium or magnesium hydroxide, simethicone, a decongestant, an antitussive, an antihistamine, a diuretic, a proton pump inhibitor, a bradykinin-1 antagonist, a sodium channel blocker, a 5-HT agonist or a CGRP antagonist.
- 15 More specifically compounds for use in combination with the compounds of the present invention include, but is not limited to, prednisone (CAS Registry Number: 53-03-2); dexamethasone (CAS Registry Number: 50-02-2); any of the selective glucocorticoid receptor agonists (SEGRAs) exemplified by A276575 (Lin, C. et al. *Mol. Pharm.*, **2002**, 62, 297-303), and ZK209614 (Schäcke, H. et al, *Proc. Natl. Acad. Sci. USA.*, **2004**, 101, 227-232); aspirin
- 20 (CAS Registry Number: 50-78-2); indomethacin (CAS Registry Number: 53-86-1) particularly dosed as local treatment with gel or spray; ibuprofen (CAS Registry Number: 15687-27-1); piroxicam (CAS Registry Number: 36322-90-4; CTLA4-Ig agonists/antagonists (Kremer, J. M. et al, *N Engl J Med.* **2003**, 349, 1907-1915); Inosine-5'-monophosphate dehydrogenase inhibitors (Whitby, F. G. et al., *Biochemistry*, 1997, 36, 10666-10674), such as mycophenolate (CAS
- 25 Registry Number: 24280-93-1); tumor necrosis factor (TNF) antagonists as infliximab (CAS Registry Number: 170277-31-3); adalimumab (CAS Registry Number: 331731-18-1); etanercept (CAS Registry Number: 185243-69-0) and pentoxifylline (CAS Registry Number: 6493-05-6); orazipone (OR-1384); integrin antagonists; cell adhesion inhibitors; interferon gamma antagonists; budesonide (CAS Registry Number: 51333-22-3); clofazimine (CAS Registry
- 30 Number: 2030-63-9); selective thyroid hormone agonists such as GC-1 (Johansson, L. et al., *Proc. Natl. Acad. Sci. USA.* **2005**, 102, 10297-10302), KB2115 (Berkenstam, A. et al., *Proc. Natl. Acad. Sci. USA.* **2008**, 105, 663-667); KB-141 (Grover, G. J. et al., *Proc. Natl. Acad. Sci. USA.* **2003**, 100, 10067-10072); and MB07811 (Erion, MD et al., *Proc. Natl. Acad. Sci. USA.* **2007**, 104, 15490-15495); selective farnesoid X receptor agonists (FXRs) such as WAY-362450
- 35 (Flatt, B. et al., *J. Med. Chem.* **2009**, 52, 904-907); CD4 antagonists such as priliximab (CAS

Registry Number: 147191-91-1); p38 mitogen-activated protein kinase inhibitors such as SB203580 (CAS Registry Number: 152121-47-6); mesalazine (CAS Registry Number: 89-57-6); azathioprine (CAS Registry Number: 446-86-6); sumatriptan (CAS Registry Number: 103628-46-2); paracetamol (CAS Registry Number: 103-90-2); fast-acting bronchodilators such as salbutamol (CAS Registry Number: 18559-94-9) and ephedrine (CAS Registry Number: 299-42-3); rituximab; NO-releasing drugs such as nitroglycerine (CAS Registry Number: 55-63-0) and isosorbide dinitrate (CAS Registry Number: 87-33-2); Selective Estrogen Receptor Modulators (SERMs) such as tamoxifen (CAS Registry Number: 10540-29-1); raloxifene (CAS Registry Number: 84449-90-1) and toremifene (CAS Registry Number: 89778-26-7); selective Liver X receptor (LXR) agonists such as T0901317 (CAS Registry Number: 293754-55-9, Repa, J. J. et al., *Science*, **2000**, 289, 1524-1529) and GW3965 (CAS Registry Number: 405911-17-3); anti-depressant drugs and pain-relievers, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as desvenlafaxine (CAS Registry Number: 93413-62-8); duloxetine (CAS Registry Number: 116539-59-4); milnacipran (CAS Registry Number: 92623-85-3); tramadol (CAS Registry Number: 27203-92-5) and bicipadine (CAS Registry Number: 71195-57-8).

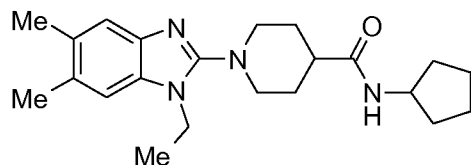
The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition.

The term "patients" include mammalian (including human) patients.

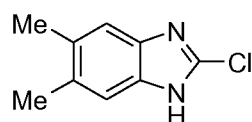
The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

The invention is illustrated by the following non-limiting Examples. In connection to these Examples, it should be noted that unless otherwise indicated, the expression "purified on reverse-phase hplc" will mean utilizing a preparative hplc-system comprising the following conditions and equipment: Shimadzu LC8A, C₁₈ column (22 x 250 mm, 10µm), acetonitrile/water gradient (0.1% trifluoroacetic acid), flowrate 15 mL/min.

EXAMPLES

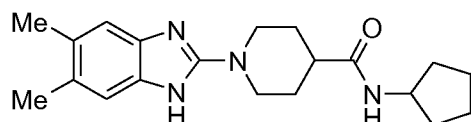
Example 1: *N*-cyclopentyl-1-(1-ethyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

(a) Preparation of the intermediary compound 2-chloro-5,6-dimethyl-1*H*-benzo[d]imidazole:



To a solution of sodium nitrite (3.77 g, 54.6 mmol) in water (220 mL) was added an aqueous solution of copper(II) chloride (12.24 g, 91.06 mmol, in 160 mL of water). The mixture was stirred at room temperature for 5 minutes and 5,6-dimethyl-1*H*-benzo[d]imidazol-2-amine (2.936 g, 18.21 mmol) was added to the mixture in portions for 5 minutes. The reaction mixture was stirred at room temperature for 1 hour, heated at 100°C for 1 hour and cooled down. The resulting reaction mixture was extracted with ethyl acetate (3 x 300 mL), the combined organic phases washed with brine (200 mL) and dried over anhydrous magnesium sulphate. After concentration *in vacuo*, the residue was subjected to column chromatography (silica gel, methanol/dichloromethane gradient elution consisting of 1-5% methanol), to give 1.054 g (29 % yield, 90 % purity) of 2-chloro-5,6-dimethyl-1*H*-benzo[d]imidazole that was used directly in the next step.

(b) Preparation of the intermediary compound *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:

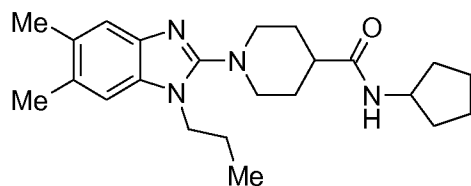


2-Chloro-5,6-dimethyl-1*H*-benzo[d]imidazole (3.59 mmol), *N*-cyclopentylpiperidine-4-carboxamide (3.95 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 927.3 mg, 7.18 mmol) and 1,4-dioxane (2 mL) were mixed in a microwave vial and sealed. The reaction mixture was heated at 180°C in a microwave oven for 1 hour. After cooling down the reaction mixture, the resulting slurry was filtered, the precipitate washed with 1,4-dioxane (5 mL) and dried under

vacuum over night. This gave 796 mg (65% yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 341.2 (M+1).

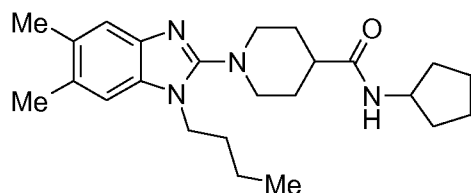
(c) *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), iodoethane (9.4 mg, 0.06 mmol), caesium carbonate (32.6 mg, 0.1 mmol) and acetonitrile (2 mL) were mixed and heated at 100°C. After 2 hours additional iodoethane was added and the reaction mixture was continued to be stirred over night at 100°C. After concentration *in vacuo*, the residue was subjected to column chromatography (Silica gel, methanol/dichloromethane gradient elution 0-10% methanol) to afford 5.4 mg (29% yield) of the title *N*-cyclopentyl-1-(1-ethyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 369.3 (M+1).

Example 2: *N*-cyclopentyl-1-(5,6-dimethyl-1-propyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), 1-iodopropane (17.0 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol) and acetonitrile (2 mL) were mixed and the reaction mixture heated at 100°C over night. After concentration *in vacuo*, the residue was subjected to column chromatography (Silica gel, methanol/dichloromethane gradient elution 0-10% methanol) to give 10.1 mg (53% yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-propyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 383.3 (M+1).

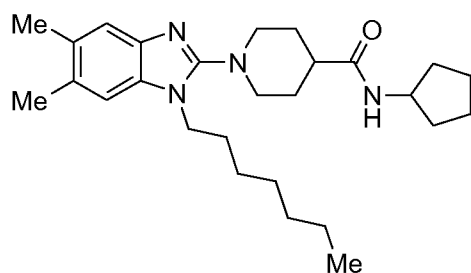
Example 3: 1-(1-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



1-(1-Butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-

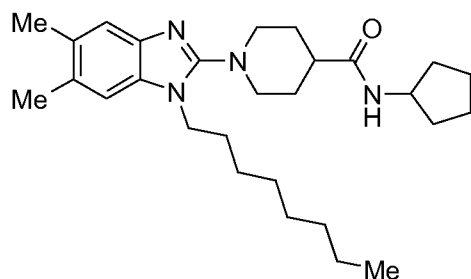
carboxamide (17.0 mg, 0.05 mmol), 1-iodobutane (18.4 mg, 0.1 mmol), caesium carbonate (48.9 mg, 0.15 mmol) and acetonitrile (2 mL), using the method described in Example 2 to give 6.9 mg (36% yield) of the title compound. LC-MS (m/z) 397.3 (M+1).

Example 4: *N*-cyclopentyl-1-(1-heptyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



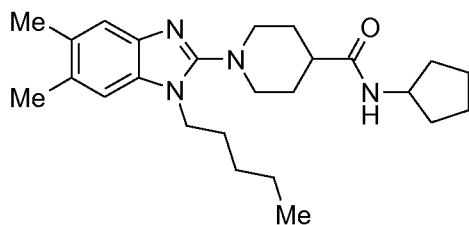
N-cyclopentyl-1-(1-heptyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), 1-bromoheptane (17.9 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol) and acetonitrile (2 mL), using the method described in Example 2 to give 12.2 mg (56 % yield) of the title compound. LC-MS (m/z) 439.4 (M+1).

Example 5: *N*-cyclopentyl-1-(5,6-dimethyl-1-octyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



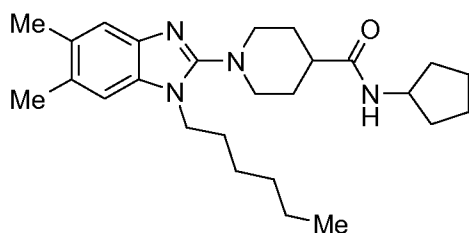
N-cyclopentyl-1-(5,6-dimethyl-1-octyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), 1-bromooctane (19.3 mg, 0.1 mmol), caesium carbonate (48.9 mg, 0.15 mmol) and acetonitrile (2 mL), using the method described in Example 2. This gave 8.4 mg (37% yield) of the title compound. LC-MS (m/z) 453.4 (M+1).

Example 6: *N*-cyclopentyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



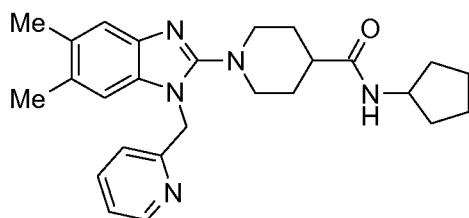
N-cyclopentyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), 1-bromopentane (15.1 mg, 0.1 mmol), caesium carbonate (48.9 mg, 0.15 mmol) and acetonitrile (2 mL), using the method described in Example 2 to give 9.2 mg (45 % yield) of the title compound. LC-MS (*m/z*) 411.4 (M+1).

Example 7: *N*-cyclopentyl-1-(1-hexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (34 mg, 0.10 mmol), 1-chlorohexane (14.5 mg, 16 mL, 0.120 mmol), caesium carbonate (65.2 mg, 0.20 mmol) and acetonitrile (2 mL) were mixed and stirred at 60°C over night, filtered, concentrated *in vacuo* and subjected to column chromatography (silica gel, methanol/ dichloromethane gradient elution 3-10 % methanol) to give 4.7 mg (11 %) of *N*-cyclopentyl-1-(1-hexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide.

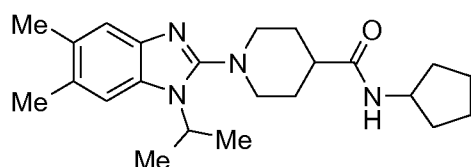
Example 8: *N*-cyclopentyl-1-(5,6-dimethyl-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (17.0 mg, 0.05 mmol), 2-(chloromethyl)pyridine hydrochloride (16.4 mg, 0.1 mmol), caesium carbonate

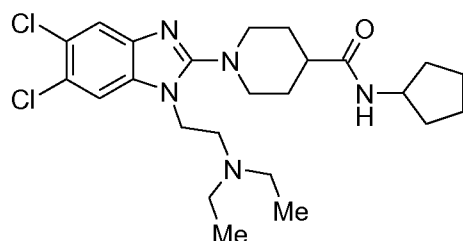
(65.16 mg, 0.3 mmol) and *N,N*-dimethylformamide (1.0 mL) were mixed in a microwave vial. The vial was sealed and irradiated in a microwave oven at 150°C for 30 minutes. The reaction mixture was concentrated in vacuo and purified on preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection). This gave 0.7 mg (3 % yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 432.3 (M+1).

Example 9: *N*-cyclopentyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

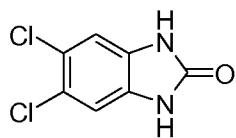


N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (356 mg, 1.046 mmol), caesium carbonate (1022 mg, 3.137 mmol), acetonitrile (30 mL), *N,N*-dimethylformamide (3 mL) and 2-bromopropane (386 mg, 3.14 mmol) were mixed and heated at 60°C over night. The reaction mixture was filtered, concentrated *in vacuo* and subjected to column chromatography (silica gel, methanol/dichloromethane, gradient elution using 1-5 % methanol) to give 314 mg (78 %) of *N*-cyclopentyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 383.2 (M+1).

Example 10: *N*-cyclopentyl-1-(1-(2-(diethylamino)ethyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

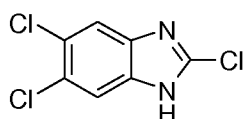


(a) Preparation of the intermediary compound 5,6-dichloro-1*H*-benzo[d]imidazol-2(3*H*)-one:



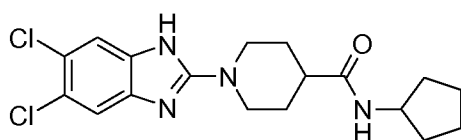
To a stirred solution of 4,5-dichlorobenzene-1,2-diamine (1.0 g, 5.6 mmol) in tetrahydrofuran (10 mL) was added N,N-carbonyl diimidazole (CDI, 1.36g, 8.4 mmol). The mixture was stirred at room temperature for 8 hours under Argon. The reaction mixture was concentrated in vacuo, the residue partitioned between diethyl ether (60 mL) and aqueous sodium hydroxide (60 mL, 1.0 N). The aqueous extract was acidified to reach a pH of approximately 5 by careful addition of aqueous hydrochloric acid (1.5 N). The resulting off-white solid was filtered off, washed with water (3 ×20 mL) and dried under high vacuum to give 0.68 mg (60 % yield) 5,6-dichloro-1*H*-benzo[d]imidazol-2(3*H*)-one.

10 (b) Preparation of the intermediary compound 2,5,6-trichloro-1 -benzo[d]imidazole:



To 5,6-dichloro-1*H*-benzo[d]imidazol-2(3*H*)-one (1.0 g, 4.5 mmol) was added phosphoryl trichloride (4 mL) and the reaction mixture was heated in a screw-cap pressure tube at 120°C for 2 hours. The reaction mixture was concentrated in vacuo, the residue was diluted with water (30 mL) and the resulting off-white solid was filtered off. The precipitate was washed with water (3×20 mL) and dried under high vacuum to afford 0.77 g (71 % yield) of 2,5,6-trichloro-1*H*-benzo[d]imidazole.

(c) Preparation of the intermediary compound N-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:

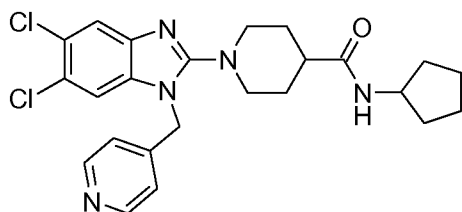


To a suspension of 2,5,6-trichloro-1*H*-benzo[d]imidazole (1g, 4.5mmol) in 1,4-dioxane (5 mL) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.094 mL, 5.4 mmol) followed by N-cyclopentylpiperidine-4-carboxamide. The mixture was heated in a screw cap pressure tube at 180°C for 2 hours. The reaction mixture was concentrated in vacuo, the residue washed with water and filtered off to afford 1.1 g (65 % yield) of N-cyclopentyl-1-(5,6-dichloro-1*H*-

benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 381.3 (M+1).

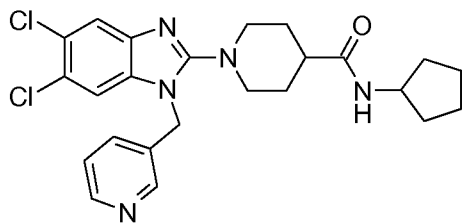
(d) To a suspension of sodium hydride (0.021 g, 0.52 mmol) in *N,N*-dimethylformamide (0.5 mL) was added *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.10 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) drop-wise at 0°C under Nitrogen. The reaction mixture was stirred at room temperature for 30 min and 2-bromo-*N,N*-diethylethylamine (0.101 g, 0.39 mmol) was added drop-wise. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with ice-water and extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) to obtain 12 mg (9.6 % yield) of *N*-cyclopentyl-1-(1-(2-(diethylamino)ethyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (m/z) 480.3 (M+1).

Example 11: *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-4-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



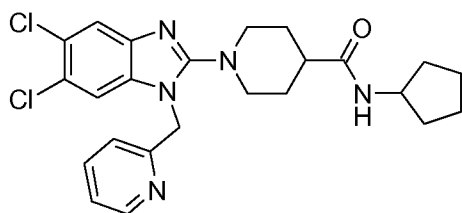
To a suspension of sodium hydride (0.021 g, 0.52 mmol) in *N,N*-dimethylformamide (0.5 mL) was added *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.10 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) drop-wise at 0°C under nitrogen gas. The reaction mixture was stirred at room temperature for 30 minutes and 4-(bromomethyl)pyridine hydrochloride (110 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 12 hours, quenched with ice and extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was subjected to preparative reverse-phase hplc to afford 81 mg (74 %) of *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-4-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (m/z) 472.1 (M+1).

Example 12: *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



5 N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from sodium hydride (72 mg, 0.30 mmol) in *N,N*-dimethylformamide (2 mL), *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (80 mg, 0.20 mmol) in *N,N*-dimethylformamide (2 mL) and 3-bromomethyl pyridinium hydrobromide (0.063g, 0.25mmol), using the method described in Example 11 to give 5 mg (5 % yield) of the title compound. LC-MS (*m/z*) 472.3 (M+1).

Example 13: *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

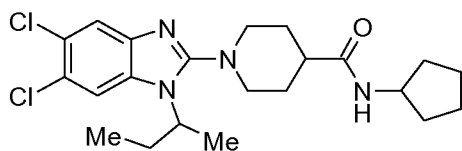


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N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from sodium hydride (72 mg, 0.30 mmol) in *N,N*-dimethylformamide (2 mL), *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (80 mg, 0.20 mmol) in *N,N*-dimethylformamide (2 mL) and 2-bromomethyl pyridinium hydrobromide (0.063g, 0.25mmol), using the method described in Example 11 to give 5 mg (5 % yield) of the title compound. LC-MS (*m/z*) 472.2 (M+1).

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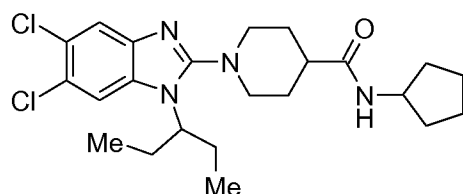
Example 14: 1-(1-sec-butyl-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



20 To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.10 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) caesium carbonate (0.33

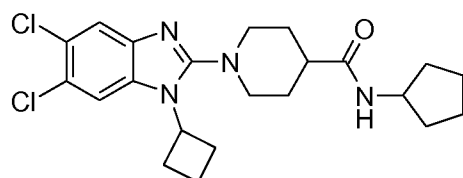
g, 1.0 mmol) and dichloro-bis(triphenylphosphine)palladium (II) ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, (0.019 g, 0.026 mmol) were added, followed by 2-bromobutane (0.07 mL, 0.46 mmol). The resulting reaction mixture was subjected to microwave irradiation for 45 min at 120°C. The reaction mixture was concentrated *in vacuo*, the solid residue filtered off, washed with ethyl acetate and the filtrate extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel) to give 81 mg (74 % yield) of 1-(1-sec-butyl-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. LC-MS (*m/z*) 437.5 (M+1).

Example 15: *N*-cyclopentyl-1-(5,6-dichloro-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



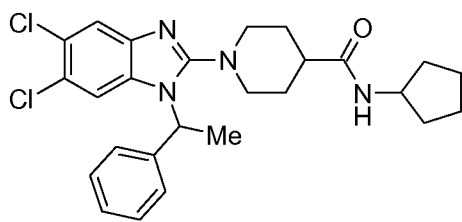
To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.10 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) caesium carbonate (0.33g, 1 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($\text{PdCl}_2(\text{dppf})$, 1.0 mg, 0.0026 mmol) were added, followed by 3-bromopentane (59 mg, 0.39 mmol). The reaction mixture was heated at 120°C for 12 hours, concentrated *in vacuo* and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was subjected to column chromatography (silica gel) to give 10 mg (17%) of *N*-cyclopentyl-1-(5,6-dichloro-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 451.3 (M+1).

Example 16: *N*-cyclopentyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



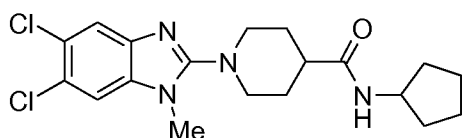
To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.050 g, 0.13 mmol) in *N,N*-dimethylformamide (0.5 mL) caesium carbonate (169 mg, 0.52 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 1.0 mg, 0.0013 mmol) were added, followed by cyclobutyl bromide (26 mg, 0.19 mmol). The reaction mixture was heated at 100°C for 12 hours, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel) to give 31 mg (54 %) of *N*-cyclopentyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 435.3 (M+1).

Example 17: *N*-cyclopentyl-1-(5,6-dichloro-1-(1-phenylethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



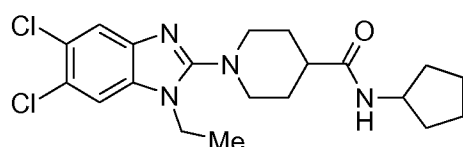
To a suspension of sodium hydride (0.011 g, 0.46 mmol) in *N,N*-dimethylformamide (0.5 mL) was added *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) drop-wise at 0°C under nitrogen gas. The reaction mixture was stirred at room temperature for 30 min, 2-bromoethylbenzene (57 mg, 0.31 mmol) was added in portions and stirred at room temperature for 16 hours. The reaction mixture was quenched with ice water and extracted with ethyl acetate (2 × 15 mL). The collected organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to obtain 8 mg (6 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-(1-phenylethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 485.3 (M+1).

Example 18: *N*-cyclopentyl-1-(5,6-dichloro-1-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



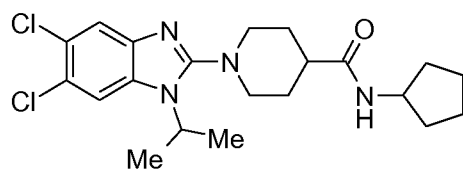
N-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (10 mg, 0.026 mmol), caesium carbonate (25.6 mg, 0.079 mmol), acetonitrile (2 mL), *N,N*-dimethylformamide (0.5 mL), iodomethane (5.6 mg, 0.039 mmol) were mixed and stirred at room temperature over night. The reaction mixture was filtered, concentrated *in vacuo* and subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using acetonitrile/water (0.05 % formaldehyde) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 1.9 mg (18 %) of the title compound. LC-MS (*m/z*) 395.2 (M+1).

Example 19: *N*-cyclopentyl-1-(5,6-dichloro-1-ethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



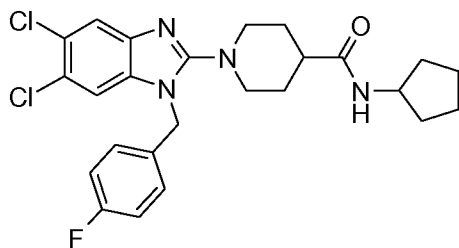
N-cyclopentyl-1-(5,6-dichloro-1-ethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (10 mg, 0.026 mmol), caesium carbonate (25.6 mg, 0.079 mmol), acetonitrile (2 mL), *N,N*-dimethylformamide (0.5 mL), iodoethane (6.1 mg, 0.039 mmol) using the method described in Example 18 to give 5.4 mg (50 % yield) of the title compound. LC-MS (*m/z*) 409.2 (M+1).

Example 20: *N*-cyclopentyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (10 mg, 0.026 mmol), caesium carbonate (25.6 mg, 0.079 mmol), acetonitrile (2 mL), *N,N*-dimethylformamide (0.5 mL), 2-bromopropane (9.7 mg, 0.079 mmol) using the method described in Example 18 to give 5.0 mg (45 % yield) of the title compound. LC-MS (*m/z*) 423.2 (M+1).

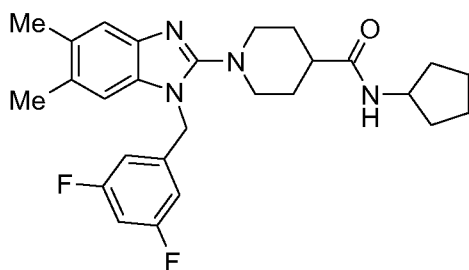
Example 21: *N*-cyclopentyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-

- 5 carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (10 mg, 0.026 mmol), caesium carbonate (25.6 mg, 0.079 mmol), acetonitrile (2 mL), *N,N*-dimethylformamide (0.5 mL), 1-(bromomethyl)-4-fluorobenzene (4.96 mg, 0.026 mmol) using the method described in Example 18 to give 4.2 mg (33 % yield) of the title compound. LC-MS (*m/z*) 489.2 (*M*+1).

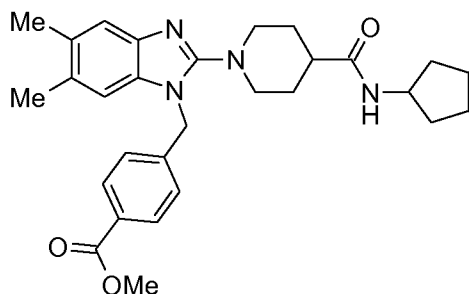
10 **Example 22: *N*-cyclopentyl-1-(1-(3,5-difluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg,

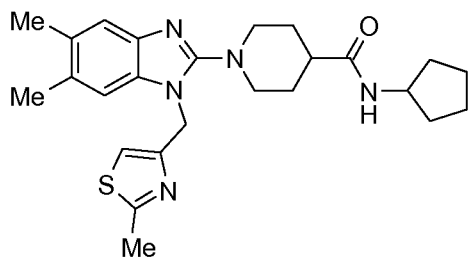
- 0.059 mmol), caesium carbonate (57.4 mg, 0.176 mmol), *N,N*-dimethylformamide (4 mL), 1-(bromomethyl)-3,5-difluorobenzene (15.2 mg, 0.073 mmol) was stirred at room temperature for 3-4 hours. The reaction mixture was filtered, the filtrate concentrated *in vacuo* and subjected to column chromatography (Silica gel, methanol/dichloromethane, gradient elution 1-15 % methanol) to give 14.2 mg (52 % yield) of *N*-cyclopentyl-1-(1-(3,5-difluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 467.3 (*M*+1).

20 **Example 23: methyl 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoate**



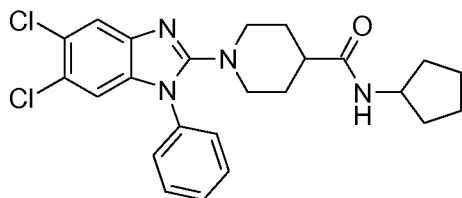
Methyl 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1H-benzo[d]imidazol-1-yl)methyl)benzoate was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.059 mmol), caesium carbonate (57.4 mg, 0.176 mmol), *N,N*-dimethylformamide (4 mL), methyl 4-(bromomethyl)benzoate (16.8 mg, 0.073 mmol) using the method described in Example 22 to give 20.4 mg (71 % yield) of the title compound. LC-MS (m/z) 489.3 (M+1).

Example 24: *N*-cyclopentyl-1-(5,6-dimethyl-1-((2-methylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



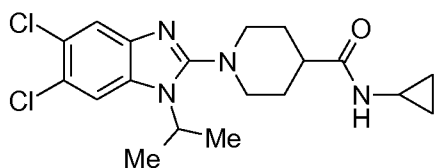
N-cyclopentyl-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.059 mmol), caesium carbonate (76.6 mg, 0.235 mmol), *N,N*-dimethylformamide (2 mL) and 4-(chloromethyl)-2-methylthiazole hydrochloride (16.2 mg, 0.088 mmol) were mixed in a microwave vial and irradiated in a microwave oven at 60°C for 1 hour and then at 100°C overnight. The reaction mixture was filtered, concentrated *in vacuo* and subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using acetonitrile/water (0.05% HCOOH) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 3.1 mg (12 % yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-((2-methylthiazol-4-yl)methyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (m/z) 452.3 (M+1).

Example 25: *N*-cyclopentyl-1-(5,6-dichloro-1-phenyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

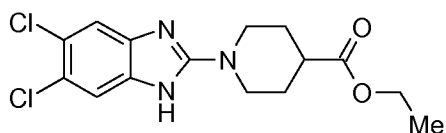


To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol) in dimethylsulfoxide (1 mL) was added caesium carbonate (119 mg, 0.36 mmol), followed by bromobenzene (0.033 mL, 0.31 mmol), 1,10-phenanthroline (9 mg, 0.39 mmol), polyethylene glycol (294 mg) and copper(I) oxide (1.8 mg, 0.013 mmol). The reaction mixture was refluxed at 110 °C for 24 hours, quenched with water and extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel) to give 5 mg (4 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 457.3 (M+1).

Example 26: *N*-cyclopropyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

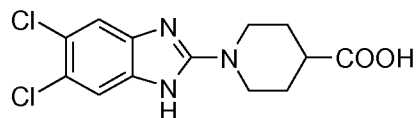


(a) Preparation of the intermediary compound ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate



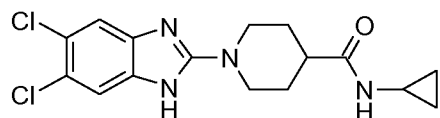
To a suspension of 2,5,6-trichloro-1*H*-benzo[d]imidazole (2.8 g, 12.6 mmol) in 1,4-dioxane (15 mL) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 6.5 mL, 38 mmol) followed by ethyl piperidine-4-carboxylate (2.38 g, 15 mmol), and the reaction mixture was heated in a screw cap pressure tube at 180 °C for 2 hours. The reaction mixture was concentrated in vacuo, the residue formed washed with water and filtered off to give 2.5 g (58 % yield) of ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate as an off-white solid.

(b) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid



Ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (2.5 g), aqueous sodium hydroxide (10 mL, 1N) and ethanol (20 mL) was stirred for 5 hours at room temperature. The reaction mixture was concentrated in vacuo, the residue partitioned between water and ethyl acetate and the aqueous layer acidified with aqueous hydrochloric acid (1.5 N) to neutral pH. The precipitate was filtered off and dried in air to give 2.3 g (99 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid as a brown solid.

(c) Preparation of the intermediary compound N-cyclopropyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:

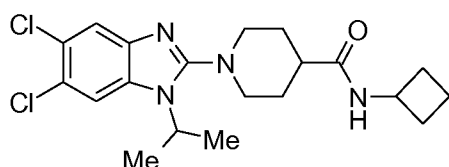


To a solution of 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.05 g, 0.16 mmol) in *N,N*-dimethylformamide (2 mL) was added 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 91 mg, 0.24 mmol) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.04 mL, 0.32 mmol) and cyclopropylamine (0.13 mL, 0.19 mmol). The reaction mixture was stirred at room temperature for 5 hours, concentrated in vacuo and extracted with ethyl acetate (2 x 20 mL). The combined organic phases were dried over anhydrous sodium sulphate and finally recrystallized from dichloromethane/*n*-hexane to give 10 mg (18 % yield) of N-cyclopropyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 353.3 (*M*+1).

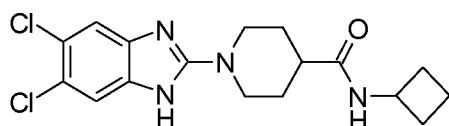
N-cyclopropyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.09 g, 0.25 mmol) was dissolved in *N,N*-dimethylformamide (1 mL). Caesium carbonate (332 mg, 1 mmol) and isopropyl bromide (56 mg, 0.45 mmol) were added, and the reaction mixture irradiated under microwave conditions at 120°C for 60 minutes. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with water (5 x 25 mL), once with brine and dried over anhydrous sodium sulfate. The organic phase was concentrated in vacuo and the residue subjected to column

chromatography (silica gel, chloroform/methanol 99:1), to give 25 mg (12 % yield) of N-cyclopropyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a light yellow solid. LC-MS (*m/z*) 395.3 (*M*+1).

Example 27: N-cyclobutyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



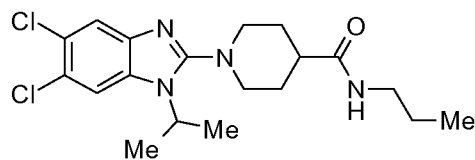
(a) Preparation of the intermediary compound N-cyclobutyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:



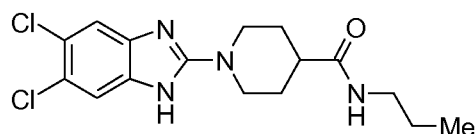
- 10 N-cyclobutyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.05 g, 0.16 mmol), *N,N*-dimethylformamide (2 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 91 mg, 0.24 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.04 mL, 0.32 mmol) and cyclobutylamine (0.16 mL, 0.19 mmol), using the method
- 15 described in Example 26(c) to give 43 mg of N-cyclobutyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 367.3 (*M*+1).

- (b) N-cyclobutyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from N-cyclobutyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.28g, 0.76mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (0.99 g, 3 mmol) and isopropyl bromide (168 mg, 1.3 mmol) using the method
- 20 described in Example 26(d) to give 61 mg (20 % yield) of the title compound as a light yellow solid. LC-MS (*m/z*) 409.5 (*M*+1).

Example 28: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide



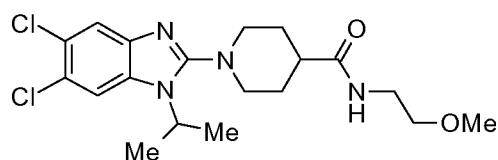
(a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide:



- 5 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.07 g, 0.22 mmol), *N,N*-dimethylformamide (4 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 127 mg, 0.33 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.052 mL, 0.45 mmol) and propan-1-amine (0.27 mmol), using the method described in
- 10 Example 26(c) to give 10 mg (13 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide. LC-MS (*m/z*) 355.3 (*M*+1).

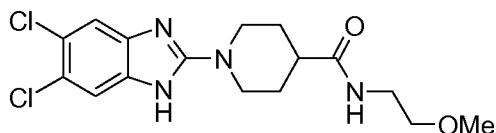
- (b) 1-(5,6-Dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide (0.05 g, 0.14 mmol), *N,N*-dimethylformamide (1 mL), caesium carbonate (0.19 g, 0.58 mmol) and isopropyl bromide (26 mg, 0.21 mmol), using the method described in Example
- 15 26(d) to give 10 mg (17 % yield) of the title compound as a light yellow solid. LC-MS (*m/z*) 397.2 (*M*+1).

Example 29: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-methoxyethyl)piperidine-4-carboxamide



20

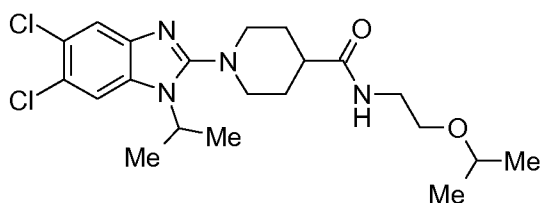
(a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-methoxyethyl)piperidine-4-carboxamide:



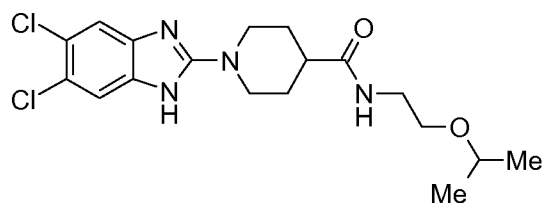
To a solution of 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.07 g, 0.22 mmol) in *N,N*-dimethylformamide (2 mL) was added 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.127 g, 0.33 mmol) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.052 mL, 0.44 mmol) and 2-methoxy-ethylamine (0.0198g, 0.24 mmol). The reaction mixture was stirred at room temperature for 5 hours, concentrated in vacuo and extracted with ethyl acetate (2 x50 mL). The combined organic phases were dried over anhydrous sodium sulphate and recrystallized from ethyl acetate/*n*-hexane to give 20 mg (24 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(2-methoxyethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 371.2 (*M*+1).

(b) 1-(5,6-Dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(2-methoxyethyl)piperidine-4-carboxamide (0.1 g, 0.27 mmol) was dissolved in *N,N*-dimethylformamide (4 mL). Caesium carbonate (0.527 mg, 1.6 mmol) and isopropyl bromide (66 mg, 0.54 mmol) were added, and the reaction mixture irradiated under microwave conditions at 120°C for 60 minutes. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 x25 mL). The combined organic phases were washed with water (5 x25 mL), once with brine and dried over anhydrous sodium sulfate. The organic phase was concentrated *in vacuo* and the residue recrystallized from ethyl acetate and *n*-hexane to give 20 mg (18 % yield) of 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-N-(2-methoxyethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 413.3 (*M*+1).

Example 30: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-N-(isopropoxymethyl)piperidine-4-carboxamide



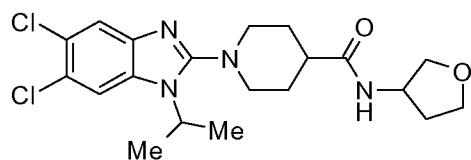
(a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(2-isopropoxyethyl)piperidine-4-carboxamide:



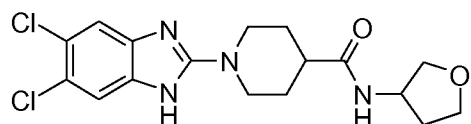
1-(5,6-Dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-isopropoxyethyl)piperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.3 g, 0.95 mmol) in *N,N*-dimethylformamide (5 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.544 g, 1.4 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.33 mL, 1.9 mmol) and 2-isopropoxyethanamine (0.118 g, 1.1 mmol), using the method described for Example 29(a) to give 0.35 g (92% yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-isopropoxyethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 399.2 (*M*+1).

(b) 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-isopropoxyethyl)piperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-isopropoxyethyl)piperidine-4-carboxamide (0.1 g, 0.25 mmol), *N,N*-dimethylformamide (1 mL), caesium carbonate (0.5 g, 1.5 mmol) and isopropyl bromide (55 mg, 0.45 mmol) using the method described in Example 29(b) to give 60 mg (18 % yield) of the title compound as a light yellow solid. LC-MS (*m/z*) 441.3 (*M*+1). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.84 (s, 1H), 7.66 (s, 1H), 4.54 (m, 1H), 3.53 (m, 1H), 3.47-3.28 (m, 4H), 3.18 (dd, 2H), 2.89 (dd, 2H), 2.36 (m, 1H), 1.79 (m, 4H), 1.51 (d, 6H), 1.09 (d, 6H).

Example 31: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



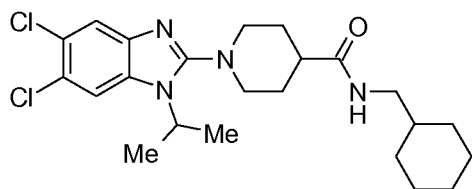
(a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



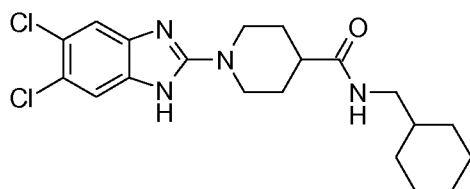
To a solution of 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.3 g, 0.95 mmol) in *N,N*-dimethylformamide (5 mL) was added 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.544 g, 1.4 mmol) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.33 mL, 1.9 mmol) and tetrahydrofuran-3-amine (0.1 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 5 hours, concentrated in vacuo and extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried over anhydrous sodium sulphate and subjected to column chromatography (chloroform/methanol 95:5) to give 0.135 g (37 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 383.2 (M+1).

(b) 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.25 mmol) was dissolved in *N,N*-dimethylformamide (1 mL). Caesium carbonate (0.5 g, 1.5 mmol) and isopropyl bromide (60 mg, 0.46 mmol) were added, and the reaction mixture irradiated under microwave conditions at 120°C for 60 minutes. The reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic phases were washed with water (5 x 25 mL), once with brine and dried over anhydrous sodium sulfate. The organic phase was concentrated in vacuo to give 75 mg (68 % yield) of 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 425.3 (M+1).

Example 32: *N*-(cyclohexylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

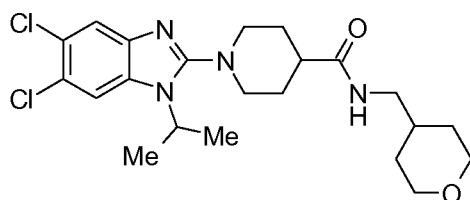


(a) Preparation of the intermediary compound *N*-(cyclohexylmethyl)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:

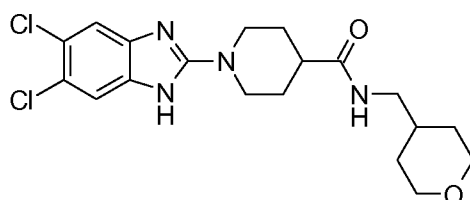


- (a) To a solution of 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.07 g, 0.22 mmol) in *N,N*-dimethylformamide (2 mL) was added 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.127 g, 0.33 mmol) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.05 mL, 0.44 mmol) and cyclohexylmethanamine (0.049 g, 0.44 mmol). The reaction mixture was stirred at room temperature for 5 hours, quenched with water to give a precipitate that was filtered off, washed with water and dried in air, to give 0.1 g (76 %) yield of *N*-(cyclohexylmethyl)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 409.3 (*M*+1).
- (b) *N*-(cyclohexylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-(cyclohexylmethyl)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.15 g, 0.36 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (0.716 g, 2.2 mmol) and isopropyl bromide (0.09 g, 0.72 mmol) using the method described in Example 29(b) to give 20 mg (12 % yield) of the title compound. LC-MS (*m/z*) 451.4 (*M*+1).

Example 33: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide



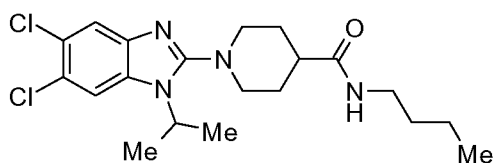
- (a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide.



To a solution of 1-(5,6-dichloro-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (0.3 g, 0.95 mmol) in *N,N*-dimethylformamide (2 mL) was added 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.544 g, 1.4 mmol) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.33 mL, 1.9 mmol) and (tetrahydro-2*H*-pyran-4-yl)methanamine (0.131 g, 1.1 mmol) was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo, the residue partitioned between water and ethyl acetate (1:3), the organic phase washed with brine and dried over anhydrous sodium sulphate. The organic phase was filtered and the filtrate concentrated in vacuo to give 0.13 g (79 %) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide. LC-MS (*m/z*) 411.3 (*M*+1).

(b) 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide (0.09 g, 0.19 mmol), *N,N*-dimethylformamide (1 mL), caesium carbonate (0.38 g, 1.1 mmol) and isopropyl bromide (43 mg, 0.35 mmol) using the method described in Example 26(d) to give 20 mg (7 % yield) of the title compound. LC-MS (*m/z*) 453.3 (*M*+1).

Example 34: *N*-butyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

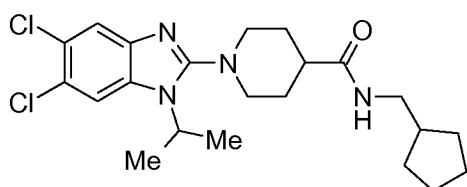


(a) The intermediary compound 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid was prepared in a similar way as described in Example 101.

(b) 1-(5,6-Dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (0.05 g, 0.16 mmol) was treated with 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.96 g, 0.25 mmol) in *N,N*-dimethylformamide (1m L) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.05 mL, 0.32 mmol), and butan-1-amine (0.18 mL, 0.19 mmol). The reaction mixture was stirred at room temperature for 4 hours, quenched with water (1 mL), extracted with ethyl acetate (2 x20 mL), washed once with brine (10mL) and dried over anhydrous sodium sulfate. The organic phase was filtered, the filtrate concentrated in vacuo and subjected to column chromatography (silica gel,

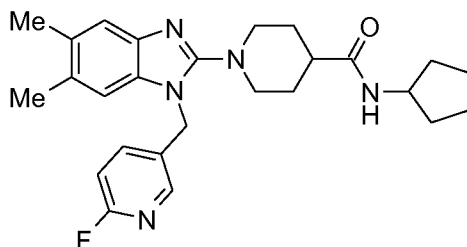
chloroform/methanol 98:2) to give 20 mg (29 % yield) of *N*-butyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 411.4 (*M*+1).

Example 35: *N*-(cyclopentylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



1-(5,6-Dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (0.15 g, 0.42 mmol) was treated with 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.24g, 0.63mmol) in *N,N*-dimethylformamide (2 mL) followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.14 mL, 0.84 mmol), and cyclopentylmethanamine hydrochloride (0.069 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 12 hours, quenched with water (1 mL), extracted with ethyl acetate (2 x20 mL), washed with brine (10 mL) and dried over anhydrous sodium sulfate. The organic phase was concentrated in vacuo, recrystallized with petroleum ether to give to give 0.02 g (11 % yield) of *N*-(cyclopentylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 437.3 (*M*+1).

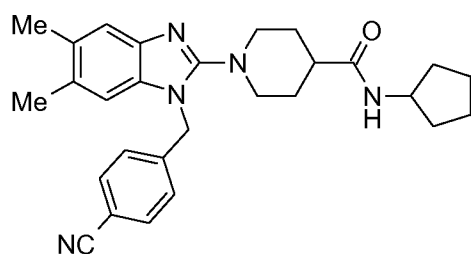
Example 36: *N*-cyclopentyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



To a solution of *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.06 g, 0.14 mmol), *N,N*-dimethylformamide (2mL) was added caesium carbonate (0.255 g, 0.87 mmol) followed by 5-(bromomethyl)-2-fluoropyridine (0.04 g, 0.26 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour. The reaction mixture was concentrated in vacuo and residue was extracted with ethyl acetate (2x15 mL). The

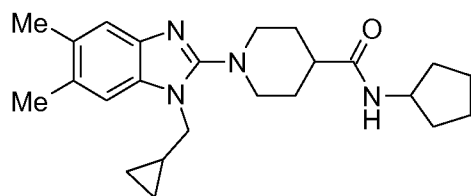
combined organic phases were washed with water (3×15 mL), dried over anhydrous sodium sulfate and concentrated. The residue was subjected to column chromatography (silica gel, 1 % chloroform/methanol, 99:1) to give 5 mg (6 % yield) of *N*-cyclopentyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 450.1 (*M*+1).

Example 37: 1-(1-(4-cyanobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.29 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.566 g, 1.7 mmol) and 4-(bromomethyl)benzonitrile (0.103 g, 0.52 mmol), using the method described in Example 36 to give 0.08 g (62 % yield) of 1-(1-(4-cyanobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 456.2 (*M*+1).

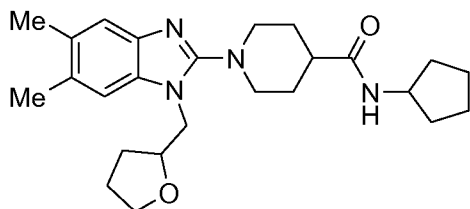
Example 38: *N*-cyclopentyl-1-(1-(cyclopropylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



To a solution of *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.08 g, 0.23 mmol) in *N,N*-dimethylformamide (3 mL) cesium carbonate (0.459 g, 1.4 mmol) was added, followed by (bromomethyl)cyclopropane (0.037 g, 0.276 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes. The reaction mixture was concentrated in vacuo and the residue was extracted with ethyl acetate (2×15 mL). The combined organic phases were washed with water (3×15 mL), dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized to give 0.05 g (54 %)

of N-cyclopentyl-1-(1-(cyclopropylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an orange solid. LC-MS (*m/z*) 395.3 (*M*+1).

Example 39: N-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

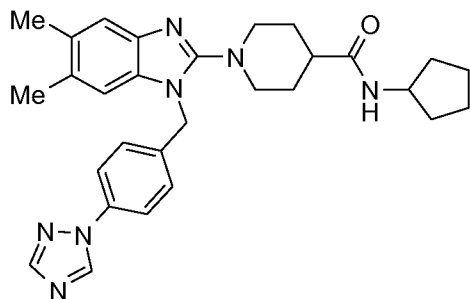


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The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.29 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.566 g, 1.7 mmol) and 2-(bromomethyl)tetrahydrofuran (0.08 g, 0.52 mmol), using the method described in Example 36, to give 11 mg (9 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 425.2 (*M*+1).

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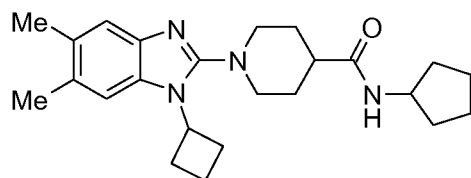
Example 40: 1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.29 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.566 g, 1.7 mmol) and 1-(4-(bromomethyl)phenyl)-1*H*-1,2,4-triazole (0.1 g, 0.52 mmol), using the method described in Example 36, to give 28 mg (19 % yield) of 1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 498.0 (*M*+1).

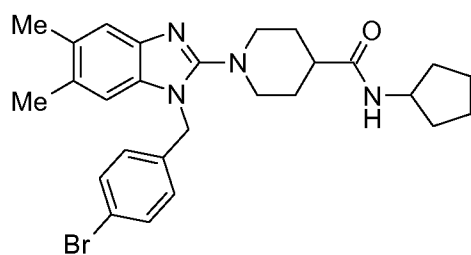
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Example 41: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide



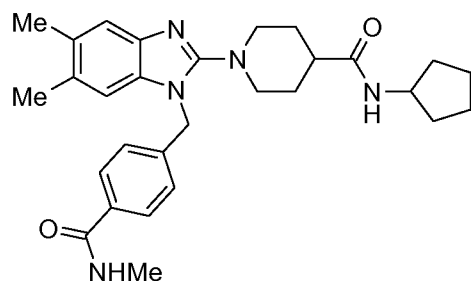
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.29 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.566 g, 1.7 mmol) and cyclobutylbromide (0.07 g, 0.527 mmol), using the method described in Example 36, to give 9 mg (8 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 395.2 (M+1).

Example 42: 1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide



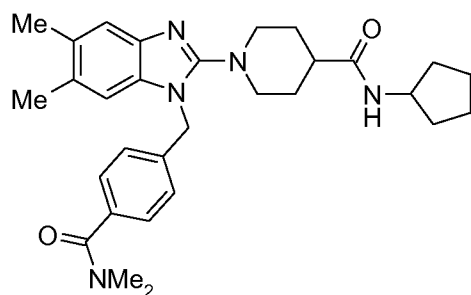
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.9 g, 2.6 mmol), *N,N*-dimethylformamide (5 mL), caesium carbonate (5 g, 15.6 mmol) and 1-bromo-4-(bromomethyl)benzene (1.18 g, 4.7 mmol), using the method described in Example 36, to give 0.5 g (38 % yield) of 1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 509.6 (M+1).

Example 43: N-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



A reaction mixture consisting of 1-(1-(4-bromobenzyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.19 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 0.089 g, 0.095 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.07 mL, 0.39 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.19 mmol), tri tertiarybutyl phosphonium hexafluoroborate [(*t*-Bu)₃PH]BF₄, 5.5 mg, 0.019 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 0.025 g, 0.095 mmol) and methyl amine hydrochloride (0.1 mg, 1.52 mmol) in 1,4-dioxane (3 mL), was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (2 x 50 mL) and the combined organic phases dried over anhydrous sodium sulphate. After concentration in vacuo, the residue was subjected to column chromatography (basic alumina, chloroform/methanol 99:1) to give 45 mg (50 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylcarbamoyl)benzyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 488.1 (*M*+1).

Example 44: N-cyclopentyl-1-(1-(4-(dimethylcarbamoyl)benzyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

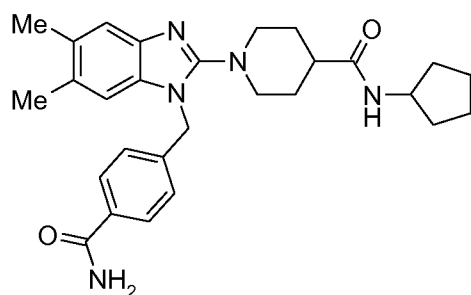


The title compound was prepared from 1-(1-(4-bromobenzyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.19 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 0.089 g, 0.095 mmol), *N,N*-diisopropylethylamine (Hünig's base, 0.07 mL, 0.39 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.028 mL, 0.19 mmol), tri tertiarybutyl phosphonium hexafluoroborate [(*t*-Bu)₃PH]BF₄, 0.0055 g, 0.019 mmol), molybdenum hexacarbonyl (Mo(CO)₆,

0.025 g, 0.095 mmol), dimethyl amine hydrochloride (0.1 g, 1.23 mmol) and 1,4-dioxane (3mL), using the method described in Example 43, to give 5 mg (5.5 % yield) of N-cyclopentyl-1-(1-(4-(dimethylcarbamoyl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 502.1 (*M*+1).

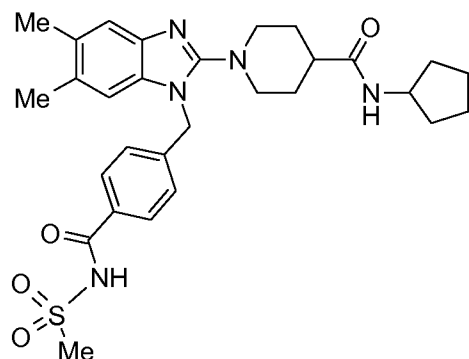
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Example 45: 1-(1-(4-carbamoylbenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



To a solution of 1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.29 mmol) in *N,N*-dimethylformamide (0.5 mL) was added caesium carbonate (0.566 g, 1.7 mmol), followed by 4-(bromomethyl)benzamide (0.112 g, 0.52 mmol, which was prepared from 4-(bromomethyl)benzoic acid by reaction with thionyl chloride (SOCl₂) and quenching the formed acid chloride with aqueous ammonia (28 %)). The resulting mixture was irradiated under microwave conditions at 120°C for 45 min. The reaction mixture was concentrated in vacuo, the residue extracted with ethyl acetate (2 × 15 mL), the combined organic phases washed with water (3 × 15 mL) and dried over anhydrous sodium sulphate. This gave 3.6 g (2.6 % yield) of 1-(1-(4-carbamoylbenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 474.1 (*M*+1).

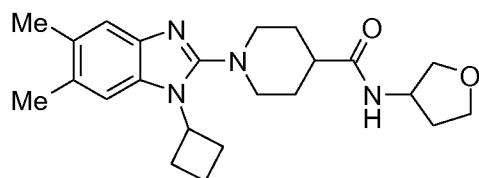
Example 46: *N*-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.19 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 0.089 g, 0.095 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.07 mL, 0.39 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.028 mL, 0.19 mmol) tri tertiarybutyl phosphonium hexafluoroborate [(*t*-Bu)₃PH]BF₄, 5.5 mg, 0.019 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 0.025 g, 0.095 mmol), methane sulfonamide (0.037 g, 0.39 mmol) and 1,4-dioxane (3 mL) was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (2 x 50 mL), the combined organic phases dried over anhydrous sodium sulfate and subjected to column chromatography (basic alumina, chloroform/methanol 99:1) to give 36 mg (33 % yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 552.0 (*M*+1).

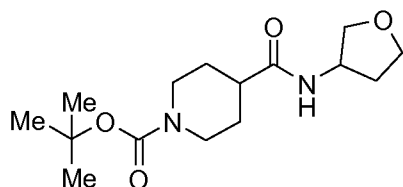
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Example 47: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



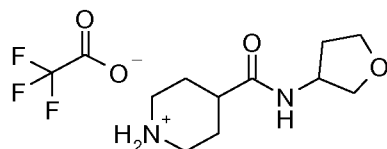
(a) Preparation of the intermediary compound *tert*-butyl 4-(tetrahydrofuran-3-ylcarbamoyl)piperidine-1-carboxylate.

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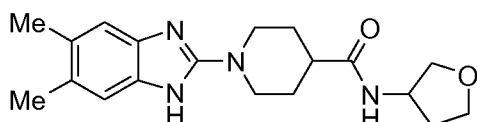
To a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.37 mmol) in dry dichloromethane (10 mL), cooled to 0 °C, was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 8.7 mmol), *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, CAS Registry Number: 25952-53-8, 8.7 mmol), 1-hydroxybenzotriazole (HOBt, CAS Registry Number: 2592-95-2, 2.2 mmol) and tetrahydrofuran-3-amine hydrochloride (5.2 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 10 hours. The reaction mixture was washed with aqueous hydrochloric acid (3 x15 mL, 2*N*), saturated aqueous sodium bicarbonate (2 x15 mL), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was recrystallized from dichloromethane/pet ether to give 1.15 g (88%) of tert-butyl 4-(tetrahydrofuran-3-ylcarbamoyl)piperidine-1-carboxylate.

(b) Preparation of the intermediary compound 4-(tetrahydrofuran-3-ylcarbamoyl)piperidinium 2,2,2-trifluoroacetate:



To a solution of *tert*-butyl 4-(tetrahydrofuran-3-ylcarbamoyl)piperidine-1-carboxylate (1.0 g, 3.36 mmol) in dichloromethane (10 mL), cooled to 0 °C, was added 2,2,2-trifluoroacetic acid (8.4 mmol). The reaction was allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated in vacuo (repeated co-evaporation with toluene), and dried under vacuum to give 4-(tetrahydrofuran-3-ylcarbamoyl)piperidinium 2,2,2-trifluoroacetate in quantitative yield.

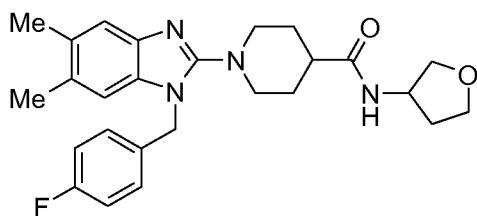
(c) Preparation of the intermediary compound 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.



To a suspension of 2-chloro-5,6-dimethyl-1*H*-benzo[d]imidazole (0.3 g, 1.6 mmol) in 1,4-dioxane (5 mL), 4-(tetrahydrofuran-3-ylcarbamoyl)piperidinium 2,2,2-trifluoroacetate (0.38 g, 1.9 mmol) in 1,4-dioxane (3 mL) was added. *N,N*-diisopropylethylamine (Hünig's base, DIEA 0.89 mL, 5.0 mmol) was added and the reaction mixture was heated in a sealed tube at 180°C for 3 hours. The reaction mixture was quenched with water, extracted with ethyl acetate, dried over anhydrous sodium sulphate and subjected to column chromatography (silica gel, chloroform/methanol 95:5), to give 0.12 g (18 % yield) of 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid.

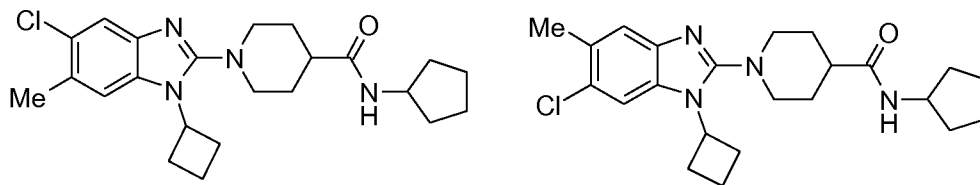
(d) To a solution of 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.05 g, 0.14 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.285 g, 0.87 mmol), followed by cyclobutylbromide (0.02 mL, 0.21 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and extracted with ethyl acetate (2×15mL). The combined organic phases were washed with water (3 ×15 mL), dried over anhydrous sodium sulfate and subjected to column chromatography (silica gel, chloroform/methanol 97.5:2.5) to give 6 mg (10 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. LC-MS (*m/z*) 397.2 (*M*+1).

Example 48: 1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

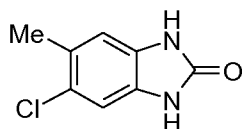


To a solution of 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.05 g, 0.14 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.285 g, 0.87 mmol), followed by 1-(bromomethyl)-4-fluorobenzene (0.032 mL, 0.17 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and extracted with ethyl acetate (2×15mL). The combined organic phases were washed with water (3 ×15 mL), dried over anhydrous sodium sulfate and recrystallized with dichloromethane and *n*-hexane to give 0.01 g (15 % yield) of 1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 451.1 (*M*+1).

Example 49: 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide

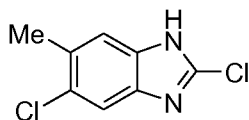


- 5 (a) Preparation of the intermediate compound 5-chloro-6-methyl-1*H*-benzo[d]imidazol-2(3*H*)-one:



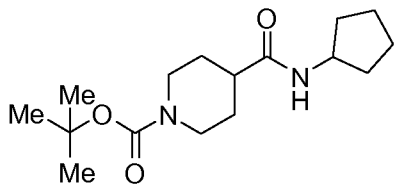
- To a stirred solution of 4-chloro-5-methylbenzene-1,2-diamine (0.3 g, 1.9 mmol) in tetrahydrofuran (5 mL) was added *N,N*-carbonyl dimidazole (CDI, 0.465 g, 2.8 mmol). The reaction mixture was stirred at room temperature for 3 hours under Argon gas, concentrated *in vacuo* and the residue partitioned between ethyl acetate (50 mL) and aqueous sodium hydroxide (50 mL, 1*N*). The aqueous extract was acidified to pH 5 via addition of aqueous hydrochloric acid (1.5*N*) and the resulting brown precipitate was filtered, washed with water (3×20mL) and dried under high vacuum to obtain 0.28 g (80 % yield) of 5-chloro-6-methyl-1*H*-benzo[d]imidazol-2(3*H*)-one.

- (b) Preparation of the intermediate compound 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole:



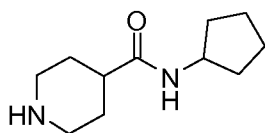
- To 5-chloro-6-methyl-1*H*-benzo[d]imidazol-2(3*H*)-one (0.25 g), phosphoryl trichloride (POCl₃, 4 mL) was added, the reaction mixture was heated in a screw cap pressure tube at 120°C for 2 hours and concentrated *in vacuo*. The residue was neutralized with sodium hydroxide, the resulting off-pale yellow solid was filtered, washed with water (3×50 mL) and dried under high vacuum to give 0.27 g (98 % yield) of 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole.

(c) Preparation of the intermediary compound *tert*-butyl 4-(cyclopentylcarbamoyl)piperidine-1-carboxylate.



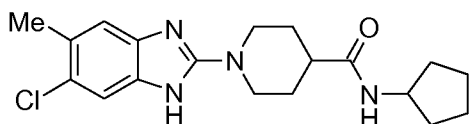
To a mixture consisting of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (6.4 g, 27.9 mmol), dry dichloromethane (66 mL), triethylamine (4.24 g, 41.9 mmol) was carefully added thionyl chloride (3.99 g, 33.5 mmol) in 16 mL dry dichloromethane. The reaction mixture was stirred for 20 minutes at room temperature, cyclopentanamine (5.94 g, 69.8 mmol) was added and the reaction mixture was heated at reflux over night under nitrogen gas. The reaction mixture was washed with aqueous hydrochloric acid (3 x 60 mL, 2*N*), saturated aqueous sodium bicarbonate (2 x 60 mL), dried over magnesium sulphate, filtered and the filtrate concentrated in vacuo. The residue was dried under vacuum to give 5.859 g of *tert*-butyl 4-(cyclopentylcarbamoyl)piperidine-1-carboxylate. LC-MS (*m/z*) 297.3 (*M*+1).

(d) Preparation of the intermediary compound 4-(cyclopentylcarbamoyl)piperidine:



tert-Butyl 4-(cyclopentylcarbamoyl)piperidine-1-carboxylate (5.859 g, 19.77 mmol), 2,2,2-trifluoroacetic acid (22.54 g, 197.66 mmol) and dichloromethane (70 mL) was stirred at room temperature. The reaction mixture was concentrated in vacuo (co-evaporation with toluene), dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous phase was concentrated in vacuo, the residue extracted with dichloromethane to give 3.21 g (83 % yield) of 4-(cyclopentylcarbamoyl)piperidine.

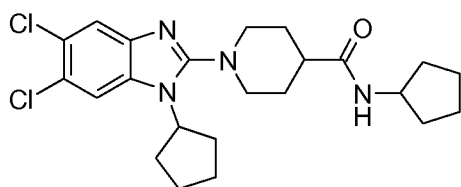
(e) Preparation of the intermediate compound 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide:



To a suspension of 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole (0.1 g, 0.49 mmol) in 1,4-dioxane (4 mL), 4-(cyclopentylcarbamoyl)piperidine (0.185 g) in 1,4-dioxane (2 mL) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.25 mL, 1.4 mmol) and heated at 180°C for 3 hours. The reaction mixture was concentrated in vacuo, partitioned between ethyl acetate (15 mL) and water (15 mL). The aqueous phase was extracted with ethyl acetate, the combined organic phases dried over anhydrous sodium sulphate and subjected to chromatography (silica gel, chloroform/methanol 98:2) to give 46 mg (26 % yield) of 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. LC-MS (*m/z*) 361.2 (*M*+1).

(f) To a solution of 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.27 mmol) in *N,N*-dimethylformamide (2 mL), caesium carbonate (0.541 g, 1.6 mmol) was added, followed by cyclobutylbromide (0.032 mL, 0.33 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf) in catalytic amounts. The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and the residue extracted with ethyl acetate (2×15mL). The combined organic phases were washed with water (3×15mL), dried over anhydrous sodium sulphate, concentrated in vacuo and subjected to column chromatography (silica gel, chloroform/methanol 98:2) to give 13 mg (11 %) of a 1:1 mixture of 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide in a mixture as a yellow solid. LC-MS (*m/z*) 415.3 (*M*+1).

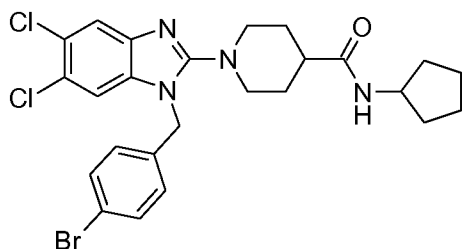
Example 50: *N*-cyclopentyl-1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) was added caesium carbonate (500 mg, 1.53 mmol), followed by cyclopentylbromide (70 mg, 0.46 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 60 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2×15 mL). The combined organic phases were washed with water (3×15 mL), dried over anhydrous sodium sulfate

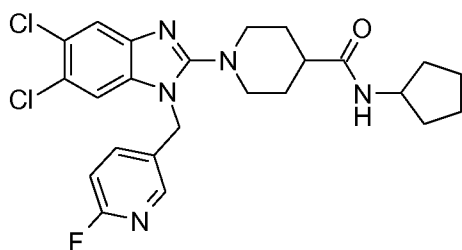
concentrated in vacuo. The residue was subjected to column chromatography (silica gel) to give 75 mg (64 % yield) *N*-cyclopentyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 449.3 (*M*+1).

Example 51: 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL), caesium carbonate (512 mg, 1.57 mmol) and 1-bromo-4-(bromomethyl)benzene (120 mg, 0.47 mmol), using the method described in Example 50 to give 60 mg (41 % yield) of the title compound. LC-MS (*m/z*) 550.6 (*M*+1).

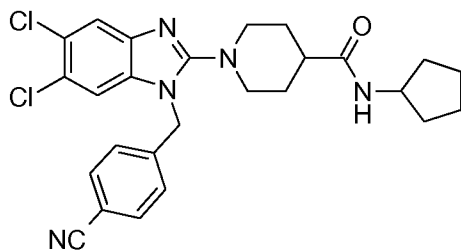
Example 52: *N*-cyclopentyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



To a solution of 1-(5,6-dichloro-1*H*-benzoimidazole-2-yl)-piperidine-4-carboxylic acid cyclopentylamide (60 mg, 0.16 mmol) in *N,N*-dimethylformamide (0.5 mL) was added caesium carbonate (300 mg, 0.94 mmol), followed by 2-fluoro-5-bromomethylpyridine (36 mg, 0.19 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was subjected to column chromatography (silica

gel) to give 20 mg (26 %) *N*-cyclopentyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 490.3 (*M*+1).

Example 53: *N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

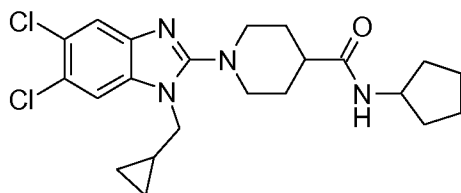


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N-cyclopentyl-1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (50 mg, 0.13 mmol), *N,N*-dimethylformamide (0.5 mL), caesium carbonate (171 mg, 0.52 mmol) and 4-(bromomethyl)benzonitrile (31 mg, 0.15 mmol), using the method described in Example 52 to give 20 mg (15 % yield) of the title compound. LC-MS (*m/z*) 496.2 (*M*+1).

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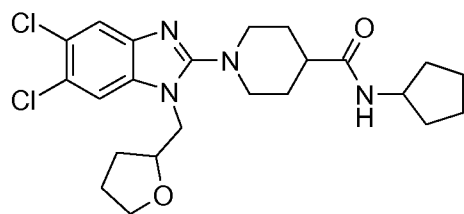
Example 54: *N*-cyclopentyl-1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol), *N,N*-dimethylformamide (0.5 mL), caesium carbonate (512 mg, 1.5 mmol) and (bromomethyl)cyclopropane (43 mg, 0.32 mmol), using the method described in Example 52 to give 19 mg (17 % yield) of the title compound. LC-MS (*m/z*) 435.3 (*M*+1).

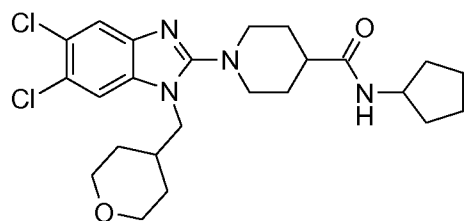
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Example 55: *N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



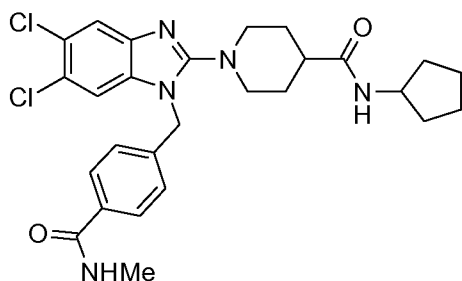
To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) was added cesium carbonate (512 mg, 1.5 mmol), followed by 2-(bromomethyl)tetrahydrofuran (77 mg, 0.47 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 min, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was washed with *n*-hexane to afford 50 mg (41 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 465.2 (*M*+1).

Example 56: *N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



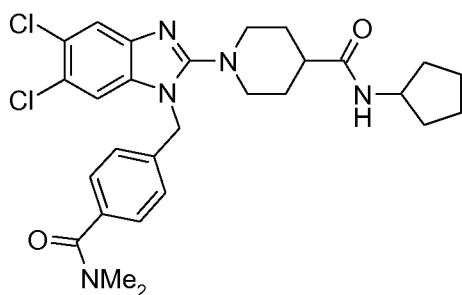
N-cyclopentyl-1-(5,6-dichloro-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (100 mg, 0.26 mmol), *N,N*-dimethylformamide (0.5 mL), caesium carbonate (512 mg, 1.5 mmol), and 4-(bromomethyl)tetrahydro-2*H*-pyran (80 mg, 0.47 mmol), using the method described in Example 55 to give 70 mg (57 % yield) of the title compound. LC-MS (*m/z*) 479.3 (*M*+1).

Example 57: *N*-cyclopentyl-1-(5,6-dichloro-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



A reaction mixture consisting of 1-(1-(4-bromobenzyl)-5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide (Example 51, 100 mg, 0.182 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 9 mg, 0.009 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.06 mL, 0.36 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.028 mL, 1.82 mmol), tri tertiarybutyl phosphonium hexafluoroborate [(*t*-Bu)₃PH]BF₄, 5 mg, 0.018 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 0.024 g, 0.09 mmol) and methyl amine (25 mg, 0.36 mmol) in 1,4-dioxane, was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (2 x 50 mL) and the combined organic phases dried over anhydrous sodium sulphate. After concentration in vacuo, the residue was subjected to column chromatography (basic alumina, chloroform/methanol 96:4) to give 12 mg (12 % yield) of N-cyclopentyl-1-(5,6-dichloro-1-(4-(methylcarbamoyl)benzyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 528.4 (*M*+1).

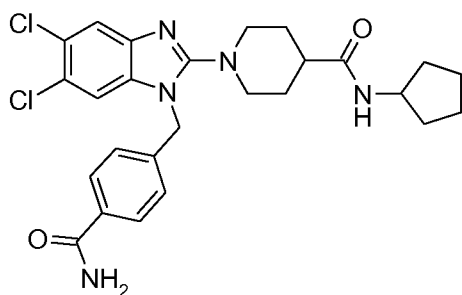
Example 58: N-cyclopentyl-1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)benzyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)benzyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was prepared from 1-(1-(4-bromobenzyl)-5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide (Example 51, 100 mg, 0.182 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 9 mg, 0.009 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.06 mL, 0.36 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.028 mL, 1.82 mmol), tri tertiarybutyl

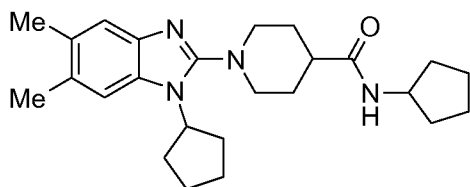
phosphonium tetrafluoroborate [(t-Bu)₃PH]BF₄ (0.005g, 0.018mmol), molybdenum hexacarbonyl (Mo(CO)₆, 24 mg, 0.09 mmol), dimethyl amine (0.029g, 0.36mmol) and 1,4-dioxane, using the method described for Example 57 to give 22 mg (22 % yield) of the title compound. LC-MS (m/z) 542.3 (M+1).

5 Example 59: 1-(1-(4-carbamoylbenzyl)-5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide



To a solution of 1-(5,6-dichloro-1H-benzoimidazole-2-yl)-piperidine-4-carboxylic acid cyclopentylamide (50 mg, 0.13 mmol) in *N,N*-dimethylformamide (0.5 mL) was added caesium carbonate (260 mg, 0.28 mmol), followed by 4-(bromomethyl)benzamide (34 mg, 0.15 mmol, that was prepared from 4-(bromomethyl)benzoic acid by reacting with thionyl chloride (SOCl₂) and quenching the resulting acid chloride with aqueous ammonia (28 %)). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes and concentrated in vacuo. The residue was extracted with ethyl acetate (2 × 15 mL), the collected organic phases washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo to afford 20 mg (30 % yield) of 1-(1-(4-carbamoylbenzyl)-5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (m/z) 514.6 (M+1).

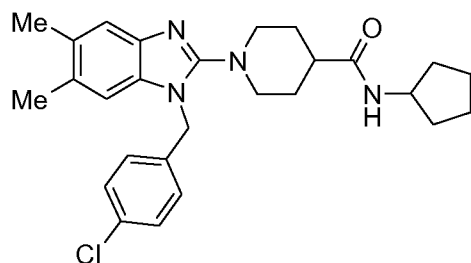
Example 60: N-cyclopentyl-1-(1-cyclopentyl-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.059 mmol), caesium carbonate (76.6 mg, 0.235 mmol), *N,N*-dimethylformamide (4 mL) and bromocyclopentane (4.96 mg, 0.026 mmol) were mixed in a microwave vial and irradiated in a

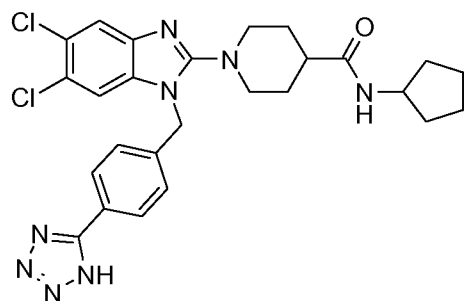
microwave oven at 60°C over night. The reaction mixture was filtered, concentrated *in vacuo* and subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using acetonitrile/water (0.05% HCOOH) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 3.6 mg (15 %) of the title compound. LC-MS (*m/z*) 409.3 (M+1).

Example 61: 1-(1-(4-chlorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



1-(1-(4-chlorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.059 mmol), caesium carbonate (57.4 mg, 0.176 mmol), *N,N*-dimethylformamide (4 mL), 1-chloro-4-(chloromethyl)benzene (11.8 mg, 0.073 mmol) using the method described in Example 60 to give 9.9 mg (27 % yield) of the title compound. LC-MS (*m/z*) 465.3 (M+1).

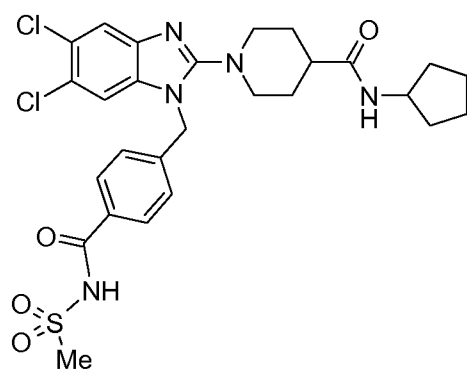
Example 62: 1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



N-cyclopentyl-1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (Example 53, 50 mg, 0.1 mmol), sodium azide (78 mg, 1.2 mmol), ammonium chloride (64 mg, 1.2 mmol), lithium chloride (catalytic amount) was refluxed in *N,N*-dimethylformamide (3 mL) for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate (2 x 25 mL), the organic phase was dried over anhydrous sodium

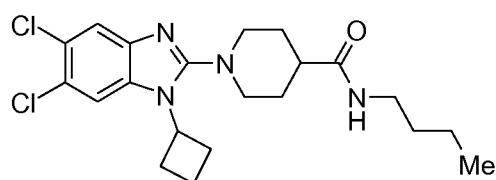
sulphate, filtered and concentrated in vacuo, to give 15 mg (28 % yield) of 1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 539.3 (M+1).

Example 63: *N*-cyclopentyl-1-(5,6-dichloro-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

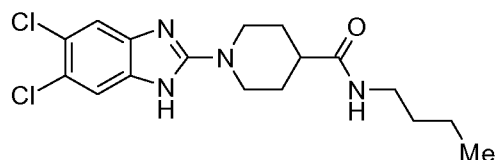


(1-(1-(4-Bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide) (Example 51, 0.1 g, 0.182 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 9 mg, 0.009 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.06 mL, 0.36 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.028 mL, 1.82 mmol), tri tertiarybutyl phosphonium hexafluoroborate [(*t*-Bu)₃PH]BF₄ (5 mg, 0.018 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 24 mg, 0.09 mmol), methane sulfonamide (34 mg, 0.36 mmol) and 1,4-dioxane was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (2 x 50 mL), the combined organic phases dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography (basic alumina, chloroform/methanol 96:4) to give 80 mg (74 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 592.4 (M+1).

Example 64: *N*-butyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



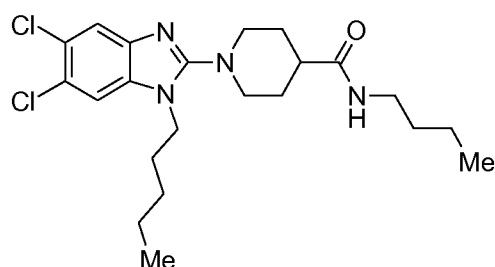
(a) Preparation of the intermediate compound *N*-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:



To a suspension of 2,5,6-trichloro-1*H*-benzo[d]imidazole (0.3 g, 1.35 mmol) in 1,4-dioxane (6 mL) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.67 mL, 4.0 mmol) followed by *N*-butylpiperidine-4-carboxamide (0.3 g, 1.6 mmol). The reaction mixture was heated in a sealed tube at 180°C for 3 hours, concentrated in vacuo, the residue washed with water and filtered off to give 0.3 g (60 %) of *N*-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 369.5 (M+1).

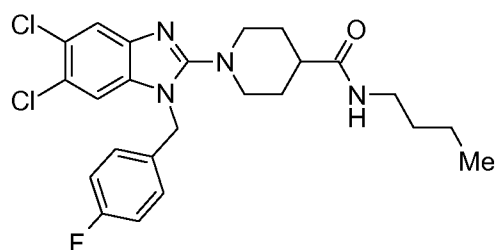
(b) To a solution of *N*-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.3 g, 0.81 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.79 g, 2.4 mmol), followed by cyclobutylbromide (0.164 mL, 1.2 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 98:2) to give 0.09 g (26 % yield) of *N*-butyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 423.3 (M+1).

Example 65: *N*-butyl-1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



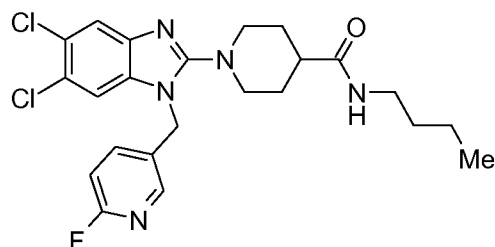
To a solution of N-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.27 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.527 g, 1.6 mmol), followed by 1-bromopentane (0.035 mL, 0.32 mmol). The resulting reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was recrystallized from dichloromethane and *n*-hexane to give 17 mg (16 % yield) of N-butyl-1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 439.4 (M+1).

10 **Example 66: N-butyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



The title compound was prepared from N-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.27 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.527 g, 1.6 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.164 mL, 1.2 mmol) using the method described in Example 64(b), to give 0.02 g (16 % yield) of N-butyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a off-white solid. LC-MS (*m/z*) 477.2 (M+1).

20 **Example 67: N-butyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**

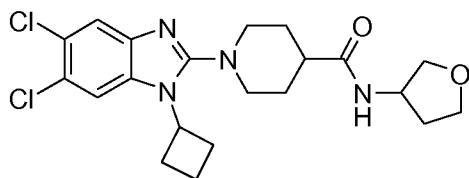


The title compound was prepared from N-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.27 mmol), *N,N*-dimethylformamide (2 mL), caesium

carbonate (0.527 g, 1.6 mmol) and 5-(bromomethyl)-2-fluoropyridine (0.092 g, 0.48 mmol) using the method described in Example 64(b), to give 2 mg (1.5 % yield) of N-butyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a off-white solid. LC-MS (*m/z*) 478.3 (M+1).

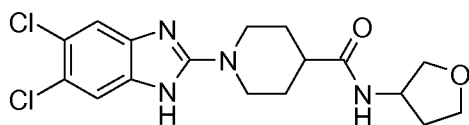
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Example 68: 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



(a) Preparation of the intermediary compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide:

10



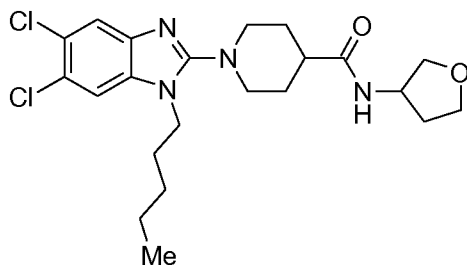
To a suspension of 2,5,6-trichloro-1*H*-benzo[d]imidazole (0.3 g, 1.36 mmol) in 1,4-dioxane (6 mL) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.36 mL, 2.0 mmol) followed by *N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.636 g, 2.0 mmol) and the reaction mixture was heated in a sealed tube at 180°C for 3 hours. The reaction mixture was concentrated in vacuo, the residue washed with water and filtered off, to give 0.14 g (26 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 383.1 (M+1).

15

(b) The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.05 g, 0.13 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.254 g, 0.78 mmol) and cyclobutylbromide (0.025 mL, 0.26 mmol) using the method described in Example 64(b), to give 0.011 g (19 % yield) of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 437.4 (M+1).

20

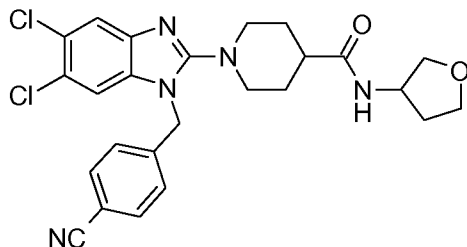
Example 69: 1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-

- 5 (tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.508 g, 1.56 mmol) and 1-bromopentane (0.033 mL, 0.31 mmol) using the method described in Example 64(b), to give 17 mg (14 % yield) of 1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 453.3 (*M*+1).

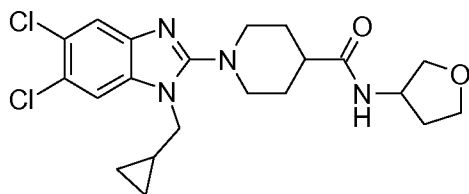
10 **Example 70: 1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide**



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-

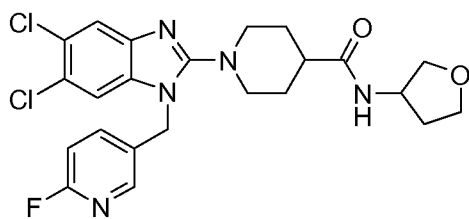
- 15 (tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.508 g, 1.56 mmol) and 4-(bromomethyl)benzonitrile (0.062 g, 0.31 mmol) using the method described in Example 64(b), to give 13 mg (10 % yield) of 1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 498.1 (*M*+1).

20 **Example 71: 1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide**



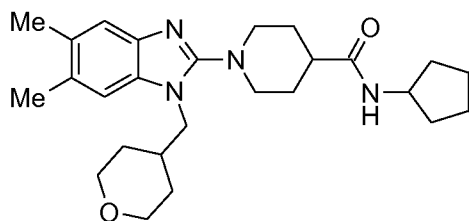
The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.508 g, 1.56 mmol) and (bromomethyl)cyclopropane (0.031 mL, 0.31 mmol) using the method described in Example 64(b), to give 14 mg (11 % yield) of 1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 437.2 (M+1).

Example 72: 1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



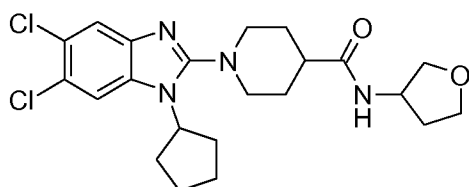
To a solution of *N*-butyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.508 g, 1.56 mmol), followed by 5-(bromomethyl)-2-fluoropyridine (0.059 mL, 0.31 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 97:3) to give 25 mg (19 % yield) of 1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 492.5 (M+1).

Example 73: *N*-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



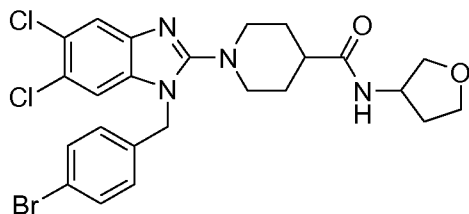
To a solution of N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.29 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.566 g, 1.7 mmol), followed by 4-(bromomethyl)tetrahydro-2*H*-pyran (0.08 g, 0.52 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and the residue extracted with ethyl acetate (2 ×15 mL). The combined organic phases were washed with water (3 ×15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 99:1) to give 0.043 g (33.5 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-
 10 ((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 439.2 (*M*+1).

Example 74: 1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



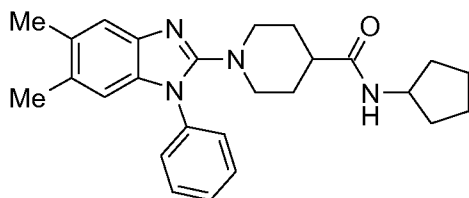
To a solution of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol) in *N,N*-dimethylformamide (2 mL) was added caesium carbonate (0.508 g, 1.56 mmol), followed by cyclopentylbromide (0.046 mL, 0.31 mmol). The resulting reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2 ×15 mL). The combined organic phases were washed with water (3 ×15 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was recrystallized from dichloromethane and *n*-hexane to give 0.02 g (17 % yield) of 1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 451.3 (*M*+1).

Example 75: 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



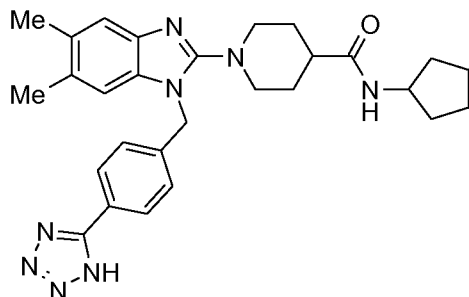
The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.508 g, 1.56 mmol) and 1-bromo-4-(bromomethyl)benzene (0.078 g, 0.31 mmol) using the method described in Example 74, to give 22 mg (15 % yield) of 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 552.5 (*M*+1). ¹H NMR (300.1 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.67 (s, 1H), 7.54 (d, 2H), 7.53 (s, 1H), 5.29 (s, 2H), 4.21 (m, 1H), 3.70 (m, 2H), 3.53 (m, 2H), 2.91 (m, 2H), 2.05 (m, 1H), 1.70 (m).

Example 76: *N*-cyclopentyl-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



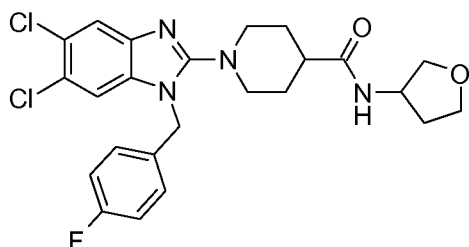
To a solution of *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.3 g, 0.87 mmol) in dimethylsulfoxide (2 mL) was added caesium carbonate (0.4 g, 1.2 mmol), followed by bromobenzene (0.011 mL, 1.0 mmol), 1,10-phenanthroline (0.031 g, 0.13 mmol), polyethylene glycol (0.882 g) and copper(I) oxide (0.006 g, 0.043 mmol). The reaction mixture was refluxed at 120°C for 24 hours, quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 99.5:0.5) to give 5 mg of *N*-cyclopentyl-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 417.1 (*M*+1).

Example 77: 1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



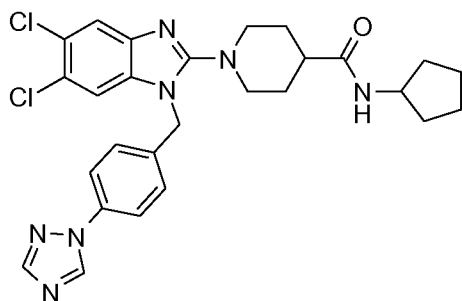
1-(1-(4-Cyanobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (Example 37, 0.06 g, 0.13 mmol), sodium azide (0.102 g, 1.5 mmol), ammonium chloride (0.08 g, 1.5 mmol), lithium chloride (catalytic amount) was refluxed in *N,N*-dimethylformamide (2 mL) for 1 hour. The reaction mixture was quenched with water and extracted with ethyl acetate (2 x25 mL), the organic phase was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo, to give 0.016 g (25 % yield) of 1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 499.0 (*M*+1).

Example 78: 1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



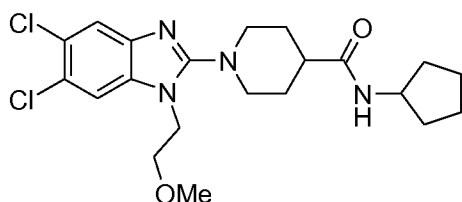
The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.508 g, 1.56 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.058 mL, 0.31 mmol) using the method described in Example 74, to give 27 mg (21 % yield) of 1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid.

Example 79: 1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



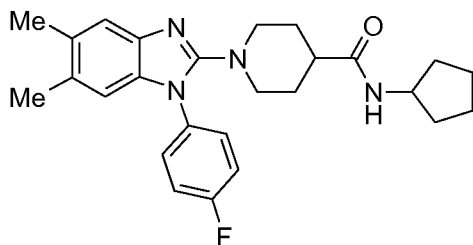
To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) was added cesium carbonate (0.512 g, 1.5 mmol), followed by 1-(4-(bromomethyl)phenyl)-1*H*-1,2,4-triazole (0.112 g, 0.47 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 45 minutes, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with water (3 × 15 mL), dried over anhydrous sodium sulphate, concentrated in vacuo and subjected to column chromatography (silica gel, chloroform/methanol 99:1), to give 0.04 g (28 % yield) of 1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 538.3 (M+1).

Example 80: *N*-cyclopentyl-1-(5,6-dichloro-1-(2-methoxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



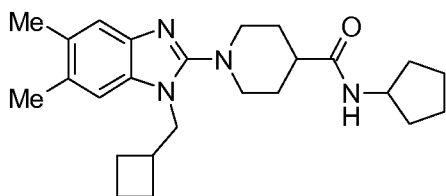
To a solution of *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) was added cesium carbonate (0.5g, 1.5mmol), followed by 1-bromo-2-methoxyethane (0.065 g, 0.47mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 60 minutes, concentrated in vacuo and the residue was extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 x 15 mL), dried over anhydrous sodium sulphate, concentrated in vacuo and the residue washed with *n*-hexane to give 0.075 g (65 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-(2-methoxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 439.3 (M+1).

Example 81: *N*-cyclopentyl-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



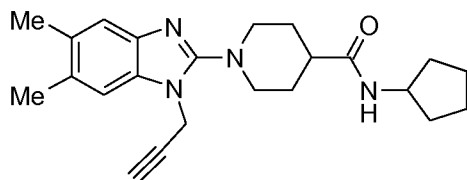
The title compound was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 1-bromo-4-iodobenzene (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 20 mg (5.2 % yield) of *N*-cyclopentyl-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 435.1 (*M*+1).

Example 82: 1-(1-(cyclobutylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



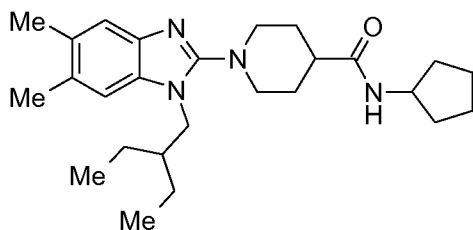
The title compound was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), (bromomethyl)cyclobutane (1.172 mmol) and dichlorobis(triphenylphosphine)palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 30 mg (25 % yield) of 1-(1-(cyclobutylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 409.1 (*M*+1).

Example 83: *N*-cyclopentyl-1-(5,6-dimethyl-1-(prop-2-ynyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



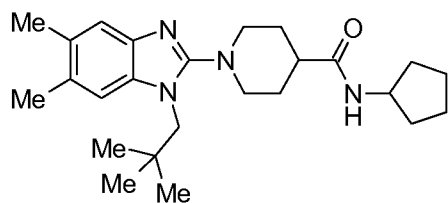
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), 3-bromoprop-1-yne (1.172 mmol) and dichlorobis(triphenylphosphine)palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 15 mg (13 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-(prop-2-ynyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 379.0 (M+1).

Example 84: N-cyclopentyl-1-(1-(2-ethylbutyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



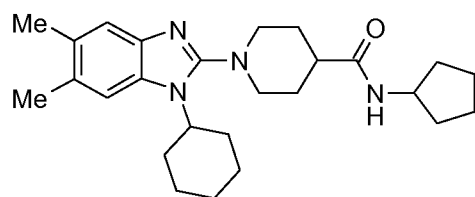
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), 3-(bromomethyl)pentane (1.172 mmol) and dichlorobis(triphenylphosphine)palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 26 mg (22 % yield) of N-cyclopentyl-1-(1-(2-ethylbutyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 425.1 (M+1).

Example 85: N-cyclopentyl-1-(5,6-dimethyl-1-neopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



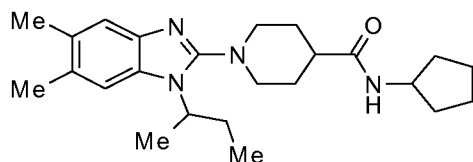
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), 1-bromo-2,2-dimethylpropane (1.172 mmol) and dichlorobis(triphenylphosphine)palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 55 mg (23 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-neopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 411.0 (M+1).

Example 86: 1-(1-cyclohexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



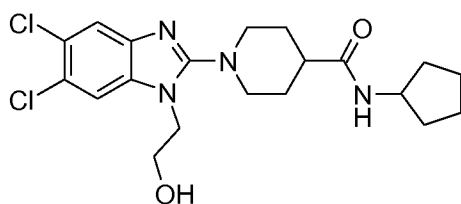
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), bromocyclohexane (1.172 mmol) and dichlorobis(triphenylphosphine)palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 8 mg (3.2 % yield) of 1-(1-cyclohexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 423.1 (M+1).

Example 87: 1-(1-sec-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



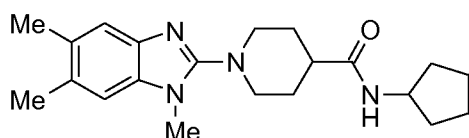
The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), 2-bromobutane (1.172 mmol) and dichlorobis(triphenylphosphine)-palladium (II) (Pd(PPh₃)₂Cl₂) (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 20 mg (8.6 % yield) of 1-(1-(1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentyl)-piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 397.0 (M+1).

Example 88: *N*-cyclopentyl-1-(5,6-dichloro-1-(2-hydroxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



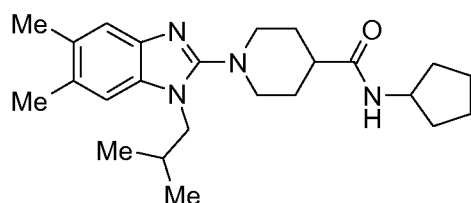
N-cyclopentyl-1-(5,6-dichloro-1-(2-methoxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide was dissolved in dichloromethane and stirred under nitrogen at 0°C for 15 minutes, treated with tribromoborane via drop-wise addition and gradually warmed to room temperature. The reaction mixture was stirred at room temperature for 1 hour, quenched with aqueous sodium hydrogencarbonate (10%) to achieve neutral pH and extracted with dichloromethane (2x 50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to give 0.02 g (42 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-(2-hydroxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 425.3 (M+1).

Example 89: *N*-cyclopentyl-1-(1,5,6-trimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



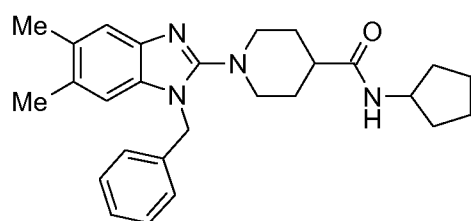
N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (6.8 mg, 0.02 mmol), iodomethane (3.4 mg, 1.5 mL, 0.024 mmol), caesium carbonate (13 mg, 0.04 mmol) and acetonitrile (0.5 mL) were mixed and stirred at room temperature. After 1 hour, additional iodoethane (3.4 mg, 1.5 mL, 0.024 mmol) was added and the reaction mixture was briefly stirred at 50°C, stirred at room temperature over night, filtered and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, methanol/dichloromethane gradient elution to give 2.3 mg (32 % yield) of *N*-cyclopentyl-1-(1,5,6-trimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 355.2 (M+1).

Example 90: *N*-cyclopentyl-1-(1-isobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



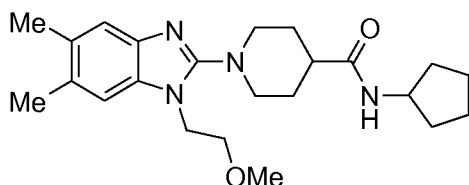
N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (6.8 mg, 0.02 mmol), 1-bromo-2-methylpropane (3.3 mg, 2.6 mL, 0.024 mmol), caesium carbonate (13 mg, 0.04 mmol) and acetonitrile (1.0 mL) and *N,N*-dimethylformamide (5 drops) were mixed and stirred at 50°C. After 75 minutes, additional 1-bromo-2-methylpropane (3.3 mg, 2.6 mL, 0.024 mmol) was added and the reaction mixture was stirred at 60°C over night, filtered and concentrated in vacuo. The residue was and purified on preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 1.7 mg (22 % yield) of *N*-cyclopentyl-1-(1-isobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 397.2 (M+1).

Example 91: 1-(1-benzyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



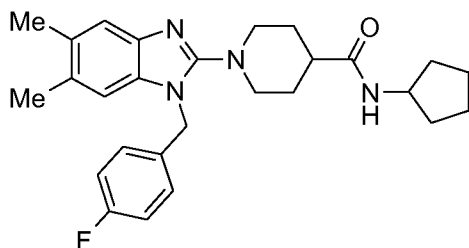
N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (34 mg, 0.1 mmol), (bromomethyl)benzene (20.5 mg, 15 mL, 0.120 mmol), caesium carbonate (65 mg, 0.20 mmol) and acetonitrile (2 mL) were mixed and stirred at 60°C over night. The reaction mixture was filtered, concentrated in vacuo and purified on preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 8.3 mg (19 % yield) of 1-(1-benzyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. LC-MS (*m/z*) 431.5 (M+1).

10 **Example 92: *N*-cyclopentyl-1-(1-(2-methoxyethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (34 mg, 0.10 mmol), 1-bromo-2-methoxyethane (16.7 mg, 11 mL, 0.120 mmol), caesium carbonate (65.2 mg, 0.20 mmol) and acetonitrile (2 mL) were mixed and stirred at 100°C over night, filtered, concentrated in vacuo and subjected to column chromatography (silica gel, methanol/dichloromethane gradient elution 3-20 % methanol) to give 4.7 mg (12 %) of *N*-cyclopentyl-1-(1-(2-methoxyethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 399.2 (M+1).

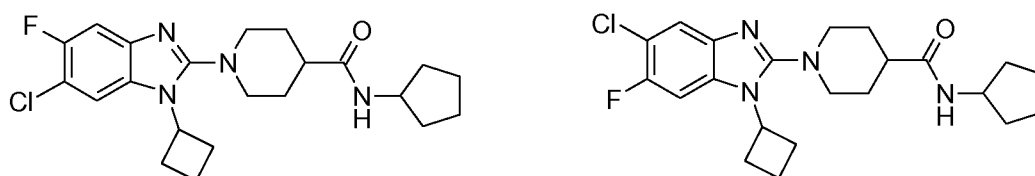
20 **Example 93: *N*-cyclopentyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



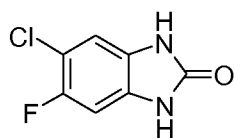
The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (34 mg, 0.10 mmol), acetonitrile (2 mL),

caesium carbonate (65.2 mg, 0.20 mmol) and 1-(bromomethyl)-4-fluorobenzene (16.7 mg, 0.12 mmol) using the method described in Example 92, to give 4.7 mg (12 % yield) of *N*-cyclopentyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 449.2 (M+1).

5 Example 94: 1-(5-chloro-1-cyclobutyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-cyclobutyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide

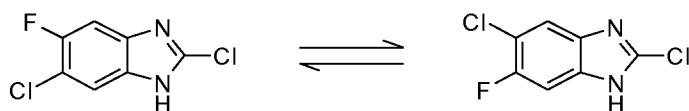


10 (a) Preparation of the intermediate compound 5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2(3*H*)-one:



To a stirred solution of 4-chloro-5-fluorobenzene-1,2-diamine (1 g, 6.22 mmol) in tetrahydrofuran (10 mL) was added *N,N*-carbonyl dimidazole (CDI, 9.33 mmol). The reaction mixture was stirred at room temperature for 3 hours under Argon gas, concentrated *in vacuo* and the residue partitioned between ethyl acetate and aqueous sodium hydroxide. The aqueous extract was acidified to pH 5 via addition of aqueous hydrochloric acid and the resulting brown precipitate was filtered, washed with water and dried to obtain 0.8 g (68 % yield) of 5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2(3*H*)-one after recrystallization from petroleum ether.

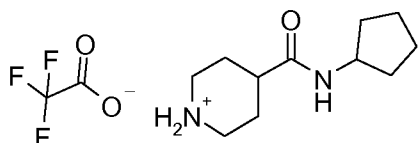
20 (b) Preparation of the intermediate compounds 2,5-dichloro-6-fluoro-1*H*-benzo[d]imidazole and 2,6-dichloro-5-fluoro-1*H*-benzo[d]imidazole.



To 5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2(3*H*)-one (1 g, 5.3 mmol), phosphoryl trichloride (POCl₃, 132 mmol) was added, the reaction mixture was heated at 120°C for 2 hours and then

concentrated *in vacuo*. The residue was neutralized with sodium hydroxide, the resulting was filtered off, washed with water and dried to give 0.85 g (77 % yield) of 2,5-dichloro-6-fluoro-1*H*-benzo[d]imidazole and 2,6-dichloro-5-fluoro-1*H*-benzo[d]imidazole after recrystallization after petroleum ether. No effort was made to determine the ratios of the tautomers.

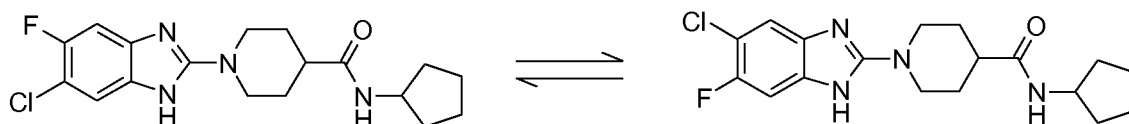
- 5 (c) Preparation of the intermediary compound 4-(cyclopentylcarbamoyl)piperidinium 2,2,2-trifluoroacetate.



To a solution of *tert*-Butyl 4-(cyclopentylcarbamoyl)piperidine-1-carboxylate (1.0 g, 3.37 mmol) in dichloromethane (10 mL), cooled to 0 °C, was added 2,2,2-trifluoroacetic acid (8.4 mmol).

- 10 The reaction was allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated *in vacuo* (repeated co-evaporation with toluene), and dried under vacuum to give 4-(cyclopentylcarbamoyl)piperidinium 2,2,2-trifluoroacetate in quantitative yield.

- (d) Preparation of the intermediary compounds 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide.

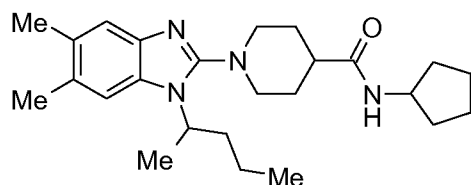


To a suspension of the tautomeric compounds 2,5-dichloro-6-fluoro-1*H*-benzo[d]imidazole and 2,6-dichloro-5-fluoro-1*H*-benzo[d]imidazole (1 g, 4.87 mmol), 1,4-dioxane (10 mL) and 4-(cyclopentylcarbamoyl)piperidinium 2,2,2-trifluoroacetate (7.3 mmol) was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 14.6 mmol) and heated at 180°C for 4 hours. After the appropriate work-up, the residue was recrystallized from a mixture of dichloromethane, petroleum ether and diethyl ether, to give 0.8 g (45 % yield) of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide.

- 25 (e) A tautomeric mixture of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-N-

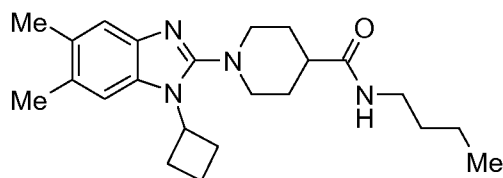
cyclopentylpiperidine-4-carboxamide (0.1 g, 0.274 mmol), bromocyclobutane (1.096 mmol), caesium carbonate (1.096 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene] dichloropalladium(II) ($\text{PdCl}_2(\text{dppf})$, 0.0274 mmol) and *N,N*-dimethyl-formamide (3 mL) was subjected to microwave conditions at 120°C for one hour in a sealed tube and purified with column chromatography, to give 5 mg (4.4 % yield) of 1-(5-chloro-1-cyclobutyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentyl-piperidine-4-carboxamide and 1-(6-chloro-1-cyclobutyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was made to determine the ratio of the regioisomers. LC-MS (m/z) 419.1 ($M+1$).

Example 95: *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

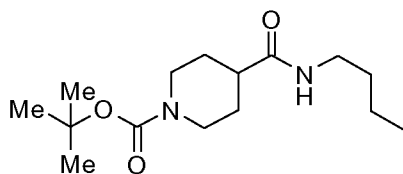


N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.059 mmol), 2-bromopentane (17.8 mg, 0.117 mmol), caesium carbonate (57.4 mg, 0.176 mmol), *N,N*-dimethylformamide (3.0 mL) was heated at 60°C over night. The reaction mixture was filtered, concentrated in vacuo and purified on preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μm , 21.2 $\times$ 150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection). This gave 7.2 mg (30 % yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (m/z) 411.4 ($M+1$).

Example 96: *N*-butyl-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

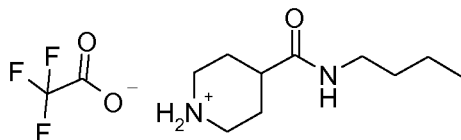


(a) Preparation of the intermediary compound *tert*-butyl 4-(*n*-butylcarbamoyl)piperidine-1-carboxylate.



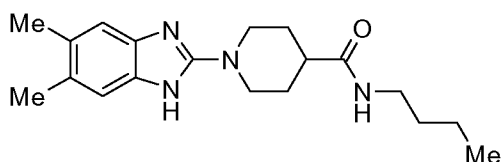
To a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.37 mmol) in dry dichloromethane (10 mL), cooled to 0 °C, was added *N,N*-diisopropylethylamine (Hünig's base, DIEA, 8.7 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 8.7 mmol, CAS Registry Number: 25952-53-8), 1-hydroxybenzotriazole (HOBt, CAS Registry Number: 2592-95-2, 2.2 mmol) and *n*-butylamine (5.2 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 8 hours. The reaction mixture was washed with aqueous hydrochloric acid (3 x 15 mL, 2 N), saturated aqueous sodium bicarbonate (2 x 15 mL), dried over magnesium sulfate, filtered and the filtrate concentrated in vacuo. The residue was recrystallized from dichloromethane/pet ether to give 1.1 g (92%) of *tert*-butyl 4-(*n*-butylcarbamoyl)piperidine-1-carboxylate.

(b) Preparation of the intermediary compound 4-(*n*-butylcarbamoyl)piperidinium 2,2,2-trifluoroacetate :



To a solution of *tert*-Butyl 4-(*n*-butylcarbamoyl)piperidine-1-carboxylate (1.0 g, 3.52 mmol) in dichloromethane (10 mL), cooled to 0 °C, was added 2,2,2-trifluoroacetic acid (8.4 mmol). The reaction was allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated in vacuo (repeated co-evaporation with toluene), and dried under vacuum to give 4-(*n*-butylcarbamoyl)piperidinium 2,2,2-trifluoroacetate in quantitative yield.

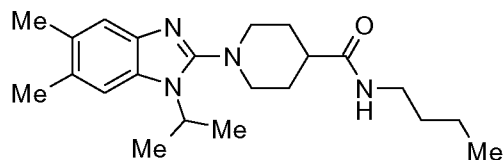
(c) Preparation of the intermediate compound *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:



To a suspension of 2-chloro-5,6-dimethyl-1*H*-benzo[d]imidazole (0.3 g, 1.6 mmol), 4-(*n*-butylcarbamoyl)piperidinium 2,2,2-trifluoroacetate (0.45 g, 2.5 mmol) and 1,4-dioxane (4 mL), was added *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 0.32 mL, 2.5 mmol). The reaction mixture was heated in a sealed tube at 180°C for 3 hours, poured out into ice-water, the precipitate filtered off, to give 0.2 g (36 % yield) of *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 329.3 (M+1).

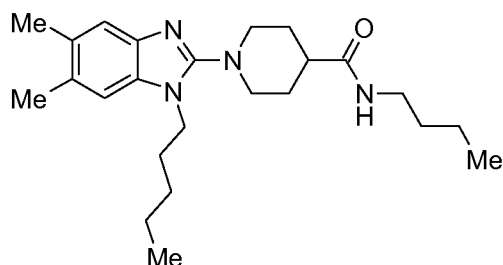
(d) To a solution of *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.3 mmol) in *N,N*-dimethylformamide (2 mL), caesium carbonate (0.6 g, 1.8 mmol) was added cyclobutylbromide (0.074 g, 0.54 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo and the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 99:8) to give 23 mg (20 % yield) of *N*-butyl-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 383.3 (M+1).

Example 97: *N*-butyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



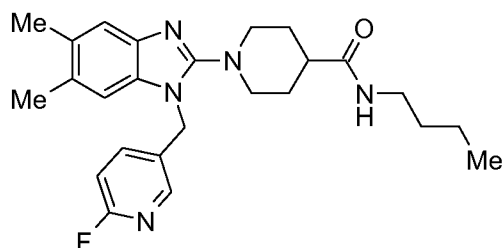
To a solution of *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.3 mmol) in *N,N*-dimethylformamide (2 mL), was added caesium carbonate (0.6 g, 1.8 mmol), followed by 2-bromopropane (67 mg, 0.54 mmol). The reaction mixture was irradiated under microwave conditions at 120°C for 1 hour, concentrated in vacuo, the residue extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with water (3 × 15 mL), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, chloroform/methanol 99:1) to give 49 mg (44 % yield) of *N*-butyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamid. LC-MS (*m/z*) 371.3 (M+1).

Example 98: *N*-butyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



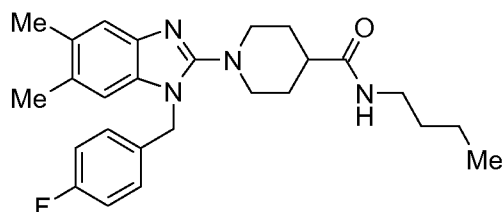
The title compound was prepared from *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.3 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.6 g, 1.8 mmol) and 1-bromopentane (0.082 g, 0.54 mmol) using the method described in Example 97, to give 25 mg (21 % yield) of *N*-butyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 399.4 (M+1).

Example 99: *N*-butyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



The title compound was prepared from *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.3 mmol), *N,N*-dimethylformamide (2 mL), caesium carbonate (0.6 g, 1.8 mmol) and 5-(bromomethyl)-2-fluoropyridine (0.1 g, 0.54 mmol) using the method described in Example 97, to give 5 mg of *N*-butyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 438.2 (M+1).

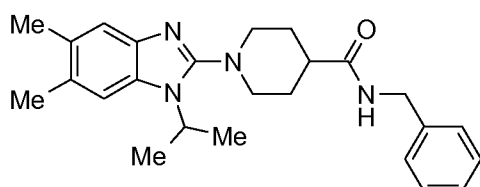
Example 100: *N*-butyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



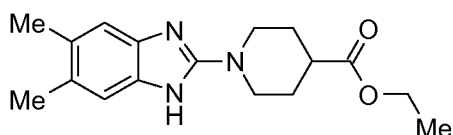
The title compound was prepared from *N*-butyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.3 mmol), *N,N*-dimethylformamide (2 mL), caesium

carbonate (0.6 g, 1.8 mmol) and 1-(bromomethyl)-4-fluorobenzene (0.1 g, 0.54 mmol) using the method described in Example 97, to give 28 mg (28 % yield) of *N*-butyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 437.1 (M+1).

Example 101: *N*-benzyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

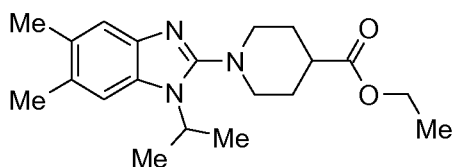


(a) Preparation of the intermediate compound ethyl 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate.



- 10 5,6-Dimethyl-1*H*-benzo[d]imidazol-2-amine (180.6 mg, 1 mmol), ethyl piperidine-4-carboxylate (157.2, 1 mmol) and 1,4-dioxane (4 mL) were mixed in a 5 mL microwave vial and irradiated under microwave conditions at 180°C for 1 hour. The reaction mixture was concentrated in vacuo, subjected to column chromatography (silica gel, dichloromethane/methanol 90:10), to give 288 mg (96 % yield) of ethyl 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate. LC-MS (*m/z*) 302.2 (M+1).

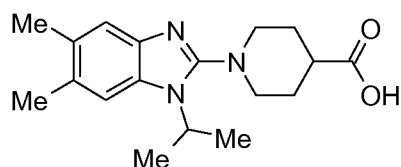
(b) Preparation of the intermediate compound ethyl 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate.



- 20 Ethyl 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (280 mg, 0.929 mmol) was dissolved in acetonitrile (25 mL) and *N,N*-dimethylformamide (5 mL). 2-Bromopropane (342.8 mg, 2.79 mmol) and potassium carbonate (385.2 mg, 2.79 mmol) was added and the reaction mixture was heated at 60°C over night. 2-Bromopropane (342.8 mg, 2.79

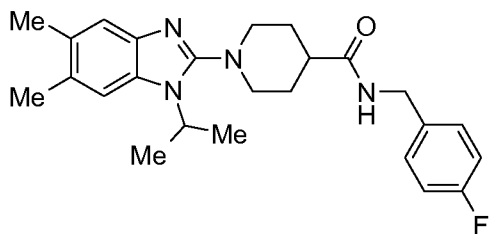
mmol) and potassium carbonate (128.4 mg, 0.929 mmol) was added, the reaction mixture was heated at 60°C for 7 hours, filtered and the filtrate concentrated in vacuo. The residue was subjected to column chromatography (silica gel, dichloromethane/methanol, gradient elution 2-10 % methanol) to give 143 mg (45 % yield, 90 % pure) of ethyl 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate. LC-MS (*m/z*) 344.3 (M+1).

(c) Preparation of the intermediate compound 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid.



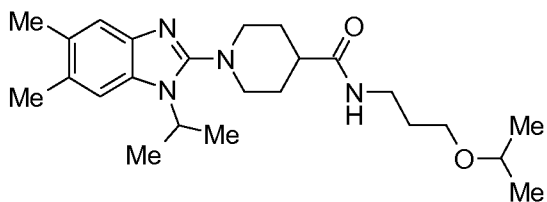
- A mixture of ethyl 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (143 mg, 0.416 mmol), sodium hydroxide (83.3 mg, 2.08 mmol) and water (1 mL) was heated at reflux for 50 minutes. Aqueous hydrochloric acid (1 mL, 2N) was added and the reaction mixture concentrated in vacuo. LC-MS (*m/z*) 344.3 (M+1). This gave 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in a mixture with sodium chloride. LC-MS (*m/z*) 316.2 (M+1).
- (d) 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (10 mg, 0.0317 mmol) was dissolved in *N,N*-dimethylformamide (2 mL). 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (13.3 mg, 0.0349 mmol), *N,N*-diisopropylethylamine (8.2 mg, 0.0634 mmol) and phenylmethanamine (4.08 mg, 0.0380 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour, concentrated in vacuo and filtered through a pad of silica gel (dichloromethane/methanol 95:5). The pooled fractions containing the title compound were concentrated in vacuo and subjected to purification on hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column with UV (214 or 254 nm) and MS (ESI) detection), using acetonitrile/water (containing 0.05 % formic acid) gradient elution 10-50 %), to give 7.3 mg (57 % yield) of *N*-benzyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 405.3 (M+1).

Example 102: *N*-(4-fluorobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



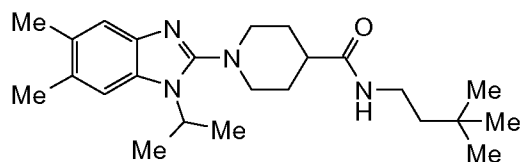
The title compound was prepared from 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (10 mg, 0.0317 mmol), *N,N*-dimethylformamide (2 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (13.3 mg, 0.0349 mmol), *N,N*-diisopropylethylamine (8.2 mg, 0.0634 mmol) and (4-fluorophenyl)methanamine (4.76 mg, 0.0380 mmol) using the method described in Example 101, to give 8.5 mg (63 % yield) of *N*-(4-fluorobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 423.3 (*M*+1).

Example 103: *N*-(3-isopropoxypropyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



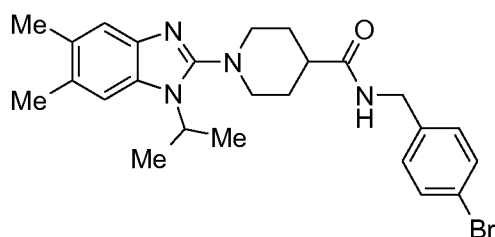
1-(1-Isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (10 mg, 0.0317 mmol) was dissolved in *N,N*-dimethylformamide (2 mL). 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (13.3 mg, 0.0349 mmol), *N,N*-diisopropylethylamine (8.2 mg, 0.0634 mmol) and 3-isopropoxypropan-1-amine (4.50 mg, 0.0380 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour, and concentrated in vacuo. The residue was subjected to purification on hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μ m, 21.2 $\times$ 150 mm) column with UV (214 or 254 nm) and MS (ESI) detection, using acetonitrile/water (containing 0.05 % formic acid) gradient elution 10-50 %), to give 9.2 mg (70 % yield) of *N*-(3-isopropoxypropyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 415.3 (*M*+1).

Example 104: *N*-(3,3-dimethylbutyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



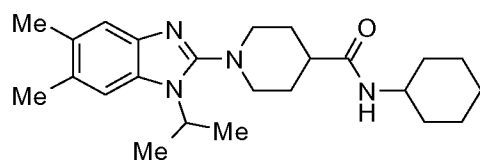
The title compound was prepared from 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (10 mg, 0.0317 mmol), *N,N*-dimethylformamide (1 mL), 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (13.3 mg, 0.0349 mmol), *N,N*-diisopropylethylamine (8.2 mg, 0.0634 mmol) and 3,3-dimethylbutan-1-amine (3.85 mg, 0.0380 mmol) using the method described in Example 103, to give 6.1 mg (48 % yield) of *N*-(3,3-dimethylbutyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 399.4 (*M*+1).

Example 105: *N*-(4-bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



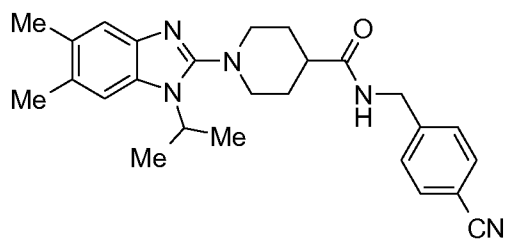
1-(1-Isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (40 mg, 0.127 mmol) was dissolved in *N,N*-dimethylformamide (4 mL). 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (53.0 mg, 0.140 mmol), *N,N*-diisopropylethylamine (49.2 mg, 0.380 mmol) and (4-bromophenyl)methanamine hydrochloride (33.9 mg, 0.152 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes, concentrated in vacuo and subjected to column chromatography (silica gel, dichloromethane/methanol, gradient elution 1-6 % methanol). This gave quantitative yield of *N*-(4-bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 483.2 (*M*+1).

Example 106: *N*-cyclohexyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



1-(1-Isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (10 mg, 0.0317 mmol) was dissolved in *N,N*-dimethylformamide (2 mL). 2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (13.3 mg, 0.0349 mmol), *N,N*-diisopropylethylamine (8.2 mg, 0.0634 mmol) and cyclohexanamine (3.77 mg, 0.0380 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes, concentrated in vacuo and filtered through a pad of silica gel (dichloromethane/methanol 95:5). The pooled fractions containing the title compound were concentrated in vacuo and subjected to purification on hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column with UV (214 or 254 nm) and MS (ESI) detection), using acetonitrile/water (containing 0.05 % formic acid) gradient elution 10-50 %), to give 5.6 mg (45 % yield) of *N*-cyclohexyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 397.3 (*M*+1).

Example 107: *N*-(4-cyanobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

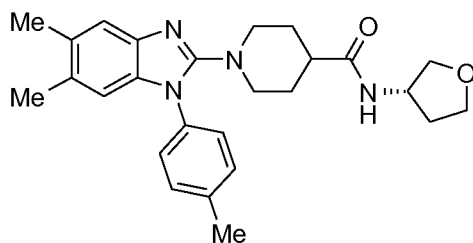


15

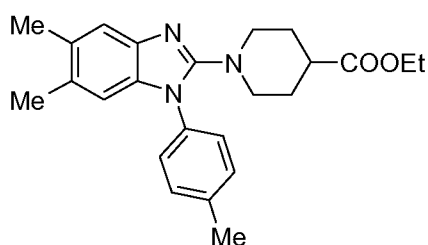
N-(4-Bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.0414 mmol), dicyanozinc (ZnCN_2 , 4.9 mg, 0.0414 mmol), bis(tri-*tert*-butylphosphine)palladium ($\text{Pd}[\text{P}(\text{t-bu})_3]_2$, 2.1 mg, 0.00414 mmol) and *N,N*-dimethylformamide (1 mL) was irradiated in a microwave oven at 150°C for 30 minutes. The reaction mixture was filtered, concentrated in vacuo, subjected to column chromatography (silica gel), to give 8.8 mg (50 % yield) of *N*-(4-cyanobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 430.3 (*M*+1).

20

Example 108: (S)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

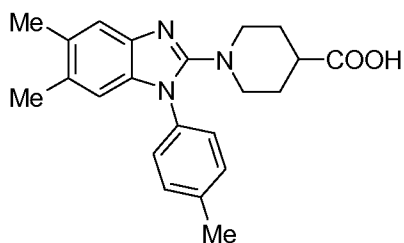


(a) Preparation of the intermediate compound ethyl 1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



- 5 Ethyl 1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80.5 mg, 0.267 mmol), 1-iodo-4-methylbenzene (116 mg, 0.534 mmol), 8-hydroxyquinoline (7.8 mg, 0.053 mmol), copper(I) oxide (3.8 mg, 0.027 mmol), polyethylene glycol 400 (107 mg, 0.267 mmol), caesium carbonate (122 mg, 0.374 mmol) and dimethylsulfoxide (0.5 mL) were mixed in a sealed reaction tube. The reaction mixture was heated to 150°C for one hour in a heating block
- 10 and then diluted with ethylacetate and water. The water phase was extracted with ethyl acetate, the combined organic phases dried over magnesium sulphate and concentrated in vacuo. The residue was purified on automated flash chromatography (silica gel, ethyl acetate/*iso*-hexane, gradient elution from 20 to 60% ethyl acetate) to give 40 mg (38 % yield) of ethyl 1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylate. LC-MS (m/z) 392.0
- 15 (M+1).

(b) Preparation of the intermediate compound 1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:

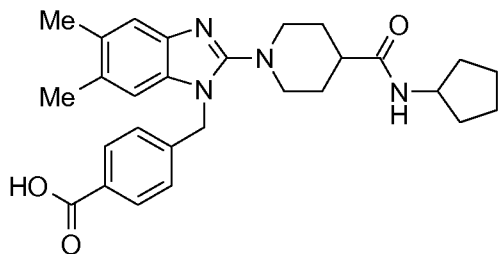


- To ethyl 1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (40 mg, 0.10 mmol) was added ethanol (2 mL) and aqueous sodium hydroxide (1 mL, 1 N) and the
- 20

reaction mixture was stirred at 50 °C for one hour. The reaction mixtures were neutralized with aqueous hydrochloric acid (1 N), concentrated in vacuo to give 1-(5,6-dimethyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in quantitative yield. LC-MS (*m/z*) 364.0 (*M*+1).

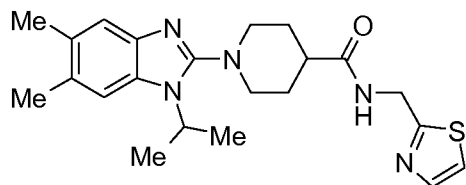
- 5 (c) 1-(5,6-Dimethyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (37 mg, 0.10 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 58 mg, 0.153 mmol), (*S*)-tetrahydrofuran-3-amine hydrochloride (18.9 mg, 0.153 mmol) and *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 170 µL, 1.02 mmol) were dissolved in *N,N*-dimethylformamide (1 mL). The reaction mixture was stirred overnight at
 10 ambient temperature, filtered and subjected to preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 33 mg (75 % yield) of (*S*)-1-(5,6-dimethyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white
 15 solid. LC-MS (*m/z*) 433.0. (*M*+1).

Example 109: 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoic acid

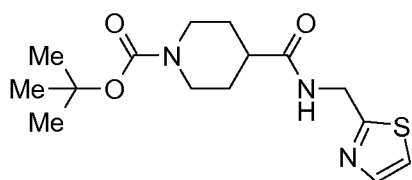


- Methyl 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoate (17 mg, 0.035 mmol) was dissolved in methanol (1 mL). Sodium hydroxide (13.9 mg, 0.348 mmol) and water (0.17 mL) was added and the reaction mixture was stirred at
 20 room temperature for 2 hours. Aqueous hydrochloride (0.085 mL, 2*N*) was added, the reaction mixture concentrated in vacuo and subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with
 25 UV (214 or 254 nm) and MS (ESI) detection) to give 8.1 mg (49 % yield) of 4-((2-(4-(cyclopentylcarbamoyl)-piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoic acid. LC-MS (*m/z*) 475.3 (*M*+1).

Example 110: 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide

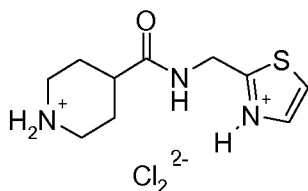


(a) Preparation of the intermediate compound tert-butyl 4-(thiazol-2-ylmethylcarbamoyl)-piperidine-1-carboxylate:



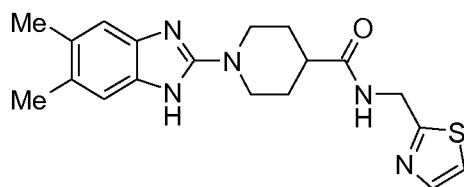
To a mixture of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (500 mg, 2.18 mmol), triethylamine (220.7 mg, 2.18 mmol) and dichloromethane (10 mL) was carefully added thionyl chloride (311.3 mg, 2.62 mmol) and the reaction mixture was stirred at room temperature (reaction mixture 1). In a separate vial was mixed 2-(chloromethyl)thiazole, triethylamine (882.7 mg, 8.723 mmol) and dichloromethane (10 mL) that was stirred and cooled on ice-batch and reaction mixture 1 was added over 5 minutes while stirring. The reaction mixture was allowed to reach room temperature, washed with aqueous hydrochloric acid (2 x 20 mL, 2 *N*), aqueous saturated sodium bicarbonate (2 x 20 mL), dried over magnesium sulphate, filtered and concentrated in vacuo. The residue was collected and the acidic and basic washes were combined and extracted with dichloromethane (3 x 30 mL), the organic phase dried over magnesium sulphate and concentrated. The two residues were combined to give 474 mg (67 % yield) of tert-butyl 4-(thiazol-2-ylmethylcarbamoyl)-piperidine-1-carboxylate. LC-MS (*m/z*) 326.2 (*M*+1).

(b) Preparation of the intermediate compound 2-((4-piperidiniumcarboxamido)methyl)-3-thiazolium dichloride:



To a solution of tert-butyl 4-(thiazol-2-ylmethylcarbamoyl)-piperidine-1-carboxylate (474 mg, 1.457 mmol) and 2-propanol (10 mL), was drop-wise added concentrated hydrochloric acid (0.18 mL) in 2-propanol (10 mL) and the reaction mixture was stirred at room temperature. After 30 minutes additional concentrated hydrochloric acid (0.18 mL) in 2-propanol (5 mL) was added and after 30 minutes followed by additional concentrated hydrochloric acid (0.54 mL). After stirring over night yet additional concentrated hydrochloric acid (2 mL) was added and the reaction mixture was refluxed for 1 hour, concentrated in vacuo and co-eluted with acetonitrile (20 mL). This gave 470 mg of 2-((4-piperidiniumcarboxamido)methyl)-3-thiazolium dichloride.

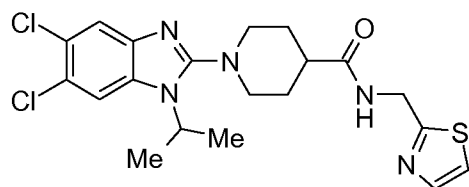
(c) Preparation of the intermediate compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide:



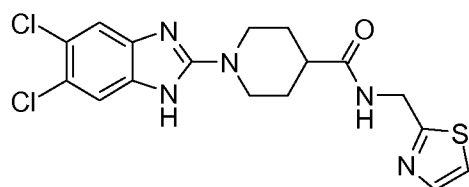
2-Chloro-5,6-dimethyl-1*H*-benzo[d]imidazole (54.2 mg, 0.30 mmol), 2-((4-piperidiniumcarboxamido)methyl)-3-thiazolium dichloride (113.4 mg, 0.39 mmol, 90 % purity), *N,N*-diisopropylethylamine (116.3 mg, 0.9 mmol) and 1,4-dioxane (2 mL) was irradiated in a microwave oven at 170°C for 1 hour. The reaction mixture was concentrated in vacuo and the residue subjected to column chromatography (silica gel, dichloromethane/methanol, gradient elution using 5-20 % methanol) to give 83 mg (75 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 370.3 (*M*+1).

(d) The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide (11.1 mg, 0.03 mmol), *N,N*-dimethylformamide (1 mL), acetonitrile (3 mL), caesium carbonate (29.3 mg, 0.09 mmol) and 2-bromopropane (11.1 mg, 0.09 mmol) using the method described in Example 111, to give 2.7 mg (22 % yield) of 1-(1-Isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 412.3 (*M*+1).

Example 111: 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide



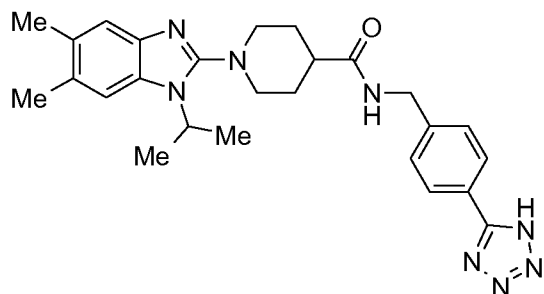
(a) Preparation of the intermediate compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide:



5 2,5,6-Trichloro-1*H*-benzo[d]imidazole (30 mg, 0.135 mmol), 2-((4-piperidinium-carboxamido)methyl)-3-thiazolium dichloride (51.2 mg, 0.176 mmol, 90 % purity), *N,N*-diisopropylethylamine (116.3 mg, 0.9 mmol) and 1,4-dioxane (2 mL) was irradiated in a microwave oven at 170°C for 1 hour. The reaction mixture was concentrated in vacuo and the residue subjected to column chromatography (silica gel, dichloromethane/methanol, gradient
10 elution using 5-20 % methanol) to give 42.2 mg (76 % yield) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 410.1 (*M*+1).

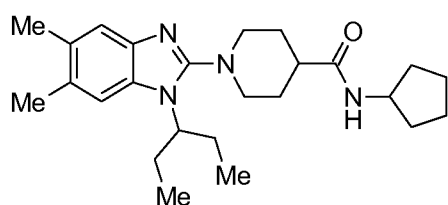
(b) 1-(5,6-Dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide (12.3 mg, 0.03 mmol), 2-bromopropane (11.1 mg, 0.09 mmol), caesium carbonate (29.3 mg, 0.09 mmol), acetonitrile (3 mL) and *N,N*-dimethylformamide (1 mL) was mixed and heated at
15 60°C over night. The reaction mixture concentrated in vacuo and subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 ×150 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 1.6 mg (12 %
20 yield) of 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide. LC-MS (*m/z*) 452.2 (*M*+1).

Example 112: *N*-(4-(1*H*-tetrazol-5-yl)benzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

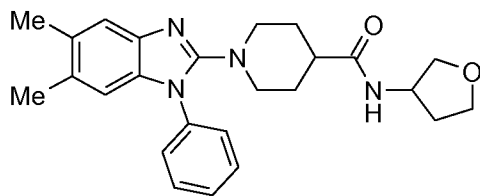


5 *N*-(4-Bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (20 mg, 0.0414 mmol), dicyanozinc (ZnCN₂, 4.9 mg, 0.0414 mmol), bis(tri-tert-butylphosphine)palladium (Pd[P(t-bu)₃]₂, 2.1 mg, 0.00414 mmol) and *N,N*-dimethylformamide (1 mL) were irradiated in a microwave oven at 140°C for 10 minutes. Sodium azide (NaN₃, 32.3 mg, 0.496 mmol) and ammonium chloride (26.6 mg, 0.496 mmol) was added to the reaction mixture, which was heated at 150°C for 40 minutes. The reaction mixture was filtered, the filtrate concentrated in vacuo and the residue subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 μm, 21.2 ×150
 10 mm) column, using acetonitrile/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 3.5 mg (18 % yield) of *N*-(4-(1*H*-tetrazol-5-yl)benzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 473.3 (M+1).

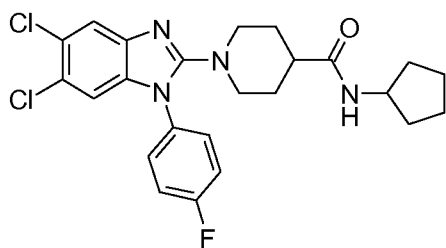
15 **Example 113: *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



The title compound was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.293 mmol), *N,N*-dimethylformamide (3 mL), caesium carbonate (1.172 mmol), 3-bromopentane (1.172 mmol) and dichlorobis(triphenylphosphine)-
 20 palladium (II) (Pd(PPh₃)₂Cl₂ (0.0293 mmol) using the method described in Example 14. The reaction mixture was heated at 120°C for 1 hour under microwave conditions and purified with column chromatography, to give 27 mg (11.2 % yield) of *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 411.1 (M+1).

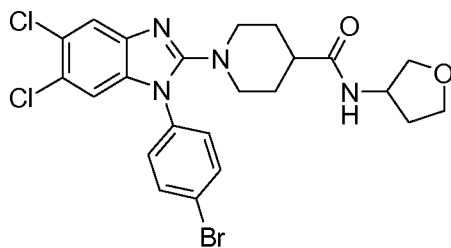
Example 114: 1-(5,6-dimethyl-1-phenyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

The title compound was prepared from 1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.877 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.51 mmol), iodobenzene (3.51 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0438 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 2.9 mg (0.8 % yield) of 1-(5,6-dimethyl-1-phenyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. LC-MS (*m/z*) 419.2 (M+1).

Example 115: N-cyclopentyl-1-(5,6-dichloro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

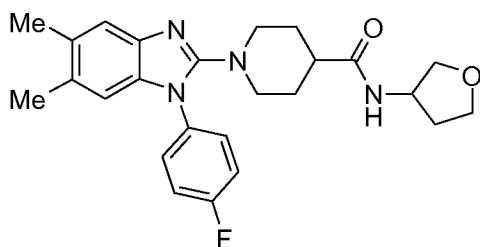
The title compound was prepared from 1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 1-fluoro-4-iodobenzene (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 21 mg (6 % yield) of N-cyclopentyl-1-(5,6-dichloro-1-(4-fluorophenyl)-1H-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 475.5 (M+1).

Example 116: 1-(1-(4-bromophenyl)-5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

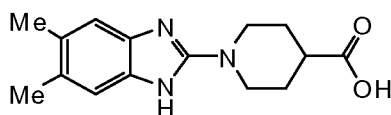


The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 1,4-dibromobenzene (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 6 mg (1.4 % yield) of 1-(1-(4-bromophenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid.

Example 117: 1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



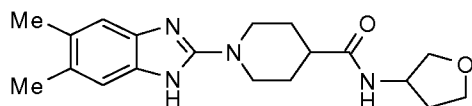
(a) Preparation of the intermediate compound 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



Ethyl 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (1.00 g, 3.31 mmol) was dissolved in ethanol (50 mL) and aqueous sodium hydroxide (1 N, 17.0 mL) was added. The reaction mixture was stirred at room temperature 1 hour, concentrated in vacuo and pH adjusted to 4-5 with addition of aqueous hydrochloric acid (6 N). The formed precipitate was filtered off, the aqueous mother liquid extracted three times with dichloromethane (50 mL) and the combined organic layers were dried with MgSO₄ and concentrated in vacuo. The precipitate and the residue

from the extraction were combined and recrystallized in petroleum ether to give 0.538 g (59%) of 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid.

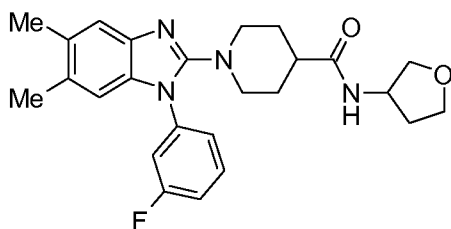
(b) Preparation of the intermediate compound 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



1-(5,6-Dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (1.0 g, 3.7 mmol), tetrahydrofuran-3-amine hydrochloride (0.54 g, 4.4 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 2.8 g, 7.4 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.96 g, 7.4 mmol) and *N,N*-dimethylformamide (25 mL) were stirred at room temperature for 1 hour. After an extractive work-up, the crude was
 10 chrystallized from dichloromethane/petroleum ether to give 1.0 g (83% yield) of 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.

(c) The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL),
 15 caesium carbonate (3.48 mmol), 1-fluoro-4-iodobenzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 9 mg (2.3 % yield) of
 20 1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 437.2 (M+1).

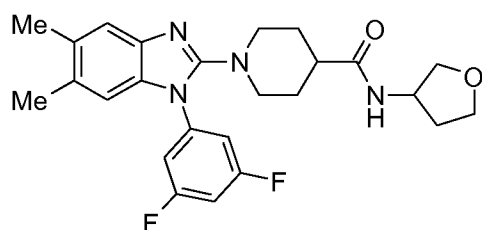
Example 118: 1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL),
 25

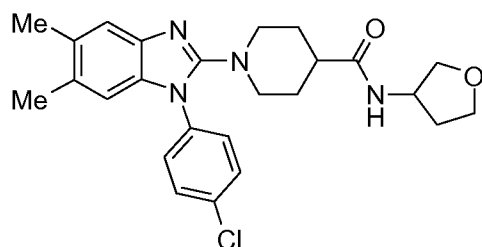
caesium carbonate (3.48 mmol), 1-bromo-3-fluorobenzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 22 mg (6 % yield) of
 5 1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 437.1 (M+1).

Example 119: 1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 1-bromo-3,5-difluorobenzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for
 15 12 hours in a sealed tube and purified with column chromatography, to give 32 mg (8 % yield) of 1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a off-white solid. LC-MS (*m/z*) 455.2 (M+1).

Example 120: 1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

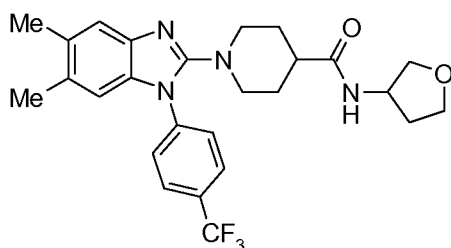


The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 1-bromo-4-chlorobenzene (3.48 mmol), 4,7-dimethoxy-1,10-

phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 61 mg (15 % yield) of 1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-

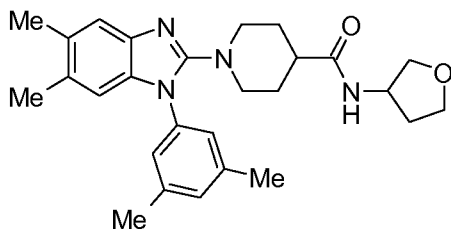
5 yl)piperidine-4-carboxamide as a off-white solid. LC-MS (*m/z*) 453.3 (M+1).

Example 121: 1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 1-bromo-4-(trifluoromethyl)benzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 54 mg (12 % yield) of 1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 487.2 (M+1).

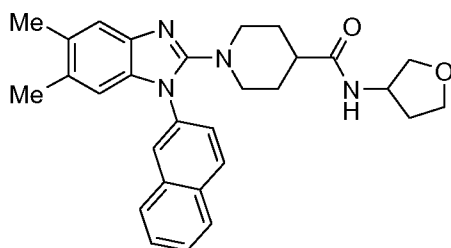
Example 122: 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 1-bromo-3,5-dimethylbenzene (3.48 mmol), 4,7-dimethoxy-

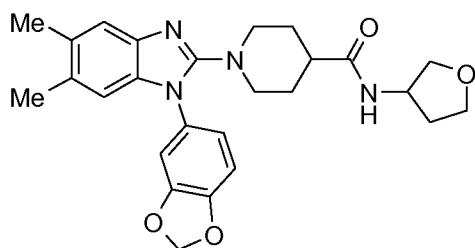
1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 24 mg (6.1 % yield) of 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 447.2 (M+1).

Example 123: 1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 2-bromonaphthalene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 5 mg (1.2 % yield) of 1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 469.1 (M+1).

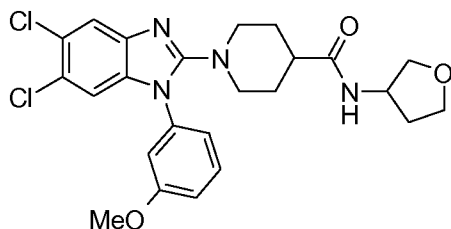
Example 124: 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 5-bromobenzo[d][1,3]dioxole (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435

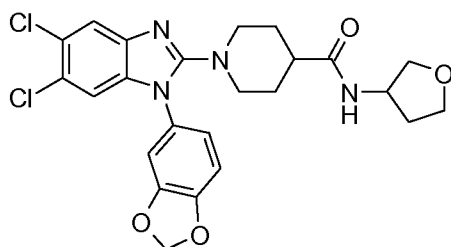
mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 24 mg (6 % yield) of 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 463.2 (M+1).

5 Example 125: 1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 1-bromo-3-methoxybenzene (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 52 mg (13.6 % yield) of 1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 489.4 (M+1).

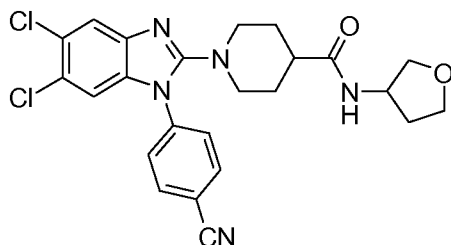
Example 126: 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 5-bromobenzo[d][1,3]dioxole (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for

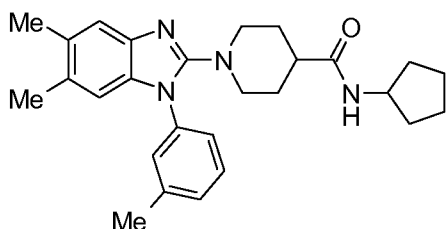
18 hours in a sealed tube and purified with column chromatography, to give 41 mg (10.5 % yield) of 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 503.4 (*M*+1).

5 Example 127: 1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 4-bromobenzonitrile (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified on preparative reverse-phase hplc, to give 13 mg (3.4 % yield) of 1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 484.4 (*M*+1).

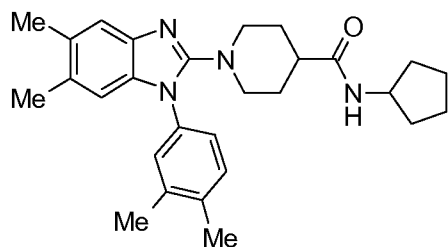
Example 128: *N*-cyclopentyl-1-(5,6-dimethyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



The title compound was prepared from *N*-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), 1-bromo-3-methylbenzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube

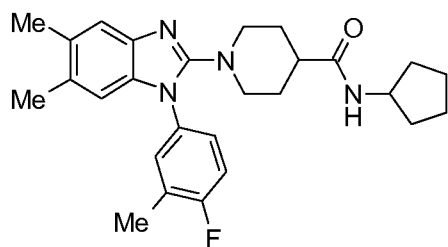
and purified with column chromatography, to give 12 mg (3.2 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 431.2 (M+1).

Example 129: N-cyclopentyl-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 4-bromo-1,2-dimethylbenzene (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 2 mg (0.52 % yield) of N-cyclopentyl-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 445.2 (M+1).

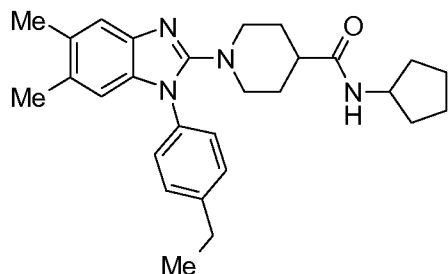
Example 130: N-cyclopentyl-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 4-bromo-1-fluoro-2-methylbenzene (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 5 mg (1.3 % yield) of

N-cyclopentyl-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 449.1 (M+1).

Example 131: N-cyclopentyl-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



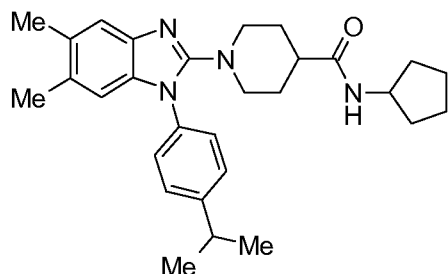
5

The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 1-bromo-4-ethylbenzene (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 10 mg (2.5 % yield) of N-cyclopentyl-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 445.2 (M+1).

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Example 132: N-cyclopentyl-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

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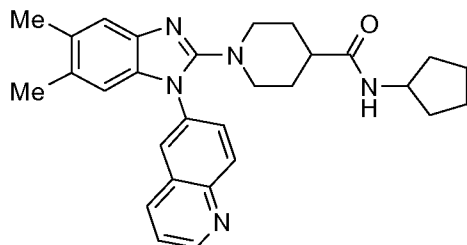


The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 1-bromo-4-isopropylbenzene (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 6 mg (1.5 % yield) of

20

N-cyclopentyl-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 459.2 (M+1).

Example 133: N-cyclopentyl-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

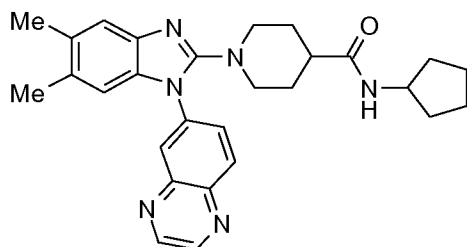


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The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 6-bromoquinoline (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 16 mg (3.9 % yield) of N-cyclopentyl-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 468.2 (M+1).

Example 134: N-cyclopentyl-1-(5,6-dimethyl-1-(quinoxalin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide

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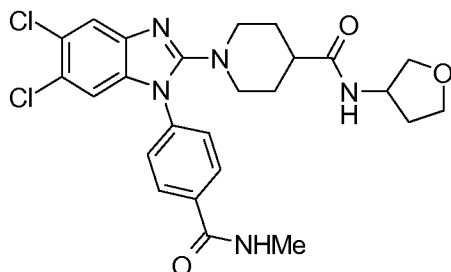


The title compound was prepared from N-cyclopentyl-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.829 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.316 mmol), 6-bromoquinoxaline (3.316 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.044 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 15 mg (3.6 % yield) of N-cyclopentyl-1-

20

(5,6-dimethyl-1-(quinoxalin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 469.2 (M+1).

Example 135: 1-(5,6-dichloro-1-(4-(methylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

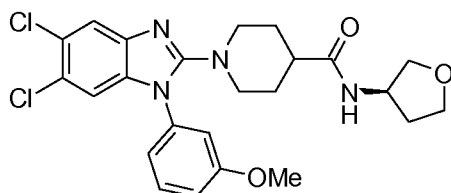


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A reaction mixture consisting of 1-(1-(4-bromophenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.19 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 0.0095 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.38 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.19 mmol), tri tertiarybutyl phosphonium tetrafluoroborate ([*t*-Bu)₃PH]BF₄, 0.019 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 0.095 mmol) and methyl amine hydrochloride (0.38 mmol) in 1,4-dioxane (3 mL), was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (2 x 50 mL) and the combined organic phases dried over anhydrous sodium sulphate. After concentration in vacuo, the residue was subjected to column chromatography to give 10 mg (10 % yield) of 1-(5,6-dichloro-1-(4-(methylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.

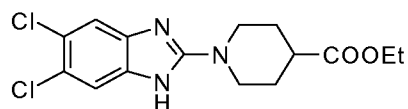
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Example 136: (R)-1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



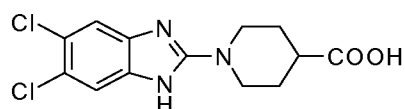
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(a) Preparation of the intermediate compound ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate



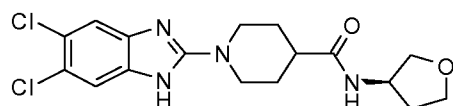
2,5,6-trichloro-1*H*-benzo[d]imidazole (1 g, 5.0 mmol) was mixed with 1,4-dioxane (9 mL) and ethyl piperidine-4-carboxylate (0.85 g, 5.0 mmol) was added, followed by *N,N*-diisopropylethylamine (Hünig's base, DIEA, 1.034 g, 8 mmol). The reaction mixture was subjected to microwave conditions for one hour at 180°C, purified on column (silica gel, hexane/ethyl acetate, gradient elution, 20-70 % ethyl acetate) to give 1.33 g (87 % yield) of ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate as a brown solid. LC-MS (*m/z*) 342.0 (*M*+1).

(b) Preparation of the intermediate compound 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid



Ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (0.60 g, 2.0 mmol) was dissolved in ethanol (150 mL) and aqueous sodium hydroxide (1 N, 17.5 mL) was added. The reaction mixture was stirred at room temperature for two days, concentrated in vacuo and pH adjusted to 4-5 with addition of aqueous hydrochloric acid (1 N). The formed precipitate was filtered off, the aqueous mother liquid extracted three times with dichloromethane (100 mL) and the combined organic phases concentrated in vacuo. The crude carboxylic acid (precipitate and the residue from the extraction) was purified on column (silica gel, ethyl acetate/methanol/formic acid, gradient elution 10-15 % methanol, 0.1 % formic acid) to give 0.53 g (90% purity) of 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid that was used directly in the next step.

(c) Preparation of the intermediate compound (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



1-(5,6-Dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (628 mg, 2.0 mmol), (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (622 mg, 2.4 mmol), 2-(7-aza-1*H*-

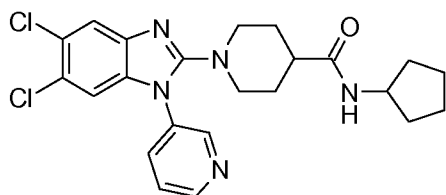
benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 912 mg, 2.4 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 775 mg, 6.0 mmol) and *N,N*-dimethylformamide (25 mL) was stirred at room temperature for 100 minutes. The reaction mixture was concentrated in vacuo, the residue purified on column (silica gel, flash

5 chromatography, dichloromethane/methanol, gradient elution 4-20 % methanol) and finally precipitated from chloroform to give 378 mg (49 % yield) of (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 382.9 (M+1).

(d) A mixture of (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (57.5 mg, 0.15 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (68.4 mg, 0.21 mmol), 1-iodo-3-methoxybenzene (70.2 mg, 0.3 mmol), 8-hydroxyquinoline (4.4 mg, 0.03 mmol), polyethylene glycol 400 (60 mg, 0.15 mmol) and copper(I) oxide (2.1 mg, 0.015 mmol) was subjected to microwave conditions for one hour at 150°C. The reaction mixture was filtered and subjected to preparative hplc (performed on a

15 Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using methanol/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 21.7 mg (30 % yield) of (R)-1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 488.9 (M+1).

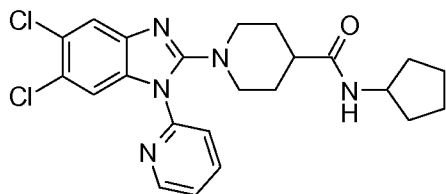
20 **Example 137: *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide**



The title compound was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (38 mg, 0.0997 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (32 mg, 0.0997 mmol), 3-iodopyridine (61.3 mg, 0.299 mmol), 8-hydroxyquinoline (3 mg, 0.0199 mmol), polyethylene glycol 400 (20 mg, 0.0498 mmol) and copper(I) oxide (1.4 mg, 0.00997 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc,

to give 12 mg (26 % yield) of N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a brown solid. LC-MS (*m/z*) 458.0 (*M*+1).

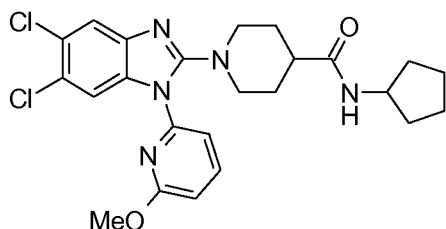
Example 138: N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



5

The title compound was prepared from N-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (38 mg, 0.0997 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (32 mg, 0.0997 mmol), 2-bromopyridine (47.2 mg, 0.299 mmol), 8-hydroxyquinoline (3 mg, 0.0199 mmol), polyethylene glycol 400 (20 mg, 0.0498 mmol) and copper(I) oxide (1.4 mg, 0.00997 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc, to give 13 mg (28 % yield) of N-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a brownish solid. LC-MS (*m/z*) 458.0 (*M*+1).

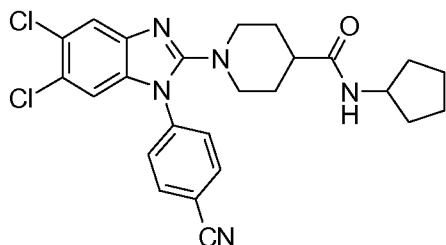
Example 139: N-cyclopentyl-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



The title compound was prepared from N-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (38 mg, 0.0997 mmol), dimethylsulfoxide (0.5 mL), caesium carbonate (32 mg, 0.0997 mmol), 2-bromo-6-methoxypyridine (56.2 mg, 0.299 mmol), 8-hydroxyquinoline (3 mg, 0.0199 mmol), polyethylene glycol 400 (20 mg, 0.0498 mmol) and copper(I) oxide (1.4 mg, 0.00997 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc, to give 22 mg (45 % yield) of N-cyclopentyl-1-(5,6-dichloro-1-

(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a beige solid. LC-MS (*m/z*) 488.0 (*M*+1).

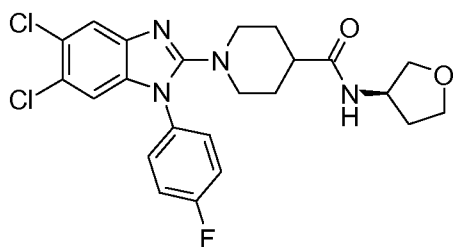
Example 140: *N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



5

The title compound was prepared from *N*-cyclopentyl-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (38 mg, 0.0997 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.5 mg, 0.14 mmol), 4-iodobenzonitrile (68.5 mg, 0.299 mmol), 8-hydroxyquinoline (3 mg, 0.0199 mmol), polyethylene glycol 400 (20 mg, 0.0498 mmol) and copper(I) oxide (1.4 mg, 0.00997 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc, to give 10.5 mg (22 % yield) of *N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a brownish solid. LC-MS (*m/z*) 482.0 (*M*+1).

Example 141: (R)-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

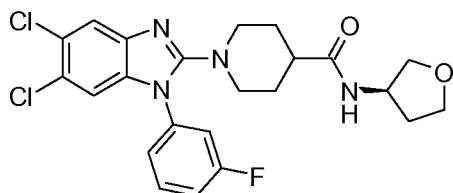


The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (38.3 mg, 0.10 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.6 mg, 0.14 mmol), 1-fluoro-4-iodobenzene (44.4 mg, 0.20 mmol), 8-hydroxyquinoline (2.9 mg, 0.02 mmol), polyethylene glycol 400 (40 mg, 0.1 mmol) and copper(I) oxide (1.4 mg, 0.01 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified

20

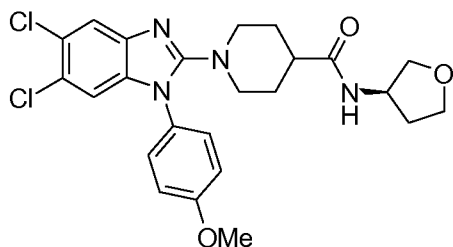
on reverse-phase hplc, to give 14 mg (29 % yield) of (R)-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]-imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 476.9 (*M*+1).

Example 142: (R)-1-(5,6-dichloro-1-(3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (38.3 mg, 0.10 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.6 mg, 0.14 mmol), 1-fluoro-3-iodobenzene (44.4 mg, 0.20 mmol), 8-hydroxyquinoline (2.9 mg, 0.02 mmol), polyethylene glycol 400 (40 mg, 0.1 mmol) and copper(I) oxide (1.4 mg, 0.01 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc, to give 6 mg (13 % yield) of (R)-1-(5,6-dichloro-1-(3-fluorophenyl)-1*H*-benzo[d]-imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 477.0 (*M*+1).

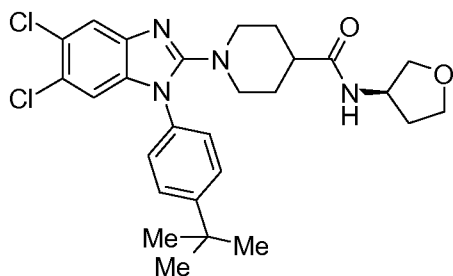
Example 143: (R)-1-(5,6-dichloro-1-(4-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (38.3 mg, 0.10 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.6 mg, 0.14 mmol), 1-iodo-4-methoxybenzene (46.8 mg, 0.20 mmol), 8-hydroxyquinoline (2.9 mg, 0.02 mmol), polyethylene glycol 400 (40 mg, 0.1 mmol) and copper(I) oxide (1.4 mg, 0.01 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently

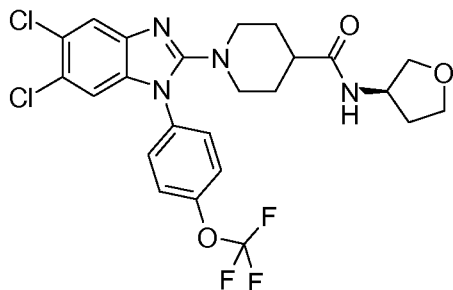
purified on reverse-phase hplc, to give 9.5 mg (49 % yield) of (R)-1-(5,6-dichloro-1-(4-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 489.0 (*M*+1).

Example 144: (R)-1-(1-(4-*tert*-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (38.3 mg, 0.10 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.6 mg, 0.14 mmol), 1-bromo-4-*tert*-butylbenzene (42.6 mg, 0.20 mmol), 8-hydroxyquinoline (5.8 mg, 0.04 mmol), polyethylene glycol 400 (40 mg, 0.1 mmol) and copper(I) oxide (2.9 mg, 0.02 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for one hour at 150°C and subsequently purified on reverse-phase hplc, to give 8.2 mg (16 % yield) of (R)-1-(1-(4-*tert*-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 515.0 (*M*+1).

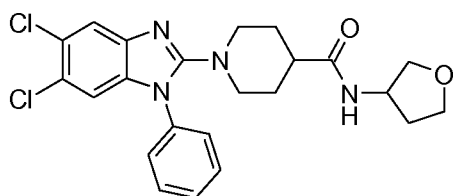
Example 145: (R)-1-(5,6-dichloro-1-(4-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (38.3 mg, 0.10 mmol), dimethylsulfoxide (0.7 mL), caesium carbonate (45.6 mg, 0.14 mmol), 1-iodo-4-(trifluoromethoxy)benzene (57.6 mg, 0.20 mmol), 8-hydroxyquinoline (2.9 mg, 0.02 mmol), polyethylene glycol 400 (40 mg, 0.1

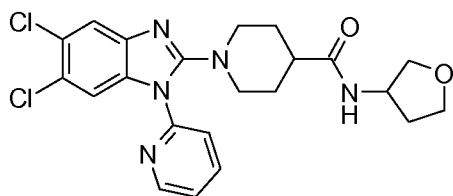
mmol) and copper(I) oxide (1.4 mg, 0.01 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 150°C, filtered and subsequently purified on reverse-phase hplc, to give 15.2 mg (28 % yield) of (R)-1-(5,6-dichloro-1-(4-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 543.0 (M+1).

Example 146: 1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), iodobenzene (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 10 mg (2.8 % yield) of 1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. LC-MS (*m/z*) 459.1 (M+1).

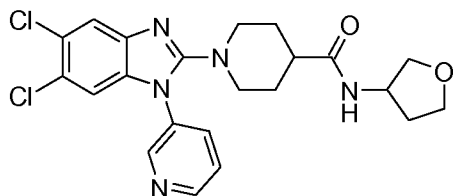
Example 147: 1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 2-bromopyridine (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 26 mg (7.2 %

yield) of 1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 460.6 (M+1).

Example 148: 1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



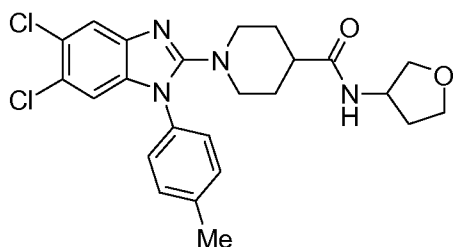
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The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 3-bromopyridine (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 5 mg (1.4 % yield) of 1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 460.5 (M+1).

10

Example 149: 1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

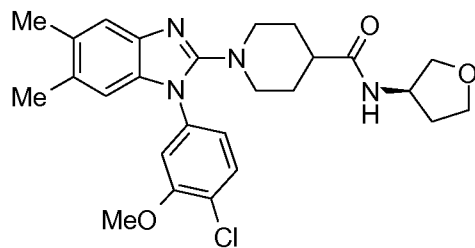
15



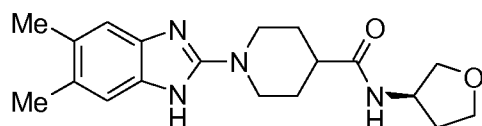
The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.3 g, 0.78 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.092 mmol), 4-bromotoluene (0.936 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.117 mmol), polyethylene glycol (0.039 mmol) and copper(I) oxide (0.039 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 18 hours in a sealed tube and purified with column chromatography, to give 27 mg (7.3 % yield) of 1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 473.4 (M+1).

20

Example 150: (R)-1-(1-(4-chloro-3-methoxyphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



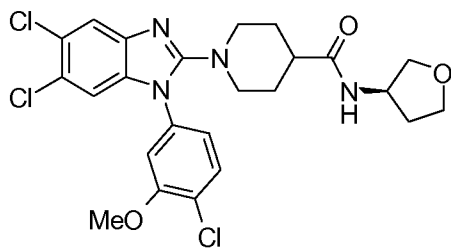
(a) Preparation of the intermediate compound (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide:



1-(5,6-Dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (1.0 g, 3.6 mmol), (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (4.3 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 7.2 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 7.2 mmol) and *N,N*-dimethylformamide (25 mL) was stirred at room temperature for 1 hour. After the appropriate work-up, the residue was recrystallized from dichloromethane/petroleum ether to give 0.96 g (77 % yield) of (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.

(b) The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 4-bromo-1-chloro-2-methoxybenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 15 mg (10 % yield) of (R)-1-(1-(4-chloro-3-methoxyphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 483.3 (*M*+1).

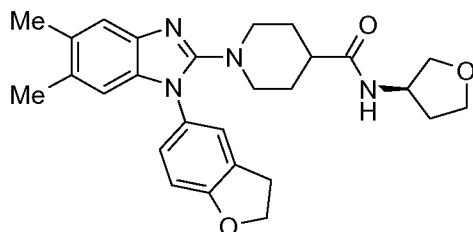
Example 151: (R)-1-(5,6-dichloro-1-(4-chloro-3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 4-bromo-1-chloro-2-methoxybenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 23 mg (17 % yield) of (R)-1-(5,6-dichloro-1-(4-chloro-3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid.

LC-MS (*m/z*) 523.5 (*M*+1).

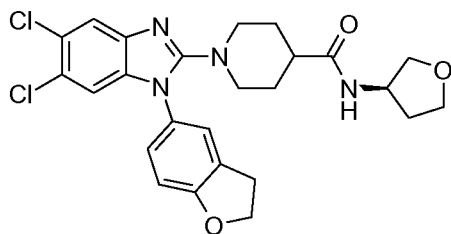
Example 152: (R)-1-(1-(2,3-dihydrobenzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 5-bromo-2,3-dihydrobenzofuran (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.7 % yield) of (R)-1-(1-(2,3-dihydrobenzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid.

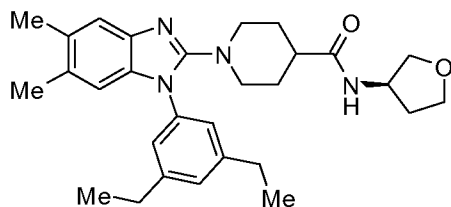
LC-MS (*m/z*) 461.2 (*M*+1).

Example 153: (R)-1-(5,6-dichloro-1-(2,3-dihydrobenzofuran-5-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



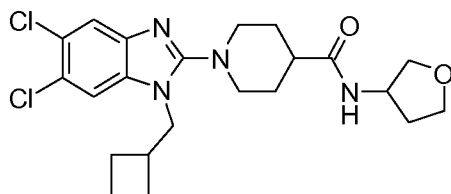
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 5-bromo-2,3-dihydrobenzofuran (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 7 mg (5.3 % yield) of (R)-1-(5,6-dichloro-1-(2,3-dihydrobenzofuran-5-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (m/z) 501.6 (M+1).

Example 154: (R)-1-(1-(3,5-diethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



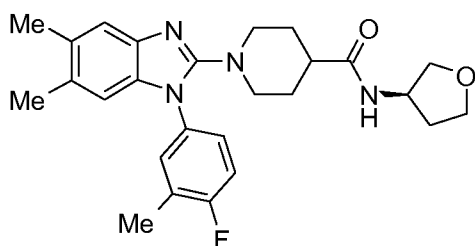
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (200 mg, 0.584 mmol) dimethylsulfoxide (2 mL), caesium carbonate (1.17 mmol), 1-bromo-3,5-diethylbenzene (1.75 mmol), 8-hydroxyquinoline (0.234 mmol), polyethylene glycol (0.292 mmol) and copper(I) oxide (0.117 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 4 mg (1.5 % yield) of (R)-1-(1-(3,5-diethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. LC-MS (m/z) 475.2 (M+1).

Example 155: 1-(5,6-dichloro-1-(cyclobutylmethyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



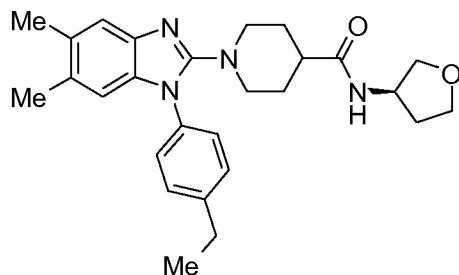
The title compound was prepared from 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.26 mmol), (bromomethyl)cyclobutane (1.04 mmol), caesium carbonate (1.04 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.026 mmol) and *N,N*-dimethylformamide (8 mL) using the method described in Example 16. The reaction mixture was heated at 130°C for two hours in a sealed tube and purified with column chromatography, to give 15 mg (12.8 % yield) of 1-(5,6-dichloro-1-(cyclobutylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 449.3 (M+1).

Example 156: (R)-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



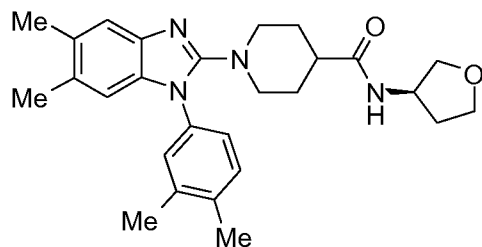
(c) The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 4-bromo-1-fluoro-2-methylbenzene (1.4 mmol), 8-hydroxyquinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 30.5 mg (30 % yield) of (R)-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 451.1 (M+1).

Example 157: (R)-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



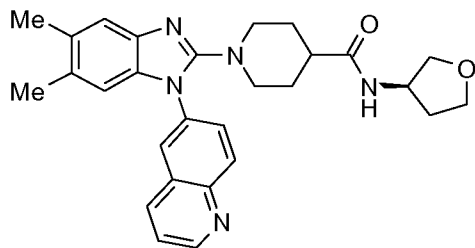
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 1-bromo-4-ethylbenzene (1.4 mmol), 8-hydroxyquinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography (silica gel), to give 19 mg (12 % yield) of (R)-1-(1-(4-ethylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 447.2 (M+1). ¹H NMR (400 MHz, DMSO-d⁶): (for the aromatic region and -NH-) δ 8.03 (1H, NH), 7.44 (4H), 7.21 (1H), 6.82 (1H).

Example 158: (R)-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



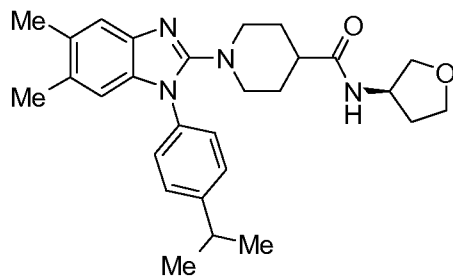
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 4-bromo-1,2-dimethylbenzene (1.4 mmol), 8-hydroxyquinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 25 mg (16 % yield) of (R)-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 447.1 (M+1).

Example 159: (R)-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



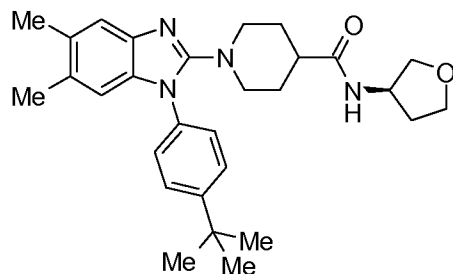
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 6-bromoquinoline (1.4 mmol), 8-hydroxyquinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 15 mg (9 % yield) of (R)-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 470.1 (*M*+1).

Example 160: (R)-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



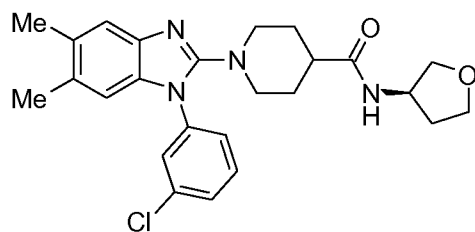
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 1-bromo-4-isopropylbenzene (1.4 mmol), 8-hydroxyquinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 5 mg (3 % yield) of (R)-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 461.2 (*M*+1).

Example 161: (R)-1-(1-(4-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



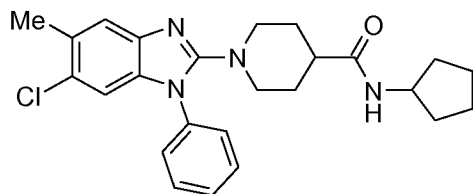
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 1-bromo-4-tert-butylbenzene (1.4 mmol), 8-hydroxy-quinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 27 mg (16 % yield) of (R)-1-(1-(4-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 475.2 (*M*+1).

Example 162: (R)-1-(1-(3-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

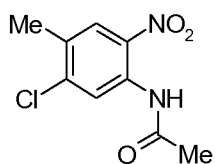


The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.35 mmol), dimethylsulfoxide (6 mL), caesium carbonate (1.4 mmol), 1-bromo-3-chlorobenzene (1.4 mmol), 8-hydroxy-quinoline (0.07 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0175 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on column chromatography, to give 54 mg (34 % yield) of (R)-1-(1-(3-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 453.2 (*M*+1).

Example 163: 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



(a) Preparation of the intermediary compound *N*-(5-chloro-4-methyl-2-nitrophenyl)acetamide:

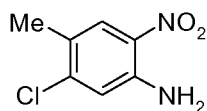


5

Potassium nitrate (10.11 g, 0.10 mol) in concentrated sulphuric acid (21.3 mL) was added dropwise to *N*-(3-chloro-4-methylphenyl)acetamide (18.36 g, 0.10 mol) in concentrated sulphuric acid (101.3 mL) at 5°C. After 5 hours stirring below 5°C, the reaction mixture was carefully poured out on ice water (500 mL), the formed precipitate filtered off, and washed with water (50 mL), *iso*-propanol (10 mL) and *iso*-hexane (30 mL). The precipitate was recrystallized from ethanol (160 mL, 95 %) to give 10.3 g (45 % yield) of *N*-(5-chloro-4-methyl-2-nitrophenyl)-acetamide.

10

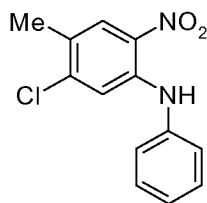
(b) Preparation of the intermediary compound 5-chloro-4-methyl-2-nitroaniline:



Sodium ethoxide (8.27 g, 45.9 mmol) in ethanol (10 mL) was added to (*N*-(5-chloro-4-methyl-2-nitrophenyl)acetamide (7.0 g, 30.6 mmol) in ethanol (10 mL) while stirring at room temperature. After one hour the reaction mixture was poured out in water (100 mL), the precipitate filtered off, and washed with a mixture of *iso*-propanol and *iso*-hexane (1:3, 10 mL) followed by *iso*-hexane (10 mL). This gave 5.71 g (85 % yield) of 5-chloro-4-methyl-2-nitroaniline. LC-MS (*m/z*) 187.0 (*M*+1).

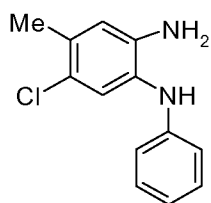
20

(c) Preparation of the intermediary compound 5-chloro-4-methyl-2-nitro-*N*-phenylaniline



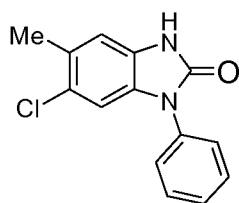
5-Chloro-4-methyl-2-nitroaniline (560 mg, 3.0 mmol), bromobenzene (3.0 g, 0.019 mmol), tripotassium phosphate (1.27 g, 6 mmol), bis(tri-tert-butylphosphine)palladium(0) ($\text{Pd}[\text{P}(\text{t-Bu})_3]_2$, 0.05, 0.0978 mmol) and toluene (5 mL) was heated at 120°C under nitrogen gas over night. The reaction mixture was purified on column (silica gel, flash chromatography, gradient elution iso-hexane/ethyl acetate 100-90 % : 0-10 %) to give 503 mg (64 %) of 5-chloro-4-methyl-2-nitro-N-phenylaniline. LC-MS (m/z) 262.9 ($\text{M}+1$).

(d) Preparation of the intermediary compound 5-chloro-4-methyl-N¹-phenylbenzene-1,2-diamine



A solution of tin(II) chloride dehydrate (1.89 g, 8.39 mmol) in concentrated hydrochloric acid (2.5 mL) was added to a stirred suspension of 5-chloro-4-methyl-2-nitro-N-phenylaniline in a mixture of ethanol and concentrated hydrochloric acid (4 mL, 1:1 mixture) at room temperature. The reaction mixture was heated at 90°C, poured out on water (20 mL), stirred for 5 minutes and filtered. The solid was added to water, the mixture made alkaline with sodium hydroxide and stirred for 5 minutes. The precipitate was filtered off, washed with water (5 mL) and dried under vacuum to give 395 mg (91 % yield) of 5-chloro-4-methyl-N¹-phenylbenzene-1,2-diamine. LC-MS (m/z) 233.0 ($\text{M}+1$).

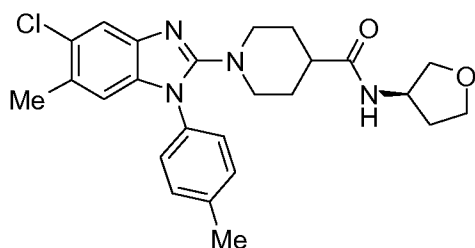
(e) Preparation of the intermediary compound 6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2(3*H*)-one.



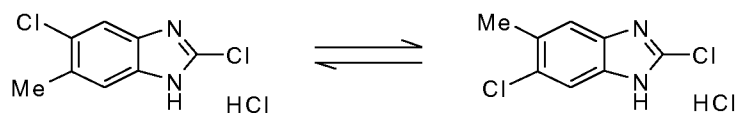
To a stirred slurry of 5-chloro-4-methyl-N¹-phenylbenzene-1,2-diamine (100 mg, 0.43 mmol) in tetrahydrofuran (5 mL) at room temperature was added 1,1'-carbonyldiimidazole (CDI, 104.5 mg, 0.645 mmol) over 10 min. The reaction mixture was stirred at 40°C over night, concentrated in vacuo, and partitioned between diethyl ether (10 mL) and aqueous sodium hydroxide (1 N, 10 mL). The aqueous layer was washed with diethyl ether (10 mL) and neutralized with aqueous hydrochloric acid. The formed precipitate was washed with water (2 mL) and dried under vacuum to give 66.6 mg (60 %) of 6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2(3*H*)-one. LC-MS (*m/z*) 258.9 (M+1).

(f) 6-Chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2(3*H*)-one (42.4 mg, 0.164 mmol) was stirred in phosphoryl trichloride (POCl₃, 5 g) at reflux for 6 hours and concentrated in vacuo (co-evaporation with toluene). Water (10 ml) was added to the residue, followed by an aqueous saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted twice with dichloromethane (20 mL), the combined organic layer dried over magnesium sulfate and concentrated in vacuo. The residue, N-cyclopentylpiperidine-4-carboxamide (29. mg, 0.136 mmol) and 1,2-dimethoxyethane (DME, 0.8 mL) was subjected to microwave conditions for one hour at 180°C. After work-up, the residue was subjected to preparative hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using methanol/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 2.8 mg of 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-cyclopentylpiperidine-4-carboxamide. LC-MS (*m/z*) 437.1 (M+1).

Example 164: (R)-1-(5-chloro-6-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

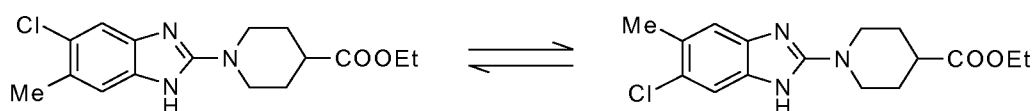


(a) Preparation of the intermediary tautomeric compounds 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole hydrochloride and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole hydrochloride :



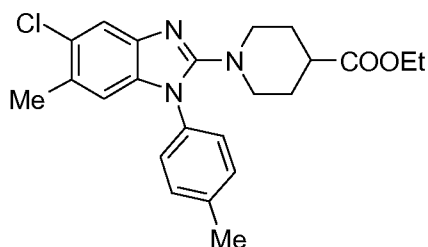
To 5-chloro-6-methyl-1*H*-benzo[d]imidazol-2(3*H*)-one (0.627 g, 3.43 mmol), phosphoryl trichloride (POCl₃, 21.1 g, 0.137 mol) was added, the reaction mixture was heated at 100°C for 6 hours and subsequently cooled down to room temperature. The formed precipitate was filtered off and washed with toluene. The filtrate was concentrated in vacuo and collected. This gave 674 mg (83 % yield) of 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole hydrochloride and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole hydrochloride. LC-MS (*m/z*) 200.9 (M+1).

(b) Preparation of the intermediary tautomeric compounds ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate :



2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole hydrochloride and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole hydrochloride (0.60 g, 2.526 mmol), 1,4-dioxane (10 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.979 g, 7.578 mmol) and ethyl piperidine-4-carboxylate (0.477 g, 3.03 mmol) was subjected to microwave conditions for one hour at 190°C. The reaction mixture was concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol 98:2) to give 0.498 g (61 % yield) of ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate. No effort was done to determine the ratio of the tautomers. LC-MS (*m/z*) 321.9 (M+1)

(c) Preparation of the intermediary intermediate compound ethyl 1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



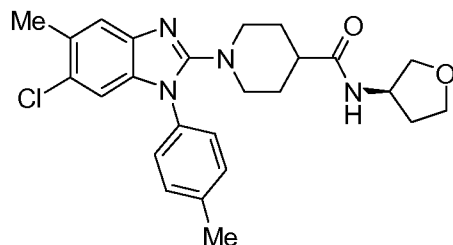
A mixture of ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and its tautomer ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (56 mg, 0.174 mmol), dimethylsulfoxide (0.5 mL), caesium carbonate (79.4 mg, 0.24 mmol), 1-iodo-4-methylbenzene (75.9 mg, 0.348 mmol), 8-hydroxyquinoline (5.1 mg, 0.035 mmol),

polyethylene glycol 400 (34.8 mg) and copper(I) oxide (2.5 mg, 0.017 mmol) was subjected to microwave conditions for 50 minutes at 150°C. The reaction mixture was poured out on aqueous saturated sodium bicarbonate (50 mL), extracted three times with dichloromethane (30 mL), the combined organic phases washed with water, dried over magnesium sulphate and finally purified on column (Silica gel, automated flash chromatography, dichloromethane/methanol, gradient elution using 0.6-0.9 % methanol). This gave 7.0 mg of ethyl 1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate that eluted before ethyl 1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate on the column. The identity of ethyl 1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate was confirmed using the Nuclear Overhauser enhancement spectroscopy (NOESY) experiment. Separate NMR spectas was also runned for ethyl 1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate: ¹H NMR (400 MHz, CDCl₃): δ 7.56 (s, 1H), 7.38-7.31 (m, 4H), 6.89 (s, 1H), 4.11 (q, J=7.1 Hz, 2H), 3.63-3.55 (m, 2H), 2.94-2.84 (m, 2H), 2.48-2.33 (m, 7H), 1.90-1.81 (m, 2H), 1.73-1.58 (m, 2H), 1.25 (t, J=7.1 Hz, 3H); as well as for ethyl 1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate: ¹H NMR (400 MHz, CDCl₃): δ 7.43 (s, 1H), 7.38-7.31 (m, 4H), 7.04 (s, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.66-3.52 (m, 2H), 2.97-2.86 (m, 2H), 2.48-2.36 (m, 7H), 1.91-1.83 (m, 2H), 1.74-1.62 (m, 2H), 1.25 (t, J=7.1 Hz, 3H). NMR spectra were conducted on a Varian Mercury plus spectrometer, ¹H at 400 MHz and ¹³C at 100.6 MHz at ambient temperature.

(d) Ethyl 1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (7 mg), ethanol (1 mL) and aqueous sodium hydroxide (1 mL, 1 N) was stirred at room temperature for two hours. Aqueous hydrochloric acid (0.5 mL, 2 N) was added and the reaction mixture concentrated in vacuo. The residue was mixed with N,N-dimethylformamide (3 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.02 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 10 mg) and (R)-(+)-tetrahydro-3-furylamine *p*-toluenesulfonate salt (6.5 mg, CAS Registry Number: 111769-27-8). The reaction mixture was stirred at room temperature for one hour, concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol, gradient elution using 2.5-5.0 % methanol) to give 11.2 mg of :

(R)-1-(5-chloro-6-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 452.9 (M+1).

Example 165: (R)-1-(6-chloro-5-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

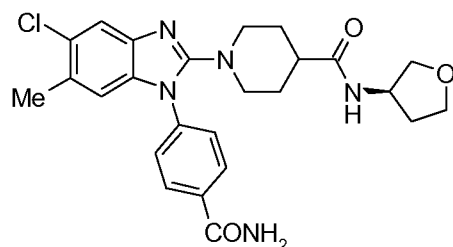


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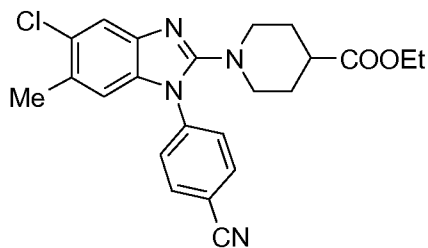
Ethyl 1-(6-chloro-5-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (4.5 mg, eluting second after (R)-1-(5-chloro-6-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as described in example 164d), ethanol (1 mL) and aqueous sodium hydroxide (1 mL, 1 N) was stirred at room temperature for two hours.

- 10 Aqueous hydrochloric acid (0.5 mL, 2 N) was added and the reaction mixture concentrated in vacuo. The residue was mixed with N,N-dimethylformamide (3 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.02 mL), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 10 mg) and (R)-(+)-tetrahydro-3-furylamine p-toluenesulfonate salt (6.5 mg, CAS Registry Number: 111769-27-8). The reaction mixture was
- 15 stirred at room temperature for one hour, concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol, gradient elution using 2.5-5.0 % methanol) to give 3.3 mg of : (R)-1-(5-chloro-6-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide after further purification on preparative reverse-phase hplc (performed on a Gilson-Finnigan ThermoQuest AQA system equipped with a Zorbax SB-C8 (5
- 20 μ m, 21.2 x 150 mm) column, using methanol/water (0.05 % formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI) detection). LC-MS (*m/z*) 452.9 (M+1).

Example 166: (R)-1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

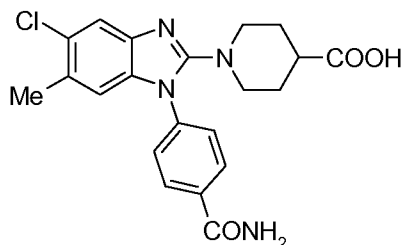


(a) Preparation of the intermediary compound ethyl 1-(5-chloro-1-(4-cyanophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



A tautomeric mixture of ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80.4 mg, 0.25 mmol), dimethylsulfoxide (0.5 mL), caesium carbonate (114 mg, 0.35 mmol), 4-iodobenzonitrile (115.5 mg, 0.5 mmol), 8-hydroxy-quinoline (7.3 mg, 0.05 mmol), polyethylene glycol 400 (100 mg, 0.25 mmol) and copper(I) oxide (3.6 mg, 0.025 mmol) was subjected to microwave conditions for one hour at 150°C. The reaction mixture was poured out on water (5 mL) and loaded on a short column reverse-phase material (Silica gel 60, C₁₈). The short column was washed with a mixture of acetonitrile and water (approximately 10 mL, 1:3), and then eluted with acetonitrile. The elute was concentrated in vacuo and further purified on column (silica gel, iso-hexane/ethyl acetate, gradient elution using 25-40 % ethyl acetate), to give 23.2 mg (22 % yield) of ethyl 1-(5-chloro-1-(4-cyanophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate, eluting ahead of ethyl 1-(6-chloro-1-(4-cyanophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (22.1 mg, 21 % yield) on the column. LC-MS (*m/z*) 422.9 (*M*+1).

(b) Preparation of the intermediate compound 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:

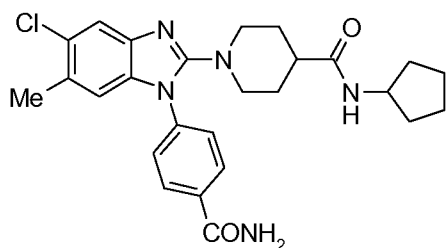


Ethyl 1-(5-chloro-1-(4-cyanophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (23.2 mg), ethanol (2 mL) and aqueous sodium hydroxide (1 mL, 1 N) was stirred at 50°C for one hour. The reaction mixture was neutralized with aqueous hydrochloric acid and concentrated in vacuo to give 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-

benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in quantitative yield. LC-MS (m/z) 412.9 (M+1).

(c) 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (11.6 mg, 0.0281 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 10.9 mg, 0.0843 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 12.8 mmol, 0.034 mmol) and (R)-(+)-tetrahydro-3-furylamine *p*-toluenesulfonate salt (8.7 mg, 0.0337 mmol, CAS Registry Number: 111769-27-8). The reaction mixture was stirred at room temperature over night, concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol, gradient elution using 5.0-10 % methanol) to give 10.3 mg (76 % yield) of (R)-1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 481.9 (M+1).

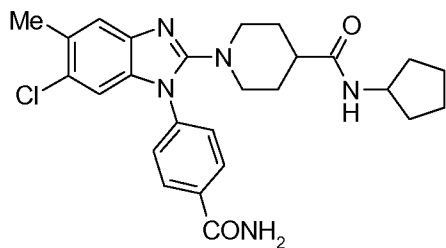
Example 167: 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



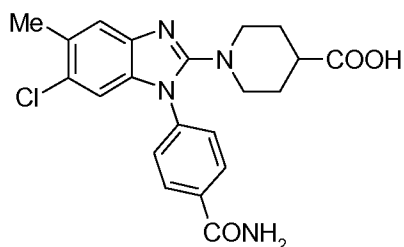
15

The title compound was prepared from 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (11.6 mg, 0.0281 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 10.9 mg, 0.0843 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 12.8 mmol, 0.034 mmol) and cyclopentanamine (2.9 mg, 0.0337 mmol) using the method described in Example 166 c). The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using 2.5-7.0 % methanol), to give 10.6 mg (79 % yield) of 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. LC-MS (m/z) 480.0 (M+1).

Example 168: 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



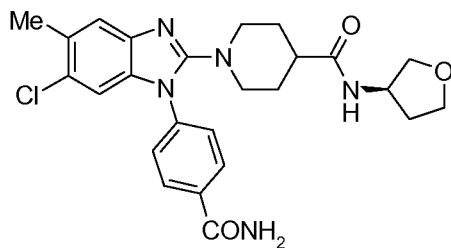
(a) Preparation of the intermediate compound 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



- 5 Ethyl 1-(6-chloro-1-(4-cyanophenyl)-5-methyl-1*H*-benzo[d]-imidazol-2-yl)piperidine-4-carboxylate (22.1 mg, eluting second after ethyl 1-(5-chloro-1-(4-cyanophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate as described in Example 166), ethanol (2 mL) and aqueous sodium hydroxide (1 mL, 1 N) was stirred at 50°C for one hour. The reaction mixture was neutralized with aqueous hydrochloric acid and concentrated in vacuo to give 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in quantitative yield. LC-MS (*m/z*) 412.9 (*M*+1).

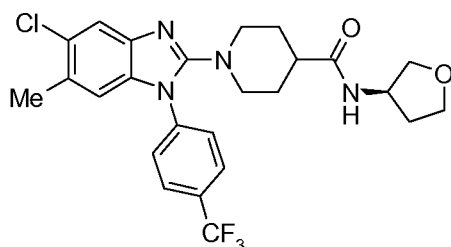
- (b) The title compound was prepared from 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (11 mg, 0.0266 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 10.3 mg, 0.0799 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 12.2 mg, 0.033 mmol) and cyclopentanamine (2.7 mg, 0.032 mmol) using the method described in Example 166 c). The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using 2.5-7.0 % methanol), to give 10.0 mg (78 % yield) of 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. LC-MS (*m/z*) 480.0 (*M*+1).

Example 169: (R)-1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

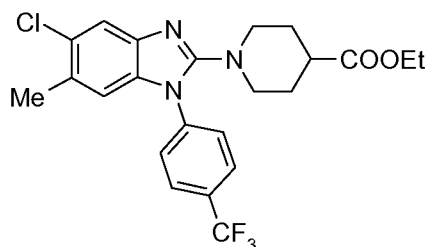


The title compound was prepared from 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (11 mg, 0.0266 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 10.3 mg, 0.0799 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 12.2 mmol, 0.033 mmol) and (R)-(+)-tetrahydro-3-furylamine p-toluenesulfonate salt (8.3 mg, 0.032 mmol, CAS Registry Number: 111769-27-8) using the method described in Example 166 c). The reaction mixture was purified on column chromatography (silica gel, dichloromethane/methanol, gradient elution using 5-10 % methanol), to give 10.9 mg (85 % yield) of (R)-1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 481.9 (*M*+1).

Example 170: (R)-1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



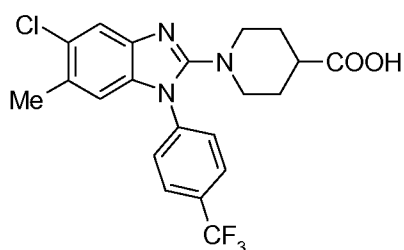
a) Preparation of the intermediate compound ethyl 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



This compound was prepared from a tautomeric mixture of ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80.4 mg, 0.25 mmol), dimethylsulfoxide (0.7

mL), caesium carbonate (114 mg, 0.35 mmol), 1-iodo-4-(trifluoromethyl)benzene (136 mg, 0.5 mmol), 8-hydroxyquinoline (7.3 mg, 0.05 mmol), polyethylene glycol 400 (100 mg, 0.25 mmol) and copper(I) oxide (3.6 mg, 0.025 mmol) using the method described in Example 166. This gave, after column chromatography (silica gel), 30.4 mg (26 % yield) of ethyl 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (26.4 mg, 23 % yield) eluting ahead of ethyl 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate on the column. LC-MS (*m/z*) 465.9 (*M*+1).

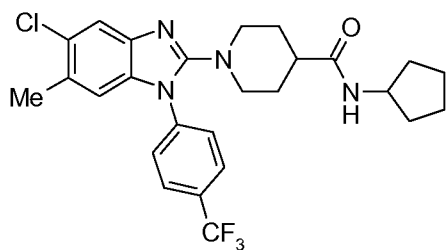
b) Preparation of the intermediate compound 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



Ethyl 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (30.4 mg), ethanol (2 mL) and aqueous sodium hydroxide (0.5 mL, 1 N) was stirred at room temperature for one hour. The reaction mixture was neutralized with aqueous hydrochloric acid and concentrated in vacuo to give 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in quantitative yield. LC-MS (*m/z*) 437.8 (*M*+1).

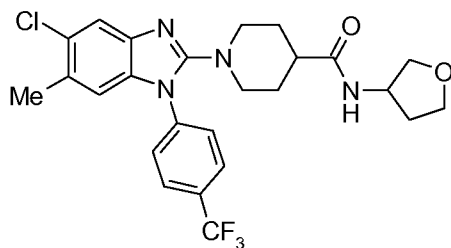
c) The title compound was prepared from 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (9.4 mg, 0.021 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 8.3 mg, 0.064 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 9.8 mg, 0.026 mmol) and (R)-(+)-tetrahydro-3-furylamine p-toluenesulfonate salt (6.7 mg, 0.026 mmol, CAS Registry Number: 111769-27-8) using the method described in Example 166 c). The reaction mixture was purified on column chromatography (silica gel, dichloromethane/methanol, gradient elution using 2-10 % methanol), to give (R)-1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]-imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 506.9 (*M*+1).

Example 171: 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



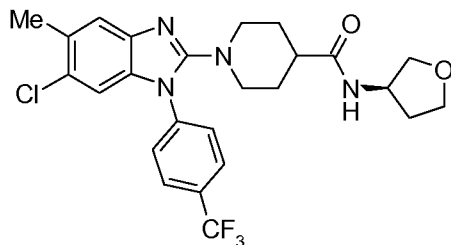
The title compound was prepared from 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (9.4 mg, 0.0215 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 8.3 mg, 0.0644 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 9.79 mg, 0.026 mmol) and cyclopentanamine (2.2 mg, 0.0258 mmol) using the method described in Example 166 c). The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using 2-7 % methanol), to give 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 504.9 (*M*+1).

Example 172: 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

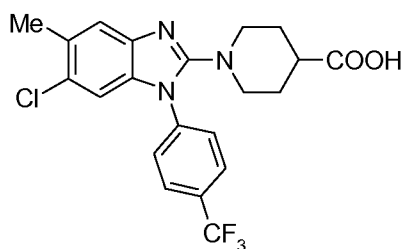


The title compound was prepared from 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (9.4 mg, 0.021 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 8.3 mg, 0.064 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 9.8 mg, 0.026 mmol) and cyclopentanamine hydrochloride (3.2 mg, 0.026 mmol) using the method described in Example 166. The reaction mixture was purified on column chromatography (silica gel, dichloromethane/methanol, gradient elution using 2 to 8 % methanol), to give 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 506.9 (*M*+1).

Example 173: (R)-1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]-imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



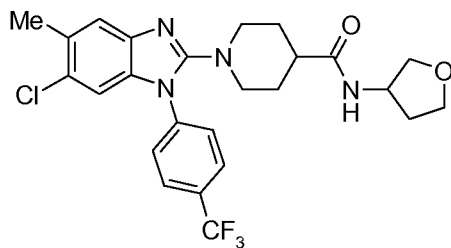
- a) Preparation of the intermediate compound 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



- Ethyl 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (26.4 mg, eluting after of ethyl 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate as described in Example 170), ethanol (2 mL) and aqueous sodium hydroxide (0.5 mL, 1 N) was stirred at room temperature for one hour. The reaction mixture was neutralized with aqueous hydrochloric acid and concentrated in vacuo to give 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid in quantitative yield. LC-MS (*m/z*) 437.8 (M+1).

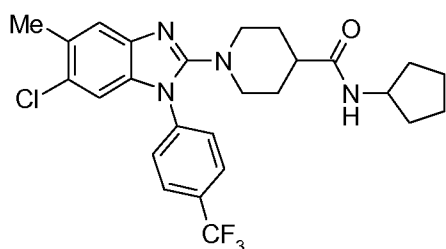
- (b) The title compound was prepared from 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (8.3 mg, 0.019 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 7.4 mg, 0.0569 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 8.6 mg, 0.023 mmol) and (R)-(+)-tetrahydro-3-furylamine *p*-toluenesulfonate salt (5.9 mg, 0.023 mmol, CAS Registry Number: 111769-27-8) using the method described in Example 166 c). The reaction mixture was purified on column chromatography (silica gel, dichloromethane/methanol, gradient elution using 2-8 % methanol), to give (R)-1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 506.9 (M+1).

Example 174: 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (8.5 mg, 0.019 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 7.5 mg, 0.058 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 8.8 mg, 0.023 mmol) and tetrahydrofuran-3-amine hydrochloride (2.9 mg, 0.023 mmol, CAS Registry Number: 204512-94-7) using the method described in Example 166 c). The reaction mixture was purified on column chromatography (silica gel, dichloromethane/methanol, gradient elution using 2-8 % methanol), to give 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 506.9 (M+1).

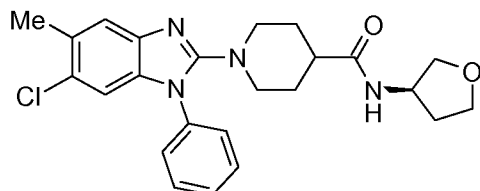
Example 175: 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide:



The title compound was prepared from 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (8.3 mg, 0.019 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 7.4 mg, 0.057 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 8.6 mg, 0.023 mmol) and cyclopentanamine (1.9 mg, 0.0227 mmol) using the method described in Example 166. The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using from 2 to 8 % methanol), to give 1-(6-chloro-

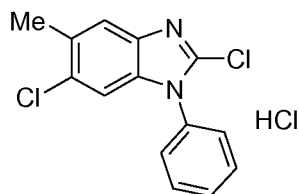
5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide in quantitative yield. LC-MS (*m/z*) 504.9 (*M*+1).

Example 176: (R)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



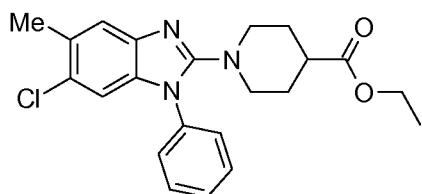
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(a) Preparation of the intermediate compound 2,6-dichloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazole hydrochloride



10 6-Chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2(3*H*)-one (100 mg, 0.387 mmol) was stirred in phosphoryl trichloride (POCl₃, 5.926 g) over night at reflux, and concentrated in vacuo (co-evaporation with toluene), to give 2,6-dichloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazole hydrochloride in quantitative yield.

(b) Preparation of the intermediary compound ethyl 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



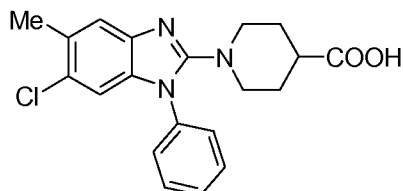
15

2,6-dichloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazole hydrochloride (121.2 mg, 0.387 mmol), ethyl piperidine-4-carboxylate (303.8 mg, 0.2 mmol), toluene (2 mL) and *N,N*-dimethylformamide (0.5 mL) was subjected to microwave conditions at 200°C. After 30 minutes the reaction mixture was concentrated in vacuo, the residue purified on column (silica gel, iso-hexane/ethyl acetate, gradient elution from 10 to 100 % ethyl acetate) to give 27.5 mg (18 %

20

yield) of ethyl 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]-imidazol-2-yl)piperidine-4-carboxylate. LC-MS (*m/z*) 398.0 (M+1).

(c) Preparation of the intermediary compound 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



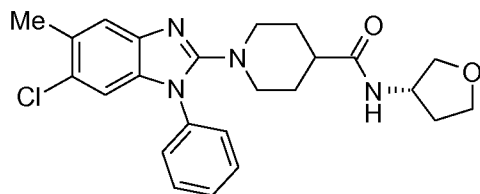
5

A mixture of ethyl 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]-imidazol-2-yl)piperidine-4-carboxylate (17.5 mg, 0.044 mmol), sodium hydroxide (8.8 mg in 1 mL water), ethanol (1 mL) was stirred at 40°C for two hours. The reaction mixture was neutralized with hydrochloric acid (2 N) and concentrated in vacuo, to give a quantitative yield of 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid. LC-MS (*m/z*) 369.9 (M+1).

(d) The title compound was prepared from 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (9.3 mg, 0.025 mmol), *N,N*-dimethylformamide (3.0 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 6.5 mg, 0.050 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 9.6 mg, 0.025 mmol) and (R)-(+)-tetrahydro-3-furylamine *p*-toluenesulfonate salt (6.5 mg, 0.025 mmol, CAS Registry Number: 111769-27-8) using the method described in Example 166. The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using 0 to 8 % methanol), to give 7.3 mg (66 % yield) of (R)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 439.0 (M+1). On measure on optical rotation this compound gave (+)-rotation. ¹H NMR (400 MHz, CD₃OD): δ 7.67-7.60 (m, 2H), 7.55-7.48 (m, 3H), 7.34 (s, 1H), 7.01 (s, 1H), 4.34-4.28 (m, 1H), 3.91-3.72 (m, 3H), 3.65-3.52 (m, 3H), 2.90-2.81 (m, 2H), 2.40 (s, 3H), 2.36-2.27 (m, 1H), 2.23-2.13 (m, 1H), 1.83-1.74 (m, 1H), 1.70-1.60 (m, 4H).

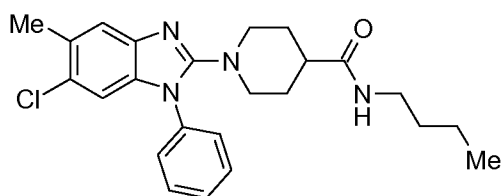
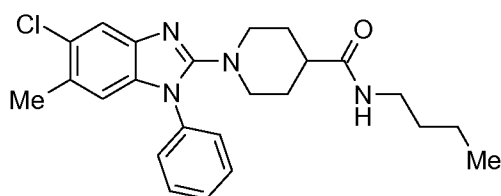
Example 177: (S)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

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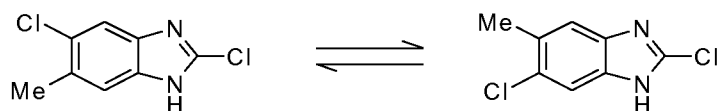


The title compound was prepared from 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (16.3 mg, 0.044 mmol), *N,N*-dimethylformamide (4.0 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 17.1 mg, 0.132 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 20.1 mg, 0.053 mmol) and (*S*)-tetrahydrofuran-3-amine hydrochloride (6.5 mg, 0.0529 mmol) using the method described in Example 166 c). The reaction mixture was purified on column (silica gel, dichloromethane/methanol, gradient elution using from 2 to 8 % methanol), to give 15.5 mg (81 % yield) of (*S*)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. On measure on optical rotation this compound gave (-)-rotation. LC-MS (*m/z*) 438.9 (*M*+1). ¹H NMR (400 MHz, CD₃OD): δ 7.67-7.60 (m, 2H), 7.55-7.48 (m, 3H), 7.34 (s, 1H), 7.01 (s, 1H), 4.34-4.28 (m, 1H), 3.91-3.72 (m, 3H), 3.65-3.52 (m, 3H), 2.90-2.81 (m, 2H), 2.40 (s, 3H), 2.36-2.27 (m, 1H), 2.23-2.13 (m, 1H), 1.83-1.74 (m, 1H), 1.70-1.60 (m, 4H).

Example 178: *N*-butyl-1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and *N*-butyl-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



(a) Preparation of the intermediary tautomeric compounds 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole:

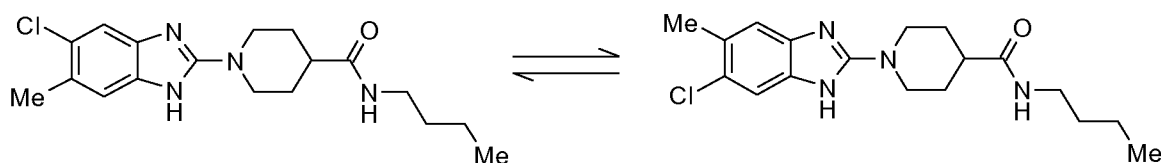


To 5-chloro-6-methyl-1*H*-benzo[d]imidazol-2(3*H*)-one (1.0 g, 5.48 mmol), phosphoryl trichloride (POCl₃, 0.137 mol) was added, the reaction mixture was heated at 120°C for 3 hours

and subsequently cooled down to room temperature. The reaction mixture was quenched with ice (without evaporating POCl_3) and neutralized with aqueous sodium hydroxide (10%) to pH 7.

The solid thus obtained was filtered off and the residue was recrystallized from petroleum ether to give 850 mg (86 % yield) of 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole.

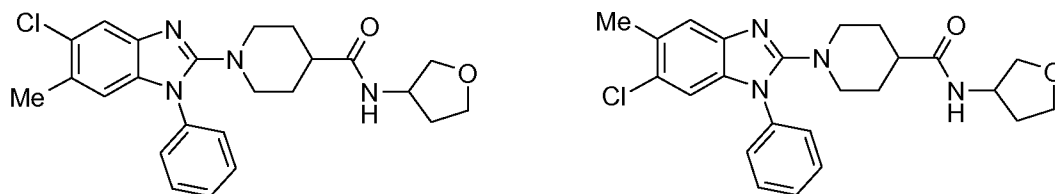
(b) Preparation of the intermediary tautomeric compounds N-butyl-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and N-butyl-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide:



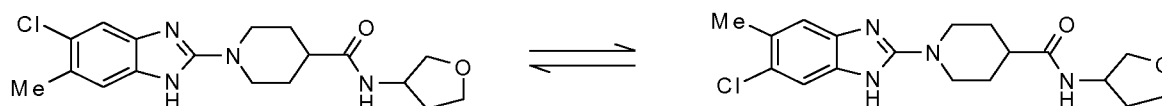
2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole (1 g, 4.98 mmol), 1,4-dioxane (10 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 14.9 mmol) and 4-(*n*-butylcarbamoyl)piperidin-1-yl 2,2,2-trifluoroacetate (7.47 mmol) was heated at 180°C for 4 hours. The reaction mixture was concentrated in vacuo and recrystallized from methanol and methyl tert-butyl ether to give 1.1 g (65 % yield) of N-butyl-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and N-butyl-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide. No effort was done in order to determine the ratios of the tautomers.

(c) The title compounds was prepared from N-butyl-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and N-butyl-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.30 g, 0.87 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.48 mmol), iodobenzene (3.48 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.130 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0435 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 10 mg (2.7 % yield) of N-butyl-1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and N-butyl-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 425.3 (*M*+1).

Example 179: 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



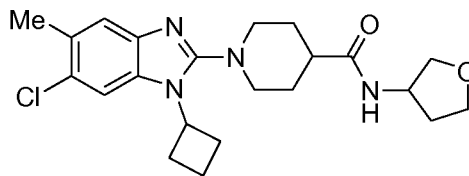
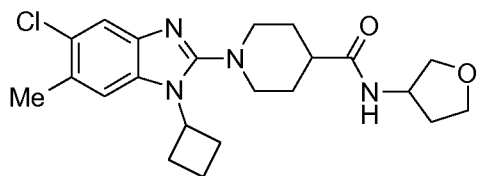
- 5 (a) Preparation of the intermediate tautomeric compounds 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide:



- 10 2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole (1 g, 4.98 mmol), 1,4-dioxane (10 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 14.9 mmol) and 4-(tetrahydrofuran-3-ylcarbamoyl)piperidinium 2,2,2-trifluoroacetate (7.47 mmol) was heated at 180°C for 4 hours. The reaction mixture was concentrated in vacuo and recrystallized from petroleum ether to give 1.1 g (65 % yield) 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. No effort was done in order to determine the ratios of the tautomers.

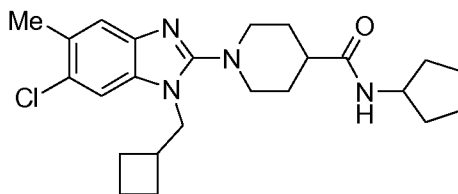
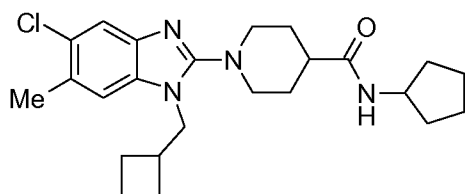
- (b) The title compounds was prepared from 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.83 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.32 mmol), iodobenzene (3.32 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.124 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0415 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 22 mg (6 % yield) of 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. No effort was done in order to determine the ratios of the compounds. LC-MS (*m/z*) 439.1 (*M*+1).

Example 180: 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide compound and 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

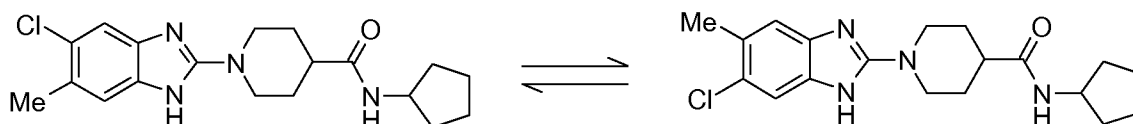


- 5 1-(5-Chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.1 g, 0.28 mmol), bromocyclobutane (1.12 mmol), caesium carbonate (1.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.028 mmol) and *N,N*-dimethylformamide (3 mL) was subjected to microwave
- 10 conditions at 120°C for one hour. The reaction mixture was purified with column chromatography, to give 12 mg (10 % yield) of 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. No effort was done in order to determine the ratios of the
- 15 compounds. LC-MS (*m/z*) 417.1 (M+1).

Example 181: 1-(5-chloro-1-(cyclobutylmethyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-(cyclobutylmethyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



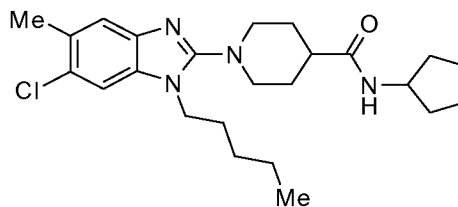
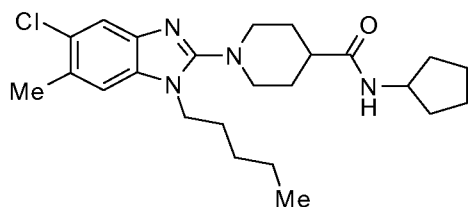
- 20 (a) Preparation of the intermediate tautomeric compounds 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide.



2,5-dichloro-6-methyl-1*H*-benzo[d]imidazole and 2,6-dichloro-5-methyl-1*H*-benzo[d]imidazole (1 g, 4.98 mmol), 1,4-dioxane (10 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 14.9 mmol) and 4-(cyclopentylcarbamoyl)piperidinium 2,2,2-trifluoroacetate (7.47 mmol) was heated at 180°C for 4 hours. The reaction mixture was concentrated in vacuo and recrystallized from petroleum ether to give 1.1 g (65 % yield) of 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide. No effort was done in order to determine the ratios of the tautomers.

(b) The title compounds were prepared from a tautomeric mixture of 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.28 mmol), bromocyclobutane (1.12 mmol), caesium carbonate (1.12 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.028 mmol) and *N,N*-dimethylformamide (3 mL) using the method described in Example 180. This gave 20 mg (17 % yield) of 1-(5-chloro-1-(cyclobutylmethyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-(cyclobutylmethyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a brown solid. No effort was done in order to determine the regioisomeric ratio of the compounds. LC-MS (*m/z*) 429.1 (M+1).

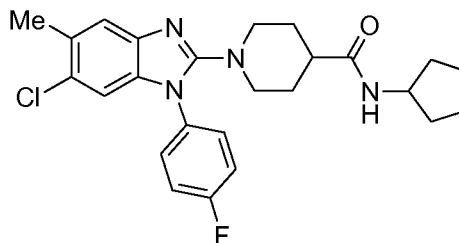
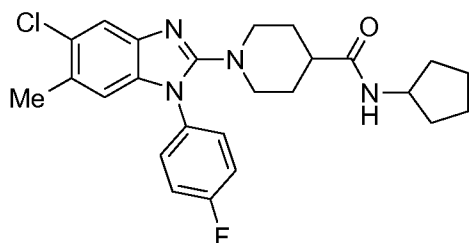
Example 182: 1-(5-chloro-6-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compounds were prepared from 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.28 mmol), 1-bromopentane (1.12 mmol), caesium carbonate (1.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.028 mmol) and *N,N*-dimethylformamide (3 mL) using the method described in Example 180. This gave 20 mg (17 % yield) of 1-(5-chloro-6-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-

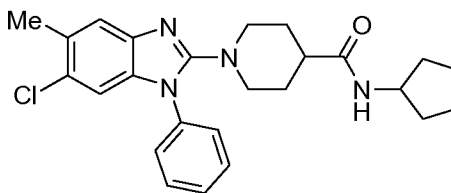
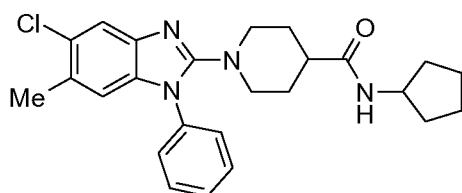
pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was done in order to determine the ratios of the compounds. LC-MS (*m/z*) 431.3 (*M*+1).

Example 183: 1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compounds was prepared from 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.30 g, 0.83 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.32 mmol), 1-fluoro-4-iodobenzene (3.32 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.124 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0415 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 11 mg (2.9 % yield) of 1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a brown solid. No effort was done in order to determine the regioisomeric ratio of the compounds.

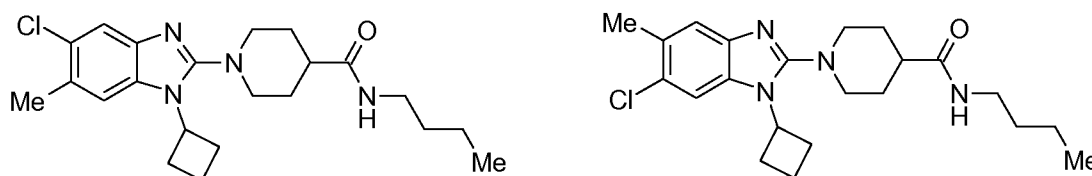
Example 184: 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compounds was prepared from 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-

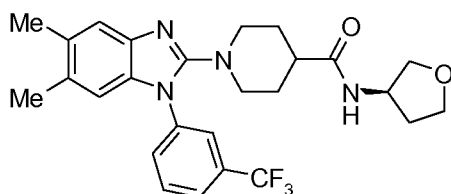
cyclopentylpiperidine-4-carboxamide (0.30 g, 0.83 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.32 mmol), iodobenzene (3.32 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.124 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0415 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 5 mg (1.4 % yield) of 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as a white solid. No effort was done in order to determine the ratios of the compounds. LC-MS (*m/z*) 437.7 (*M*+1).

Example 185: *N*-butyl-1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and *N*-butyl-1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide



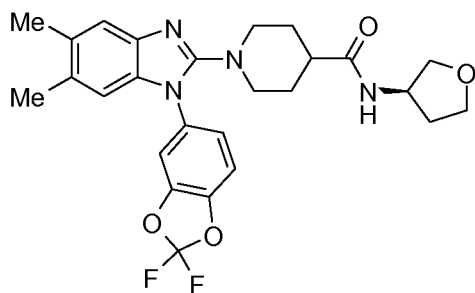
The title compounds were prepared from *N*-butyl-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and *N*-butyl-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide (0.1 g, 0.28 mmol), bromocyclobutane (1.12 mmol), caesium carbonate (1.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.028 mmol) and *N,N*-dimethylformamide (3 mL) using the method described in Example 180. This gave 15 mg (13 % yield) of *N*-butyl-1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide and *N*-butyl-1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide as a white solid. No effort was done in order to determine the ratios of the compounds. LC-MS (*m/z*) 403.3 (*M*+1).

Example 186: (R)-1-(5,6-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



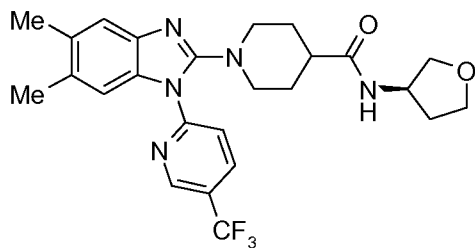
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (150 mg, 0.438 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.657 mmol), 1-bromo-3-(trifluoromethyl)benzene (1.31 mmol), 8-hydroxyquinoline (0.175 mmol), polyethylene glycol (0.219 mmol) and copper(I) oxide (0.0876 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 150°C and subsequently purified on reverse-phase hplc, to give 63 mg (30 % yield) of (R)-1-(5,6-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 487.1 (M+1).

Example 187: (R)-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (150 mg, 0.438 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.657 mmol), 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (1.31 mmol), 8-hydroxyquinoline (0.175 mmol), polyethylene glycol (0.219 mmol) and copper(I) oxide (0.0876 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 150°C and subsequently purified on reverse-phase hplc, to give 10 mg (4.6 % yield) of (R)-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 499.2 (M+1).

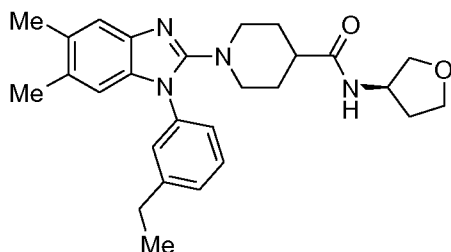
Example 188: (R)-1-(5,6-dimethyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (150 mg, 0.438 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.657 mmol), 2-bromo-5-(trifluoromethyl)pyridine (1.31 mmol), 8-hydroxyquinoline (0.175 mmol), polyethylene glycol (0.219 mmol) and copper(I) oxide (0.0876 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 150°C and subsequently purified on reverse-phase hplc, to give 37 mg (17 % yield) of (R)-1-(5,6-dimethyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid.

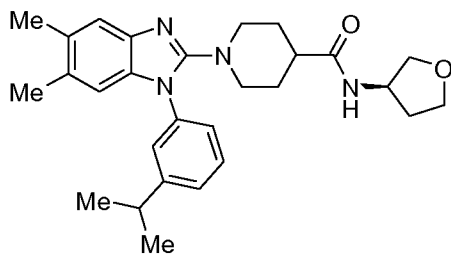
LC-MS (*m/z*) 488.1 (*M*+1).

Example 189: (R)-1-(1-(3-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



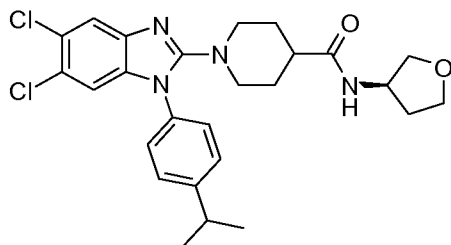
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (150 mg, 0.438 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.657 mmol), 1-bromo-3-ethylbenzene (1.31 mmol), 8-hydroxyquinoline (0.175 mmol), polyethylene glycol (0.219 mmol) and copper(I) oxide (0.0876 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 15 mg (7.6 % yield) of (R)-1-(1-(3-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 447.2 (*M*+1).

Example 190: (R)-1-(1-(3-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



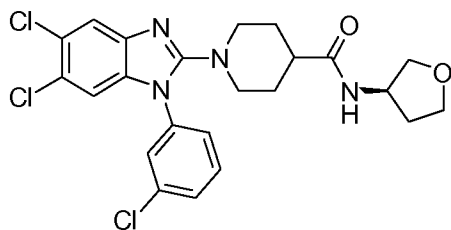
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (150 mg, 0.438 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.657 mmol), 1-bromo-3-isopropylbenzene (1.31 mmol), 8-hydroxyquinoline (0.175 mmol), polyethylene glycol (0.219 mmol) and copper(I) oxide (0.0876 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (2.5 % yield) of (R)-1-(1-(3-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 461.4 (*M*+1).

Example 191: (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



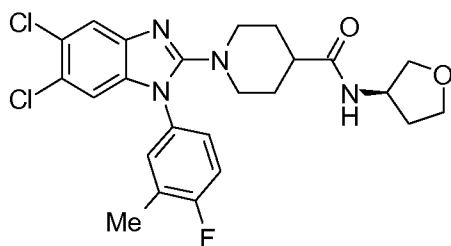
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-4-isopropylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 6 mg (5 % yield) of (R)-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 501.5 (*M*+1).

Example 192: (R)-1-(5,6-dichloro-1-(3-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



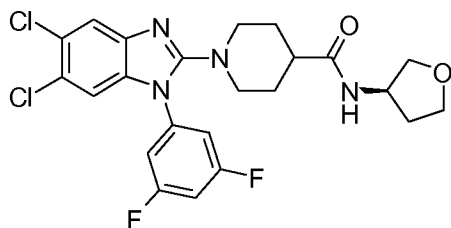
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-chlorobenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 2 mg (2 % yield) of (R)-1-(5,6-dichloro-1-(3-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 493.1 (M+1).

Example 193: (R)-1-(5,6-dichloro-1-(4-fluoro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



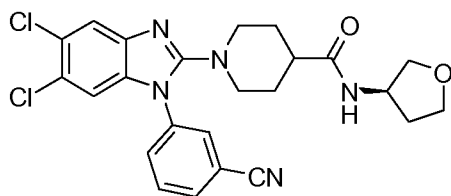
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 4-bromo-1-fluoro-2-methylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 15 mg (12 % yield) of (R)-1-(5,6-dichloro-1-(4-fluoro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 491.1 (M+1).

Example 194: (R)-1-(5,6-dichloro-1-(3,5-difluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



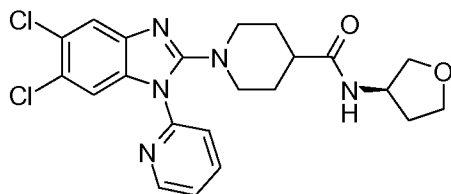
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3,5-difluorobenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (2.3 % yield) of (R)-1-(5,6-dichloro-1-(3,5-difluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 495.4 (*M*+1).

Example 195: (R)-1-(5,6-dichloro-1-(3-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



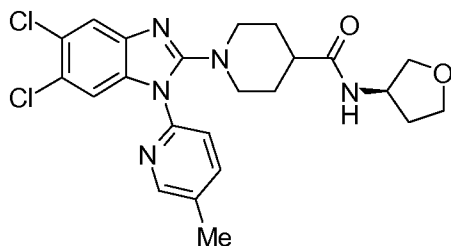
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 3-bromobenzonitrile (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.9 % yield) of (R)-1-(5,6-dichloro-1-(3-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 484.1 (*M*+1).

Example 196: (R)-1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



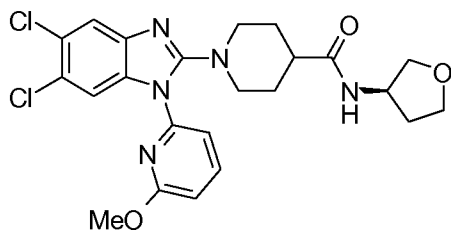
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-iodopyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 30 mg (25 % yield) of (R)-1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 460.3 (*M*+1).

Example 197: (R)-1-(5,6-dichloro-1-(5-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



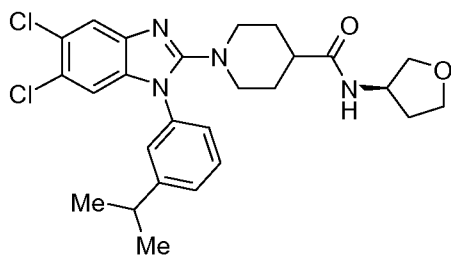
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-5-methylpyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 13 mg (11 % yield) of (R)-1-(5,6-dichloro-1-(5-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 474.4 (*M*+1).

Example 198: (R)-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



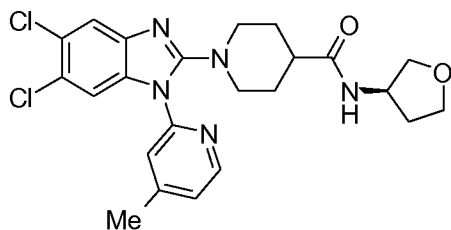
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-6-methoxypyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (2.3 % yield) of (R)-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 490.4 (*M*+1).

Example 199: (R)-1-(5,6-dichloro-1-(3-isopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



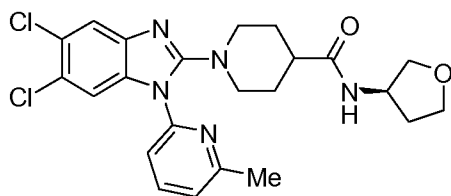
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-isopropylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.8 % yield) of (R)-1-(5,6-dichloro-1-(3-isopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 501.2 (*M*+1).

Example 200: (R)-1-(5,6-dichloro-1-(4-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



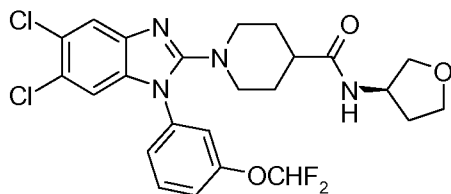
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-4-methylpyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.9 % yield) of (R)-1-(5,6-dichloro-1-(4-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 474.2 (*M*+1).

Example 201: (R)-1-(5,6-dichloro-1-(6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



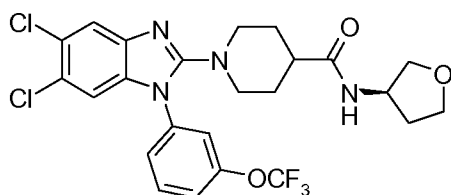
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-6-methylpyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 25 mg (20 % yield) of (R)-1-(5,6-dichloro-1-(6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 474.2 (*M*+1).

Example 202: (R)-1-(5,6-dichloro-1-(3-(difluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



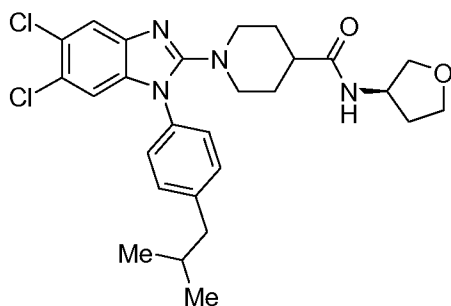
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-(difluoromethoxy)benzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.6 % yield) of (R)-1-(5,6-dichloro-1-(3-(difluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a gray solid. LC-MS (m/z) 525.2 (M+1).

Example 203: (R)-1-(5,6-dichloro-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



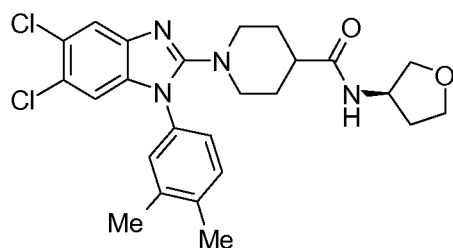
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-(trifluoromethoxy)benzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 9 mg (6.4 % yield) of (R)-1-(5,6-dichloro-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 543.0 (M+1).

Example 204: (R)-1-(5,6-dichloro-1-(4-isobutylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



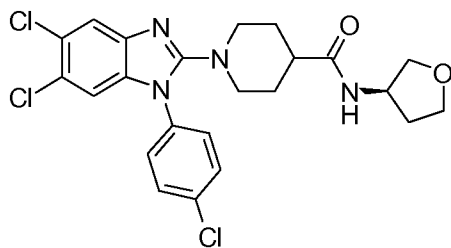
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-4-isobutylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 10 mg (7.4 % yield) of (R)-1-(5,6-dichloro-1-(4-isobutylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 515.5 (*M*+1).

Example 205: (R)-1-(5,6-dichloro-1-(3,4-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



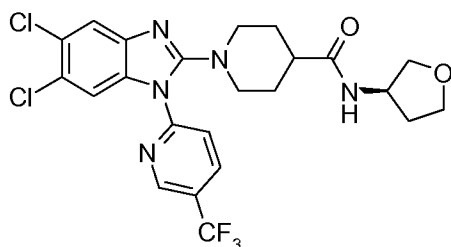
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 1-bromo-3-(cyclopentyloxy)benzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.2 % yield) of (R)-1-(5,6-dichloro-1-(3,4-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 487.2 (*M*+1).

Example 206: (R)-1-(5,6-dichloro-1-(4-chlorophenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



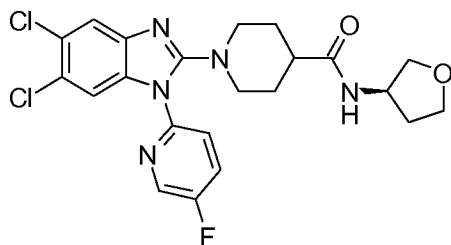
The title compound was prepared from (R)-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (200 mg, 0.522 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.783 mmol), 1-chloro-4-iodobenzene (1.565 mmol), 8-hydroxyquinoline (0.209 mmol), polyethylene glycol (0.261 mmol) and copper(I) oxide (0.104 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 9 mg (3.6 % yield) of (R)-1-(5,6-dichloro-1-(4-chlorophenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 493.5 (M+1).

Example 207: (R)-1-(5,6-dichloro-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



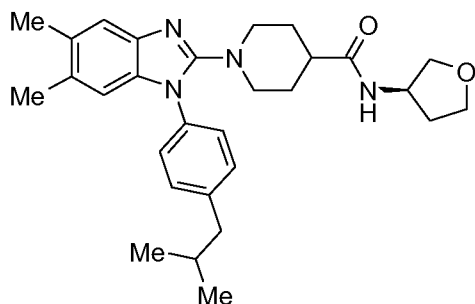
The title compound was prepared from (R)-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (150 mg, 0.391 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.587 mmol), 2-bromo-5-(trifluoromethyl)pyridine (1.17 mmol), 8-hydroxyquinoline (0.157 mmol), polyethylene glycol (0.196 mmol) and copper(I) oxide (0.0783 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (2.5 % yield) of (R)-1-(5,6-dichloro-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (m/z) 528.3 (M+1).

Example 208: (R)-1-(5,6-dichloro-1-(5-fluoropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



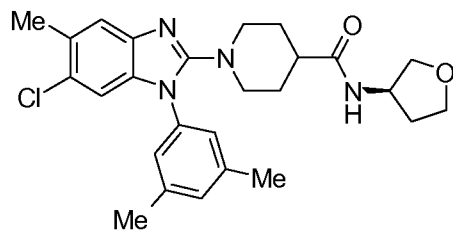
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (150 mg, 0.391 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.587 mmol), 2-bromo-5-fluoropyridine (1.17 mmol), 8-hydroxyquinoline (0.157 mmol), polyethylene glycol (0.196 mmol) and copper(I) oxide (0.0783 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 35 mg (19 % yield) of (R)-1-(5,6-dichloro-1-(5-fluoropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 478.2 (*M*+1).

Example 209: (R)-1-(1-(4-isobutylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

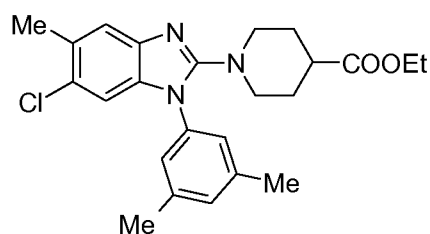


The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 1-bromo-4-isobutylbenzene (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 19 mg (11 % yield) of (R)-1-(1-(4-isobutylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 475.2 (*M*+1).

Example 210: (R)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



a) Preparation of the intermediate compound ethyl 1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate

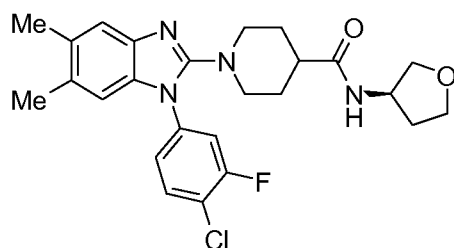


A tautomeric mixture of ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80 mg, 0.249 mmol), dimethylsulfoxide (0.5 mL), caesium carbonate (113 mg, 0.348 mmol), 1-bromo-3,5-dimethylbenzene (138 mg, 0.746 mmol), 8-hydroxy-quinoline (14.4 mg, 0.099 mmol), polyethylene glycol 400 (50.0 mg, 0.124 mmol) and copper(I) oxide (7.1 mg, 0.05 mmol) was heated at 150°C for 4 hours. The reaction mixture was filtered, washed with *N,N*-dimethylformamide, the filtrate concentrated in vacuo (co-evaporation with *N,N*-dimethylformamide) and purified on column (silica gel, iso-hexane/ethyl acetate, gradient elution from 20 to 30 % ethyl acetate). This gave 16.3 mg (15 % yield) of ethyl 1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (LC-MS (*m/z*) 426.0 (*M*+1)) that eluted as the second peak after ethyl 1-(5-chloro-1-(3,5-dimethylphenyl)-6-methyl-1*H*-benzo[d]-imidazol-2-yl)piperidine-4-carboxylate (18.0 mg, 17 % yield).

(b) To ethyl 1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (8.6 mg) was added ethanol (2 mL) and aqueous sodium hydroxide (1 mL, 2 N). The reaction mixture was stirred at 40°C for two hours, neutralized with aqueous hydrochloric acid (2 N) and concentrated in vacuo. The residue was mixed (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (6.3 mg, 0.024 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-

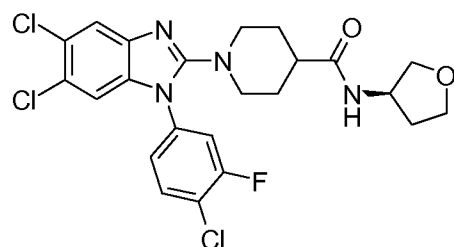
tetramethyluronium hexafluorophosphate (HATU, 9.2 mg, 0.024 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 7.8 mg, 0.060 mmol) and *N,N*-dimethylformamide (5 mL) was stirred at room temperature over the weekend. The reaction mixture was concentrated in vacuo, the residue subjected to preparative hplc (Preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI detection) to give 7.7 mg (82 % yield) (R)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. MS (*m/z*) 467.0 (M+1).

Example 211: (R)-1-(1-(4-chloro-3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



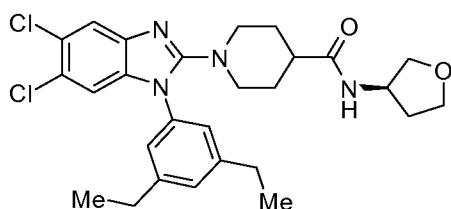
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 4-bromo-1-chloro-2-fluorobenzene (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (1.8 % yield) of (R)-1-(1-(3-fluoro-5-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 471.2 (M+1).

Example 212: (R)-1-(5,6-dichloro-1-(4-chloro-3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



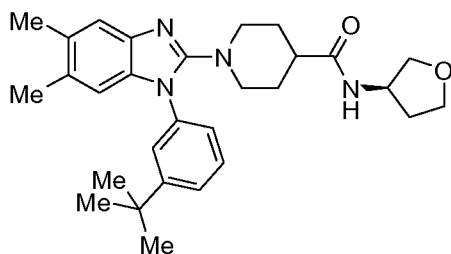
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 4-bromo-1-chloro-2-fluorobenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 13 mg (9.9 % yield) of (R)-1-(5,6-dichloro-1-(4-chloro-3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 511.8 (*M*+1).

Example 213: (R)-1-(5,6-dichloro-1-(3,5-diethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



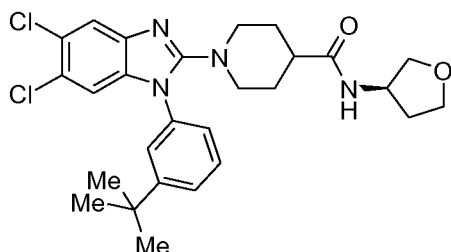
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (200 mg, 0.522 mmol) dimethylsulfoxide (2 mL), caesium carbonate (1.04 mmol), 1-bromo-3,5-diethylbenzene (1.57 mmol), 8-hydroxyquinoline (0.209 mmol), polyethylene glycol (0.261 mmol) and copper(I) oxide (0.104 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (1.9 % yield) of (R)-1-(5,6-dichloro-1-(3,5-diethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 515.5 (*M*+1).

Example 214: (R)-1-(1-(3-*tert*-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



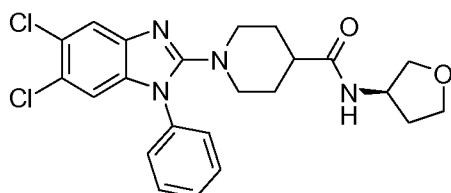
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 1-bromo-3-tert-butylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 2 mg (1.4 % yield) of (R)-1-(1-(3-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 475.2 (M+1).

Example 215: (R)-1-(1-(3-tert-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



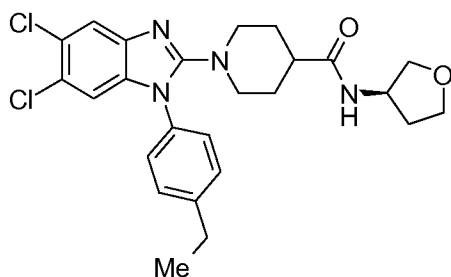
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-tert-butylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.7 % yield) of (R)-1-(1-(3-tert-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off- white solid. LC-MS (m/z) 515.5 (M+1).

Example 216: (R)-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



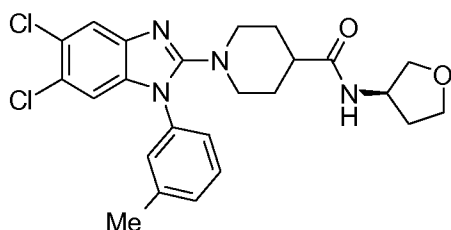
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), iodobenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 13 mg (11 % yield) of (R)-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale brown solid. LC-MS (m/z) 459.1 (M+1).

Example 217: (R)-1-(5,6-dichloro-1-(4-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



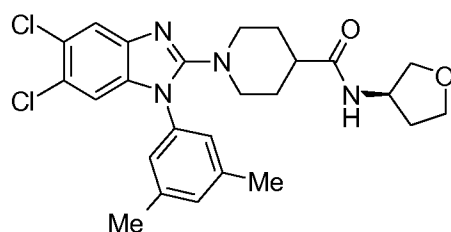
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-4-ethylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 34 mg (27 % yield) of (R)-1-(5,6-dichloro-1-(4-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (m/z) 487.1 (M+1).

Example 218: (R)-1-(5,6-dichloro-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



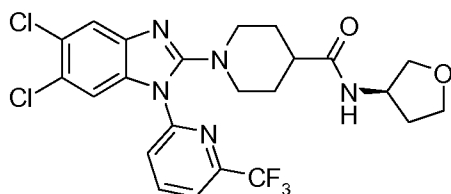
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-methylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 13 mg (10 % yield) of (R)-1-(5,6-dichloro-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 473.1 (M+1).

Example 219: (R)-1-(5,6-dichloro-1-(3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



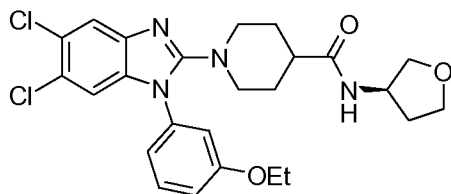
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-ethylbenzene (0.783 mmol), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 31 mg (24 % yield) of (R)-1-(5,6-dichloro-1-(3-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (m/z) 487.2 (M+1).

Example 221: (R)-1-(5,6-dichloro-1-(6-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



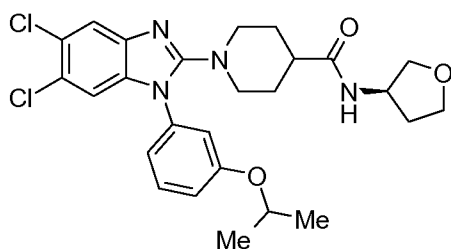
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-6-(trifluoromethyl)pyridine (0.783 mmol), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 25 mg (18 % yield) of (R)-1-(5,6-dichloro-1-(6-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (m/z) 528.4 (M+1). ¹H NMR (400 MHz, CDCl₃): δ 8.11-8.06 (m, 1H), 7.98-7.93 (m, 1H), 7.74 (s, 1H), 7.71-7.68 (m, 1H), 7.61 (s, 1H), 5.77 (br s, 1H), 4.48-4.40 (m, 1H), 3.90-3.82 (m, 1H), 3.77-3.68 (m, 2H), 3.65-3.55 (m, 3H), 3.07-2.91 (m, 2H), 2.26-2.16 (m, 2H), 1.86-1.77 (m, 6H).

Example 222: (R)-1-(5,6-dichloro-1-(3-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



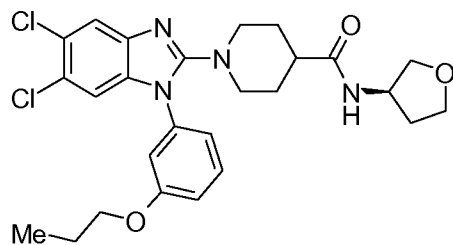
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-ethoxybenzene (0.783 mmol, CAS Registry Number: 2655-84-7), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.8 % yield) of (R)-1-(5,6-dichloro-1-(3-ethoxyphenyl)-1*H*-benzo[d]-imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 503.2 (*M*+1).

Example 223: (R)-1-(5,6-dichloro-1-(3-isopropoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



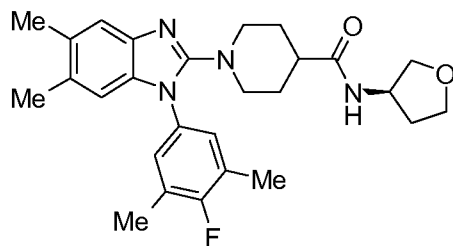
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-isopropoxybenzene (0.783 mmol, CAS Registry Number: 131738-73-3), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 2 mg (1.2 % yield) of (R)-1-(5,6-dichloro-1-(3-isopropoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 517.2 (*M*+1).

Example 224: (R)-1-(5,6-dichloro-1-(3-propoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



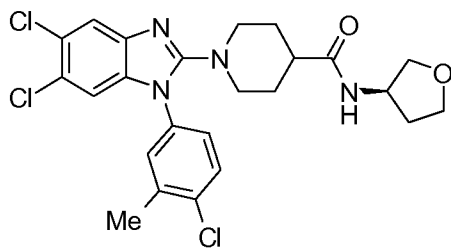
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-propoxybenzene (0.783 mmol, CAS Registry Number: 149557-17-5), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 14 mg (10 % yield) of (R)-1-(5,6-dichloro-1-(3-propoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 517.5 (*M*+1).

Example 225: (R)-1-(1-(4-fluoro-3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



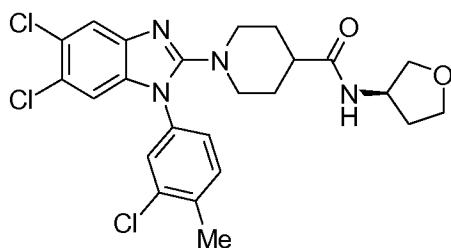
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 5-bromo-2-fluoro-1,3-dimethylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase hplc, to give 17 mg (13 % yield) of (R)-1-(1-(4-fluoro-3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 465.2 (*M*+1).

Example 226: (R)-1-(5,6-dichloro-1-(4-chloro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



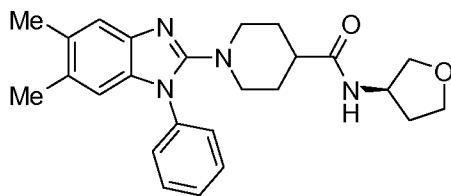
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 4-bromo-1-chloro-2-methylbenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc (Shimadzu LC8A, C₁₈ column (22 x 250 mm, 10µm), acetonitrile/water gradient (0.1% trifluoroacetic acid), flowrate 15 mL/min) , to give 15 mg (11 % yield) of (R)-1-(5,6-dichloro-1-(4-chloro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale brown solid. LC-MS (m/z) 507.8 (M+1).

Example 227: (R)-1-(5,6-dichloro-1-(3-chloro-4-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



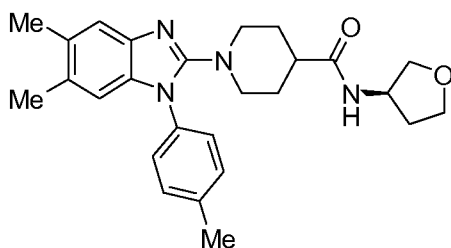
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 4-bromo-2-chloro-1-methylbenzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (2 % yield) of (R)-1-(5,6-dichloro-1-(3-chloro-4-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a gray solid. LC-MS (m/z) 507.3 (M+1).

Example 228: (R)-1-(5,6-dimethyl-1-phenyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



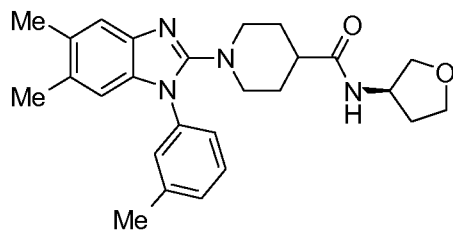
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), iodobenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 34 mg (28 % yield) of (R)-1-(5,6-dimethyl-1-phenyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 419.1 (M+1).

Example 229: (R)-1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



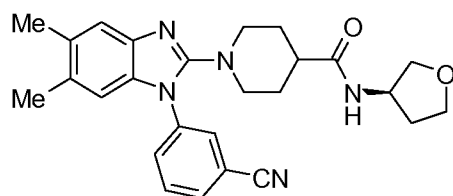
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 1-bromo-4-methylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (2.3 % yield) of (R)-1-(5,6-dimethyl-1-p-tolyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 433.3 (M+1).

Example 230: (R)-1-(5,6-dimethyl-1-m-tolyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



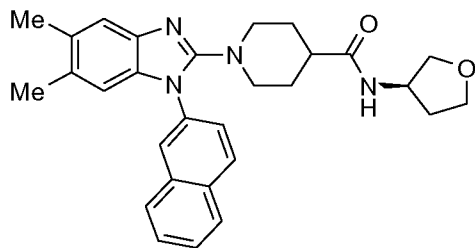
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 1-bromo-3-methylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 4 mg (2.6 % yield) of (R)-1-(5,6-dimethyl-1-m-tolyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 433.3 (M+1).

Example 231: (R)-1-(1-(3-cyanophenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



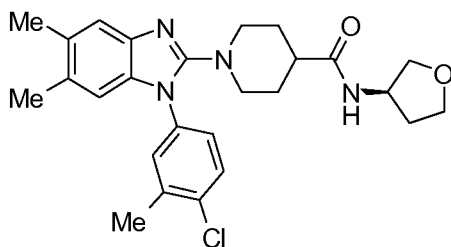
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 3-bromobenzonitrile (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 8 mg (4.6 % yield) of (R)-1-(1-(3-cyanophenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (m/z) 444.1 (M+1).

Example 232: (R)-1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



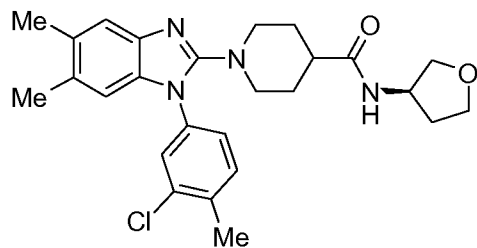
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 2-bromonaphthalene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (2.2 % yield) of (R)-1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 469.1 (*M*+1).

Example 233: (R)-1-(1-(4-chloro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



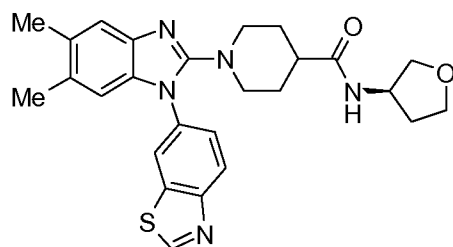
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 4-bromo-1-chloro-2-methylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 35 mg (26 % yield) of (R)-1-(1-(4-chloro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 467.2 (*M*+1).

Example 234: (R)-1-(1-(3-chloro-4-methylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



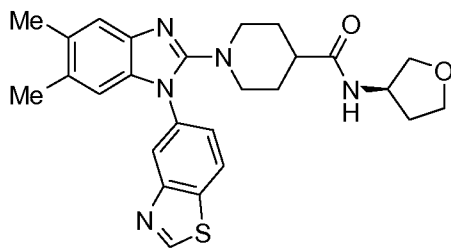
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.438 mmol), 4-bromo-2-chloro-1-methylbenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 20 mg (15 % yield) of (R)-1-(1-(3-chloro-4-methylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (m/z) 467.2 (M+1).

Example 235: (R)-1-(1-(benzo[d]thiazol-6-yl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



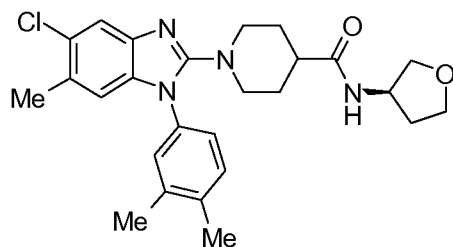
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.526 mmol), 6-bromobenzo[d]thiazole (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 3 mg (1.8 % yield) of (R)-1-(1-(benzo[d]thiazol-6-yl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 476.2 (M+1).

Example 236: (R)-1-(1-(benzo[d]thiazol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

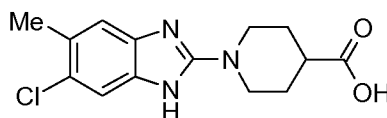
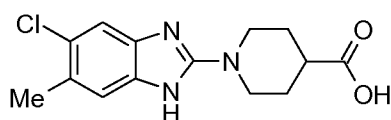


The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.526 mmol), 5-bromobenzo[d]thiazole (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 120°C and subsequently purified on reverse-phase hplc, to give 5 mg (3 % yield) of (R)-1-(1-(benzo[d]thiazol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 476.1 (*M*+1).

Example 237: (R)-1-(5-chloro-1-(3,4-dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

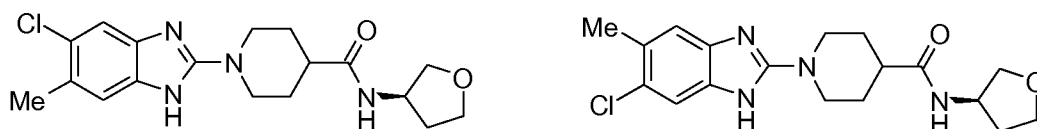


(a) Preparation of the intermediate tautomeric mixture 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid



A tautomeric mixture of 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid ethyl ester and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid ethyl ester (1.0 g, 3.1 mmol) was dissolved in ethanol (70 mL) and aqueous sodium hydroxide (1 N, 16 mL) was added. The reaction mixture was stirred at room temperature two hours, concentrated in vacuo and pH adjusted to 4-5 with addition of aqueous hydrochloric acid (6 N). The formed precipitate was filtered off, the aqueous mother liquid extracted three times with dichloromethane (50 mL) and the combined organic layers were dried with MgSO₄ and concentrated in vacuo. The precipitate and the residue from the extraction were combined and recrystallized in petroleum ether to give 0.82 g (90%) of a tautomeric mixture of 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic.

(b) Preparation of the intermediate tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide:

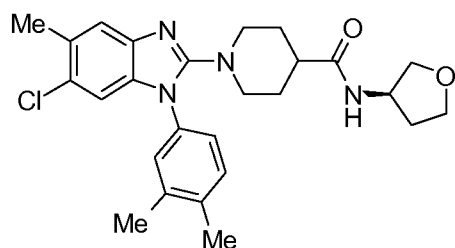


A tautomeric mixture of 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid and 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (1.0 g, 3.4 mmol), (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (4.1 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 6.8 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 6.8 mmol) and *N,N*-dimethylformamide (25 mL) was stirred at room temperature for 1 hour. After the appropriate work-up, the residue was recrystallized from dichloromethane/petroleum ether to give 1.0 g (83 % yield) of a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.

(c) The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500 mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.07 mmol), 4-bromo-1,2-dimethylbenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689

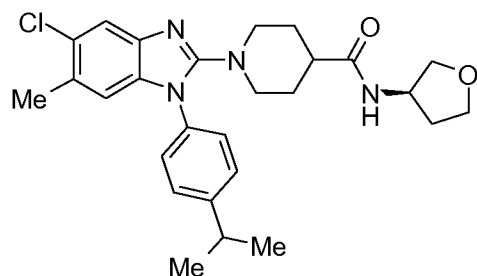
mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 15 mg (2.3 % yield) of (R)-1-(5-chloro-1-(3,4-dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid, eluting after (R)-1-(6-chloro-1-(3,4-dimethylphenyl)-5-methyl-1*H*-benzo[d]-imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (*m/z*) 467.2 (*M*+1).

Example 238: (R)-1-(6-chloro-1-(3,4-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was obtained as described in Example 237 eluting ahead of (R)-1-(5-chloro-1-(3,4-dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 16 mg (2.5 % yield) of (R)-1-(6-chloro-1-(3,4-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. MS (*m/z*) 467.2 (*M*+1).

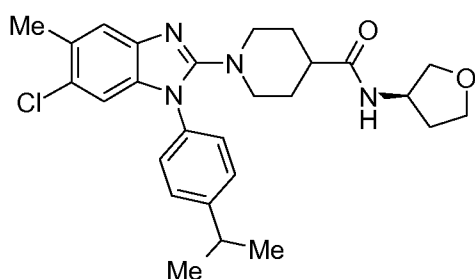
Example 239: (R)-1-(5-chloro-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500 mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.07 mmol), 1-bromo-4-isopropylbenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689

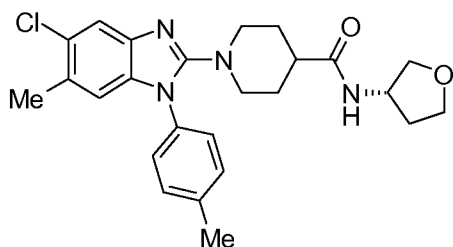
mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 27 mg (4.3 % yield) of (R)-1-(5-chloro-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid, eluting after (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (m/z) 481.2 (M+1).

Example 240: (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was obtained as described in Example 239 eluting ahead of (R)-1-(5-chloro-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 4 mg (6 % yield) of (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. MS (m/z) 481.3 (M+1).

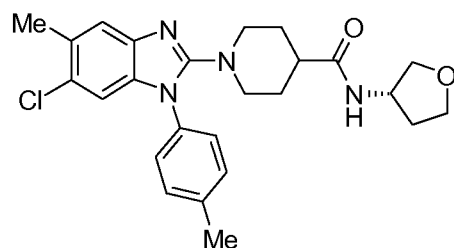
Example 241: (S)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



A tautomeric mixture of ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80.5 mg, 0.25 mmol) dimethylsulfoxide (0.5 mL), caesium carbonate (114 mg, 0.35 mmol), 1-iodo-4-methylbenzene (109 mg, 0.50 mmol), 8-hydroxyquinoline (7.3 mg, 0.05 mmol), polyethylene glycol 400 (60.4 mg, 0.515 mmol) and copper(I) oxide (3.6 mg, 0.025 mmol) was

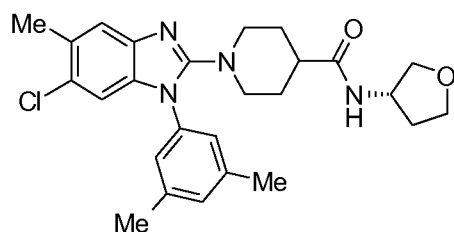
heated at 150°C for 4 hours. The temperature was lowered to 90°C and water (0.004 mL) was added to the reaction mixture, which was stirred for one hour. Aqueous sodium hydroxide (0.5 mL, 1 N) and ethanol (1 mL) was added and the reaction mixture stirred over night. Aqueous hydrochloric acid (0.25 mL, 2 N) was added and the reaction mixture concentrated in vacuo. The residue was mixed with N,N-dimethylformamide (5 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 97 mg, 0.75 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 114 mg, 0.3 mmol) and (S)-tetrahydrofuran-3-amine hydrochloride (31 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 90 minutes, concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol 96:4) to give 4.6 mg (4 % yield) of (S)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 452.9 (*M*+1). Also eluting from the column was the other regioisomer (S)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide.

Example 242: (S)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



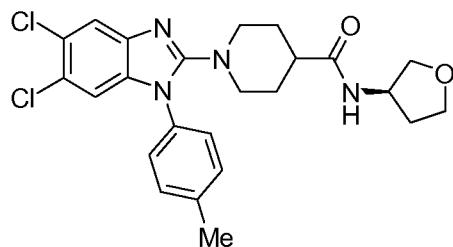
The title compound was obtained as described in Example 241 to give 5.8 mg (5 % yield) of (S)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 452.9 (*M*+1).

Example 243: (S)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



A tautomeric mixture of ethyl 1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate and ethyl 1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (100 mg, 0.311 mmol) dimethylsulfoxide (0.5 mL), caesium carbonate (142 mg, 0.435 mmol), 1-1-bromo-3,5-dimethylbenzene (115 mg, 0.621 mmol), 8-hydroxyquinoline (9.0 mg, 0.062 mmol), polyethylene glycol 400 (75 mg, 0.188 mmol) and copper(I) oxide (4.4 mg, 0.031 mmol) was heated at 150°C for 4 hours. The reaction mixture was purified using column chromatography, the appropriate combined fractions concentrated in vacuo and dissolved in ethanol. Aqueous sodium hydroxide (0.5 mL, 1 N) was added and the reaction mixture was stirred at room temperature over night. Aqueous hydrochloric acid (0.25 mL, 2 N) was added and the reaction mixture concentrated in vacuo. The residue was mixed with N,N-dimethylformamide (5 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 73 mg, 0.563 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 85.7 mg, 0.225 mmol) and (*S*)-tetrahydrofuran-3-amine hydrochloride (23 mg, 0.188 mmol). The reaction mixture was stirred at room temperature for 105 minutes, concentrated in vacuo and purified on column (silica gel, dichloromethane/methanol, gradient elution using from 3 to 7 % methanol) and further on hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 µm, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 15 mL/min with UV (214 or 254 nm) and MS (ESI detection) to give 1.9 mg of (*S*)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 466.9 (*M*+1).

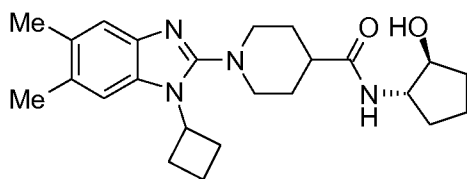
Example 244: (*R*)-1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



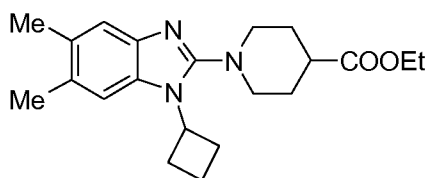
Ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (110 mg, 0.321 mmol) dimethylsulfoxide (1 mL), caesium carbonate (147 mg, 0.45 mmol), 1-iodo-4-methylbenzene (140 mg, 0.643 mmol), 8-hydroxyquinoline (9.3 mg, 0.064 mmol), polyethylene glycol 400 (64.3 mg, 0.161 mmol) and copper(I) oxide (4.6 mg, 0.032 mmol) was subjected to microwave conditions for one hour at 150°C. The reaction mixture was diluted with N,N-dimethyl-

formamide (4 mL), filtered and the filtrate concentrated in vacuo. The residue was dissolved in ethanol (4 mL) and aqueous sodium hydroxide (2 mL, 1 N), and stirred at room temperature over the weekend. The reaction mixture was treated with aqueous hydrochloric acid (1 mL, 2 N) and concentrated. The residue was mixed with N,N-dimethylformamide (13 mL), N,N-diisopropylethylamine (Hünig's base, DIEA, 19.2 mg, 0.148 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU, 14.1 mg, 0.037 mmol) and (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (9.6 mg, 0.0371 mmol). The reaction mixture was stirred at room temperature for 2 hours, concentrated in vacuo and purified on hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 7.7 mg of (R)-1-(5,6-dichloro-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 473.1 (*M*+1).

Example 245: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide

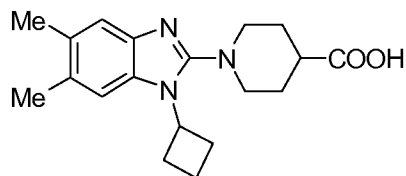


(a) Preparation of the intermediate compound ethyl 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



This compound was prepared from ethyl 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (1 g, 3.3 mmol), bromocyclobutane (13.2 mmol), caesium carbonate (13.2 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.033 mmol) and N,N-dimethylformamide (8 mL) using the method described in Example 16. The reaction mixture was heated at 130°C for two hours in a sealed tube and purified with column chromatography, to give 510 mg (43 % yield) of ethyl 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate.

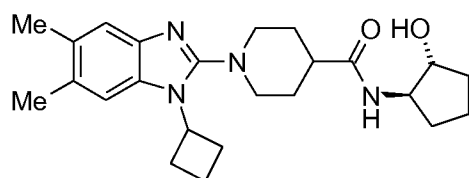
(b) Preparation of the intermediate compound 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



Ethyl 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (1 g, 2.79 mmol), aqueous sodium hydroxide (14 mmol), ethanol and water (50 mL) was stirred at room temperature for 30 minutes. After the appropriate work-up, the target compound was recrystallized from petroleum ether to give 500 mg (54 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid.

(c) The title compound was prepared from 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (0.1 g, 0.3 mmol), *N,N*-dimethylformamide (3 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.6 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.6 mmol) and (1*S*,2*S*)-2-aminocyclopentanol (0.36 mmol) using the method described in Example 166. The reaction mixture was stirred at room temperature for one hour and purified with recrystallization from petroleum ether, to give 47 mg (37 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 410.9 (*M*+1).

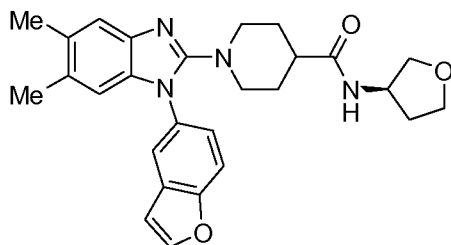
Example 246: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)piperidine-4-carboxamide



The title compound was prepared from 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (0.1 g, 0.3 mmol), *N,N*-dimethylformamide (3 mL), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.6 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 0.6 mmol) and (1*R*,2*R*)-2-aminocyclopentanol (0.36 mmol) using the method described in Example 166. The reaction

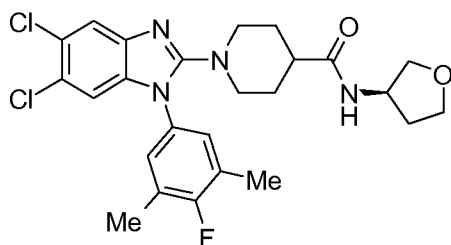
mixture was stirred at room temperature for one hour and purified with recrystallization from petroleum ether, to give 10 mg (8 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 410.9 (*M*+1).

5 Example 247: (R)-1-(1-(benzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 5-bromobenzofuran (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on preparative hplc (Shimadzu LC8A, C₁₈ column (22 x 250 mm, 10µm), acetonitrile/water gradient (0.1% trifluoroacetic acid), flowrate 15 mL/min), to give 5 mg (3.1 % yield) of (R)-1-(1-(benzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 459.2 (*M*+1).

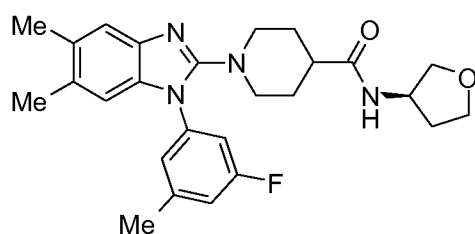
Example 248: (R)-1-(5,6-dichloro-1-(4-fluoro-3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 5-bromo-2-fluoro-1,3-dimethylbenzene (0.783 mmol), 8-

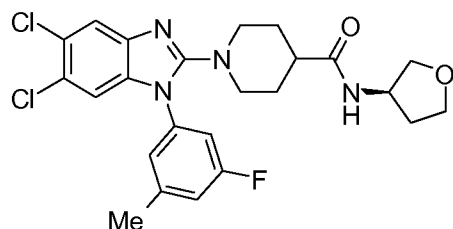
hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on preparative hplc (Shimadzu LC8A, C₁₈ column (22 x 250 mm, 10µm), acetonitrile/water gradient (0.1% trifluoroacetic acid), flowrate 15 mL/min), to give 10 mg (7.6 % yield) of (R)-1-(5,6-dichloro-1-(4-fluoro-3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow. solid. LC-MS (m/z) 505.4 (M+1).

Example 249: (R)-1-(1-(3-fluoro-5-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 1-bromo-3-fluoro-5-methylbenzene (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 3 mg (1.9 % yield) of (R)-1-(1-(3-fluoro-5-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (m/z) 451.1 (M+1).

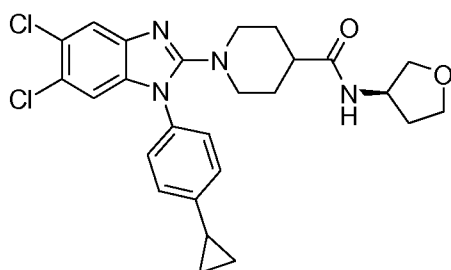
Example 250: (R)-1-(5,6-dichloro-1-(3-fluoro-5-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2

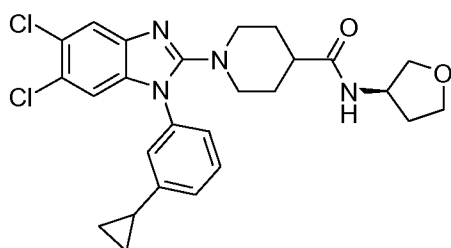
mL), caesium carbonate (0.470 mmol), 1-bromo-3-fluoro-5-methylbenzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 14 mg (9.1 % yield) of (R)-1-(5,6-dichloro-1-(3-fluoro-5-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 491.5 (M+1).

Example 251: (R)-1-(5,6-dichloro-1-(4-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



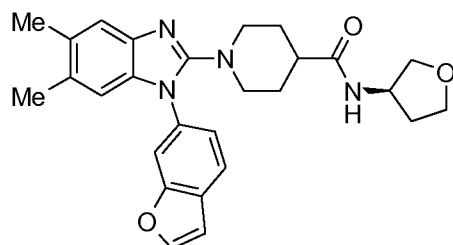
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 1-bromo-4-cyclopropylbenzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.2 % yield) of (R)-1-(5,6-dichloro-1-(4-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 499.3 (M+1).

Example 252: (R)-1-(5,6-dichloro-1-(3-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



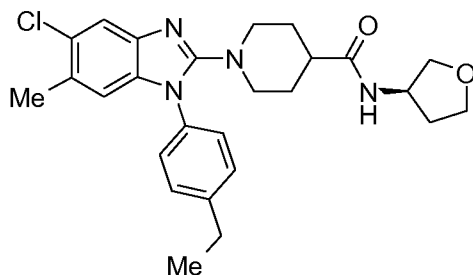
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 1-bromo-3-cyclopropylbenzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 17 mg (11 % yield) of (R)-1-(5,6-dichloro-1-(3-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 499.4 (M+1).

Example 253: (R)-1-(1-(benzofuran-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



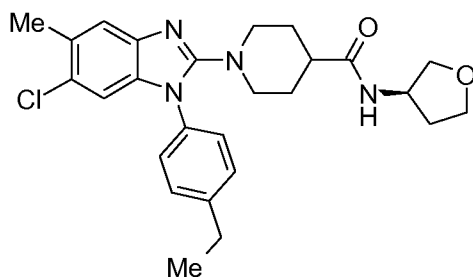
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 6-bromobenzofuran (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 20 mg (12 % yield) of (R)-1-(1-(benzofuran-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (m/z) 459.1 (M+1).

Example 254: (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



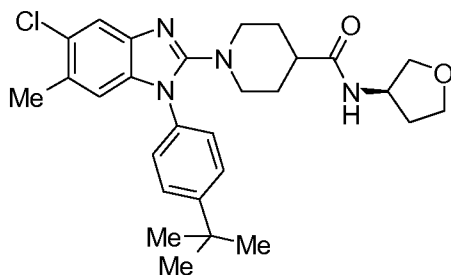
The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500 mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.76 mmol), 1-bromo-4-ethylbenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689 mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase reverse-phase hplc, to give 20 mg (3.3 % yield) of (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid solid, eluting after (R)-1-(6-chloro-1-(4-ethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (*m/z*) 467.2 (*M*+1).

Example 255: (R)-1-(6-chloro-1-(4-ethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



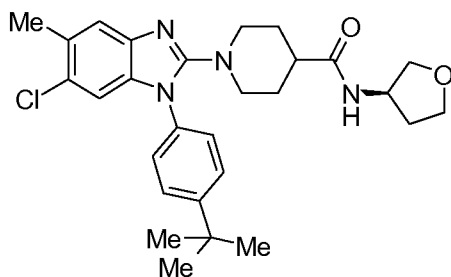
The title compound was obtained as described in Example 254 as eluting before (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 24 mg (3.7 % yield) of (R)-1-(6-chloro-1-(4-ethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. MS (*m/z*) 467.2 (*M*+1).

Example 256: (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



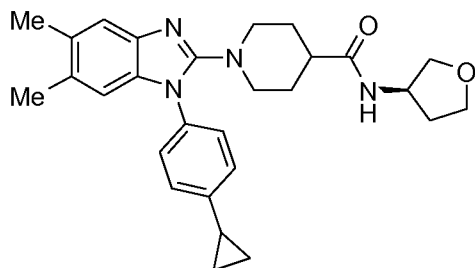
The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500 mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.76 mmol), 1-bromo-4-tert-butylbenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689 mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase reverse-phase hplc, to give 69 mg (10 % yield) of (R)-1-(1-(4-tert-butylphenyl)-5-chloro-6-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid, eluting after (R)-1-(1-(4-tert-butylphenyl)-6-chloro-5-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (m/z) 495.3 (M+1).

Example 257: (R)-1-(1-(4-tert-butylphenyl)-6-chloro-5-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



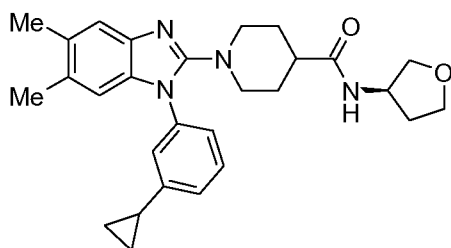
The title compound was obtained as described in Example 256 eluting before (R)-1-(1-(4-tert-butylphenyl)-5-chloro-6-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 63 mg (9 % yield) of (R)-1-(1-(4-tert-butylphenyl)-6-chloro-5-methyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. MS (m/z) 495.3 (M+1).

Example 258: (R)-1-(1-(4-cyclopropylphenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



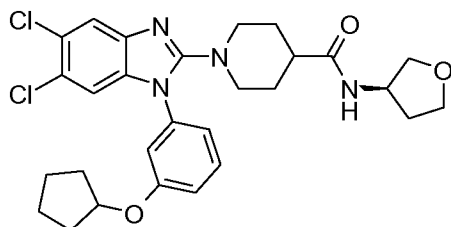
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 1-bromo-4-cyclopropylbenzene (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hours at 140°C and subsequently purified on reverse-phase hplc, to give 13 mg (8.1 % yield) of (R)-1-(1-(4-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 459.1 (*M*+1).

Example 259: (R)-1-(1-(3-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



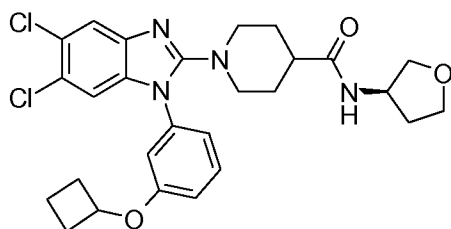
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 1-bromo-3-cyclopropylbenzene (1.051 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.1 % yield) of (R)-1-(1-(3-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 459.2 (*M*+1).

Example 260: (R)-1-(5,6-dichloro-1-(3-(cyclopentyloxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-(cyclopentyloxy)benzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 2 mg (1.4 % yield) of (R)-1-(5,6-dichloro-1-(3-(cyclopentyloxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 543.2 (*M*+1).

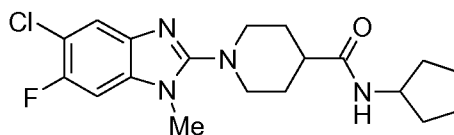
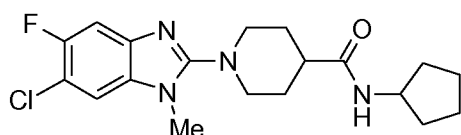
Example 261: (R)-1-(5,6-dichloro-1-(3-cyclobutoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 1-bromo-3-cyclobutoxybenzene (0.783 mmol, prepared by alkylation of 3-bromophenol using bromocyclobutane and potassium carbonate in *N,N*-dimethylformamide), 8-hydroxy-quinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for two hour at 120°C and subsequently purified on reverse-phase hplc, to give 2 mg (1.5 % yield) of (R)-1-(5,6-dichloro-1-(3-

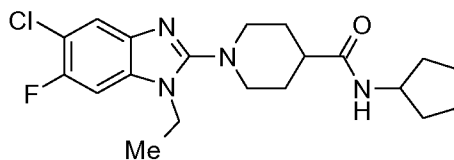
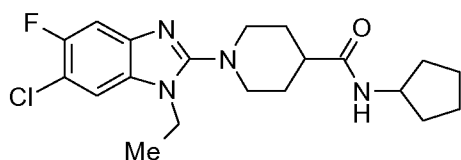
cyclobutoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 529.4 (*M*+1).

Example 262: 1-(5-chloro-6-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.27 mmol), methyl iodide (1.096 mmol), caesium carbonate (1.096 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.0274 mmol) and *N,N*-dimethyl-formamide (3 mL) using the method described in Example 94. This gave 30 mg (29 % yield) of 1-(5-chloro-6-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was made to determine the ratio of the regioisomers. LC-MS (*m/z*) 379.1 (*M*+1).

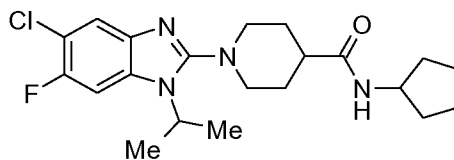
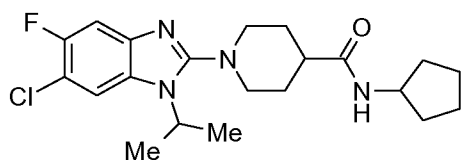
Example 263: 1-(5-chloro-1-ethyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-ethyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.27 mmol), ethyl iodide (1.096 mmol), caesium carbonate (1.096 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.0274 mmol) and *N,N*-dimethyl-formamide (3 mL) using the method described in Example 94. This gave 35 mg (33 % yield) of 1-(5-chloro-1-ethyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-1-

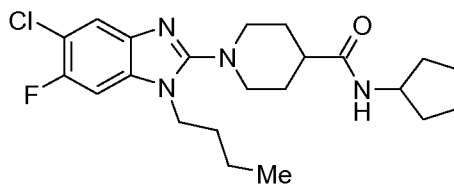
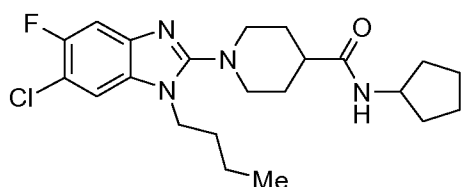
ethyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was made to determine the ratio of the regioisomers. LC-MS (*m/z*) 393.0 (*M*+1).

Example 264: 1-(5-chloro-6-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.27 mmol), isopropyl iodide (1.096 mmol), caesium carbonate (1.096 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.0274 mmol) and *N,N*-dimethyl-formamide (3 mL) using the method described in Example 94. This gave 50 mg (45 % yield) of 1-(5-chloro-6-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was made to determine the ratio of the regioisomers. LC-MS (*m/z*) 407.1 (*M*+1).

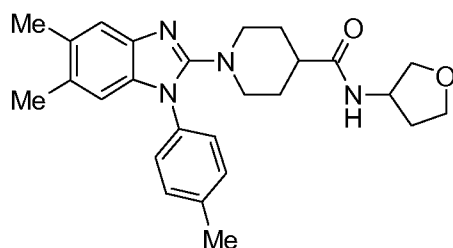
Example 265: 1-(1-butyl-5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(1-butyl-6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of 1-(5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide (0.1 g, 0.27 mmol), 1-bromobutane (1.096 mmol), caesium carbonate (1.096 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.0274 mmol) and *N,N*-dimethyl-

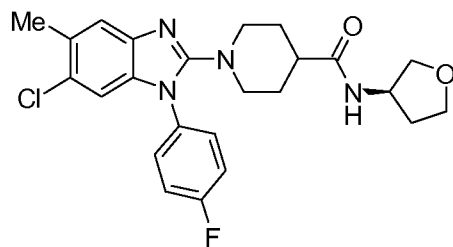
formamide (3 mL) using the method described in Example 94. This gave 8 mg (6.8 % yield) of 1-(1-butyl-5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide and 1-(1-butyl-6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide as an off-white solid. No effort was made to determine the ratio of the regioisomers. LC-MS (*m/z*) 421.1 (M+1).

Example 266: 1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from 1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (0.30 g, 0.877 mmol), dimethylsulfoxide (6 mL), caesium carbonate (3.51 mmol), 1-iodo-4-methylbenzene (3.51 mmol), 4,7-dimethoxy-1,10-phenanthroline (0.132 mmol), polyethylene glycol (0.89 g) and copper(I) oxide (0.0438 mmol) using the method described in Example 76. The reaction mixture was heated at 120°C for 12 hours in a sealed tube and purified with column chromatography, to give 43 mg (11.3 % yield) of 1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale green solid. LC-MS (*m/z*) 432.2 (M+1).

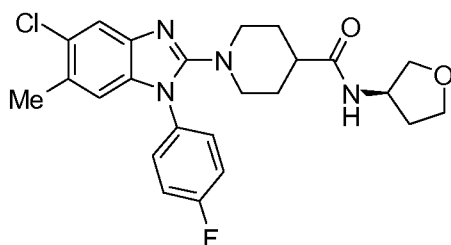
Example 267: (R)-1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500 mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.76 mmol), 4-fluoro

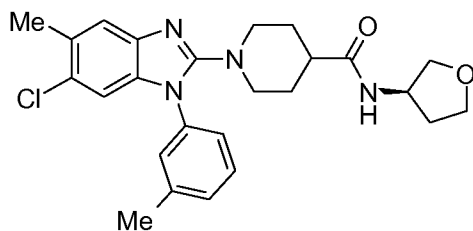
iodobenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689 mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and subsequently purified on reverse-phase reverse-phase hplc, to give 42 mg (6.6 % yield) of (R)-1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid, eluting ahead of (R)-1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. MS (m/z) 457.1 (M+1).

Example 268: (R)-1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was obtained as described in Example 267 eluting after (R)-1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 47 mg (7.4 % yield) of (R)-1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 457.1 (M+1).

Example 269: (R)-1-(6-chloro-5-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

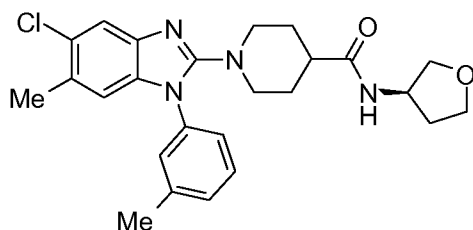


The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500

mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.76 mmol), 1-bromo-3-methylbenzene (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689 mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and

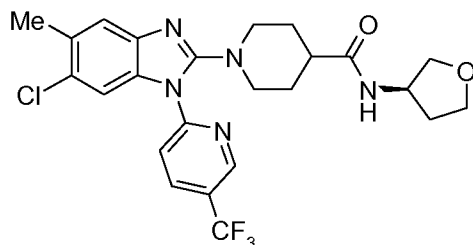
subsequently purified on reverse-phase reverse-phase hplc, to give 24 mg (3.8 % yield) of (R)-1-(6-chloro-5-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a pale yellow solid, eluting ahead of (R)-1-(5-chloro-6-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (*m/z*) 453.2 (*M*+1).

Example 270: (R)-1-(5-chloro-6-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was obtained as described in Example 269 eluting after (R)-1-(6-chloro-5-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. This gave 23 mg (3.7 % yield) of (R)-1-(5-chloro-6-methyl-1-m-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 453.3 (*M*+1).

Example 271: (R)-1-(5-chloro-6-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



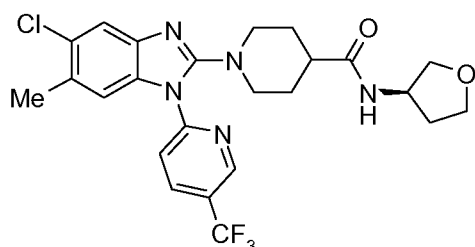
The title compound was prepared from a tautomeric mixture of (R)-1-(5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide and (R)-1-(6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (500

mg, 1.38 mmol) dimethylsulfoxide (2 mL), caesium carbonate (2.76 mmol), 2-bromo-5-(trifluoromethyl)pyridine (4.13 mmol), 8-hydroxyquinoline (0.551 mmol), polyethylene glycol (0.689 mmol) and copper(I) oxide (0.276 mmol) using the method described in Example 136.

The reaction mixture was subjected to microwave conditions for 150 minutes at 120°C and

- 5 subsequently purified on reverse-phase reverse-phase hplc, to give 12 mg (1.7 % yield) of (R)-1-(5-chloro-6-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a yellow solid, eluting ahead of (R)-1-(6-chloro-5-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide on the column. LC-MS (*m/z*) 508.3 (*M*+1).

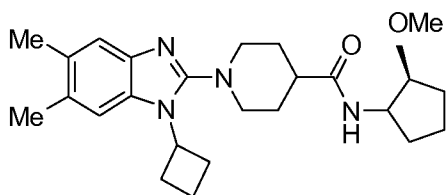
10 **Example 272: (R)-1-(6-chloro-5-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide**



The title compound was obtained as described in Example 271 eluting after (R)-1-(5-chloro-6-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-

- 15 yl)piperidine-4-carboxamide on the column. This gave 16 mg (2.3 % yield) of (R)-1-(6-chloro-5-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an yellow solid. LC-MS (*m/z*) 508.2 (*M*+1).

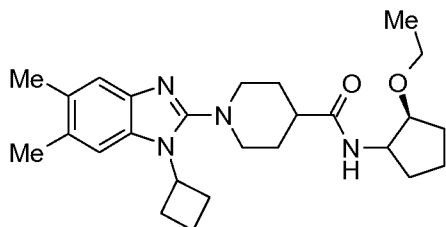
Example 273: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-((2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide



A solution of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamid (0.10 g, 0.24 mmol) in *N,N*-dimethylformamide (DMF, 2 mL) was cooled to 0 °C. Sodium hydride (0.26 mmol) was added followed by methyl iodide (0.24 mmol) and the reaction was stirred at 0 °C for 3 h. The reaction mixture was poured

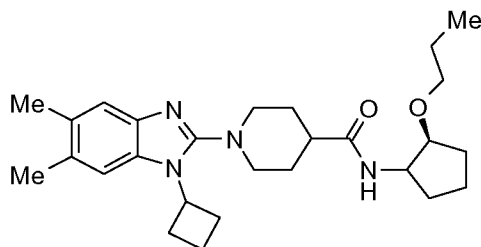
onto ice and the precipitate was collected by filtration. The crude was rechrystallized from petroleum ether to give 17 mg (17%) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide as a pale yellow solid. LC-MS (*m/z*) 425.2 (*M*+1).

5 Example 274: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide



A solution of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamid (0.10 g, 0.24 mmol) in *N,N*-dimethylformamide (DMF, 2 mL) was cooled to 0 °C. Sodium hydride (0.48 mmol) was added followed by ethyl iodide (0.48 mmol) and the reaction was stirred at 0 °C for 3 h. The reaction mixture was poured onto ice and the precipitate was collected by filtration. The crude was rechrystallized from petroleum ether to give 42 mg (39%) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 439.2 (*M*+1).

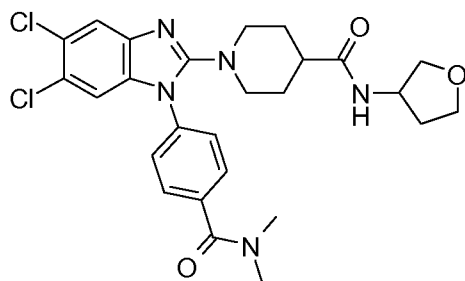
Example 275: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-propoxycyclopentyl)piperidine-4-carboxamide



A solution of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamid (0.10 g, 0.24 mmol) in *N,N*-dimethylformamide (DMF, 2 mL) was cooled to 0 °C. Sodium hydride (0.48 mmol) was added followed by 1-iodopropane (0.48 mmol) and the reaction was stirred at 0 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the crude purified by silica chromatography

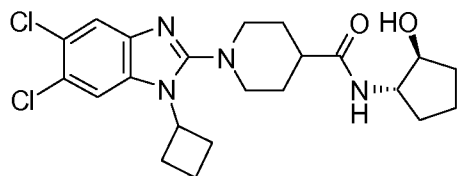
(chloroform/methanol gradient) to give 51 mg (46%) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-propoxycyclopentyl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 453.2 (*M*+1).

Example 276: 1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

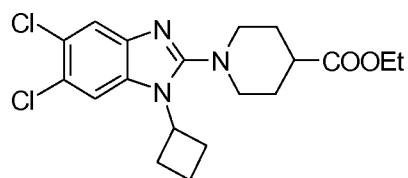


A reaction mixture consisting of 1-(1-(4-bromophenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.19 mmol), *trans*-di(μ -acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (Hermann palladacycle, 0.0095 mmol), *N,N*-diisopropylethylamine (Hünig's base, DIEA, 0.38 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.19 mmol), tri tertiarybutyl phosphonium tetrafluoroborate ([*t*-Bu)₃PH]BF₄, 0.019 mmol), molybdenum hexacarbonyl (Mo(CO)₆, 0.095 mmol) and *N,N*-dimethyl amine hydrochloride (0.38 mmol) in 1,4-dioxane (3 mL), was irradiated under microwave conditions at 150°C for 30 minutes. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (2 x 50 mL) and the combined organic phases dried over anhydrous sodium sulphate. After concentration in vacuo, the residue was subjected to column chromatography to give 5 mg (5 % yield) of 1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 530.5 (*M*+1).

Example 277: 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide

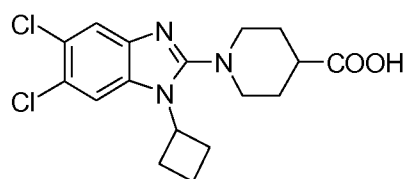


(a) Preparation of the intermediate compound ethyl 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate:



5 Ethyl 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate was prepared from ethyl 1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (1.0 g, 2.9 mmol), (bromomethyl)cyclobutane (11.6 mmol), caesium carbonate (11.6 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (PdCl₂(dppf), 0.29 mmol) and *N,N*-dimethylformamide (8 mL) using the method described in Example 16. The reaction mixture was heated at 130°C for two hours in a sealed tube and purified with column chromatography, to give 480 mg (42 % yield) of ethyl 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate as a pale yellow solid. LC-MS (*m/z*) 451.3 (*M*+1).

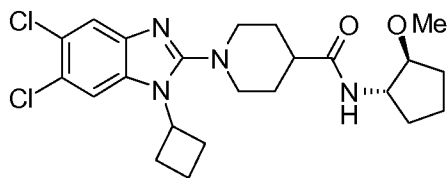
10 (b) Preparation of the intermediate compound 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:



15 Ethyl 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (1.0 g, 2.5 mmol), aqueous sodium hydroxide (12.5) and ethanol/water (4:1) was stirred for 30 minutes at room temperature. After the appropriate work-up, the residue was recrystallized from petroleum ether, to give 0.70 g (83 % yield) of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid.

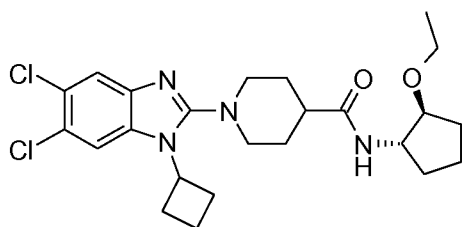
20 (c) 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (1.0 mg, 2.7 mmol), *N,N*-dimethylformamide (10 mL), *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 5.4 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 5.4 mmol) and (1*S*,2*S*)-2-aminocyclopentanol (3.24 mmol) was stirred at room temperature for one hour. After the appropriate work-up, the residue was recrystallized from petroleum ether, to give 1.0 g (83 % yield) of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide.

Example 278: 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide



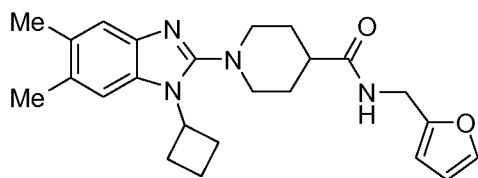
A solution of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide (0.10 g, 0.22 mmol) in *N,N*-dimethylformamide (DMF, 3 mL) was cooled to 0 °C. Sodium hydride (0.24 mmol) was added followed by methyl iodide (0.22 mmol) and the reaction was stirred at 0 °C for 30 minutes. The reaction mixture was poured onto ice and the precipitate was collected by filtration. The crude was recrystallized from petroleum ether to give 5 mg (5%) of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide as a yellow solid. LC-MS (*m/z*) 465.4 (*M*+1).

Example 279: 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide



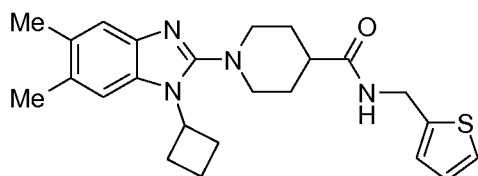
A solution of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide (0.10 g, 0.22 mmol) in *N,N*-dimethylformamide (DMF, 3 mL) was cooled to 0 °C. Sodium hydride (0.44 mmol) was added followed by ethyl iodide (0.44 mmol) and the reaction was stirred at 0 °C for 3 hours. The reaction mixture was poured onto ice and the precipitate was collected by filtration. The crude was recrystallized from petroleum ether to give 30 mg (28 % yield) of 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide as an yellow solid. LC-MS (*m/z*) 479.5 (*M*+1).

Example 280: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(furan-2-ylmethyl)piperidine-4-carboxamide



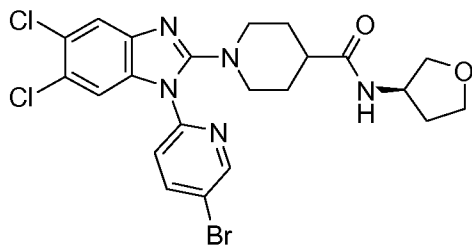
1-(1-Cyclobutyl-5,6-dimethyl-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (30 mg, 0.092 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 42 mg, 0.11 mmol), 2-aminomethylfuran (25 μ L, 0.28 mmol) and *N,N*-diisopropylethylamine (Hünig's base, DIEA, 46 μ L, 0.28 mmol) were dissolved in *N,N*-dimethylformamide (DMF, 1 mL). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was filtered and the crude product was purified on preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 18.2 mg (72 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(furan-2-ylmethyl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 407.0 ($M+1$).

Example 281: 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide



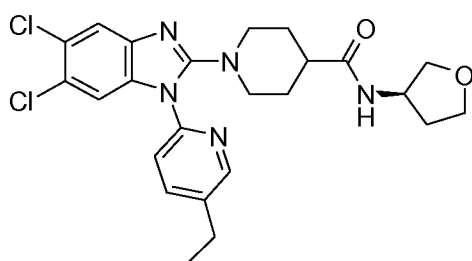
1-(1-Cyclobutyl-5,6-dimethyl-1*H*-benzoimidazol-2-yl)-piperidine-4-carboxylic acid (30 mg, 0.092 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 42 mg, 0.11 mmol), 2-thiophenemethylamine (28 μ L, 0.28 mmol) and *N,N*-diisopropylethylamine (Hünig's base, DIEA, 153 μ L, 0.916 mmol) were dissolved in *N,N*-dimethylformamide (DMF, 1 mL). The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was filtered and the crude product was purified on preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 2.5 mg (6 % yield) of 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide as an off-white solid. LC-MS (m/z) 423.0 ($M+1$).

Example 282: (R)-1-(1-(5-bromopyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



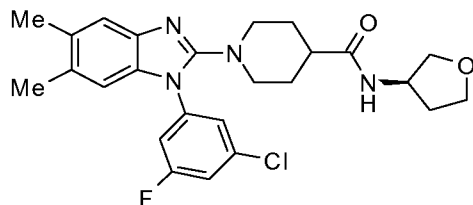
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (290 mg, 0.757 mmol) dimethylsulfoxide (1 mL), caesium carbonate (345 mg, 1.06 mmol), 2,5-dibromopyridine (0.72 g, 3.0 mmol), 8-hydroxyquinoline (0.15 mmol), polyethylene glycol 400 (0.38 mmol) and copper(I) oxide (0.076 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 60 minutes at 150°C. Most of the DMSO was removed under reduced pressure and the residue purified by silica chromatography (0-6% MeOH in dichloromethane) to give 97 mg (37 % yield) of (R)-1-(1-(5-bromopyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a brown solid. LC-MS (*m/z*) 540.2 (M+1).

Example 283: (R)-1-(1-(5-ethylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



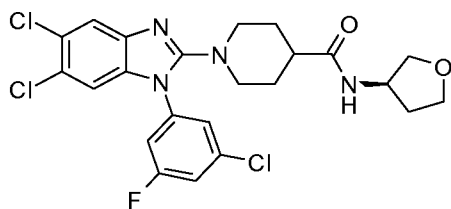
To a solution of (R)-1-(1-(5-bromopyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (20 mg, 0.037 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) (CAS Registry Number: 53199-31-8, 1.2 mg, 0.0024 mmol) in dry tetrahydrofuran under nitrogen was added diethylzinc (1 N in hexane, 0.11 mL, 0.11 mmol) and the mixture microwave heated at 120 °C for 1 hour. The reaction mixture was purified by preparative reversed phase HPLC to give 7.7 mg (43 % yield) of (R)-1-(1-(5-ethylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as a white solid. LC-MS (*m/z*) 488.2 (M+1).

Example 284: (R)-1-(1-(3-chloro-5-fluorophenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



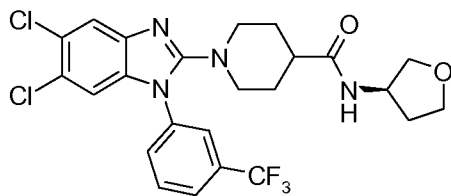
The title compound was prepared from (R)-1-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 3-chloro-5-fluoro-bromobenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 10 mg (7 % yield) of (R)-1-(1-(3-chloro-5-fluorophenyl)-5,6-dimethyl-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 471.2 (*M*+1).

Example 285: (R)-1-(5,6-dichloro-1-(3-chloro-5-fluorophenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



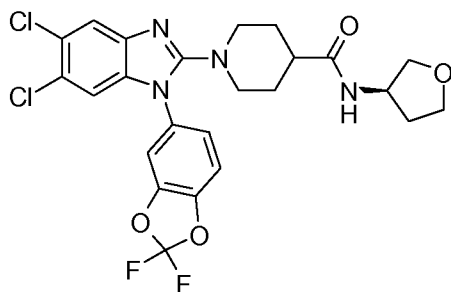
The title compound was prepared from (R)-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol), dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 3-chloro-5-fluoro-bromobenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 9 mg (7 % yield) of (R)-1-(5,6-dichloro-1-(3-chloro-5-fluoro-phenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 511.3 (*M*+1).

Example 286: (R)-1-(5,6-dichloro-1-(3-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



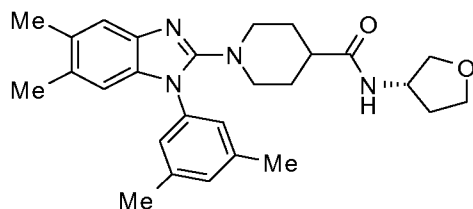
The title compound was prepared from (R)-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol), dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 3-bromo-benzotrifluoride (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 12 mg (9 % yield) of (R)-1-(5,6-dichloro-1-(3-trifluoromethylphenyl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 527.4 (M+1).

Example 287: (R)-1-(5,6-dichloro-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide

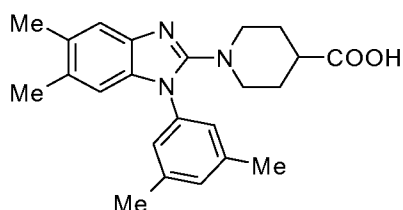


The title compound was prepared from (R)-1-(5,6-dichloro-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol), dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 5-bromo-2,2-difluorobenzo[d][1,3]dioxol (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 11 mg (8 % yield) of (R)-1-(5,6-dichloro-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 539.3 (M+1).

Example 288 (S)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



(a) Preparation of the intermediate compound 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid:

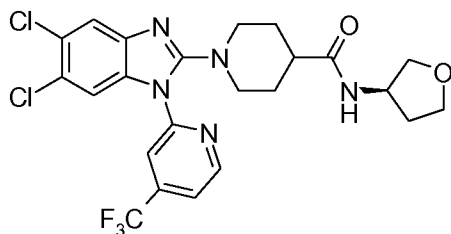


Ethyl 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylate (80.5 mg, 0.267 mmol), 1-bromo-3,5-dimethylbenzene (73 μ L, 0.534 mmol), 8-hydroxyquinoline (7.8 mg, 0.053 mmol), copper(I) oxide (3.8 mg, 0.027 mmol), polyethylene glycol 400 (107 mg, 0.267 mmol), caesium carbonate (122 mg, 0.374 mmol) and dimethylsulfoxide (0.5 mL) were mixed in a sealed reaction tube. The reaction mixture was heated at 150°C for two hour in a heating block and then diluted with ethylacetate and water. The water phase was extracted with ethyl acetate, the combined organic phases was dried over magnesium sulphate and concentrated in vacuo. To the residue was added ethanol (2 mL) and aqueous sodium hydroxide (1 mL, 1 N). The reaction mixture was stirred at 50 °C for one hour, neutralized with aqueous hydrochloric acid (1 N) and concentrated in vacuo. This gave 90 mg of 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid. LC-MS (m/z) 378.0 (M+1).

(b) 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (90 mg, 0.24 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 136 mg, 0.358 mmol), (S)-(-)-tetrahydrofuran-3-amine hydrochloride (29.5 mg, 0.238 mmol) and *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 994 μ L, 5.96 mmol) were dissolved in *N,N*-dimethylformamide (1 mL). The reaction mixture was stirred overnight at ambient temperature, filtered and subjected to preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m,

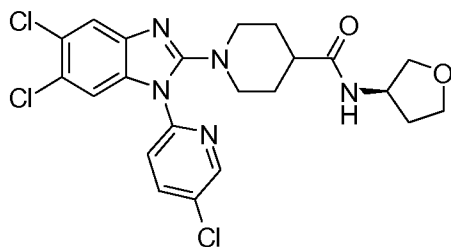
21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 2 mg (2 % yield) of (S)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 447.0 (*M*+1).

5 Example 289: (R)-1-(5,6-dichloro-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol), dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-4-trifluoromethylpyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 41 mg (30 % yield) of (R)-1-(5,6-dichloro-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 528.2 (*M*+1).

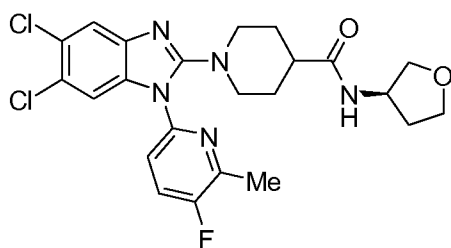
Example 290: (R)-1-(5,6-dichloro-1-(5-chloropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (100 mg, 0.261 mmol), dimethylsulfoxide (2 mL), caesium carbonate (0.392 mmol), 2-bromo-4-chloropyridine (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522

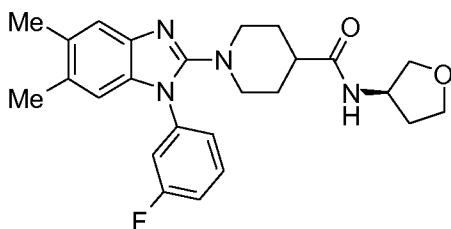
mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 20 mg (17 % yield) of (R)-1-(5,6-dichloro-1-(5-chloropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 494.3 (M+1).

Example 291: (R)-1-(5,6-dichloro-1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 2-bromo-5-fluoro-6-methylpyridine (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 5 mg (3.2 % yield) of (R)-1-(5,6-dichloro-1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamid. LC-MS (*m/z*) 492.3 (M+1).

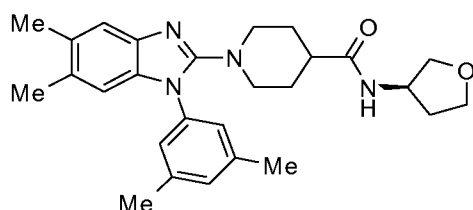
Example 292: (R)-1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 3-fluoro-bromobenzene (0.876 mmol), 8-

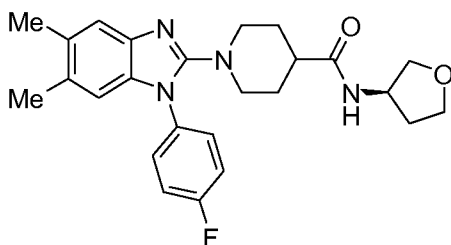
hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 7 mg (6 % yield) of (R)-1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 437.1 (M+1).

Example 293: (R)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (90 mg, 0.24 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 136 mg, 0.358 mmol), (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (61.8 mg, 0.238 mmol) and *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 994 μ L, 5.96 mmol) were dissolved in *N,N*-dimethylformamide (1 mL). The reaction mixture was stirred overnight at ambient temperature, filtered and subjected to preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 11 mg (10 % yield) of (R)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamid as an off-white solid. LC-MS (m/z) 447.0 (M+1).

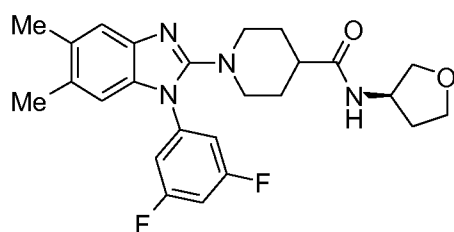
Example 294: (R)-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2

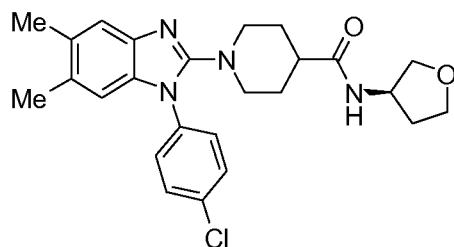
mL), caesium carbonate (0.584 mmol), 4-fluoro-bromobenzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 25 mg (22 % yield) of (R)-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 437.1 (M+1).

Example 295: (R)-1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



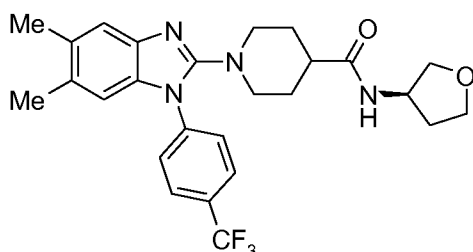
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 3,5-difluoro-bromobenzene (1.05 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 31 mg (19 % yield) of (R)-1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 455.1 (M+1).

Example 296: (R)-1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



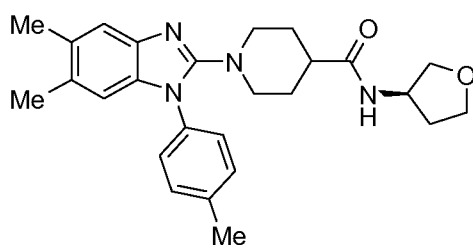
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 4-chloro-bromobenzene (1.05 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 10 mg (6 % yield) of (R)-1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 453.2 (M+1).

Example 297: (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



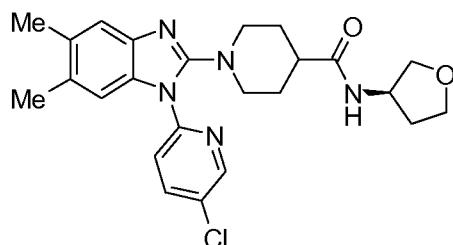
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 4-bromo-benzotrifluoride (1.05 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 3 mg (1.8 % yield) of (R)-1-(1-(4-trifluoromethyl-phenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 487.1 (M+1).

Example 298: (R)-1-(5,6-dimethyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



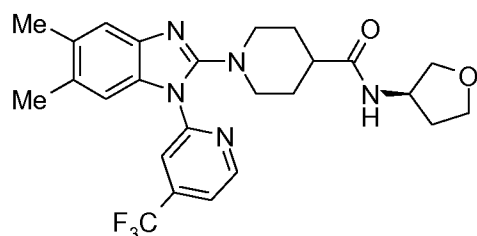
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 3-chloro-5-fluoro-benzene (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 39 mg (31 % yield) of (R)-1-(1-(4-methyl-phenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 434.1 (M+1).

Example 299: (R)-1-(1-(5-chloropyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



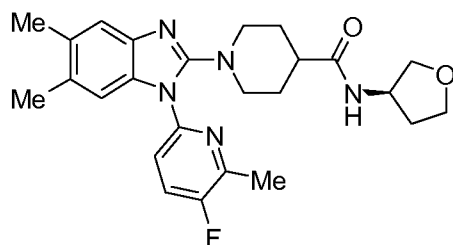
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 2-bromo-5-chloropyridine (1.05 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 18 mg (12 % yield) of (R)-1-(1-(5-chloropyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 454.2 (M+1).

Example 300: (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



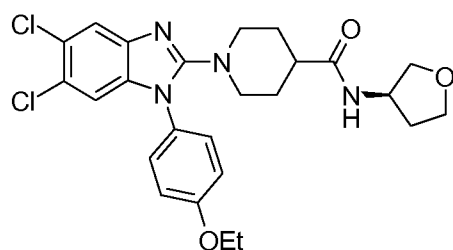
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (100 mg, 0.292 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.584 mmol), 2-bromo-4-trifluoromethylpyridine (0.876 mmol), 8-hydroxyquinoline (0.117 mmol), polyethylene glycol (0.146 mmol) and copper(I) oxide (0.0584 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 25 mg (18 % yield) of (R)-1-(1-(4-(trifluoromethyl)pyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 488.1 (M+1).

Example 301: (R)-1-(1-(5-fluoro-6-methylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



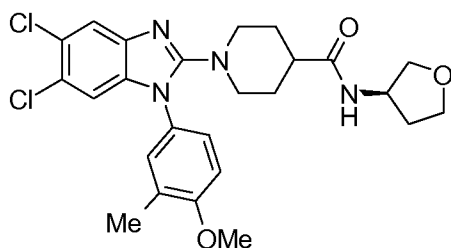
The title compound was prepared from (R)-1-(5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide, (120 mg, 0.350 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.701 mmol), 2-bromo-5-fluoro-6-methylpyridine (1.05 mmol), 8-hydroxyquinoline (0.140 mmol), polyethylene glycol (0.175 mmol) and copper(I) oxide (0.0701 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 11 mg (7 % yield) of (R)-1-(1-(5-fluoro-6-methylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (m/z) 452.1 (M+1).

Example 302: (R)-1-(5,6-dichloro-1-(4-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



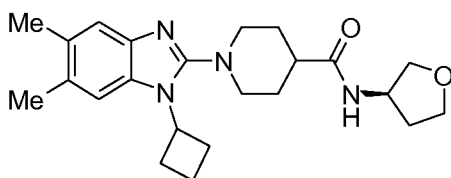
The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 4-ethoxybenzene (0.783 mmol), 8-hydroxyquinoline (0.104 mmol), polyethylene glycol (0.511 mmol) and copper(I) oxide (0.0522 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 35 mg (30 % yield) of (R)-1-(5,6-dichloro-1-(4-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 503.5 (M+1).

Example 303: (R)-1-(5,6-dichloro-1-(4-methoxy-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



The title compound was prepared from (R)-1-(5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide (120 mg, 0.313 mmol) dimethylsulfoxide (2 mL), caesium carbonate (0.470 mmol), 4-methoxy-3-methylbenzene (0.939 mmol), 8-hydroxyquinoline (0.125 mmol), polyethylene glycol (0.157 mmol) and copper(I) oxide (0.0626 mmol) using the method described in Example 136. The reaction mixture was subjected to microwave conditions for 150 minutes at 140°C and subsequently purified on reverse-phase hplc, to give 15 mg (10 % yield) of (R)-1-(5,6-dichloro-1-(4-methoxy-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide. LC-MS (*m/z*) 503.4 (M+1).

Example 304: (R)-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-N-(tetrahydrofuran-3-yl)piperidine-4-carboxamide



1-(1-Cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxylic acid (30 mg, 0.092 mmol), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU (42 mg, 0.11 mmol), (R)-(+)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (71 mg, 0.28 mmol) and *N,N*-diisopropyl-ethylamine (Hünig's base, DIEA, 153 μ L, 0.916 mmol) were dissolved in *N,N*-dimethylformamide (1 mL). The reaction mixture was stirred overnight at ambient temperature, filtered and subjected to preparative hplc (preparative RP-LC was performed on a Gilson system equipped with a Zorbax SB-C8 (5 μ m, 21.2 x 150 mm) column, using methanol/water (0.05% formic acid) gradients at a flow rate of 4 mL/min with UV (214 or 254 nm) and MS (ESI) detection) to give 17 mg (46 % yield) of (R)-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide as an off-white solid. LC-MS (*m/z*) 397.0 (*M*+1).

BIOLOGICAL TESTS

Prostaglandin detection kits were purchased from Cayman Chemicals and used according to the instruction of the manufacturer.

15

Thiobarbituric acid assay (TBA-MDA assay or Malondialdehyde assay):

Malondialdehyde is a product of lipid peroxidation and reacts with thiobarbituric acid forming a red product that absorbs at 535 nm (W.G. Niehaus, Jr and B. Samuelsson, Eur. J. Biochem 6, 126 (1968) and is also fluorescent. The extinction coefficient of the TBA-MDA conjugate is $1.56 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$ (E.D. Wills. Biochem. J. 113, 315 (1969). The method used for detection of inhibition of mPGEs-1 is based on the detection of the amount of remaining PGH₂. This method was described more than 20 years ago by Basevich et al (Bioorg. Khim. 1983, 9(5), 658-665).

20

The assay used was a modified variant and used citric acid instead of the TCA-TBA-HCl reagent described in the original assay. In this assay recombinant, membrane-bound human or rat mPGEs-1 was incubated with PGH₂. The reaction was stopped by adding citric acid with a final pH of 3 and a large excess of iron(II) chloride (20 mM) to convert any remaining PGH₂ into MDA and 12-HHT. TBA reagent was finally added (0.67 %) and the samples were heated at 80 °C for 30 min. The fluorescence of the conjugate was measured at 485/545 nm.

30

The product of mPGEs-1 (PGE₂) was not measured directly in this assay, but rather the remaining substrate (PGH₂) indirectly by adding FeCl₂ that converts PGH₂ into MDA and 12-HHT. As a positive control a known mPGEs-1 inhibitor, MK-886, was used and the new inhibitors were compared with the inhibition of MK-886.

Selected results from the human and rat mPGEs-1 TBA-MDA assay (IC₅₀ in μ M) are shown in Table 1.

5 A549 cell-assay

A549 lung carcinoma cells, seeded at a density of 10, 000 cells/well, were grown in 96 well tissue culture plates. TNF α (5 ng/mL) and IL-1 β (5 ng/mL) were added and the cells were incubated for 16 hours. Cells were washed in PBS and test compounds at the appropriate concentration in HBSS/0.1% BSA were added. After 30 minutes incubation with test compounds, 10 μ M arachidonic acid was added and cells were further incubated for 30 minutes. Supernatant was collected and analyzed for PGE₂ content by EIA according to manufacturer's instructions. Selected results from the A549 cell-assay are shown in Table 1.

Table 1. Inhibition of human and rat mPGEs-1 and cellular PGE₂ synthesis.

Example	Human mPGEs-1 IC ₅₀ (μ M)	Rat mPGEs-1 IC ₅₀ (μ M)	A549 cell-assay IC ₅₀ (μ M)
1	0.19	0.65	0.75
2	0.18	0.22	0.45
3	0.10	0.12	0.51
4	0.17	0.37	0.37
5	0.31	0.45	0.19
6	0.079	0.36	0.071
7	0.12	0.52	0.13
8	>3	-	-
9	0.18	0.92	0.67
10	0.28	-	-
11	0.21	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
12	0.14	2.5	0.24
13	0.088	0.27	0.30
14	0.18	-	-
15	0.24	-	-
16	0.050	0.62	0.11
17	0.52	-	-
18	0.11	0.075	0.46
19	0.065	0.080	0.39
20	0.085	0.83	0.33
21	0.15	0.42	0.21
22	0.10	1.0	0.26
23	0.082	0.46	0.075
24	>3	-	-
25	0.071	0.38	0.10
26	2.04	-	-
27	0.33	0.34	0.21
28	0.94	6.2	1.4
29	1.36	-	-
30	>3	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
31	0.34	1.7	0.73
32	0.27	-	-
33	1.06	-	-
34	0.38	1.7	0.77
35	0.26	2.0	0.99
36	0.17	2.5	0.43
37	0.18	-	-
38	0.08	0.12	0.25
39	0.49	-	-
40	0.083	0.61	0.19
41	0.064	0.25	0.13
42	0.077	0.44	0.052
43	0.86	-	-
44	>3	-	-
45	>3	-	-
46	>3	-	-
47	0.24	-	-
48	0.34	-	-
49	0.045	0.27	0.073

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
50	0.043	0.17	0.044
51	0.072	0.27	0.022
52	0.10	6.7	0.14
53	0.071	>50	0.11
54	0.038	0.88	0.13
55	0.10	0.28	0.25
56	0.10	11	0.061
57	0.17	-	-
58	0.41	-	-
59	0.19	-	-
60	0.22	-	-
61	0.11	0.54	0.62
62	0.37	-	-
63	>3	-	-
64	0.18	-	-
65	0.11	1.6	0.078
66	0.23	-	-
67	-	-	-
68	0.10	0.65	0.39

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
69	0.093	0.94	0.11
70	0.14	-	-
71	0.10	-	0.68
72	0.77	-	-
73	0.38	-	-
74	0.13	0.44	0.47
75	0.058	-	-
76	0.061	0.12	0.36
77	>3	-	-
78	0.11	1.6	0.25
79	0.032	1.1	0.10
80	0.22	-	-
81	0.070	-	0.013
82	0.074	-	0.051
83	0.46	-	-
84	0.057	-	0.051
85	0.16	-	-
86	0.070	-	0.067
87	0.49	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
88	0.63	-	-
89	0.29	1.6	0.53
90	0.26	1.3	0.46
91	0.12	0.25	0.16
92	1.09	-	-
93	0.11	0.31	0.046
94	0.048	-	0.054
95	0.35	-	-
96	0.27	-	-
97	0.89	-	-
98	0.23	-	-
99	1.04	-	-
100	0.42	-	-
101	>3	-	-
102	0.38	-	-
103	>3	-	-
104	>3	-	-
105	0.26	-	-
106	0.30	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
107	0.65	-	-
108	0.15	-	-
109	>3	-	-
110	>3	-	-
111	>3	-	-
112	>3	-	-
113	1.3	-	-
114	0.23	-	-
117	0.21	-	-
118	0.11	-	0.28
119	0.12	-	-
120	0.10	-	-
121	0.15	-	-
122	0.025	0.027	0.078
123	0.011	0.037	0.042
124	0.083	0.088	0.38
125	0.074	0.24	0.29
126	0.054	0.14	0.28
127	0.30	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
128	0.037	-	0.015
129	0.019	0.045	0.031
130	0.025	0.060	0.027
131	0.042	0.10	0.014
132	0.059	0.14	0.037
133	0.026	0.068	0.12
134	0.043	0.085	0.15
136	0.10	0.28	0.089
137	0.43	-	-
138	0.076	0.44	0.10
139	0.028	0.21	0.017
140	0.045	0.048	0.011
141	0.12	0.38	0.073
142	0.053	0.13	0.096
143	0.054	0.15	0.13
144	0.052	0.36	0.063
145	0.094	-	-
146	0.074	-	0.084
147	0.29	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
148	1.7	-	-
149	0.08	0.13	0.13
150	0.10	-	-
151	0.093	-	-
152	0.036	-	-
153	0.035	-	-
154	0.085	-	-
155	0.041	0.51	0.11
156	0.045	0.048	0.011
157	0.063	0.091	0.061
158	0.051	0.032	0.008
159	0.065	0.071	0.066
160	0.075	0.10	0.065
161	0.050	0.070	0.049
162	0.052	0.018	0.093
163	0.060	0.27	0.12
164	0.14	-	-
165	0.059	0.37	0.11
166	0.25	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
167	0.081	-	1.4
168	0.070	-	1.5
169	0.20	-	-
170	0.078	0.41	0.089
171	0.082	0.37	0.042
172	0.089	0.44	0.076
173	0.090	0.38	0.091
174	0.12	-	-
175	0.10	0.28	0.10
176	0.073	0.18	0.21
177	0.12	0.17	0.58
178	0.18	-	-
179	0.070	0.14	0.11
180	0.12	-	0.076
181	0.061	0.42	0.13
182	0.080	-	0.077
183	0.068	-	0.040
184	0.061	0.20	0.019
185	0.24	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
186	0.042	0.046	0.056
187	0.074	0.085	-
188	0.13		-
189	0.042	-	0.027
190	0.11	-	-
191	0.26	-	-
192	0.036	-	0.080
193	0.072	-	-
194	0.073	-	-
195	0.19	-	-
196	0.15	-	-
197	0.053	-	0.11
198	0.022	-	0.046
199	0.18	-	-
200	0.063	-	0.20
201	0.12	-	-
202	0.14	-	-
203	0.35	-	-
204	0.077	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
205	0.040	-	0.056
206	0.045	-	0.12
207	0.016	-	0.026
208	0.22	-	-
209	0.091	-	-
210	0.039	0.057	0.024
211	0.11	-	-
212	0.078	-	-
213	0.081	-	-
214	0.12	-	-
215	0.070	-	-
216	0.083	0.17	0.34
217	0.13	0.22	-
218	0.034	0.069	0.021
219	0.049	0.065	0.024
220	0.066	-	-
221	0.024	-	-
222	0.21	-	-
223	0.11	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
224	0.19	-	-
225	0.044	-	-
226	0.044	-	-
227	0.029	-	-
228	0.073	0.072	0.22
229	0.051	0.068	0.09
230	0.071	0.043	0.21
231	0.23	-	-
232	0.038	0.030	0.039
233	0.047	-	-
234	0.035	-	-
235	0.056	-	-
236	0.10	-	-
237	0.047	-	-
238	0.12	-	-
239	0.073	-	-
240	0.059	-	-
241	0.085	-	0.050
242	0.074	-	0.048

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
243	0.057	-	0.014
244	0.057	0.20	0.12
245	0.24	-	-
246	0.43	-	-
247	0.041	-	-
248	0.046	-	-
249	0.051	-	-
250	0.040	-	-
251	0.13	-	-
252	0.058	-	-
253	0.045	-	-
254	0.10	-	-
255	0.032	-	-
256	0.097	-	-
257	0.098	-	-
258	0.048	-	-
259	0.054	-	-
260	0.73	-	-
261	0.14	-	-

Example	Human mPGEs-1	Rat mPGEs-1	A549 cell-assay
	IC₅₀ (μM)	IC₅₀ (μM)	IC₅₀ (μM)
262	0.35	-	-
263	0.13	-	-
264	0.13	-	-
265	0.071	0.54	0.13
266	0.070	0.089	0.26
267	0.066	-	-
268	0.13	-	-
269	0.033	-	-
270	0.046	-	-
271	0.054	-	-
272	0.067	-	-
273	0.18	-	-
274	0.16	-	-
275	0.14	-	-
276	0.89	-	-
277	0.072	0.78	0.22
278	0.10	-	0.22
279	0.083	1.3	0.36
280	1.1	-	-

Example	Human mPGEs-1 IC ₅₀ (μM)	Rat mPGEs-1 IC ₅₀ (μM)	A549 cell-assay IC ₅₀ (μM)
281	1.5	-	-
288	0.081	-	0.042
304	1.500	-	-

The human mPGEs-1 IC₅₀ values of the compounds of Examples 284-287, 289-292 and 294-303 are within the range of 10-250 nM (i.e. 0.01-0.25 μM).

5 Carrageenan-induced paw edema

Method

Chemicals

λ-Carrageenan (Fluka, Switzerland), Carboxymethyl cellulose (CMC) (Sigma, USA), Dimethyl sulfoxide (DMSO) (Merck, Germany), Pyrogen free saline (Sintong, R. O. C.) and Tween 80 (Sigma, USA).

Equipment

Animal cage (Allentown, USA), Glass syringes (1 mL, 2 mL, Mitsuba, Japan), Hypodermic needle 27G x 1" (Top Corporation, Japan), Paw/Tail stimulator analgesia meter (IITC Model-336G, IITC, USA), Plethysmometer (PV-01, Paw Volume Apparatus, SINGA Technology Co., R. O. C), Rat oral needle (Natsume, Japan) and Rat scale (1 g ~ 1000 g, TANITA, Japan).

Animals

Male Wistar rats weighing 165 ± 15 g were provided by BioLasco Taiwan (under Charles River Laboratories Technology Licensee). Space allocation for 5 animals was 45 x 23 x 21 cm.

Animals were housed in animal cages and maintained in a controlled temperature (21 - 23°C) and humidity (50% - 70%) environment with 12 hours light/dark cycles for at least three days at test site prior to use. The rats were divided into groups of eight, each group to receive either

vehicle (1% Tween 80/0.5% CMC), or 10, 30 or 100 mg/kg bodyweight of the compound of EXAMPLE 41 (in the following referred to as "EXAMPLE 41"). The rats were fasted overnight prior to use. EXAMPLE 41 was suspended in vehicle and administered intraperitoneally immediately before the right hind paw received intraplantar injection of carrageenan (0.1 mL of 1% suspension). Hind paw edema, a measure of inflammation, was recorded 6 hours after carrageenan administration using a plethysmometer.

Results

Intraperitoneal administration of EXAMPLE 41 at 10, 30 and 100 mg/kg bodyweight to rats resulted in a decrease in paw swelling of 22%, 34% and 39%, respectively, compared to vehicle-treated rats (figure qz1).

Conclusion

EXAMPLE 41 is capable of reducing carrageenan-induced paw swelling, a symptom of inflammation, in rats.

Complete Freund's Adjuvant-induced arthritis

EXAMPLE 41, was evaluated for anti-inflammatory activity in Complete Freund's Adjuvant (CFA)-induced arthritis in rats. EXAMPLE 41 at 3, 10 and 30 mg/kg was administered orally once daily for 5 consecutive days; the first dose given one hour before CFA was injected into the right hind paw on day 1. The right hind paw volume was measured on day 0 (before CFA), 4 hours after the single CFA injection (denoted day 1) and on days 5, 8, 11, 14, 18 and 21 (acute phase), while the left hind paw (without CFA) volume was measured on days 0 (before CFA), 14, 18 and 21 (delayed phase).

Method

Test Substance and Dosing Pattern

EXAMPLE 41 at 3, 10 and 30 mg/kg was administered orally once daily for 5 consecutive days, with the first dose given one hour before CFA (Complete Freund's Adjuvant) challenge. A dosing volume of 2 mL/kg was used.

Animals

Female Lewis rats weighing 210 ± 10 g were obtained from Charles River USA Inc. Space allocation for 5 animals was 45 x 23 x 21 cm. All animals were maintained in a controlled temperature (21-23°C) and humidity (50% - 70%) environment with 12 hours light/dark cycles

for at least three days at test site prior to use. Free access to standard lab chow for rats and water was granted.

EXAMPLE 41 at 3, 10 and 30 mg/kg was administered orally (PO) on day 1 beginning one hour before injection of CFA; once daily dosing was performed for 5 consecutive days. A well-ground suspension of killed *Mycobacterium butyricum* (0.3 mg in 0.1 mL of light mineral oil; CFA, was administered in a single dose into the subplantar region of the right hind paw 1 hour following the first dose of test substance (denoted day 1). Right hind paw volume was measured by plethysmometry on day 0 (before CFA treatment), day 1 (4 hr after CFA treatment) and days 5, 8, 11, 14, 18 and 21 after CFA treatment. The left paw volume measured days 0 (before CFA treatment), 14, 18 and 21 after administration of CFA in the right paw. For CFA-injected rats, the increase in paw volume (net swelling) on days 1, 5, 8, 11, 14, 18 and 21 was obtained by subtracting the volume at day 0 (acute phase of inflammation); and the left paw volume on days 14, 18 and 21 was obtained by subtracting the volume at day 0 (delayed phase of inflammation). The net swelling of each treatment group was then compared to vehicle-treated group and expressed as percentage of inhibition. Anti-inflammatory activity in this model was denoted by values calculated during the acute phase as well as the delayed phase.

Equipment

Animal cage (Allentown, USA), Glass syringe (1 mL, Mitsuba, Japan), Hypodermic needle (27G x 1", Top Corporation, Japan), Stainless forceps (Klappenecker, Germany), Stainless scissors (Klappenecker, Germany) and TERUMO Syringe with the needle (1 mL, TERUMO CO., Philippines). Plethysmometer (PV-01 Paw volume apparatus, SINGA Technology Co. R. O. C), Rat scale (1 ~ 1000 g, TANITA, Japan) and Rat oral needle (Natsume, Japan), Centrifuge 5810R (Eppendorf, Germany), Eppendorf tube (2 mL, Safe-lock, Eppendorf, Germany), Micropipettes (100 P & 200 P, Gilson, France)

Results

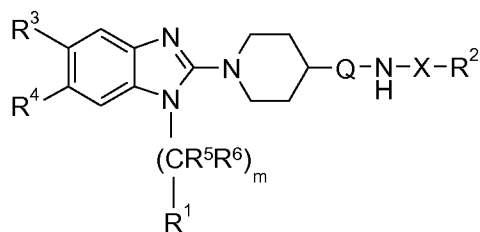
Maximum inhibition of paw swelling in EXAMPLE 41-treated animals compared to vehicle-treated animals was recorded on day 1 and 14 for acute and delayed phase, respectively (figure qz2).

Conclusion

Oral administration of EXAMPLE 41 inhibits CFA-induced paw swelling in rats.

CLAIMS

1. A compound of formula (I)



5 (I)

wherein

R¹ is selected from branched or unbranched C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl; C₃-C₁₀ cycloalkyl; C₄-C₁₀ cycloalkenyl; C₈-C₁₀ cycloalkynyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or cycloalkynyl moiety optionally is substituted with 1, 2 or 3 groups R^a; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b;

R² is selected from branched or unbranched C₁-C₉ alkyl, C₂-C₉ alkenyl, or C₂-C₉ alkynyl; C₃-C₆ cycloalkyl; C₄-C₆ cycloalkenyl; C₈-C₁₀ cycloalkynyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or cycloalkynyl moiety optionally is substituted with 1, 2 or 3 groups R^a; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b;

R³ and R⁴ are each independently selected from C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₄ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; halogen; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; and C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; wherein any alkyl, alkenyl, alkynyl or cycloalkyl moiety optionally is substituted with 1, 2, or 3 groups R^c;

R⁵ and R⁶ are independently selected from hydrogen; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; and halogen; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2, or 3 groups R^c;

X represents a bond or branched or unbranched C₁-C₃ alkyl, C₂-C₃ alkenyl or C₂-C₃ alkynyl;

Q represents carbonyl, sulfonyl or sulfinyl;

m is an integer of 0, 1 or 2;

each R^a is independently selected from halogen; hydroxy; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^b is independently selected from halogen; carboxy; hydroxy; cyano; C₁-C₅ heteroaryl; C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₂-C₄ alkenyloxy; C₂-C₄ alkynyloxy; C₃-C₅ cycloalkyloxy; C₁-C₄ alkylthio; C₂-C₄ alkenylthio; C₂-C₄ alkynylthio; C₃-C₅ cycloalkylthio; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amino; aminocarbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary amido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl carbonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl sulfonyl; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary sulphonamido; C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl secondary or tertiary acylsulphonamido; C₁-C₄ alkyloxy, C₂-C₄ alkenyloxy, or C₂-C₄ alkynyloxy carbonyl; C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^c is independently selected from fluorine and chlorine;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

R¹ is selected from branched or unbranched C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1, 2 or 3 groups R^a; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b;

R² is selected from branched or unbranched C₁-C₉ alkyl; C₃-C₆ cycloalkyl; C₁-C₉ heterocyclyl; and C₆-C₁₀ aryl; wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or cycloalkynyl moiety optionally is substituted with 1, 2 or 3 groups R^a; and any heterocyclyl or aryl moiety optionally is substituted with 1, 2, 3, 4 or 5 groups R^b;

R³ and R⁴ are each independently selected from C₁-C₄ alkyl and halogen, wherein any alkyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

R⁵ and R⁶ are independently selected from hydrogen and C₁-C₄ alkyl, wherein any alkyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

X represents a bond or branched or unbranched C₁-C₃ alkyl;

Q represents carbonyl;

m is 0 or 1;

each R^a is independently selected from hydroxy; C₁-C₄ alkyloxy; C₁-C₄ alkyl secondary or tertiary amino; wherein any alkyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^b is independently selected from halogen; carboxy; cyano; C₁-C₅ heteroaryl, C₁-C₄ alkyl; C₃-C₅ cycloalkyl; C₁-C₄ alkyloxy; C₃-C₅ cycloalkyloxy; aminocarbonyl; C₁-C₄ alkyl secondary or tertiary amido; C₁-C₄ alkyl carbonyl; C₁-C₄ alkyloxy carbonyl; C₁-C₄ alkyl secondary or tertiary acylsulphonamido; and C₁-C₅ heterocyclyl; wherein any alkyl, alkenyl or alkynyl moiety optionally is substituted with 1, 2 or 3 groups R^c;

each R^c is fluoro or is absent;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2, wherein

R¹ is selected from branched or unbranched C₁-C₁₀ alkyl; C₃-C₆ cycloalkyl; 5- or 6-membered C₃-C₅ heterocyclyl; and phenyl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a; and any heterocyclyl or phenyl moiety optionally is substituted with 1 or 2 groups R^b;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3, wherein R¹ is selected from branched or unbranched C₁-C₁₀ alkyl, optionally substituted with 1 or 2 groups R^a;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 3, wherein R^1 is selected from C_3 - C_6 cycloalkyl, optionally substituted with 1 or 2 groups R^a ;
or a pharmaceutically acceptable salt thereof.

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6. A compound according to claim 3, wherein R^1 is selected from 5- or 6-membered C_3 - C_5 heterocyclyl optionally substituted with 1 or 2 groups R^b ;
or a pharmaceutically acceptable salt thereof.

10 7. A compound according to any one of the claims 1-6, wherein R^2 is selected from branched or unbranched C_1 - C_6 alkyl; C_3 - C_6 cycloalkyl; 5- or 6-membered C_3 - C_5 heterocyclyl; and phenyl; wherein any alkyl or cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a ; and any heterocyclyl or phenyl moiety optionally is substituted with 1 or 2 groups R^b ;
or a pharmaceutically acceptable salt thereof.

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8. A compound according to claim 7, wherein R^2 is selected from C_3 - C_6 cycloalkyl, 5-membered C_3 - C_4 heterocyclyl and 6-membered C_3 - C_5 heterocyclyl, wherein any cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a ; and any heterocyclyl moiety optionally is substituted with 1 or 2 groups R^b ;

20 or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 7, wherein R^2 is selected from C_4 - C_6 cycloalkyl and 5- or 6-membered C_4 - C_5 heterocyclyl, wherein any cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a ; and any heterocyclyl moiety optionally is substituted with 1 or 2 groups R^b ; or a
25 pharmaceutically acceptable salt thereof.

10. A compound according to claim 7, wherein R^2 is selected from C_4 - C_6 cycloalkyl and 5-membered C_3 - C_4 heterocyclyl, wherein any cycloalkyl moiety optionally is substituted with 1 or 2 groups R^a ; and any heterocyclyl moiety optionally is substituted with 1 or 2 groups R^b ;
30 or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 7, wherein R^2 is selected from pentyl, optionally substituted with 1 or 2 groups R^a ; and tetrahydrofuryl, optionally substituted with 1 or 2 groups R^b ;
or a pharmaceutically acceptable salt thereof.

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12. A compound according to claim 7, wherein R^2 is selected from branched or unbranched C_1 - C_6 alkyl;
or a pharmaceutically acceptable salt thereof.
- 5 13. A compound according to any one of the claims 1-12, wherein R^3 and R^4 are each independently selected from methyl and chloro, wherein any methyl optionally is substituted with 1, 2 or 3 groups R^c ;
or a pharmaceutically acceptable salt thereof.
- 10 14. A compound according to any one of the claims 1-13, wherein R^5 and R^6 are each independently selected from hydrogen and methyl, wherein any methyl optionally is substituted with 1, 2 or 3 groups R^c ;
or a pharmaceutically acceptable salt thereof.
- 15 15. A compound according to claim 14, wherein R^5 and R^6 are each hydrogen;
or a pharmaceutically acceptable salt thereof.
16. A compound according to claim 14, wherein R^5 is hydrogen and R^6 is methyl;
or a pharmaceutically acceptable salt thereof.
- 20 17. A compound according to any one of the claims 1-16, wherein X represents a bond or methylene;
or a pharmaceutically acceptable salt thereof.
- 25 18. A compound according to claim 17, wherein X represents a bond;
or a pharmaceutically acceptable salt thereof.
19. A compound according to any one of the claims 1 to 18, wherein m is 0;
or a pharmaceutically acceptable salt thereof.
- 30 20. A compound according to any one of the claims 1 to 19, wherein R^c is absent;
or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 1, wherein R¹ represents C₁-C₁₀ alkyl; R² represents C₄-C₆ cycloalkyl or C₄-C₅ heterocyclyl; R³ and R⁴ are independently selected from methyl and chlorine; R⁵ is hydrogen; X represents a bond; and Q represents carbonyl; or a pharmaceutically acceptable salt thereof.

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22. A compound according to claim 1, wherein R¹ represents C₃-C₆ cycloalkyl; R² represents C₄-C₆ cycloalkyl or C₄-C₅ heterocyclyl; R³ and R⁴ are independently selected from methyl and chlorine; X represents a bond and Q represents carbonyl; or a pharmaceutically acceptable salt thereof.

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23. A compound according to claim 1, wherein R¹ represents phenyl or C₄-C₅ heterocyclyl; R² represents C₄-C₆ cycloalkyl or C₄-C₅ heterocyclyl; R³ and R⁴ are independently selected from methyl or chlorine; X represents a bond; and Q represents carbonyl; or a pharmaceutically acceptable salt thereof.

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24. A compound according to claim 1, wherein R¹ represents phenyl or C₄-C₅ heterocyclyl, optionally substituted with one or more R^b; R² represents cyclopentyl; R³ and R⁴ are independently selected from methyl and chlorine; the integer m is equal to 1 or 0 (zero); R⁵ and R⁶ are hydrogen; X represents a bond; and Q represents carbonyl;

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or a pharmaceutically acceptable salt thereof.

25. A compound according to claim 1, wherein R¹ represents C₁-C₁₀ alkyl; R² represents C₁-C₉ alkyl; R³ and R⁴ are independently selected from methyl and chlorine; R⁵ and R⁶ are hydrogen; and Q represents carbonyl;

25

or a pharmaceutically acceptable salt thereof.

26. A compound according to claim 1, wherein R¹ represents C₄-C₅ saturated heterocyclyl; R² represents cyclopentyl; R³ and R⁴ are independently selected from methyl and chlorine; the integer m is equal to 1; R⁵ and R⁶ are hydrogen; X represents a bond; and Q represents carbonyl; or a pharmaceutically acceptable salt thereof.

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27. A compound according to claim 1, wherein R¹ represents C₃-C₅ cycloalkyl; R² represents cyclopentyl or tetrahydrofuranyl; R³ and R⁴ are independently selected from methyl and chlorine; the integer m is equal to either 0 (zero) or 1; R⁵ and R⁶ are hydrogen; X represents a bond; and Q represents carbonyl;

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or a pharmaceutically acceptable salt thereof.

28. A compound according to claim 1, selected from

- N*-cyclopentyl-1-(1-ethyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-propyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-heptyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-octyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 *N*-cyclopentyl-1-(1-hexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 15 *N*-cyclopentyl-1-(1-(2-(diethylamino)ethyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-4-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 20 *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-2-ylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-sec-butyl-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(1-phenylethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 30 *N*-cyclopentyl-1-(5,6-dichloro-1-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-ethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- N*-cyclopentyl-1-(1-(3,5-difluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- methyl 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoate;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-((2-methylthiazol-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopropyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 *N*-cyclobutyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-propylpiperidine-4-carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(2-methoxyethyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(isopropoxymethyl)piperidine-4-
- 15 carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- N*-(cyclohexylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 20 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)piperidine-4-carboxamide;
- N*-butyl-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(cyclopentylmethyl)-1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-cyanobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(cyclopropylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 30 carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;

- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-(4-bromobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-(dimethylcarbamoyl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-carbamoylbenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentyl-piperidine-4-carboxamide;
- 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 20 carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 25 *N*-cyclopentyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 30 carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydrofuran-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- N*-cyclopentyl-1-(5,6-dichloro-1-(4-(methylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 1-(1-(4-carbamoylbenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(1-cyclopentyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-chlorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(4-(methylsulfonylcarbamoyl)benzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 15 *N*-butyl-1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-butyl-1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-
- 20 4-carboxamide;
1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(5,6-dichloro-1-(4-cyanobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-(cyclopropylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-((6-fluoropyridin-3-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-
- 30 3-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(5,6-dichloro-1-cyclopentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- 1-(1-(4-bromobenzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(4-(1*H*-tetrazol-5-yl)benzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-
5 cyclopentylpiperidine-4-carboxamide;
1-(5,6-dichloro-1-(4-fluorobenzyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
1-(1-(4-(1*H*-1,2,4-triazol-1-yl)benzyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
10 *N*-cyclopentyl-1-(5,6-dichloro-1-(2-methoxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-(cyclobutylmethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
15 carboxamide;
N-cyclopentyl-1-(5,6-dimethyl-1-(prop-2-ynyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1-(2-ethylbutyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
20 *N*-cyclopentyl-1-(5,6-dimethyl-1-neopentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
1-(1-cyclohexyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
1-(1-sec-butyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentyl-piperidine-4-
25 carboxamide;
N-cyclopentyl-1-(5,6-dichloro-1-(2-hydroxyethyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1,5,6-trimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1-isobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
30 1-(1-benzyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
N-cyclopentyl-1-(1-(2-methoxyethyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
N-cyclopentyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;

- 1-(5-chloro-1-cyclobutyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-1-cyclobutyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(5,6-dimethyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 *N*-butyl-1-(1-((6-fluoropyridin-3-yl)methyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-butyl-1-(1-(4-fluorobenzyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-benzyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 15 *N*-(4-fluorobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(3-isopropoxypropyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(3,3-dimethylbutyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 20 carboxamide;
- N*-(4-bromobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclohexyl-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-(4-cyanobenzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 25 carboxamide;
- (*S*)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 4-((2-(4-(cyclopentylcarbamoyl)piperidin-1-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)methyl)benzoic acid
- 30 1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiazol-2-ylmethyl)piperidine-4-carboxamide;
- N*-(4-(1*H*-tetrazol-5-yl)benzyl)-1-(1-isopropyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-
- 35 yl)piperidine-4-carboxamide;

- N*-cyclopentyl-1-(5,6-dimethyl-1-(pentan-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(1-(4-bromophenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(1-(benzo[d][1,3]dioxol-5-yl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 *N*-cyclopentyl-1-(5,6-dimethyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 35

- N*-cyclopentyl-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 5 *N*-cyclopentyl-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dimethyl-1-(quinoxalin-6-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 10 1-(5,6-dichloro-1-(4-(methylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 15 *N*-cyclopentyl-1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- N*-cyclopentyl-1-(5,6-dichloro-1-(4-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 20 carboxamide;
- (*R*)-1-(5,6-dichloro-1-(4-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (*R*)-1-(5,6-dichloro-1-(4-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(4-tert-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(4-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-
- 30 (tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- 1-(5,6-dichloro-1-(pyridin-3-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(1-(4-chloro-3-methoxyphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-chloro-3-methoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(2,3-dihydrobenzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5,6-dichloro-1-(2,3-dihydrobenzofuran-5-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3,5-diethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 1-(5,6-dichloro-1-(cyclobutylmethyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-fluoro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-(quinolin-6-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(1-(4-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-*tert*-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- (R)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(6-chloro-5-methyl-1-p-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(1-(4-carbamoylphenyl)-5-chloro-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- (R)-1-(1-(4-carbamoylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 15 1-(5-chloro-6-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 1-(6-chloro-5-methyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;;
- (R)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (S)-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- N*-butyl-1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide; *N*-butyl-1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-
- 30 4-carboxamide;
- 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- 1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5-chloro-1-(cyclobutylmethyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 5 1-(6-chloro-1-(cyclobutylmethyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(5-chloro-6-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-5-methyl-1-pentyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
- 1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 15 1-(5-chloro-6-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-5-methyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- N*-butyl-1-(5-chloro-1-cyclobutyl-6-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-
- 20 carboxamide;
- N*-butyl-1-(6-chloro-1-cyclobutyl-5-methyl-1*H*-benzo[d]imidazol-2-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dimethyl-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (*R*)-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dimethyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-ethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 30 yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-isopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(3-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-fluoro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dichloro-1-(3,5-difluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-cyanophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5,6-dichloro-1-(5-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(6-methoxypyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(3-isopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(5,6-dichloro-1-(3-(difluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-(trifluoromethoxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5,6-dichloro-1-(4-isobutylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3,4-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-chlorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 (R)-1-(5,6-dichloro-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(5-fluoropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(1-(4-isobutylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(1-(4-chloro-3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-chloro-3-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3,5-diethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(1-(3-tert-butylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-tert-butylphenyl)-5,6-dichloro-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-
- 20 carboxamide;
- (R)-1-(5,6-dichloro-1-(3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-ethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5,6-dichloro-1-(6-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-isopropoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 30 yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-propoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-fluoro-3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(4-chloro-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-chloro-4-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(5,6-dimethyl-1-phenyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-
- 10 carboxamide;
- (R)-1-(1-(3-cyanophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-(naphthalen-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(1-(4-chloro-3-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-chloro-4-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(benzo[d]thiazol-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 20 yl)piperidine-4-carboxamide;
- (R)-1-(1-(benzo[d]thiazol-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(3,4-dimethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(6-chloro-1-(3,4-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-isopropylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-1-(4-isopropylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-
- 30 3-yl)piperidine-4-carboxamide;
- (S)-1-(5-chloro-6-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (S)-1-(6-chloro-5-methyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (S)-1-(6-chloro-1-(3,5-dimethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;
- (R)-1-(1-(benzofuran-5-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(5,6-dichloro-1-(4-fluoro-3,5-dimethylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-fluoro-5-methylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dichloro-1-(3-fluoro-5-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-cyclopropylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(1-(benzofuran-6-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(6-chloro-1-(4-ethylphenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-1-(4-ethylphenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-*tert*-butylphenyl)-6-chloro-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 (R)-1-(1-(4-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3-cyclopropylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(3-(cyclopentyloxy)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(3-cyclobutoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 1-(5-chloro-6-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(6-chloro-5-fluoro-1-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(5-chloro-1-ethyl-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 10 carboxamide;
- 1-(6-chloro-1-ethyl-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(5-chloro-6-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 15 1-(6-chloro-5-fluoro-1-isopropyl-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-butyl-5-chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-carboxamide;
- 1-(1-butyl-6-chloro-5-fluoro-1*H*-benzo[d]imidazol-2-yl)-*N*-cyclopentylpiperidine-4-
- 20 carboxamide;
- 1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-1-(4-fluorophenyl)-5-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5-chloro-1-(4-fluorophenyl)-6-methyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-5-methyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-6-methyl-1-*m*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-
- 30 yl)piperidine-4-carboxamide;
- (R)-1-(5-chloro-6-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(6-chloro-5-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide;
- 5 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((2*S*)-2-propoxycyclopentyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-(4-(dimethylcarbamoyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)piperidine-4-carboxamide;
- 10 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-methoxycyclopentyl)piperidine-4-carboxamide;
- 1-(5,6-dichloro-1-cyclobutyl-1*H*-benzo[d]imidazol-2-yl)-*N*-((1*S*,2*S*)-2-ethoxycyclopentyl)piperidine-4-carboxamide;
- 15 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(furan-2-ylmethyl)piperidine-4-carboxamide;
- 1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(thiophen-2-ylmethyl)piperidine-4-carboxamide;
- (*R*)-1-(1-(5-bromopyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (*R*)-1-(1-(5-ethylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(1-(3-chloro-5-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (*R*)-1-(5,6-dichloro-1-(3-chloro-5-fluorophenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(3-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 (*S*)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (*R*)-1-(5,6-dichloro-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;

- (R)-1-(5,6-dichloro-1-(5-chloropyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 5 (R)-1-(1-(3-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(3,5-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-fluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 10 (R)-1-(1-(3,5-difluorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(4-chlorophenyl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 15 (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dimethyl-1-*p*-tolyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(5-chloropyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 20 (R)-1-(5,6-dimethyl-1-(4-(trifluoromethyl)pyridin-2-yl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(1-(5-fluoro-6-methylpyridin-2-yl)-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 25 (R)-1-(5,6-dichloro-1-(4-ethoxyphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- (R)-1-(5,6-dichloro-1-(4-methoxy-3-methylphenyl)-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide; and
- (R)-1-(1-cyclobutyl-5,6-dimethyl-1*H*-benzo[d]imidazol-2-yl)-*N*-(tetrahydrofuran-3-yl)piperidine-4-carboxamide;
- 30 or a pharmaceutically acceptable salt thereof.

29. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use as a medicament.

30. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, in admixture with at least one pharmaceutically acceptable adjuvant, diluent or carrier.

5 31. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of an inflammatory disease, said disease preferably being selected from rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, psoriasis, eczema, swelling and periodontitis.

10 32. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of nociceptive pain, said pain preferably being selected from inflammatory pain, post-operative pain, fibromyalgia, dysmenorrhea, migraine, arthrotic pain, arthritic pain, pain in connection with osteoarthritis, cephalalgia, pain due to gall-stones, pain due to metastasis, pain due to ankylosing spondylitis, pain due to gout,
15 toothache and pain due to rheumatic fever, or for use in the preemptive treatment of surgical pain.

33. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of an autoimmune disease, said
20 autoimmune disease preferably being selected from rheumatoid arthritis and multiple sclerosis.

34. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a breathing disorder, said disorder preferably being selected from apnea or other respiratory distress symptoms in adults and
25 children, sudden infant death syndrome (SIDS), asthma and other chronic obstructive lung-diseases and sarcoidosis.

35. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of cancer, said cancer preferably being
30 selected from familial adenomatous polyposis (FAP) condition, colorectal cancer, breast cancer, gastric tumorigenesis and epithelial ovarian cancer, or cellular neoplastic transformations and metastatic tumor growth.

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36. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of a cardiovascular disease due to atherosclerosis, such as myocardial infarction and stroke.

5 37. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of fever-related or inflammation-related anorexia.

10 38. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of Alzheimer's disease.

39. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of endometriosis.

15 40. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of hemophilic arthropathy.

41. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of diabetic retinopathy.

20 42. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of and tumor angiogenesis.

25 43. A compound according to any one of the claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of premature labor.

44. A combination product comprising: (A) a compound according to any one of the claims 1 to 28, or a pharmaceutically-acceptable salt thereof, and (B) another therapeutic agent, wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable
30 adjuvant, diluent or carrier.

45. A combination product as claimed in claim 44, wherein the other therapeutic agent is an agent useful in the treatment of inflammation.

46. A combination product as claimed in claim 44 or claim 45, which comprises a kit of parts comprising components: (A) a pharmaceutical formulation including a compound as defined above, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and (B) a pharmaceutical formulation including another therapeutic agent in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

47. A method of treatment of a disorder selected from an inflammatory disease, nociceptive pain, an autoimmune disease, a breathing disorder, cancer, a cardiovascular disease due to atherosclerosis, fever or inflammation-related anorexia, or Alzheimer's disease, which method comprises administration of a therapeutically effective amount of a compound according to any one of the claims 1 to 28, or a pharmaceutically-acceptable salt thereof, to a mammal subject suffering from, or susceptible to, such a disorder.

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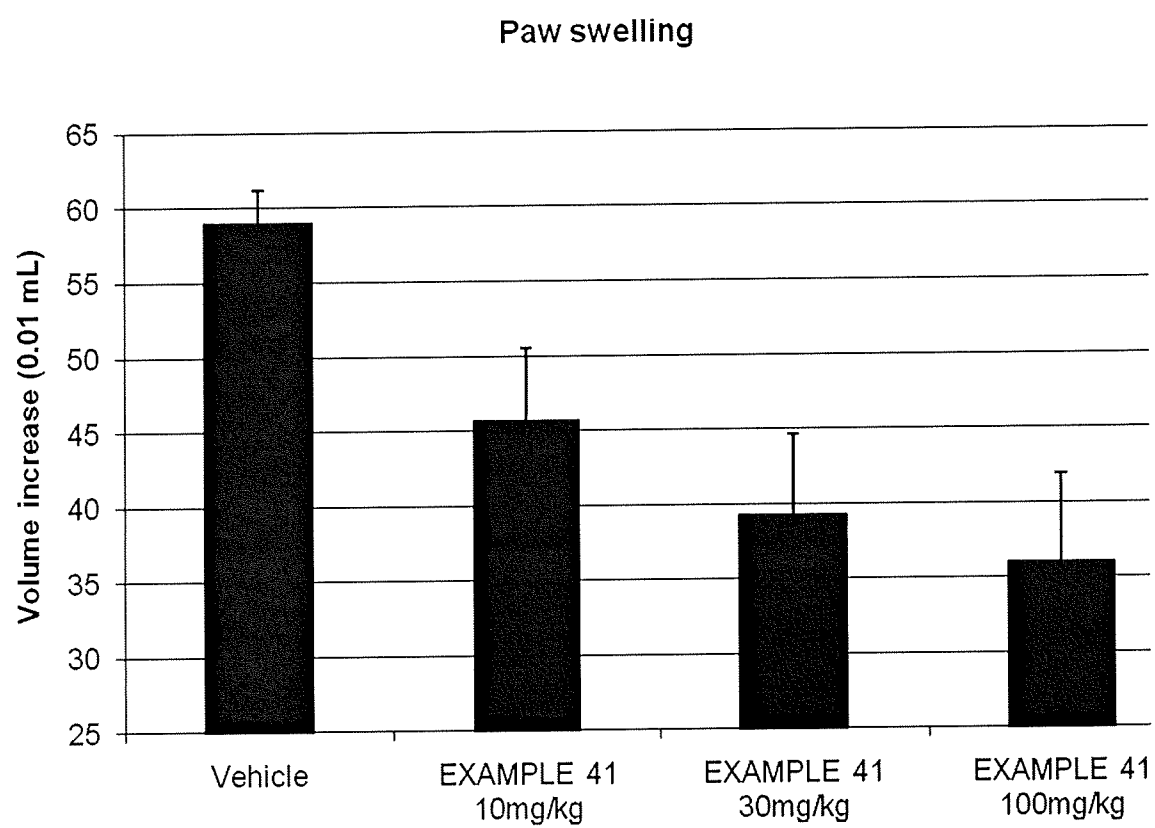


Fig. 1

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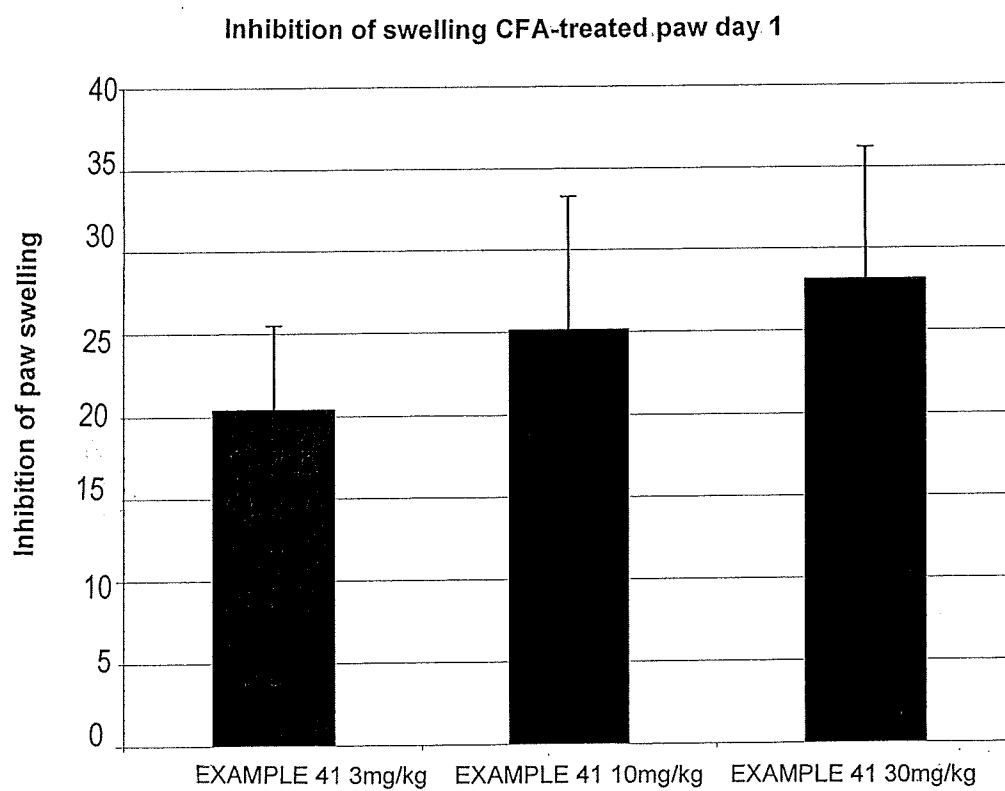


Fig. 2A

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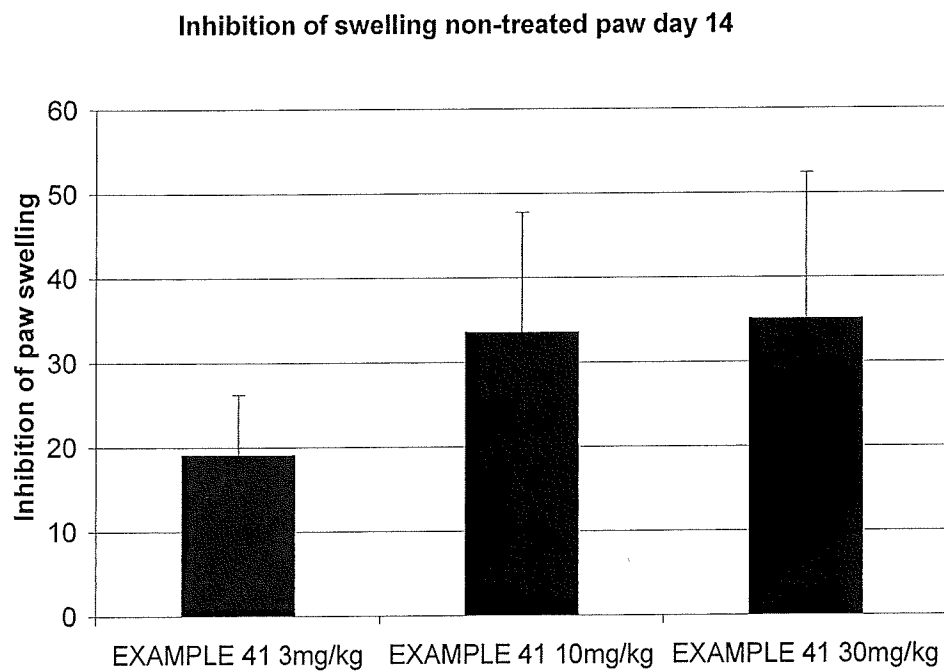


Fig. 2B

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/062596

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D401/14 C07D407/14 C07D417/14 A61K31/454
A61K31/454 A61P9/00 A61P11/00 A61P25/28 A61P29/00
A61P35/00 A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

A	WO 2008/084218 A (BOEHRINGER INGELHEIM INT [DE]; BIOLIPOX AB [SE]; HAUER NORBERT [DE]; A) 17 July 2008 (2008-07-17) cited in the application claims 1, 14, 16 pages 58-65; examples 22-30	1-47

A	JACHAK S M: "PGE synthase inhibitors as an alternative to COX-2 inhibitors" CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 8, no. 5, 1 May 2007 (2007-05-01), pages 411-415, XP009124702 ISSN: 1472-4472 the whole document	1-47

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

15 October 2010

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22/10/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/062596

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008084218 A	17-07-2008	NONE	